4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

EDITOR
STEPHEN L. HAUSER

ASSOCIATE EDITOR
S. ANDREW JOSEPHSON

Mc Graw Hill Education

www.ketabpezeshki.com (021) 66485457 - 66485438

4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

www.ketabpezeshki.com (021) 66485457 - 66485438

Derived from Harrison's Principles of Internal Medicine, 19th Edition

Editors

DENNIS L. KASPER, md
William Ellery Channing Professor of Medicine,
Professor of Microbiology and Immunobiology,
Department of Microbiology and Immunobiology,
Harvard Medical School; Division of Infectious Diseases,
Brigham and Women's Hospital, Boston, Massachusetts

ANTHONY S. FAUCI, md
Chief, Laboratory of Immunoregulation; Director,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, Maryland

STEPHEN L. HAUSER, md
Director, UCSF Weill Institute for Neurosciences,
Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology, University of California,
San Francisco, San Francisco, California

DAN L. LONGO, md
Professor of Medicine, Harvard Medical School; Senior Physician,
Brigham and Women's Hospital; Deputy Editor, New England
Journal *of* Medicine, Boston, Massachusetts

J. LARRY JAMESON, md, phd
Robert G. Dunlop Professor of Medicine; Dean,
Perelman School of Medicine at the University of Pennsylvania;
Executive Vice President, University of Pennsylvania for the Health
System, Philadelphia, Pennsylvania

JOSEPH LOSCALZO, md, phd
Hersey Professor of the T eory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine,
and Physician-in-Chief, Brigham and Women's Hospital,
Boston, Massachusetts

www.ketabpezeshki.com (021) 66485457 - 66485438

4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

EDITOR

Stephen L. Hauser, MD
Director, UCSF Weill Institute for Neurosciences
Robert A. Fishman Distinguished Professor and Chairman
Department of Neurology
University of California, San Francisco, San Francisco, California

ASSOCIATE EDITOR

S. Andrew Josephson, MD
C. Castro-Franceschi and G. Mitchell Endowed Neurohospitalist Professor
Senior Executive Vice-Chairman, Department of Neurology
University of California, San Francisco, San Francisco, California

Mc Graw Hill Education

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

www.ketabpezeshki.com (021) 66485457 - 66485438

کتاب پزشکی

66485457 - 66485438

www.ketabpezeshki.com

Copyright © 2017 by McGraw-Hill Education. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-25-983587-2
MHID: 1-26-001210-7.

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-986096-6,
MHID: 1-25-986096-5.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Dr. Fauci's work as an editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

www.ketabpezeshki.com (021) 66485457 - 66485438

CONTENTS

Contributors ix

Preface xiii

SECTION I
INTRODUCTION TO NEUROLOGY

1 Approach to the Patient with Neurologic Disease . . 2
Daniel H. Lowenstein, Joseph B. Martin, Stephen L. Hauser

2 T e Neurologic Screening Exam 11
Daniel H. Lowenstein

3 Video Atlas of the Detailed Neurologic Examination 12
Martin A. Samuels

4 Neuroimaging in Neurologic Disorders 13
William P. Dillon

5 Atlas of Neuroimaging 27
Andre D. Furtado, William P. Dillon

6 Electrodiagnostic Studies of Nervous System Disorders: EEG, Evoked Potentials, and EMG . . . 71
Michael J. Amino*ff*

7 Technique of Lumbar Puncture 80
Elizabeth Robbins, Stephen L. Hauser

SECTION II
CLINICAL MANIFESTATIONS OF NEUROLOGIC DISEASE

8 Pain: Pathophysiology and Management 88
James P. Rathmell, Howard L. Fields

9 Headache 100
Peter J. Goadsby, Neil H. Raskin

10 Back and Neck Pain 107
John W. Engstrom, Richard A. Deyo

11 Syncope 125
Roy Freeman

12 Dizziness and Vertigo 135
Mark F. Walker, Robert B. Daro*ff*

13 Fatigue 140
Je*ff*rey M. Gel*f*and, Vanja C. Douglas

14 Neurologic Causes of Weakness and Paralysis . . . 144
Michael J. Amino*ff*

15 Numbness, Tingling, and Sensory Loss 150
Michael J. Amino*ff*

16 Gait and Balance Disorders 157
Lewis Sudarsky

17 Video Library of Gait Disorders 163
Gail Kang, Nicholas B. Galif anakis, Michael D. Geschwind

18 Confusion and Delirium 164
S. Andrew Josephson, Bruce L. Miller

19 Coma 171
Allan H. Ropper

20 Examination of the Comatose Patient 181
S. Andrew Josephson

21 Dementia 182
William W. Seeley, Bruce L. Miller

22 Aphasia, Memory Loss, and Other Focal Cerebral Disorders 191
M.-Marsel Mesulam

23 Primary Progressive Aphasia, Memory Loss, and Other Focal Cerebral Disorders 204
Maria Luisa Gorno-*T*empini, Jenni*f*er Ogar, Joel Kramer, Bruce L. Miller, Gil Rabinovici, Maria Carmela *T*artaglia

24 Sleep Disorders 205
Charles A. Czeisler, T omas E. Scammell, Cli*ff*ord B. Saper

25 Disorders of the Eye 221
Jonathan C. Horton

26 Use of the Hand-Held Ophthalmoscope 245
Homayoun *T*abandeh, Morton F. Goldberg

27 Video Library of Neuro-Ophthalmology 253
Shirley H. Wray

28 Disorders of Smell and Taste 255
Richard L. Doty, Steven M. Bromley

29 Disorders of Hearing 264
Anil K. Lalwani

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION III
DISEASES OF THE NERVOUS SYSTEM

30 Biology of Neurologic Diseases 278
Stephen L. Hauser, Stanley B. Prusiner, M. Flint Beal

31 Seizures and Epilepsy 297
Daniel H. Lowenstein

32 Cerebrovascular Diseases 323
Wade S. Smith, S. Claiborne Johnston, J. Claude Hemphill

33 Neurologic Critical Care, Including Hypoxic-Ischemic Encephalopathy, and Subarachnoid Hemorrhage 361
J. Claude Hemphill, III, Wade S. Smith, Daryl R. Gress

34 Migraine and Other Primary Headache Disorders 376
Peter J. Goadsby, Neil H. Raskin

35 Alzheimer's Disease and Other Dementias 392
William W. Seeley, Bruce L. Miller

36 Parkinson's Disease and Other Movement Disorders 408
C. Warren Olanow, Anthony H.V. Schapira, Jose A. Obeso

37 Ataxic Disorders 435
Roger N. Rosenberg

38 Classification of the Spinocerebellar Ataxias 443
Roger N. Rosenberg

39 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases 449
Robert H. Brown, Jr.

40 Prion Diseases 459
Stanley B. Prusiner, Bruce L. Miller

41 Disorders of the Autonomic Nervous System . . . 469
Phillip A. Low, John W. Engstrom

42 Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders 481
M. Flint Beal, Stephen L. Hauser

43 Diseases of the Spinal Cord 490
Stephen L. Hauser, Allan H. Ropper

44 Concussion and Other Traumatic Brain Injuries 505
Allan H. Ropper

45 Multiple Sclerosis and Other Demyelinating Diseases 513
Stephen L. Hauser, Douglas S. Goodin

46 Meningitis, Encephalitis, Brain Abscess, and Empyema 533
Karen L. Roos, Kenneth L. Tyler

47 Chronic and Recurrent Meningitis 568
Walter J. Koroshetz, Avindra Nath

48 HIV Neurology 577
Anthony S. Fauci, H. Clifford Lane

49 Primary and Metastatic Tumors of the Nervous System 591
Lisa M. DeAngelis, Patrick Y. Wen

50 Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis 606
Josep Dalmau, Myrna R. Rosenfeld

51 Anterior Pituitary Tumor Syndromes 615
Shlomo Melmed, J. Larry Jameson

52 Disorders of the Neurohypophysis 635
Gary L. Robertson

53 Peripheral Neuropathy 648
Anthony A. Amato, Richard J. Barohn

54 Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies 681
Stephen L. Hauser, Anthony A. Amato

55 Myasthenia Gravis and Other Diseases of the Neuromuscular Junction 691
Daniel B. Drachman, Anthony A. Amato

56 Muscular Dystrophies and Other Muscle Diseases 700
Anthony A. Amato, Robert H. Brown, Jr.

57 Polymyositis, Dermatomyositis, and Inclusion Body Myositis 730
Marinos C. Dalakas

58 Special Issues in Inpatient Neurologic Consultation 742
S. Andrew Josephson, Martin A. Samuels

SECTION IV
CHRONIC FATIGUE SYNDROME

59 Chronic Fatigue Syndrome 752
Gijs Bleijenberg, Jos W. M. van der Meer

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION V
PSYCHIATRIC DISORDERS

60 Biology of Psychiatric Disorders 758
Robert O. Messing, Eric J. Nestler

61 Mental Disorders 765
Victor I. Reus

62 Neuropsychiatric Illnesses in War Veterans 788
Charles W. Hoge

SECTION VI
ALCOHOLISM AND DRUG DEPENDENCY

63 Alcohol and Alcoholism 798
Marc A. Schuckit

64 Opioid-Related Disorders 807
T omas R. Kosten, Colin N. Haile

65 Cocaine and Other Commonly Abused Drugs 813
Nancy K. Mello, Jack H. Mendelson

66 Nicotine Addiction 821
David M. Burns

Appendix
Laboratory Values of Clinical Importance 827
Alexander Kratz, Michael A. Pesce, Robert C. Basner, Andrew J. Einstein

Review and Self-Assessment 849
Charles M. Wiener, Cynthia D. Brown, Brian Houston

Index 887

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or co-written by the contributor.

Anthony A. Amato, MD
Professor of Neurology, Harvard Medical School; Vice-Chairman, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [53–56]

Michael J. Aminoff, MD, DSc, FRCP
Professor of Neurology, School of Medicine, University of California, San Francisco, San Francisco, California [6, 14, 15]

Richard J. Barohn, MD
Chairman, Department of Neurology; Gertrude and Dewey Ziegler Professor of Neurology, University of Kansas Medical Center, Kansas City, Kansas [53]

Robert C. Basner, MD
Professor of Clinical Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York [Appendix]

M. Flint Beal, MD
University Professor of Neurology and Neuroscience; Neurologist, New York Presbyterian Hospital; Weill Cornell Medical College, New York, New York [30, 42]

Gijs Bleijenberg, PhD
Professor Emeritus, Expert Centre for Chronic Fatigue, Radboud University Medical Centre, Nijmegen, T e Netherlands [59]

Steven M. Bromley, MD
Director, Outpatient Services, Virtua Neuroscience, Voorhees, New Jersey; Director, Bromley Neurology, PC, Audubon, New Jersey [28]

Cynthia D. Brown, MD
Associate Professor of Clinical Medicine, Division of Pulmonary, Critical Care, Sleep and Occupational Medicine, Indiana University, Indianapolis, Indiana [Review and Self-Assessment]

Robert H. Brown, Jr., MD, PhD
Chairman, Department of Neurology, University of Massachusetts Medical School, Worchester, Massachusetts [39, 56]

David M. Burns, MD
Professor Emeritus, Department of Family and Preventive Medicine, University of California, San Diego School of Medicine, San Diego, California [66]

Charles A. Czeisler, MD, PhD
Frank Baldino, Jr., PhD Professor of Sleep Medicine, Professor of Medicine, and Director, Division of Sleep Medicine, Harvard Medical School; Chief, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, Massachusetts [24]

Marinos C. Dalakas, MD
Professor of Neurology, University of Athens Medical School, Athens, Greece; T omas Jefferson University, Philadelphia, Pennsylvania [57]

Josep Dalmau, MD, PhD
ICREA Professor, Institut d'Investigació Biomèdica August Pi i Sunyer, University of Barcelona, Barcelona, Spain; Adjunct Professor, University of Pennsylvania, Philadelphia, Pennsylvania [50]

Robert B. Daroff, MD
Professor and Chair Emeritus, Department of Neurology, Case Western Reserve University School of Medicine; University Hospitals–Case Medical Center, Cleveland, Ohio [12]

Lisa M. DeAngelis, MD
Professor of Neurology, Weill Cornell Medical College; Chair, Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York [49]

Richard A. Deyo, MD, MPH
Kaiser Permanente Professor of Evidence-Based Family Medicine, Department of Family Medicine, Department of Medicine, Department of Public Health and Preventive Medicine, Oregon Institute of Occupational Health Sciences; Oregon Health and Science University; Clinical Investigator, Kaiser Permanente Center for Health Research, Portland, Oregon [10]

William P. Dillon, MD
Professor and Executive Vice-Chair; Chief, Section of Neuroradiology, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California [4, 5]

Richard L. Doty, PhD, MA
Director, T e Smell and Taste Center; Professor, Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania [28]

Vanja C. Douglas, MD
Assistant Professor of Clinical Neurology and Sara and Evan Williams Foundation Endowed Neurohospitalist Chair, University of California, San Francisco, San Francisco, California [13]

Daniel B. Drachman, MD
Professor of Neurology and Neuroscience, W. W. Smith Charitable Trust Professor of Neuroimmunology, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland [55]

Andrew J. Einstein, MD, PhD
Victoria and Esther Aboodi Assistant Professor of Medicine; Director, Cardiac CT Research; Co-Director, Cardiac CT and MRI, Department of Medicine, Cardiology Division, Department of Radiology, Columbia University College of Physicians and Surgeons, New York-Presbyterian Hospital, New York, New York [Appendix]

John W. Engstrom, MD
Betty Anker Fife Distinguished Professor and Vice-Chairman; Neurology Residency Program Director, University of California, San Francisco, San Francisco, California [10, 41]

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [48]

Howard L. Fields, MD, PhD
Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [8]

www.ketabpezeshki.com (021) 66485457 - 66485438

Roy Freeman, MD
Professor of Neurology, Harvard Medical School; Director, Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, Boston, Massachusetts [11]

Andre D. Furtado, MD
Assistant Professor, Department of Radiology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania [5]

Nicholas B. Galif anakis, MD, MPH
Assistant Clinical Professor, Surgical Movement Disorders Center, Department of Neurology, University of California, San Francisco, San Francisco, California [17]

Jeffrey M. Gelfand, MD, MAS
Assistant Professor of Clinical Neurology, Department of Neurology, University of California, San Francisco, San Francisco, California [13]

Michael D. Geschwind, MD, PhD
Associate Professor of Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [17]

Peter J. Goadsby, MD, PhD, DSc, FRACp, FRCP
Professor, NIHR-Wellcome Trust Clinical Research Facility, King's College, London, United Kingdom; Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [9, 34]

Morton F. Goldberg, MD, FACS, FAOS
Director Emeritus and Joseph Green Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore, Maryland [26]

Douglas S. Goodin, MD
Professor, Department of Neurology, School of Medicine, University of California, San Francisco, San Francisco, California [45]

Maria Luisa Gorno-Tempini, MD, PhD
Professor, Department of Neurology; Language Neurobiology Lab, Memory and Aging Center; Dyslexia Center, University of California, San Francisco, San Francisco, California [23]

Daryl R. Gress, MD, FAAN, FCCM, FNCS
Associate Professor of Neurology, University of Virginia, Charlottesville, Virginia [33]

Colin N. Haile, MD, PhD
Assistant Professor, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine; Michael E. DeBakey VA Medical Center, Houston, Texas [64]

Stephen L. Hauser, MD
Director, UCSF Weill Institute for Neurosciences, Robert A. Fishman Distinguished Professor and Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California [1, 7, 30, 42, 43, 45, 54]

J. Claude Hemphill, III, MD, MAS
Professor of Neurology and Neurological Surgery, University of California, San Francisco; Chief of Neurology, San Francisco General Hospital, San Francisco, California [32, 33]

Charles W. Hoge, MD
Senior Scientist, Center for Psychiatry and Neuroscience, Walter Reed Army Institute of Research, Silver Spring, Maryland [62]

Jonathan C. Horton, MD, PhD
William F. Hoyt Professor of Neuro-ophthalmology, Professor of Ophthalmology, Neurology, and Physiology, University of California, San Francisco School of Medicine, San Francisco, California [25]

Brian Houston, MD
Division of Cardiology, Department of Medicine Johns Hopkins Hospital Baltimore, Maryland [Review and Self-Assessment]

J. Larry Jameson, MD, PhD
Robert G. Dunlop Professor of Medicine; Dean, Perelman School of Medicine at the University of Pennsylvania; Executive Vice President, University of Pennsylvania for the Health System, Philadelphia, Pennsylvania [51]

S. Clairborne Johnston, MD, PhD
Dean, Dell Medical School; Frank Denius Distinguished Dean's Chair in Medical Leadership; Vice President for Medical Affairs, University of Texas, Austin, Austin, Texas [32]

S. Andrew Josephson, MD
Carmen Castro Franceschi and Gladyne Mitchell Neurohospitalist Distinguished Professor Senior Executive Vice-Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California [18, 20, 58]

Gail Kang, MD
San Francisco, California [17]

Walter J. Koroshetz, MD
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland [47]

T omas R. Kosten, MD
J. H. Waggoner Professor of Psychiatry, Pharmacology, Immunology, Neuroscience, Baylor College of Medicine, Houston, Texas [64]

Joel Kramer, PsyD
Professor of Neuropsychology in Neurology; Director of Neuropsychology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

Alexander Kratz, MD, MPH, PhD
Associate Professor of Clinical Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Core Laboratory, Columbia University Medical Center and New York Presbyterian Hospital; Director, Allen Hospital Laboratory, New York, New York [Appendix]

Anil K. Lalwani, MD
Professor and Vice Chair for Research; Director, Division of Otology, Neurotology, and Skull Base Surgery; Director, Columbia Cochlear Implant Center, Columbia University College of Physicians and Surgeons, New York, New York [29]

H. Clifford Lane, MD
Clinical Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [48]

Phillip A. Low, MD, FRACP, FRCP(Hon)
Robert D. and Patricia E. Kern Professor of Neurology, Mayo Clinic, College of Medicine, Rochester, Minnesota [41]

Daniel H. Lowenstein, MD
Dr. Robert B. and Mrs. Ellinor Aird Professor of Neurology; Director, Epilepsy Center, University of California, San Francisco, San Francisco, California [1, 2, 31]

Joseph B. Martin, MD, PhD
Edward R. and Anne G. Lefler Professor, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts [1]

www.ketabpezeshki.com (021) 66485457 - 66485438

Nancy K. Mello,[1] PhD
Professor of Psychology (Neuroscience), Harvard Medical School, Boston, Massachusetts; Director, Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, Massachusetts [65]

Shlomo Melmed, MD
Senior Vice President and Dean of the Medical Faculty, Cedars-Sinai Medical Center, Los Angeles, California [51]

Jack H. Mendelson,[1] MD
Professor of Psychiatry (Neuroscience), Harvard Medical School, Belmont, Massachusetts [65]

Robert O. Messing, MD
Professor, Division of Pharmacology and Toxicology, College of Pharmacy; Associate Director, Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, Texas [60]

M.-Marsel Mesulam, MD
Professor of Neurology, Psychiatry and Psychology, Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois [22]

Bruce L. Miller, MD
A. W. and Mary Margaret Clausen Distinguished Professor of Neurology, University of California, San Francisco School of Medicine, San Francisco, California [18, 21, 23, 35, 40]

Avindra Nath, MD
Chief, Section of Infections of the Nervous System; Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland [47]

Eric J. Nestler, MD, PhD
Nash Family Professor and Chair, Department of Neuroscience; Director, Friedman Brain Institute, Ichan School of Medicine at Mount Sinai, New York, New York [60]

Jose A. Obeso, MD
Professor of Neurology and Director, CIINAC, Hospital de Madrid; Medical School, CEU-San Pablo, Madrid, Spain [36]

Jennifer Ogar, MS CCC-SLP
Speech-Language Pathologist, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

C. Warren Olanow, MD, FRCPC, FRCP(hon)
Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology; Professor, Department of Neuroscience, Mount Sinai School of Medicine, New York, New York [36]

Michael A. Pesce, PhD
Professor Emeritus of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Biochemical Genetics Laboratory, Columbia University Medical Center, New York Presbyterian Hospital, New York, New York [Appendix]

Stanley B. Prusiner, MD
Director, Institute for Neurodegenerative Diseases; Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [30, 40]

Gil Rabinovici, MD
Associate Professor in Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

Neil H. Raskin, MD
Department of Neurology, University of California, San Francisco, San Francisco, California [9, 34]

James P. Rathmell, MD
Henry Knowles Beecher Professor of Anesthesiology, Harvard Medical School; Executive Vice Chair and Chief, Division of Pain Medicine, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts [8]

Victor I. Reus, MD
Department of Psychiatry, University of California, San Francisco School of Medicine; Langley Porter Neuropsychiatric Institute, San Francisco, California [61]

Elizabeth Robbins, MD
Clinical Professor of Pediatrics, University of California, San Francisco, San Francisco, California [7]

Gary L. Robertson, MD
Emeritus Professor of Medicine, Northwestern University School of Medicine, Chicago, Illinois [52]

Karen L. Roos, MD
John and Nancy Nelson Professor of Neurology; Professor of Neurological Surgery, Indiana University School of Medicine, Indianapolis, Indiana [46]

Allan H. Ropper, MD, FRCP, FACP
Professor of Neurology, Harvard Medical School; Raymond D. Adams Master Clinician; Executive Vice Chair, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [19, 43, 44]

Roger N. Rosenberg, MD
Zale Distinguished Chair and Professor of Neurology, Department of Neurology, University of Texas Southwestern Medical Center, Dallas, Texas [37, 38]

Myrna R. Rosenfeld, MD, PhD
Department of Neurology, Hospital Clínic/IDIBAPS, Barcelona, Spain [50]

Martin A. Samuels, MD
Professor of Neurology, Harvard Medical School; Chair, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [3, 58]

Clifford B. Saper, MD, PhD
James Jackson Putnam Professor of Neurology and Neuroscience, Harvard Medical School; Chairman, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts [24]

T omas E. Scammell, MD
Professor, Harvard Medical School; Beth Israel Deaconess Medical Center; Boston Children's Hospital, Boston, Massachusetts [24]

Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci
Chair and Professor of Clinical Neurosciences, UCL Institute of Neurology, London, United Kingdom [36]

Marc A. Schuckit, MD
Distinguished Professor of Psychiatry, University of California, San Diego School of Medicine, La Jolla, California [63]

[1]Deceased

www.ketabpezeshki.com (021) 66485457 - 66485438

William W. Seeley, MD
Associate Professor of Neurology and Pathology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [21, 35]

Wade S. Smith, MD, PhD
Professor of Neurology, Daryl R. Gress Endowed Chair of Neurocritical Care and Stroke; Director, University of California, San Francisco Neurovascular Service, San Francisco, California [32, 33]

Lewis Sudarsky, MD
Associate Professor of Neurology, Harvard Medical School; Director of Movement Disorders, Brigham and Women's Hospital, Boston, Massachusetts [16]

Homayoun Tabandeh, MD
Retina-Vitreous Associates Medical Group, Los Angeles, California [26]

Maria Carmela Tartaglia, MD
Assistant Professor, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada [23]

Kenneth L. Tyler, MD
Reuler-Lewin Family Professor and Chair of Neurology; Professor of Medicine, Immunology, and Microbiology, University of Colorado School of Medicine, Aurora, Colorado; Neurologist, Denver Veterans Affairs Medical Center, Denver, Colorado [46]

Jos W. M. van der Meer, MD, PhD
Professor of Medicine; Head, Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, T e Netherlands [59]

Mark F. Walker, MD
Associate Professor, Neurology, Case Western Reserve University; Cleveland VA Medical Center, Cleveland, Ohio [12]

Patrick Y. Wen, MD
Professor of Neurology, Harvard Medical School; Director, Center for Neuro-Oncology, Dana-Farber Cancer Institute; Director, Division of Neuro-Oncology, Department of Neurology, Brigham and Women's Hospital; Dana-Farber Cancer Institute, Boston, Massachusetts [49]

Charles M. Wiener, MD
Vice President of Academic Affairs Johns Hopkins Medicine International Professor of Medicine and Physiology Johns Hopkins School of Medicine Baltimore, Maryland [Review and Self-Assessment]

Shirley H. Wray, MD, PhD, FRCP
Professor of Neurology, Harvard Medical School; Master Clinician, Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts [27]

www.ketabpezeshki.com (021) 66485457 - 66485438

PREFACE

T e first three editions of Harrison's Neurology in Clinical Medicine were unqualified successes. Readers responded enthusiastically to the convenient, attractive, expanded, and updated stand-alone volume, which was based upon the neurology and psychiatry sections from Harrison's Principles *of* Internal Medicine. Our original goal was to provide, in an easy-to-use format, full coverage of the most authoritative information available anywhere of clinically important topics in neurology and psychiatry, while retaining the focus on pathophysiology and therapy that has always been characteristic of Harrison's.

T is new fourth edition of Harrison's Neurology in Clinical Medicine has been extensively updated to highlight recent advances in the understanding, diagnosis, treatment, and prevention of neurologic and psychiatric diseases. Readers will find expanded coverage of the neurodegenerative diseases, highlighting advances in their classification and management, and delineating the new understanding of mechanisms responsible for the deposition and spread of pathogenic protein aggregates in these disorders. Neuroimmunology is another dynamic and rapidly changing field of neurology, and the new edition of Harrison's provides extensive coverage of progress in this area, including a timely summary of advances in understanding paraneoplastic syndromes, autoimmune encephalitis, and neuromyelitis optica, as well as a practical guide to navigating the large number of treatment options now available for multiple sclerosis. T e chapter on cerebrovascular diseases has also been extensively revised to reflect the exciting new opportunities for acute treatment and prevention of ischemic and hemorrhagic stroke. Sleep disorders and migraine are additional areas in which important advances are highlighted in the new edition. Many illustrative neuroimaging figures appear throughout the section, and an updated and expanded atlas of neuroimaging findings is also included. We have been extremely pleased with the warm reception that greeted the high-definition video presentations introduced in the last edition of Harrison's, and in the fourth edition we have added to the collection new videos illustrating sleep disorders and examination of the comatose patient.

For many physicians, neurologic diseases represent particularly challenging problems. Acquisition of the requisite clinical skills is often viewed as time-consuming, dif cult to master, and requiring a working knowledge of obscure anatomic facts and laundry lists of diagnostic possibilities. T e patients themselves may be dif cult, as neurologic disorders often alter an individual's capacity to recount the history of an illness or to even recognize that something is wrong. An additional obstacle is the development of independent neurology services, departments, and training programs at many medical centers, reducing the exposure of trainees in internal medicine to neurologic problems. All of these forces, acting within the fast paced environment of modern medical practice, can lead to an overreliance on unfocused neuroimaging tests, suboptimal patient care, and unfortunate outcomes. Because neurologists represent less than 1% of all physicians, the vast majority of neurologic care must be delivered by nonspecialists who are often generalists and usually internists.

T e old adage that neurologists "know everything but do nothing" has been rendered obsolete by advances in molecular medicine, imaging, bioengineering, and clinical research. Examples of new therapies include intravenous and endovascular recanalization in acute ischemic stroke, intensive monitoring of brain pressure and cerebral blood flow for brain injury, effective therapies for immune-mediated neurologic disorders, new designer drugs for migraine, the first generation of rational therapies for neurodegenerative diseases, neural stimulators for Parkinson's disease, drugs for narcolepsy and other sleep disorders, and control of epilepsy by surgical resection of small seizure foci precisely localized by functional imaging and electrophysiology. T e pipeline continues to grow, stimulated by a quickening tempo of discoveries generating opportunities for rational design of new diagnostics, interventions, and drugs.

T e founding editors of Harrison's Principles *of* Internal Medicine acknowledged the importance of neurology but were uncertain as to its proper role in a textbook of internal medicine. An initial plan to exclude neurology from the first edition (1950) was reversed at the eleventh hour, and a neurology section was hastily prepared by Houston Merritt. By the second edition, the section was considerably enlarged by Raymond D. Adams, whose influence on the textbook was profound. T e third neurology editor, Joseph B. Martin, brilliantly led the book during the 1980s and 1990s as neurology was transformed from a largely descriptive discipline to one of the most dynamic and rapidly evolving areas of medicine. With these changes, the growth of neurology coverage in Harrison's became so pronounced that Harrison suggested the book be retitled, T e Details *of* Neurology and Some Principles *of* Internal Medicine. His humorous comment, now legendary, underscores the depth of coverage

www.ketabpezeshki.com (021) 66485457 - 66485438

of neurologic medicine in Harrison's befitting its critical role in the practice of internal medicine.

T e editors are indebted to our authors, a group of internationally recognized authorities who have magnificently distilled a daunting body of information into the essential principles required to understand and manage commonly encountered neurologic problems. T anks also to Dr. Elizabeth Robbins who has served for more than 20 years as managing editor of the neurology section of Harrison's; she has overseen the complex logistics required to produce a multiauthored textbook, and has promoted exceptional standards for clarity, language, and style. Finally, we wish to acknowledge and express our great appreciation to our colleagues at McGraw-Hill. T is new volume was championed by James Shanahan and impeccably managed by Kim Davis.

We live in an electronic, wireless age. Information is downloaded rather than pulled from the shelf. Some have questioned the value of traditional books in this new era. We believe that as the volume of information, and the ways to access this information, continue to grow, the need to grasp the essential concepts of medical practice becomes even more challenging. One of our young colleagues recently remarked that he uses the Internet to find facts, but that he reads Harrison's to learn medicine. Our aim has always been to provide the reader with an integrated, organic summary of the science and the practice of medicine rather than a mere compendium of chapters, and we are delighted and humbled by the continuing and quite remarkable growth in popularity of Harrison's at a time when many "classics" in medicine seem less relevant than in years past. We are of course cognizant of the flexibility in information delivery that today's readers seek, and so we have also made the fourth edition of Harrison's Neurology in Clinical Medicine available in a number of eBook formats for all major devices, including the iPad (available via the iBookstore).

It is our sincere hope that you will enjoy using Harrison's Neurology in Clinical Medicine, Fourth Edition, as an authoritative source for the most up-to-date information in clinical neurology.

T e Editors

www.ketabpezeshki.com (021) 66485457 - 66485438

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-259-64288-3.

T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

T e genetic icons identify a clinical issue with an explicit genetic relationship.

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION I

INTRODUCTION TO NEUROLOGY

CHAPTER 1

APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE

Daniel H. Lowenstein ■ Joseph B. Martin ■ Stephen L. Hauser

Neurologic diseases are common and costly. According to estimates by the World Health Organization, neurologic disorders affect over 1 billion people worldwide, constitute 12% of the global burden of disease, and cause 14% of global deaths **(Table 1-1)**. T ese numbers are only expected to increase as the world's population ages. Most patients with neurologic symptoms seek care from internists and other generalists rather than from neurologists. Because therapies now exist for many neurologic disorders, a skillful approach to diagnosis is essential. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, while useful, do not substitute for an adequate history and examination. T e proper approach to the patient with a neurologic illness begins with the patient and focuses the clinical problem first in anatomic and then in pathophysiologic terms; only then should a specific diagnosis be entertained. T is method ensures that technology is judiciously applied, a correct diagnosis is established in an efficient manner, and treatment is promptly initiated.

TABLE 1-1

GLOBAL DISABILITY-ADJUSTED LIFE-YEARS (DALYS) AND NUMBER OF ANNUAL DEATHS FOR SELECTED NEUROLOGIC DISORDERS IN 2010

DISORDER	DALYS	DEATHS
Low back and neck pain	116,704,000	—
Cerebrovascular diseases	102,232,000	5,874,000
Meningitis and encephalitis	26,540,000	541,000
Migraine	22,362,000	—
Epilepsy	17,429,000	177,000
Dementia	11,349,000	485,000
Parkinson's disease	1,918,000	111,000
% of total DALYs or deaths for all causes that are neurologic	**12.0%**	**13.6%**
% change of DALYs for neurologic disorders between 2000 and 2010	**51.6%**	**114.3%**

Source: R Lozano et al: Lancet 380: 2095, 2012.

THE NEUROLOGIC METHOD

DEFINE THE ANATOMY

T e first priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Can the disorder be mapped to one specific location, is it multifocal, or is a diffuse process present? Are the symptoms restricted to the nervous system, or do they arise in the context of a systemic illness? Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? If in the CNS, is the cerebral cortex, basal ganglia, brainstem, cerebellum, or spinal cord responsible? Are the pain-sensitive meninges involved? If in the PNS, could the disorder be located in peripheral nerves and, if so, are motor or sensory nerves primarily affected, or is a lesion in the neuromuscular junction or muscle more likely?

T e first clues to defining the anatomic area of involvement appear in the history, and the examination is then directed to confirm or rule out these impressions and to clarify uncertainties. A more detailed examination of a particular region of the CNS or PNS is often indicated. For example, the examination of a patient who presents with a history of ascending paresthesias and weakness should be directed toward deciding, among other things, if the location of the lesion is in the spinal cord or peripheral nerves. Focal back pain, a spinal cord sensory level, and incontinence

www.ketabpezeshki.com (021) 66485457 - 66485438

suggest a spinal cord origin, whereas a stocking-glove pattern of sensory loss suggests peripheral nerve disease; areflexia usually indicates peripheral neuropathy but may also be present with spinal shock in acute spinal cord disorders.

Deciding "where the lesion is" accomplishes the task of limiting the possible etiologies to a manageable, finite number. In addition, this strategy safeguards against making serious errors. Symptoms of recurrent vertigo, diplopia, and nystagmus should not trigger "multiple sclerosis" as an answer (etiology) but "brainstem" or "pons" (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration. Similarly, the combination of optic neuritis and spastic ataxic paraparesis suggests optic nerve and spinal cord disease; multiple sclerosis (MS), CNS syphilis, and vitamin B_{12} deficiency are treatable disorders that can produce this syndrome. Once the question, "Where is the lesion?" is answered, then the question, "What is the lesion?" can be addressed.

IDENTIFY THE PATHOPHYSIOLOGY

Clues to the pathophysiology of the disease process may also be present in the history. Primary neuronal (gray matter) disorders may present as early cognitive disturbances, movement disorders, or seizures, whereas white matter involvement produces predominantly "long tract" disorders of motor, sensory, visual, and cerebellar pathways. Progressive and symmetric symptoms often have a metabolic or degenerative origin; in such cases lesions are usually not sharply circumscribed. Thus, a patient with paraparesis and a clear spinal cord sensory level is unlikely to have vitamin B_{12} deficiency as the explanation. A Lhermitte symptom (electric shock–like sensations evoked by neck flexion) is due to ectopic impulse generation in white matter pathways and occurs with demyelination in the cervical spinal cord; among many possible causes, this symptom may indicate MS in a young adult or compressive cervical spondylosis in an older person. Symptoms that worsen after exposure to heat or exercise may indicate conduction block in demyelinated axons, as occurs in MS. A patient with recurrent episodes of diplopia and dysarthria associated with exercise or fatigue may have a disorder of neuromuscular transmission such as myasthenia gravis. Slowly advancing visual scotoma with luminous edges, termed *fortification spectra*, indicates spreading cortical depression, typically with migraine.

THE NEUROLOGIC HISTORY

Attention to the description of the symptoms experienced by the patient and substantiated by family members and others often permits an accurate localization and determination of the probable cause of the complaints, even before the neurologic examination is performed. The history also helps to bring a focus to the neurologic examination that follows. Each complaint should be pursued as far as possible to elucidate the location of the lesion, the likely underlying pathophysiology, and potential etiologies. For example, a patient complains of weakness of the right arm. What are the associated features? Does the patient have difficulty with brushing hair or reaching upward (proximal) or buttoning buttons or opening a twist-top bottle (distal)? Negative associations may also be crucial. A patient with a right hemiparesis without a language deficit likely has a lesion (internal capsule, brainstem, or spinal cord) different from that of a patient with a right hemiparesis and aphasia (left hemisphere). Other pertinent features of the history include the following:

1. *Temporal course of* the illness. It is important to determine the precise time of appearance and rate of progression of the symptoms experienced by the patient. The rapid onset of a neurologic complaint, occurring within seconds or minutes, usually indicates a vascular event, a seizure, or migraine. The onset of sensory symptoms located in one extremity that spread over a few seconds to adjacent portions of that extremity and then to the other regions of the body suggests a seizure. A more gradual onset and less well-localized symptoms point to the possibility of a transient ischemic attack (TIA). A similar but slower temporal march of symptoms accompanied by headache, nausea, or visual disturbance suggests migraine. The presence of "positive" sensory symptoms (e.g., tingling or sensations that are difficult to describe) or involuntary motor movements suggests a seizure; in contrast, transient loss of function (negative symptoms) suggests a TIA. A stuttering onset where symptoms appear, stabilize, and then progress over hours or days also suggests cerebrovascular disease; an additional history of transient remission or regression indicates that the process is more likely due to ischemia rather than hemorrhage. A gradual evolution of symptoms over hours or days suggests a toxic, metabolic, infectious, or inflammatory process. Progressing symptoms associated with the systemic manifestations of fever, stiff neck, and altered level of consciousness imply an infectious process. Relapsing and remitting symptoms involving different levels of the nervous system suggest MS or other inflammatory processes. Slowly progressive symptoms without remissions are characteristic of neurodegenerative disorders, chronic infections, gradual intoxications, and neoplasms.
2. Patients' descriptions *of* the complaint. The same words often mean different things to different patients. "Dizziness" may imply impending syncope,

www.ketabpezeshki.com (021) 66485457 - 66485438

a sense of disequilibrium, or true spinning vertigo. "Numbness" may mean a complete loss of feeling, a positive sensation such as tingling, or even weakness. "Blurred vision" may be used to describe unilateral visual loss, as in transient monocular blindness, or diplopia. T e interpretation of the true meaning of the words used by patients to describe symptoms obviously becomes even more complex when there are differences in primary languages and cultures.

3. Corroboration *of* the history by others. It is almost always helpful to obtain additional information from family, friends, or other observers to corroborate or expand the patient's description. Memory loss, aphasia, loss of insight, intoxication, and other factors may impair the patient's capacity to communicate normally with the examiner or prevent openness about factors that have contributed to the illness. Episodes of loss of consciousness necessitate that details be sought from observers to ascertain precisely what has happened during the event.
4. Family history. Many neurologic disorders have an underlying genetic component. T e presence of a Mendelian disorder, such as Huntington's disease or Charcot-Marie-Tooth neuropathy, is often obvious if family data are available. More detailed questions about family history are often necessary in polygenic disorders such as MS, migraine, and many types of epilepsy. It is important to elicit family history about all illnesses, in addition to neurologic and psychiatric disorders. A familial propensity to hypertension or heart disease is relevant in a patient who presents with a stroke. T ere are numerous inherited neurologic diseases that are associated with multisystem manifestations that may provide clues to the correct diagnosis (e.g., neurofibromatosis, Wilson's disease, mitochondrial disorders).
5. Medical illnesses. Many neurologic diseases occur in the context of systemic disorders. Diabetes mellitus, hypertension, and abnormalities of blood lipids predispose to cerebrovascular disease. A solitary mass lesion in the brain may be an abscess in a patient with valvular heart disease, a primary hemorrhage in a patient with a coagulopathy, a lymphoma or toxoplasmosis in a patient with AIDS, or a metastasis in a patient with underlying cancer. Patients with malignancy may also present with a neurologic paraneoplastic syndrome **(Chap. 50)** or complications from chemotherapy or radiotherapy. Marfan's syndrome and related collagen disorders predispose to dissection of the cranial arteries and aneurysmal subarachnoid hemorrhage; the latter may also occur with polycystic kidney disease. Various neurologic disorders occur with dysthyroid states or other endocrinopathies. It is especially important to look for the presence of systemic diseases in patients with peripheral neuropathy. Most patients with coma in a hospital setting have a metabolic, toxic, or infectious cause.
6. Drug use and abuse and toxin exposure. It is essential to inquire about the history of drug use, both prescribed and illicit. Sedatives, antidepressants, and other psychoactive medications are frequently associated with acute confusional states, especially in the elderly. Aminoglycoside antibiotics may exacerbate symptoms of weakness in patients with disorders of neuromuscular transmission, such as myasthenia gravis, and may cause dizziness secondary to ototoxicity. Vincristine and other antineoplastic drugs can cause peripheral neuropathy, and immunosuppressive agents such as cyclosporine can produce encephalopathy. Excessive vitamin ingestion can lead to disease; examples include vitamin A and pseudotumor cerebri or pyridoxine and peripheral neuropathy. Many patients are unaware that over-the-counter sleeping pills, cold preparations, and diet pills are actually drugs. Alcohol, the most prevalent neurotoxin, is often not recognized as such by patients, and other drugs of abuse such as cocaine and heroin can cause a wide range of neurologic abnormalities. A history of environmental or industrial exposure to neurotoxins may provide an essential clue; consultation with the patient's coworkers or employer may be required.
7. Formulating an impression *of* the patient. Use the opportunity while taking the history to form an impression of the patient. Is the information forthcoming, or does it take a circuitous course? Is there evidence of anxiety, depression, or hypochondriasis? Are there any clues to problems with language, memory, insight, comportment, or behavior? T e neurologic assessment begins as soon as the patient comes into the room and the first introduction is made.

THE NEUROLOGIC EXAMINATION

T e neurologic examination is challenging and complex; it has many components and includes a number of skills that can be mastered only through repeated use of the same techniques on a large number of individuals with and without neurologic disease. Mastery of the complete neurologic examination is usually important only for physicians in neurology and associated specialties. However, knowledge of the basics of the examination, especially those components that are effective in screening for neurologic dysfunction, is essential for all clinicians, especially generalists.

T ere is no single, universally accepted sequence of the examination that must be followed, but most

www.ketabpezeshki.com (021) 66485457 - 66485438

clinicians begin with assessment of mental status followed by the cranial nerves, motor system, reflexes, sensory system, coordination, and gait. Whether the examination is basic or comprehensive, it is essential that it be performed in an orderly and systematic fashion to avoid errors and serious omissions. Thus, the best way to learn and gain expertise in the examination is to choose one's own approach and practice it frequently and do it in the same exact sequence each time.

The detailed description that follows describes the more commonly used parts of the neurologic examination, with a particular emphasis on the components that are considered most helpful for the assessment of common neurologic problems. Each section also includes a brief description of the minimal examination necessary to adequately screen for abnormalities in a patient who has no symptoms suggesting neurologic dysfunction. A screening examination done in this way can be completed in 3–5 min.

Several additional points about the examination are worth noting. First, in recording observations, it is important to describe what is found rather than to apply a poorly defined medical term (e.g., "patient groans to sternal rub" rather than "obtunded"). Second, subtle CNS abnormalities are best detected by carefully comparing a patient's performance on tasks that require simultaneous activation of both cerebral hemispheres (e.g., eliciting a pronator drift of an outstretched arm with the eyes closed; extinction on one side of bilaterally applied light touch, also with eyes closed; or decreased arm swing or a slight asymmetry when walking). Third, if the patient's complaint is brought on by some activity, reproduce the activity in the office. If the complaint is of dizziness when the head is turned in one direction, have the patient do this and also look for associated signs on examination (e.g., nystagmus or dysmetria). If pain occurs after walking two blocks, have the patient leave the office and walk this distance and immediately return, and repeat the relevant parts of the examination. Finally, the use of tests that are individually tailored to the patient's problem can be of value in assessing changes over time. Tests of walking a 7.5-m (25-ft) distance (normal, 5–6 s; note assistance, if any), repetitive finger or toe tapping (normal, 20–25 taps in 5 s), or handwriting are examples.

MENTAL STATUS EXAMINATION

- The bare minimum: During the interview, look *for* di*ffi*culties with communication and determine whether the patient has recall and insight into recent and past events.

The mental status examination is under way as soon as the physician begins observing and speaking with the patient. If the history raises any concern for abnormalities of higher cortical function or if cognitive problems are observed during the interview, then detailed testing of the mental status is indicated. The patient's ability to understand the language used for the examination, cultural background, educational experience, sensory or motor problems, or comorbid conditions need to be factored into the applicability of the tests and interpretation of results.

The Folstein mini-mental status examination (MMSE) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to complete. Using age-adjusted values for defining normal performance, the test is ~85% sensitive and 85% specific for making the diagnosis of dementia that is moderate or severe, especially in educated patients. When there is sufficient time available, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared.

Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations.

Level *of* consciousness is the patient's relative state of awareness of the self and the environment, and ranges from fully awake to comatose. When the patient is not fully awake, the examiner should describe the responses to the minimum stimulus necessary to elicit a reaction, ranging from verbal commands to a brief, painful stimulus such as a squeeze of the trapezius muscle. Responses that are directed toward the stimulus and signify some degree of intact cerebral function (e.g., opening the eyes and looking at the examiner or reaching to push away a painful stimulus) must be distinguished from reflex responses of a spinal origin (e.g., triple flexion response—flexion at the ankle, knee, and hip in response to a painful stimulus to the foot).

Orientation is tested by asking the person to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions.

Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllables and words).

Language is assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch, or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command.

www.ketabpezeshki.com (021) 66485457 - 66485438

Memory should be analyzed according to three main time scales: (1) immediate memory is assessed by saying a list of three items and having the patient repeat the list immediately; (2) short-term memory is tested by asking the patient to recall the same three items 5 and 15 min later; and (3) long-term memory is evaluated by determining how well the patient is able to provide a coherent chronologic history of his or her illness or personal events.

Fund *of* in*f*ormation is assessed by asking questions about major historic or current events, with special attention to educational level and life experiences.

Abnormalities of insight and judgment are usually detected during the patient interview; a more detailed assessment can be elicited by asking the patient to describe how he or she would respond to situations having a variety of potential outcomes (e.g., "What would you do if you found a wallet on the sidewalk?").

Abstract thought can be tested by asking the patient to describe similarities between various objects or concepts (e.g., apple and orange, desk and chair, poetry and sculpture) or to list items having the same attributes (e.g., a list of four-legged animals).

Calculation ability is assessed by having the patient carry out a computation that is appropriate to the patient's age and education (e.g., serial subtraction of 7 from 100 or 3 from 20; or word problems involving simple arithmetic).

CRANIAL NERVE EXAMINATION

- T e bare minimum: Check the *f*undi, visual *f*ields, pupil size and reactivity, extraocular movements, and *f*acial movements.

T e cranial nerves (CN) are best examined in numerical order, except for grouping together CN III, IV, and VI because of their similar function.

CN I (olfactory)

Testing is often omitted unless there is suspicion for inferior frontal lobe disease (e.g., meningioma). With eyes closed, ask the patient to sniff a mild stimulus such as toothpaste or coffee and identify the odorant.

CN II (optic)

Check visual acuity (with eyeglasses or contact lens correction) using a Snellen chart or similar tool. Test the visual fields by confrontation, i.e., by comparing the patient's visual fields to your own. As a screening test, it is usually sufficient to examine the visual fields of both eyes simultaneously; individual eye fields should be tested if there is any reason to suspect a problem of vision by the history or other elements of the examination, or if the screening test reveals an abnormality. Face the patient at a distance of approximately 0.6–1.0 m (2–3 ft) and place your hands at the periphery of your visual fields in the plane that is equidistant between you and the patient. Instruct the patient to look directly at the center of your face and to indicate when and where he or she sees one of your fingers moving. Beginning with the two inferior quadrants and then the two superior quadrants, move your index finger of the right hand, left hand, or both hands simultaneously and observe whether the patient detects the movements. A single small-amplitude movement of the finger is sufficient for a normal response. Focal perimetry and tangent screen examinations should be used to map out visual field defects fully or to search for subtle abnormalities. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc noted, as well as the color and texture of the retina. T e retinal vessels should be checked for size, regularity, arteriovenous nicking at crossing points, hemorrhage, exudates, etc.

CN III, IV, VI (oculomotor, trochlear, abducens)

Describe the size and shape of pupils and reaction to light and accommodation (i.e., as the eyes converge while following your finger as it moves toward the bridge of the nose). To check extraocular movements, ask the patient to keep his or her head still while tracking the movement of the tip of your finger. Move the target slowly in the horizontal and vertical planes; observe any paresis, nystagmus, or abnormalities of smooth pursuit (saccades, oculomotor ataxia, etc.). If necessary, the relative position of the two eyes, both in primary and multidirectional gaze, can be assessed by comparing the ref ections of a bright light off both pupils. However, in practice it is typically more useful to determine whether the patient describes diplopia in any direction of gaze; true diplopia should almost always resolve with one eye closed. Horizontal nystagmus is best assessed at 45° and not at extreme lateral gaze (which is uncomfortable for the patient); the target must often be held at the lateral position for at least a few seconds to detect an abnormality.

CN V (trigeminal)

Examine sensation within the three territories of the branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) on each side of the face. As with other parts of the sensory examination, testing of two sensory modalities derived from different anatomic pathways (e.g., light touch and temperature) is sufficient for a screening examination. Testing of other modalities, the corneal ref ex, and the motor component of

www.ketabpezeshki.com (021) 66485457 - 66485438

CN V (jaw clench—masseter muscle) is indicated when suggested by the history.

CN VII (facial)

Look for facial asymmetry at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, and cheek puff. Look in particular for differences in the lower versus upper facial muscles; weakness of the lower two-thirds of the face with preservation of the upper third suggests an upper motor neuron lesion, whereas weakness of an entire side suggests a lower motor neuron lesion.

CN VIII (vestibulocochlear)

Check the patient's ability to hear a finger rub or whispered voice with each ear. Further testing for air versus mastoid bone conduction (Rinne) and lateralization of a 512-Hz tuning fork placed at the center of the forehead (Weber) should be done if an abnormality is detected by history or examination. Any suspected problem should be followed up with formal audiometry. **For further discussion of assessing vestibular nerve function in the setting of dizziness, hearing loss, or coma, see Chaps. 12, 29, and 19, respectively.**

CN IX, X (glossopharyngeal, vagus)

Observe the position and symmetry of the palate and uvula at rest and with phonation ("aah"). The pharyngeal ("gag") reflex is evaluated by stimulating the posterior pharyngeal wall on each side with a sterile, blunt object (e.g., tongue blade), but the reflex is often absent in normal individuals.

CN XI (spinal accessory)

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid) against resistance.

CN XII (hypoglossal)

Inspect the tongue for atrophy or fasciculations, position with protrusion, and strength when extended against the inner surface of the cheeks on each side.

MOTOR EXAMINATION

- The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper extremity strength by checking for pronator drift and strength of wrist or finger extensors. Assess lower extremity strength by checking strength of the toe extensors and having the patient walk normally and on heels and toes.

The motor examination includes observations of muscle appearance, tone, and strength. Although gait is in part a test of motor function, it is usually evaluated separately at the end of the examination.

Appearance

Inspect and palpate muscle groups under good light and with the patient in a comfortable and symmetric position. Check for muscle fasciculations, tenderness, and atrophy or hypertrophy. Involuntary movements may be present at rest (e.g., tics, myoclonus, choreoathetosis), during maintained posture (pill-rolling tremor of Parkinson's disease), or with voluntary movements (intention tremor of cerebellar disease or familial tremor).

Tone

Muscle tone is tested by measuring the resistance to passive movement of a relaxed limb. Patients often have difficulty relaxing during this procedure, so it is useful to distract the patient to minimize active movements. In the upper limbs, tone is assessed by rapid pronation and supination of the forearm and flexion and extension at the wrist. In the lower limbs, while the patient is supine the examiner's hands are placed behind the knees and rapidly raised; with normal tone, the ankles drag along the table surface for a variable distance before rising, whereas increased tone results in an immediate lift of the heel off the surface. Decreased tone is most commonly due to lower motor neuron or peripheral nerve disorders. Increased tone may be evident as spasticity (resistance determined by the angle and velocity of motion; corticospinal tract disease), rigidity (similar resistance in all angles of motion; extrapyramidal disease), or paratonia (fluctuating changes in resistance; frontal lobe pathways or normal difficulty in relaxing). Cogwheel rigidity, in which passive motion elicits jerky interruptions in resistance, is seen in parkinsonism.

Strength

Testing for pronator drift is an extremely useful method for screening upper limb weakness. The patient is asked to hold both arms fully extended and parallel to the ground with eyes closed. This position should be maintained for ~10 s; any flexion at the elbow or fingers or pronation of the forearm, especially if asymmetric, is a sign of potential weakness. Muscle strength is further assessed by having the patient exert maximal effort for the particular muscle or muscle group being tested. It is important to isolate the muscles as much as possible, i.e., hold the limb so that only the muscles of interest are active. It is also helpful to palpate accessible muscles

www.ketabpezeshki.com (021) 66485457 - 66485438

as they contract. Grading muscle strength and evaluating the patient's effort is an art that takes time and practice. Muscle strength is traditionally graded using the following scale:

0 = no movement
1 = flicker or trace of contraction but no associated movement at a joint
2 = movement with gravity eliminated
3 = movement against gravity but not against resistance
4– = movement against a mild degree of resistance
4 = movement against moderate resistance
4+ = movement against strong resistance
5 = full power

However, in many cases, it is more practical to use the following terms:

Paralysis = no movement
Severe weakness = movement with gravity eliminated
Moderate weakness = movement against gravity but not against mild resistance
Mild weakness = movement against moderate resistance
Full strength

Noting the pattern of weakness is as important as assessing the magnitude of weakness. Unilateral or bilateral weakness of the upper limb extensors and lower limb flexors ("pyramidal weakness") suggests a lesion of the pyramidal tract, bilateral proximal weakness suggests myopathy, and bilateral distal weakness suggests peripheral neuropathy.

REFLEX EXAMINATION

- The bare minimum: Check the biceps, patellar, and Achilles reflexes.

Muscle stretch reflexes

Those that are typically assessed include the biceps (C5, C6), brachioradialis (C5, C6), and triceps (C7, C8) reflexes in the upper limbs and the patellar or quadriceps (L3, L4) and Achilles (S1, S2) reflexes in the lower limbs. The patient should be relaxed and the muscle positioned midway between full contraction and extension. Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (Jendrassik maneuver). For example, upper limb reflexes may be reinforced by voluntary teeth-clenching, and the Achilles reflex by hooking the flexed fingers of the two hands together and attempting to pull them apart. For each reflex tested, the two sides should be tested sequentially, and it is important to determine the smallest stimulus required to elicit a reflex rather than the maximum response. Reflexes are graded according to the following scale:

0 = absent
1 = present but diminished
2 = normoactive
3 = exaggerated
4 = clonus

Cutaneous reflexes

The plantar reflex is elicited by stroking, with a noxious stimulus such as a tongue blade, the lateral surface of the sole of the foot beginning near the heel and moving across the ball of the foot to the great toe. The normal reflex consists of plantar flexion of the toes. With upper motor neuron lesions above the S1 level of the spinal cord, a paradoxical extension of the toe is observed, associated with fanning and extension of the other toes (termed an extensor plantar response, or Babinski sign). However, despite its popularity, the reliability and validity of the Babinski sign for identifying upper motor neuron weakness is limited—it is far more useful to rely on tests of tone, strength, stretch reflexes, and coordination. Superficial abdominal reflexes are elicited by gently stroking the abdominal surface near the umbilicus in a diagonal fashion with a sharp object (e.g., the wooden end of a cotton-tipped swab) and observing the movement of the umbilicus. Normally, the umbilicus will pull toward the stimulated quadrant. With upper motor neuron lesions, these reflexes are absent. They are most helpful when there is preservation of the upper (spinal cord level T9) but not lower (T12) abdominal reflexes, indicating a spinal lesion between T9 and T12, or when the response is asymmetric. Other useful cutaneous reflexes include the cremasteric (ipsilateral elevation of the testicle following stroking of the medial thigh; mediated by L1 and L2) and anal (contraction of the anal sphincter when the perianal skin is scratched; mediated by S2, S3, S4) reflexes. It is particularly important to test for these reflexes in any patient with suspected injury to the spinal cord or lumbosacral roots.

Primitive reflexes

With disease of the frontal lobe pathways, several primitive reflexes not normally present in the adult may appear. The suck response is elicited by lightly touching with a tongue blade the center of the lips, and the root response the corner of the lips; the patient will move the lips to suck or root in the direction of the stimulus. The grasp reflex is elicited by touching the palm between the thumb and index finger with the examiner's fingers; a positive response is a forced grasp of the examiner's hand. In many instances, stroking the back of the hand

www.ketabpezeshki.com (021) 66485457 - 66485438

will lead to its release. The palmomental response is contraction of the mentalis muscle (chin) ipsilateral to a scratch stimulus diagonally applied to the palm.

SENSORY EXAMINATION

- The bare minimum: Ask whether the patient can *f*eel light touch and the temperature *of* a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands. Per*f*orm the Romberg maneuver.

Evaluating sensation is usually the most unreliable part of the examination because it is subjective and is difficult to quantify. In the compliant and discerning patient, the sensory examination can be extremely helpful for the precise localization of a lesion. With patients who are uncooperative or lack an understanding of the tests, it may be useless. The examination should be focused on the suspected lesion. For example, in spinal cord, spinal root, or peripheral nerve abnormalities, all major sensory modalities should be tested while looking for a pattern consistent with a spinal level and dermatomal or nerve distribution. In patients with lesions at or above the brainstem, screening the primary sensory modalities in the distal extremities along with tests of "cortical" sensation is usually sufficient.

The five primary sensory modalities—light touch, pain, temperature, vibration, and joint position—are tested in each limb. Light touch is assessed by stimulating the skin with single, very gentle touches of the examiner's finger or a wisp of cotton. Pain is tested using a new pin, and temperature is assessed using a metal object (e.g., tuning fork) that has been immersed in cold and warm water. Vibration is tested using a 128-Hz tuning fork applied to the distal phalanx of the great toe or index finger just below the nail bed. By placing a finger on the opposite side of the joint being tested, the examiner compares the patient's threshold of vibration perception with his or her own. For joint position testing, the examiner grasps the digit or limb laterally and distal to the joint being assessed; small 1- to 2-mm excursions can usually be sensed. The Romberg maneuver is primarily a test of proprioception. The patient is asked to stand with the feet as close together as necessary to maintain balance while the eyes are open, and the eyes are then closed. A loss of balance with the eyes closed is an abnormal response.

"Cortical" sensation is mediated by the parietal lobes and represents an integration of the primary sensory modalities; testing cortical sensation is only meaningful when primary sensation is intact. Double simultaneous stimulation is especially useful as a screening test for cortical function; with the patient's eyes closed, the examiner lightly touches one or both hands and asks the patient to identify the stimuli. With a parietal lobe lesion, the patient may be unable to identify the stimulus on the contralateral side when both hands are touched. Other modalities relying on the parietal cortex include the discrimination of two closely placed stimuli as separate (two-point discrimination), identification of an object by touch and manipulation alone (stereognosis), and the identification of numbers or letters written on the skin surface (graphesthesia).

COORDINATION EXAMINATION

- The bare minimum: Observe the patient at rest and during spontaneous movements. *T*est rapid alternating movements *of* the hands and *f*eet and *f*inger to nose.

Coordination refers to the orchestration and fluidity of movements. Even simple acts require cooperation of agonist and antagonist muscles, maintenance of posture, and complex servomechanisms to control the rate and range of movements. Part of this integration relies on normal function of the cerebellar and basal ganglia systems. However, coordination also requires intact muscle strength and kinesthetic and proprioceptive information. Thus, if the examination has disclosed abnormalities of the motor or sensory systems, the patient's coordination should be assessed with these limitations in mind.

Rapid alternating movements in the upper limbs are tested separately on each side by having the patient make a fist, partially extend the index finger, and then tap the index finger on the distal thumb as quickly as possible. In the lower limb, the patient rapidly taps the foot against the floor or the examiner's hand. Finger-to-nose testing is primarily a test of cerebellar function; the patient is asked to touch his or her index finger repetitively to the nose and then to the examiner's outstretched finger, which moves with each repetition. A similar test in the lower extremity is to have the patient raise the leg and touch the examiner's finger with the great toe. Another cerebellar test in the lower limbs is the heel-knee-shin maneuver; in the supine position the patient is asked to slide the heel of each foot from the knee down the shin of the other leg. For all these movements, the accuracy, speed, and rhythm are noted.

GAIT EXAMINATION

- The bare minimum: Observe the patient while walking normally, on the heels and toes, and along a straight line.

Watching the patient walk is the most important part of the neurologic examination. Normal gait requires that multiple systems—including strength, sensation, and coordination—function in a highly integrated fashion. Unexpected abnormalities may be detected that prompt

www.ketabpezeshki.com (021) 66485457 - 66485438

the examiner to return in more detail to other aspects of the examination. The patient should be observed while walking and turning normally, walking on the heels, walking on the toes, and walking heel-to-toe along a straight line. The examination may reveal decreased arm swing on one side (corticospinal tract disease), a stooped posture and short-stepped gait (parkinsonism), a broad-based unstable gait (ataxia), scissoring (spasticity), or a high-stepped, slapping gait (posterior column or peripheral nerve disease), or the patient may appear to be stuck in place (apraxia with frontal lobe disease).

NEUROLOGIC DIAGNOSIS

The clinical data obtained from the history and examination are interpreted to arrive at an anatomic localization that best explains the clinical findings **(Table 1-2)**, to narrow the list of diagnostic possibilities, and to select the laboratory tests most likely to be informative. The laboratory assessment may include (1) serum electrolytes; complete blood count; and renal, hepatic, endocrine, and immune studies; (2) cerebrospinal fluid examination; (3) focused neuroimaging studies **(Chap. 4)**; or (4) electrophysiologic studies **(Chap. 6)**. The anatomic localization, mode of onset and course of illness, other medical data, and laboratory findings are then integrated to establish an etiologic diagnosis.

The neurologic examination may be normal even in patients with a serious neurologic disease, such as seizures, chronic meningitis, or a TIA. A comatose patient may arrive with no available history, and in such cases, the approach is as described in **Chap. 19**. In other patients, an inadequate history may be overcome by a succession of examinations from which the course of the illness can be inferred. In perplexing cases it is useful to remember that uncommon presentations of common diseases are more likely than rare etiologies. Thus, even in tertiary care settings, multiple strokes are usually due to emboli and not vasculitis, and dementia with myoclonus is usually Alzheimer's disease and not a prion disorder or a paraneoplastic illness. Finally, the most important task of a primary care physician faced with a patient who has a new neurologic complaint is to assess the urgency of referral to a specialist. Here, the imperative is to rapidly identify patients likely to have nervous system infections, acute strokes, and spinal cord compression or other treatable mass lesions and arrange for immediate care.

TABLE 1-2

FINDINGS HELPFUL FOR LOCALIZATIONS WITHIN THE NERVOUS SYSTEM

	SIGNS
Cerebrum	Abnormal mental status or cognitive impairment Seizures Unilateral weakness[a] and sensory abnormalities including head and limbs Visual field abnormalities Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)
Brainstem	Isolated cranial nerve abnormalities (single or multiple) "Crossed" weakness[a] and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg
Spinal cord	Back pain or tenderness Weakness[a] and sensory abnormalities sparing the head Mixed upper and lower motor neuron findings Sensory level Sphincter dysfunction
Spinal roots	Radiating limb pain Weakness[b] or sensory abnormalities following root distribution (see Figs. 15-2 and 15-3) Loss of reflexes
Peripheral nerve	Mid or distal limb pain Weakness[b] or sensory abnormalities following nerve distribution (see Figs. 15-2 and 15-3) "Stocking or glove" distribution of sensory loss Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs Increasing weakness with exertion Sparing of sensation
Muscle	Bilateral proximal or distal weakness Sparing of sensation

[a]Weakness along with other abnormalities having an "upper motor neuron" pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.
[b]Weakness along with other abnormalities having a "lower motor neuron" pattern, i.e., flaccidity and hyporeflexia.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 2

THE NEUROLOGIC SCREENING EXAM

Daniel H. Lowenstein

Knowledge of the basic neurologic examination is an essential clinical skill. A simple neurologic screening examination—assessment of mental status, cranial nerves, motor system, sensory system, coordination, and gait—can be reliably performed in 3–5 min. Although the components of the examination may appear daunting at first, skills usually improve rapidly with repetition and practice. In this video, the technique of performing a simple and ef cient screening examination is presented.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 2–1. The Neurologic Screening Exam

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 3

VIDEO ATLAS OF THE DETAILED NEUROLOGIC EXAMINATION

Martin A. Samuels

T e comprehensive neurologic examination is an irreplaceable tool for the ef cient diagnosis of neurologic disorders. Mastery of its details requires knowledge of normal nervous system anatomy and physiology combined with personal experience performing orderly and systematic examinations on large numbers of patients and healthy individuals. In the hands of a great clinician, the neurologic examination also becomes a thing of beauty—the pinnacle of the art of medicine. In these videos, the most commonly used components of the examination are presented in detail, with a particular emphasis on those elements that are most helpful for assessment of common neurologic problems.

Videos for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 3–1. Introduction and the General Physical Examination Relevant to Neurology

Video 3–2. Mental Status

Video 3–3. Cranial Nerves

Video 3–4. Motor

Video 3–5. Sensory

Video 3–6. Ref exes

Video 3–7. Coordination and Gait

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 4

NEUROIMAGING IN NEUROLOGIC DISORDERS

William P. Dillon

The clinician caring for patients with neurologic symptoms is faced with myriad imaging options, including computed tomography (CT), CT angiography (CTA), perfusion CT (pCT), magnetic resonance (MR) imaging (MRI), MR angiography (MRA), functional MRI (fMRI), MR spectroscopy (MRS), MR neurography (MRN), diffusion and diffusion tensor imaging, susceptibility-weighted MR imaging (SWI), arterial spin label MRI (ASL) and perfusion MRI (pMRI). In addition, an increasing number of interventional neuroradiologic techniques are available, including angiography catheter embolization, coiling, and stenting of vascular structures, and spine diagnostic and interventional techniques, such as diskography, transforaminal and translaminar epidural and nerve root injections, and blood patches. Multidetector CTA (MDCTA) and gadolinium-enhanced MRA have narrowed the indications for conventional angiography, which is now reserved for patients in whom small-vessel detail is essential for diagnosis or for whom concurrent interventional therapy is planned **(Table 4-1)**.

In general, MRI is more sensitive than CT for the detection of lesions affecting the central nervous system (CNS), particularly those of the spinal cord, cranial nerves, and posterior fossa structures. Diffusion MR, a sequence sensitive to the microscopic motion of water, is the most sensitive technique for detecting acute ischemic stroke of the brain or spinal cord, and it is also useful in the detection of encephalitis, abscesses, and prion diseases. CT, however, is quickly acquired and is widely available, making it a pragmatic choice for the initial evaluation of patients with acute changes in mental status, suspected acute stroke, hemorrhage, and intracranial or spinal trauma. CT is also more sensitive than MRI for visualizing fine osseous detail and is indicated in the initial imaging evaluation of conductive hearing loss as well as lesions affecting the skull base and calvarium. MR may, however, add important diagnostic information regarding bone marrow infiltrative processes that are difficult to detect on CT.

COMPUTED TOMOGRAPHY

TECHNIQUE

The CT image is a cross-sectional representation of anatomy created by a computer-generated analysis of the attenuation of x-ray beams passed through a section of the body. As the x-ray beam, collimated to the desired slice width, rotates around the patient, it passes through selected regions in the body. X-rays that are not attenuated by body structures are detected by sensitive x-ray detectors aligned 180° from the x-ray tube. A computer calculates a "back projection" image from the 360° x-ray attenuation profile. Greater x-ray attenuation (e.g., as caused by bone), results in areas of high "density" (whiter) on the scan, whereas soft tissue structures that have poor attenuation of x-rays, such as organs and air-filled cavities, are lower (blacker) in density. The resolution of an image depends on the radiation dose, the detector size, collimation (slice thickness), the field of view, and the matrix size of the display. A modern CT scanner is capable of obtaining sections as thin as 0.5–1 mm with 0.4-mm in-plane resolution at a speed of 0.3 s per rotation; complete studies of the brain can be completed in 1–10 s.

Multidetector CT (MDCT) is now standard in most radiology departments. Single or multiple (from 4 to 320) solid-state detectors positioned opposite to the x-ray source result in multiple slices per revolution of the beam around the patient. The table moves continuously through the rotating x-ray beam, generating a continuous "helix" of information that can be reformatted into various slice thicknesses and planes. Advantages of MDCT include shorter scan times, reduced

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 4-1

GUIDELINES FOR THE USE OF CT, ULTRASOUND, AND MRI

CONDITION	RECOMMENDED TECHNIQUE
Hemorrhage	
Acute parenchymal	CT, MR
Subacute/chronic	MRI
Subarachnoid hemorrhage	CT, CTA, lumbar puncture → angiography
Aneurysm	Angiography > CTA, MRA
Ischemic infarction	
Hemorrhagic infarction	CT or MRI
Bland infarction	MRI with diffusion > CT, CTA, angiography
Carotid or vertebral dissection	MRI/MRA
Vertebral basilar insufficiency	CTA, MRI/MRA
Carotid stenosis	CTA, MRA > US
Suspected mass lesion	
Neoplasm, primary or metastatic	MRI + contrast
Infection/abscess	MRI + contrast
Immunosuppressed with focal findings	MRI + contrast
Vascular malformation	MRI ± angiography
White matter disorders	MRI
Demyelinating disease	MRI ± contrast
Dementia	MRI > CT
Trauma	
Acute trauma	CT
Shear injury/chronic hemorrhage	MRI + susceptibility-weighted imaging
Headache/migraine	CT/MRI
Seizure	
First time, no focal neurologic deficits	MRI > CT
Partial complex/refractory	MRI
Cranial neuropathy	MRI with contrast
Meningeal disease	MRI with contrast
Spine	
Low back pain	
No neurologic deficits	MRI or CT after >6 weeks
With focal deficits	MRI > CT
Spinal stenosis	MRI or CT
Cervical spondylosis	MRI, CT, CT myelography
Infection	MRI + contrast, CT
Myelopathy	MRI + contrast
Arteriovenous malformation	MRI + contrast, angiography

Abbreviations: CT, computed tomography; CTA, CT angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

patient and organ motion, and the ability to acquire images dynamically during the infusion of intravenous contrast, which can be used to construct CT angiograms of vascular structures and perfusion images **(Figs. 4-1B and C)**. CTA can be displayed in three dimensions to yield angiogram-like images **(Figs. 4-1C, 4-2E and F,** and see Fig. 32-4). CTA has proved useful in assessing the cervical and intracranial arterial and venous anatomy.

Intravenous iodinated contrast is often administered to identify both vascular structures and to detect defects in the blood-brain barrier (BBB) that are caused by tumors, infarcts, and infections. In the normal CNS, only vessels and structures lacking a BBB (e.g., the pituitary gland, choroid plexus, and dura) enhance after contrast administration. T e use of iodinated contrast agents carries a small risk of allergic reaction and adds additional expense. While helpful in characterizing mass lesions as well as essential for the acquisition of CTA studies, the decision to use contrast material should always be considered carefully.

INDICATIONS

CT is the primary study of choice in the evaluation of an acute change in mental status, focal neurologic findings, acute trauma to the brain and spine, suspected subarachnoid hemorrhage, and conductive hearing loss (Table 4-1). CT is complementary to MR in the evaluation of the skull base, orbit, and osseous structures of the spine. In the spine, CT is useful in evaluating patients with osseous spinal stenosis and spondylosis, but MRI is often preferred in those with neurologic deficits. CT can also be obtained following intrathecal contrast injection to evaluate the intracranial cisterns (CT cisternography) for cerebrospinal f uid (CSF) fistula, as well as the spinal subarachnoid space (CT myelography), although intrathecal administration of gadolinium combined with MR may also be complementary.

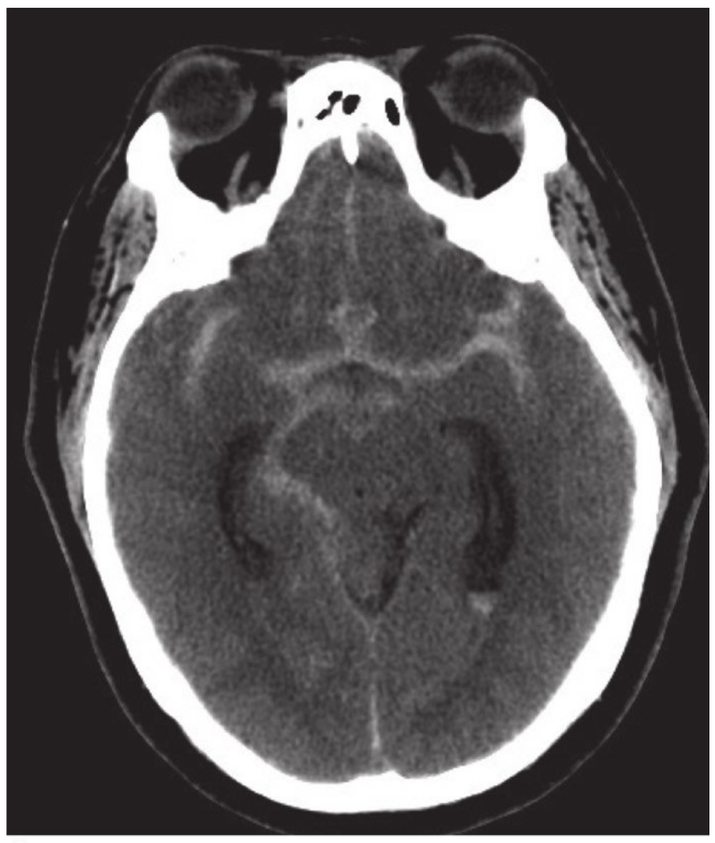
COMPLICATIONS

CT is safe, fast, and reliable. Radiation exposure depends on the dose used but is normally between 2 and 5 mSv (millisievert) for a routine brain CT study. Care must be taken to reduce exposure when imaging children. With the advent of MDCT, CTA, and CT perfusion, the benefit must be weighed against the increased radiation doses associated with these techniques. Advanced noise reduction software now permits acceptable diagnostic CT scans at 30–40% lower radiation doses.

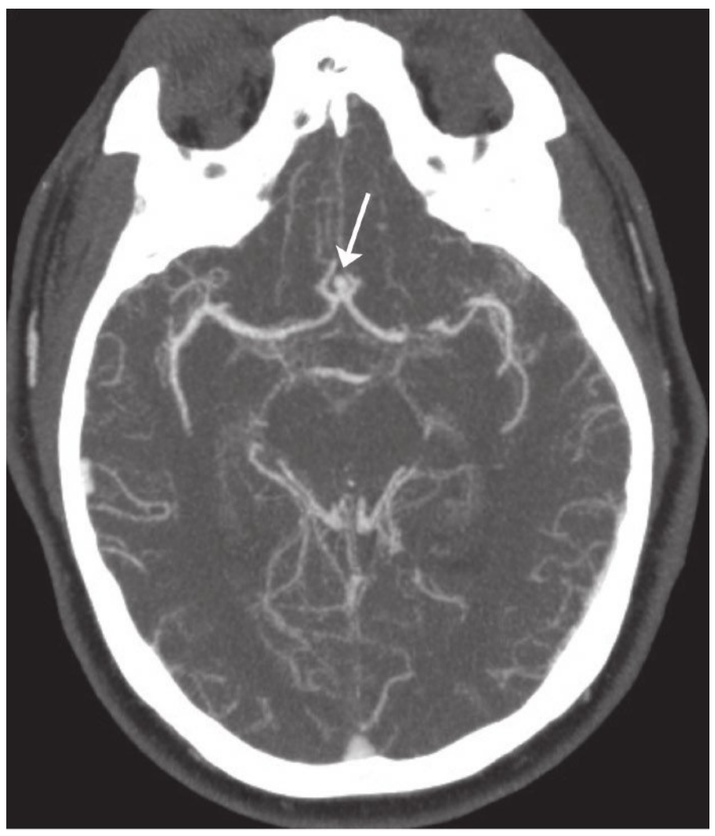
T e most frequent complications are those associated with use of intravenous contrast agents. While two broad categories of contrast media, ionic and nonionic, are in use, ionic agents have been largely replaced by safer nonionic compounds.

Contrast nephropathy may result from hemodynamic changes, renal tubular obstruction and cell damage, or immunologic reactions to contrast agents.

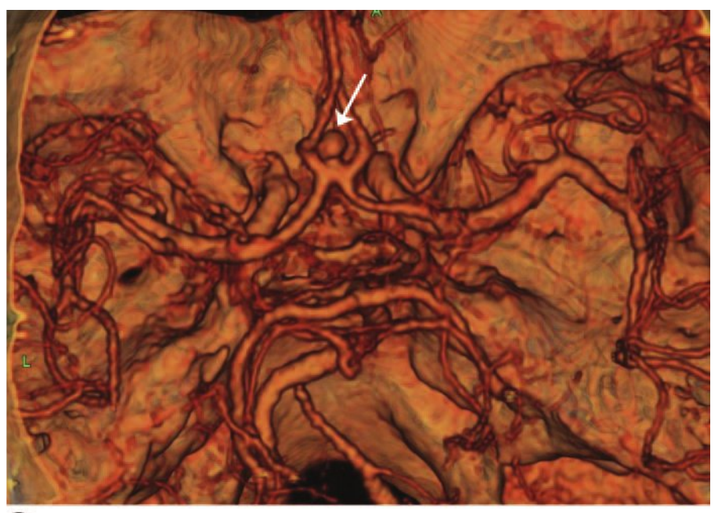
www.ketabpezeshki.com (021) 66485457 - 66485438



A



B



C

FIGURE 4-1
Computed tomography (CT) angiography (CTA) of ruptured anterior cerebral artery aneurysm in a patient presenting with acute headache. A. Noncontrast CT demonstrates subarachnoid hemorrhage and mild obstructive hydrocephalus. B. Axial maximum-intensity projection from CTA demonstrates enlargement of the anterior cerebral artery (arrow). C. Three-dimensional surface reconstruction using a workstation confirms the anterior cerebral aneurysm and demonstrates its orientation and relationship to nearby vessels (arrow). CTA image is produced by 0.5- to 1-mm helical CT scans performed during a rapid bolus infusion of intravenous contrast medium.

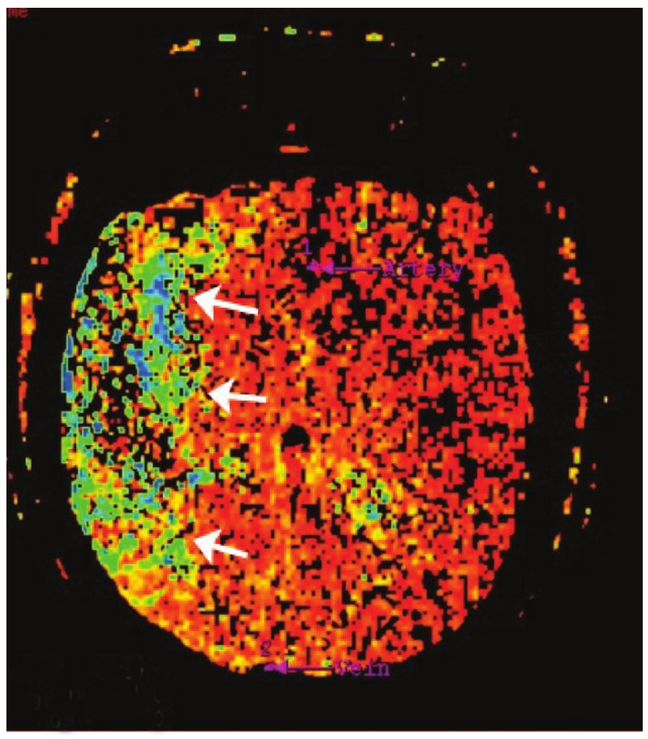
A rise in serum creatinine of at least 85 μmol/L (1 mg/dL) within 48 h of contrast administration is often used as a definition of contrast nephropathy, although other causes of acute renal failure must be excluded. The prognosis is usually favorable, with serum creatinine levels returning to baseline within 1–2 weeks. Risk factors for contrast nephropathy include advanced age (>80 years), preexisting renal disease (serum creatinine exceeding 2 mg/dL), solitary kidney, diabetes mellitus, dehydration, paraproteinemia, concurrent use of nephrotoxic medication or chemotherapeutic agents, and high contrast dose. Patients with diabetes and those with mild renal failure should be well hydrated prior to the administration of contrast agents, although careful consideration should be given to alternative imaging techniques such as MRI, noncontrast CT, or ultrasound (US). Nonionic, low-osmolar media produce fewer abnormalities in renal blood flow and less endothelial cell damage but should still be used carefully in patients at risk for allergic reaction. Estimated glomerular filtration rate (eGFR) is a more reliable indicator of renal function compared to creatinine alone because it takes into account age, race, and sex. In one study, 15% of outpatients with a normal serum creatinine had an estimated creatinine clearance of 50 mL/min/1.73 m^2 or less (normal is ≥90 mL/min/1.73 m^2). The exact eGFR threshold, below which withholding intravenous contrast should be considered, is controversial. The risk of contrast nephropathy increases in patients with an eGFR <60 mL/min/1.73 m^2; however, the majority of these patients will only have a temporary rise in creatinine. The risk of dialysis after receiving contrast significantly increases in patients with eGFR <30 mL/min/1.73 m^2. Thus, an eGFR threshold between 60 and 30 mL/min/1.73 m^2 is appropriate; however, the exact number is somewhat arbitrary. A creatinine of 1.6 in a 70-year-old, non-African-American male corresponds to an eGFR of approximately 45 mL/min/1.73 m^2. The American College of Radiology suggests using an eGFR of 45 mL/min/1.73 m^2 as a threshold below which iodinated contrast should not be given without serious consideration of the potential for contrast nephropathy. If contrast must be administered to a patient with an eGFR below 45 mL/min/1.73 m^2, the patient should be well hydrated, and a reduction in the dose of contrast should be considered. Use of other agents such as bicarbonate and acetylcysteine may reduce the incidence of contrast nephropathy.

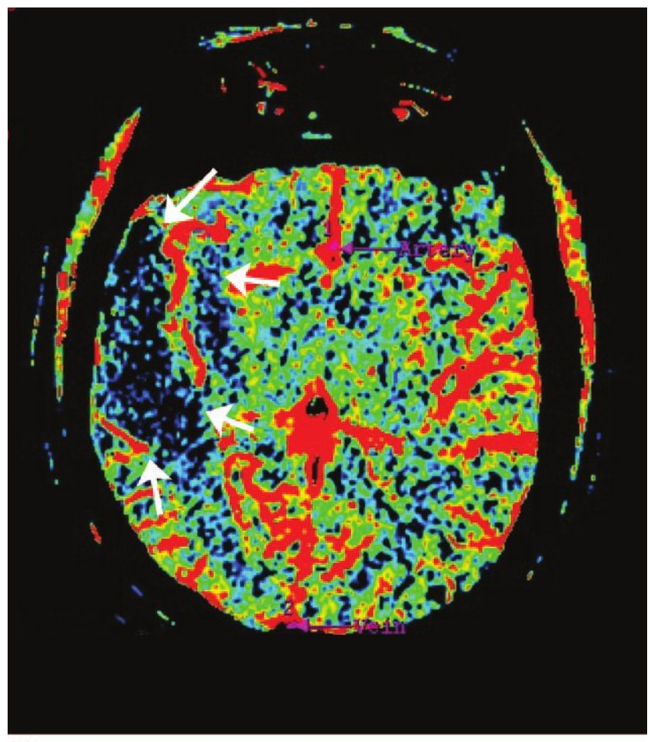
Allergy

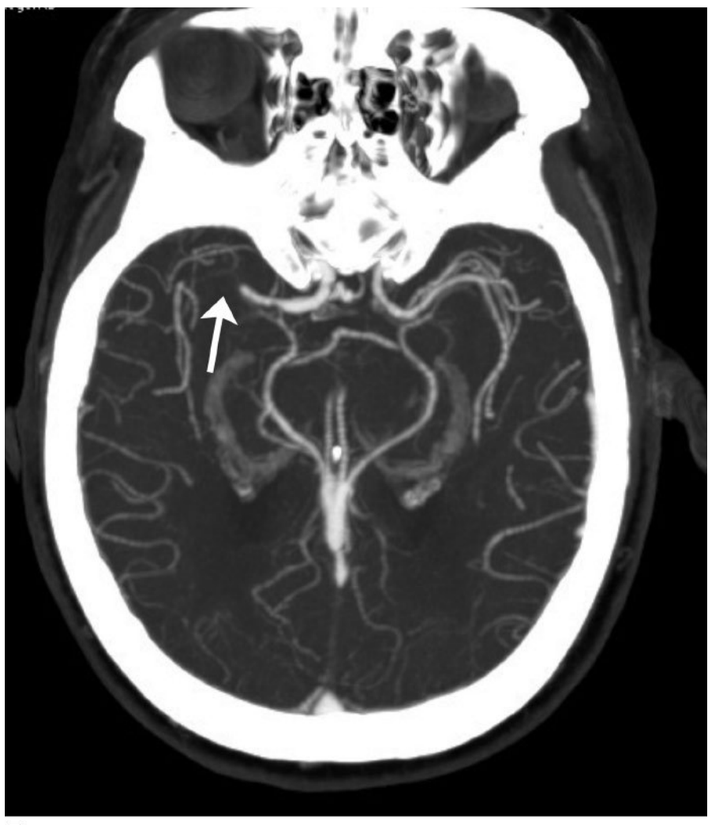
Immediate reactions following intravenous contrast media can occur through several mechanisms. The most severe reactions are related to allergic

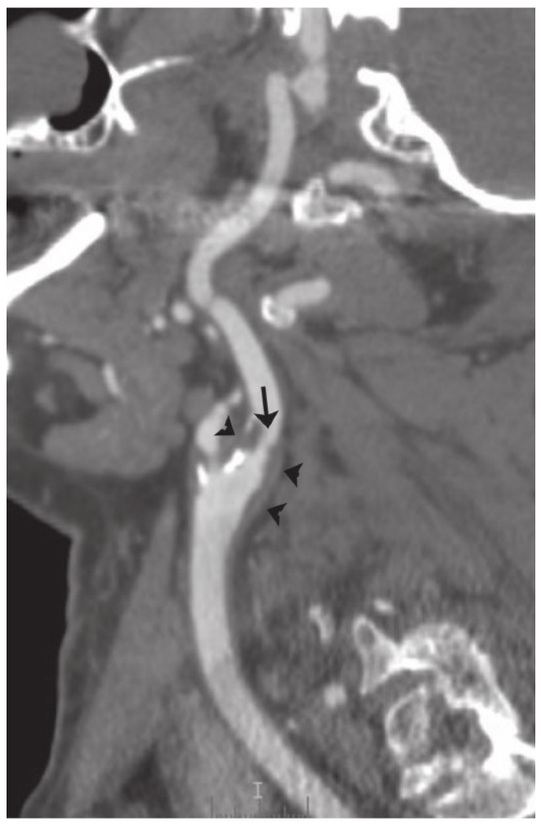
www.ketabpezeshki.com (021) 66485457 - 66485438

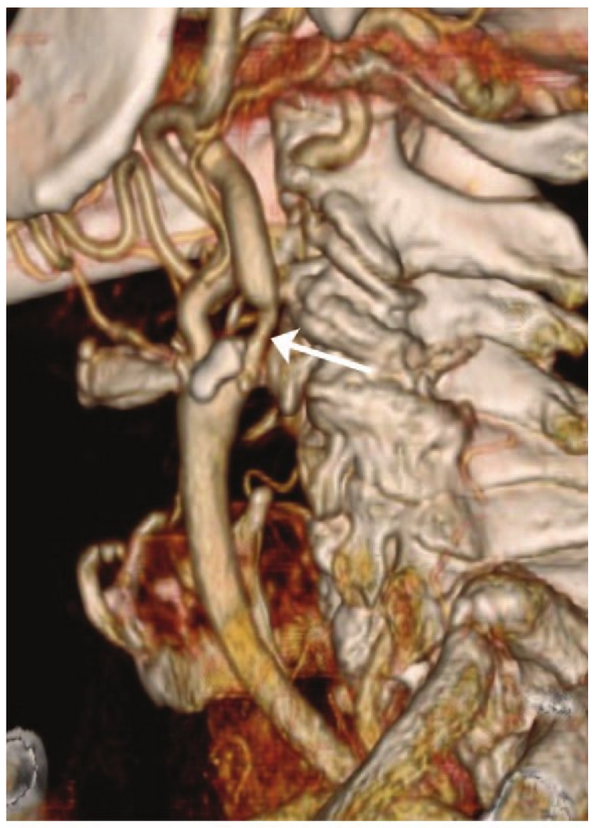
A

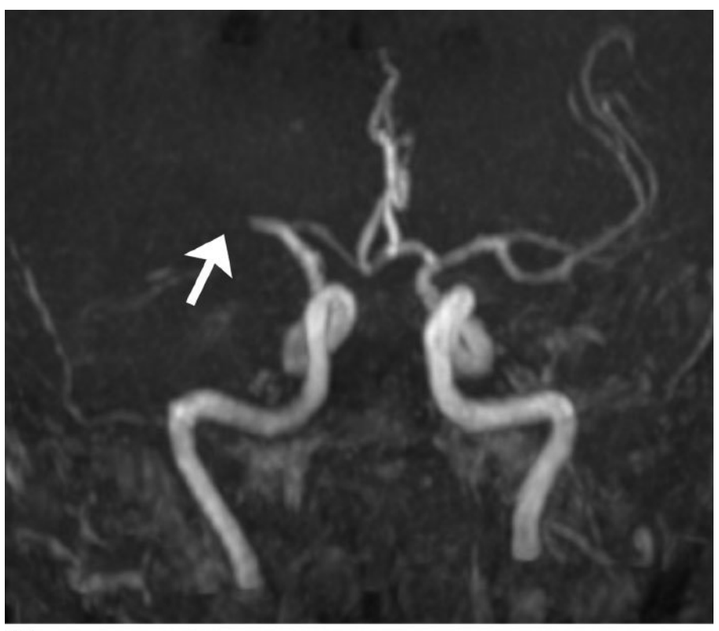

B

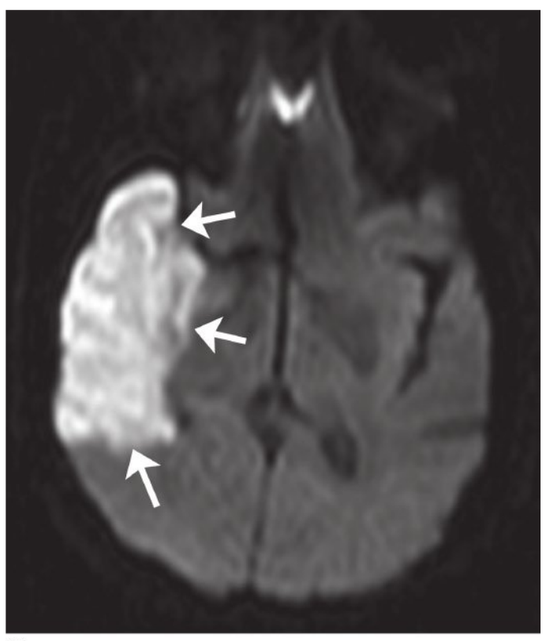

C


D


E


F


G


H

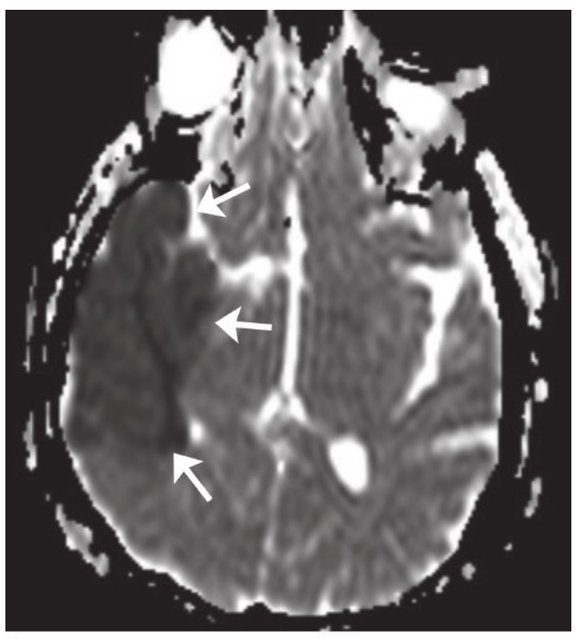

I

FIGURE 4-2

Acute left hemiparesis due to middle cerebral artery occlusion. A. Axial noncontrast computed tomography (CT) scan demonstrates high density within the right middle cerebral artery (arrow) associated with subtle low density involving the right putamen (arrowheads). B. Mean transit time CT perfusion parametric map indicating prolonged mean transit time involving the right middle cerebral territory (arrows). C. Cerebral blood volume (CBV) map shows reduced CBV involving an area within the defect shown in B, indicating a high likelihood of infarction (arrows). D. Axial maximum-intensity projection from a CT angiography (CTA) study through the circle of Willis demonstrates an abrupt occlusion of the proximal right middle cerebral artery (arrow). E. Sagittal reformation through the right internal carotid artery demonstrates a low-density lipid-laden plaque (arrowheads) narrowing the lumen (black arrow). F. Three-dimensional surface-rendered CTA image demonstrates calcification and narrowing of the right internal carotid artery (arrow), consistent with atherosclerotic disease. G. Coronal maximum-intensity projection from magnetic resonance angiography shows right middle cerebral artery (MCA) occlusion (arrow). H. and I. Axial diffusion-weighted image (H) and apparent diffusion coefficient image (I) documents the presence of a right middle cerebral artery infarction.

www.ketabpezeshki.com (021) 66485457 - 66485438

hypersensitivity (anaphylaxis) and range from mild hives to bronchospasm and death. T e pathogenesis of allergic hypersensitivity reactions is thought to include the release of mediators such as histamine, antibody-antigen reactions, and complement activation. Severe allergic reactions occur in ~0.04% of patients receiving nonionic media, sixfold lower than with ionic media. Risk factors include a history of prior contrast reaction (fivefold increased likelihood), food and or drug allergies, and atopy (asthma and hay fever). T e predictive value of specific allergies, such as those to shellfish, once thought important, actually is now recognized to be unreliable. Nonetheless, in patients with a history worrisome for potential allergic reaction, a noncontrast CT or MRI procedure should be considered as an alternative to contrast administration. If iodinated contrast is absolutely required, a nonionic agent should be used in conjunction with pretreatment with glucocorticoids and antihistamines **(Table 4-2)**; however, pretreatment does not guarantee safety. Patients with allergic reactions to iodinated contrast material do not usually react to gadolinium-based MR contrast material, although such reactions can occur. It would be wise to pretreat patients with a prior allergic history to MR contrast administration in a similar fashion. Nonimmediate (>1 h after injection) reactions are frequent and probably related to T cell–mediated immune reactions. T ese are typically urticarial but can occasionally be more severe. Drug provocation and skin testing may be required to determine the culprit agent involved as well as determine a safe alternative.

Other side effects of CT scanning are rare but include a sensation of warmth throughout the body and a metallic taste during intravenous administration of iodinated contrast media. Extravasation of contrast media, although rare, can be painful and lead to compartment syndrome. When this occurs, consultation with plastic surgery is indicated. Patients with significant cardiac disease may be at increased risk for contrast reactions, and in these patients, limits to the volume and osmolality of the contrast media should be considered. Patients who may undergo systemic radioactive iodine therapy for thyroid disease or cancer should not receive iodinated contrast media if possible, because this will decrease the uptake of the radioisotope into the tumor or thyroid (see the American College of Radiology Manual on Contrast Media, Version 9, 2013; http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf).

TABLE 4-2

GUIDELINES FOR PREMEDICATION OF PATIENTS WITH PRIOR CONTRAST ALLERGY
12 h prior to examination: Prednisone, 50 mg PO or methylprednisolone, 32 mg PO
2 h prior to examination: Prednisone, 50 mg PO or methylprednisolone, 32 mg PO and cimetidine, 300 mg PO or ranitidine, 150 mg PO
Immediately prior to examination: Benadryl, 50 mg IV (alternatively, can be given PO 2 h prior to exam)

MAGNETIC RESONANCE IMAGING

TECHNIQUE

MRI is a complex interaction between hydrogen protons in biologic tissues, a static magnetic field (the magnet), and energy in the form of radiofrequency (Rf) waves of a specific frequency introduced by coils placed next to the body part of interest. Images are made by computerized processing of resonance information received from protons in the body. Field strength of the magnet is directly related to signal-to-noise ratio. While 1.5-T magnets have become the standard high-field MRI units, 3-T magnets are now widely available and have distinct advantages in the brain and musculoskeletal systems. Even higher field magnets (7-T) and positron emission tomography (PET) MR machines promise increased resolution and anatomic-functional information on a variety of disorders. Spatial localization is achieved by magnetic gradients surrounding the main magnet, which impart slight changes in magnetic field throughout the imaging volume. Rf pulses transiently excite the energy state of the hydrogen protons in the body. Rf is administered at a frequency specific for the field strength of the magnet. T e subsequent return to equilibrium energy state (relaxation) of the hydrogen protons results in a release of Rf energy (the echo), which is detected by the coils that delivered the Rf pulses. Fourier analysis is used to transform the echo into the information used to form an MR image. T e MR image thus consists of a map of the distribution of hydrogen protons, with signal intensity imparted by both density of hydrogen protons and differences in the relaxation times (see below) of hydrogen protons on different molecules. Although clinical MRI currently makes use of the ubiquitous hydrogen proton, research into sodium and carbon imaging and spectroscopy appears promising.

T1 and T2 relaxation times

T e rate of return to equilibrium of perturbed protons is called the relaxation rate. T e relaxation rate varies among normal and pathologic tissues. T e relaxation rate of a hydrogen proton in a tissue is inf uenced by local interactions with surrounding molecules and

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 4-3

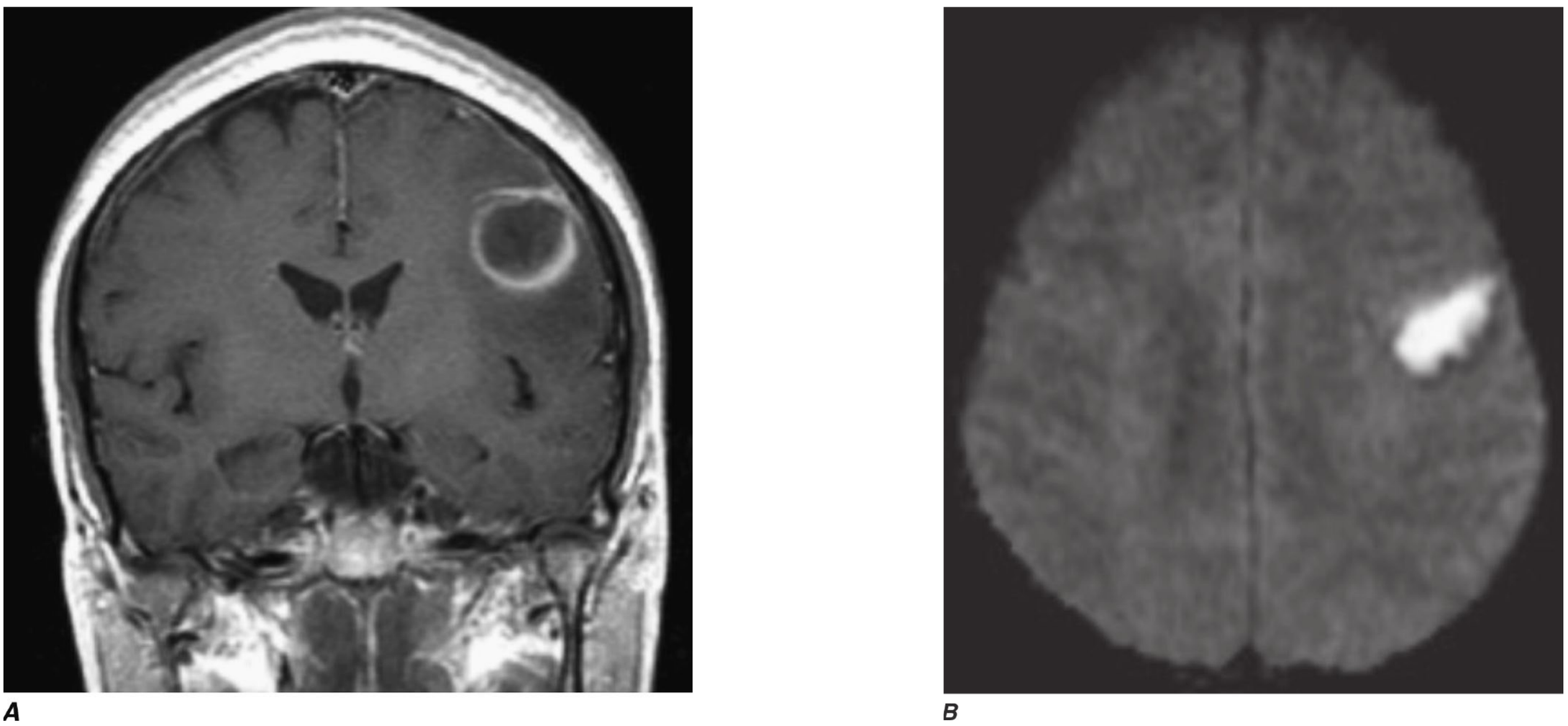
SOME COMMON INTENSITIES ON T1- AND T2-WEIGHTED MRI SEQUENCES

			SIGNAL INTENSITY			
IMAGE	TR	TE	CSF	FAT	BRAIN	EDEMA
T1W	Short	Short	Low	High	Low	Low
T2W	Long	Long	High	Low	High	High
FLAIR (T2)	Long	Long	Low	Medium	High	High

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; TE, interval between radiofrequency pulse and signal reception; TR, interval between radiofrequency pulses; T1W and T2W, T1- and T2-weighted.

atomic neighbors. Two relaxation rates, T1 and T2, influence the signal intensity of the image. The T1 relaxation time is the time, measured in milliseconds, for 63% of the hydrogen protons to return to their normal equilibrium state, whereas the T2 relaxation is the time for 63% of the protons to become dephased owing to interactions among nearby protons. The intensity and image contrast of the signal within various tissues can be modulated by altering acquisition parameters such as the interval between Rf pulses (TR) and the time between the Rf pulse and the signal reception (TE). T1-weighted (T1W) images are produced by keeping the TR and TE relatively short, whereas using longer TR and TE times produces T2-weighted (T2W) images. Fat and subacute hemorrhage have relatively shorter T1 relaxation rates and thus higher signal intensity than brain on T1W images. Structures containing more water, such as CSF and edema, have long T1 and T2 relaxation rates, resulting in relatively lower signal intensity on T1W images and higher signal intensity on T2W images **(Table 4-3)**. Gray matter contains 10–15% more water than white matter, which accounts for much of the intrinsic contrast between the two on MRI (Fig. 4-6B). T2W images are more sensitive than T1W images to edema, demyelination, infarction, and chronic hemorrhage, whereas T1W imaging is more sensitive to subacute hemorrhage and fat-containing structures.

Many different MR pulse sequences exist, and each can be obtained in various planes **(Figs. 4-2, 4-3, and 4-4)**. The selection of a proper protocol that will best answer a clinical question depends on an accurate clinical history and indication for the examination. Fluid-attenuated inversion recovery (FLAIR) is a useful pulse sequence that produces T2W images in which the normally high signal intensity of CSF is suppressed (Fig. 4-6B). FLAIR images are more sensitive than standard spin echo images for any water-containing lesions or edema. Susceptibility-weighted imaging, such as gradient echo imaging, is very sensitive to magnetic susceptibility generated

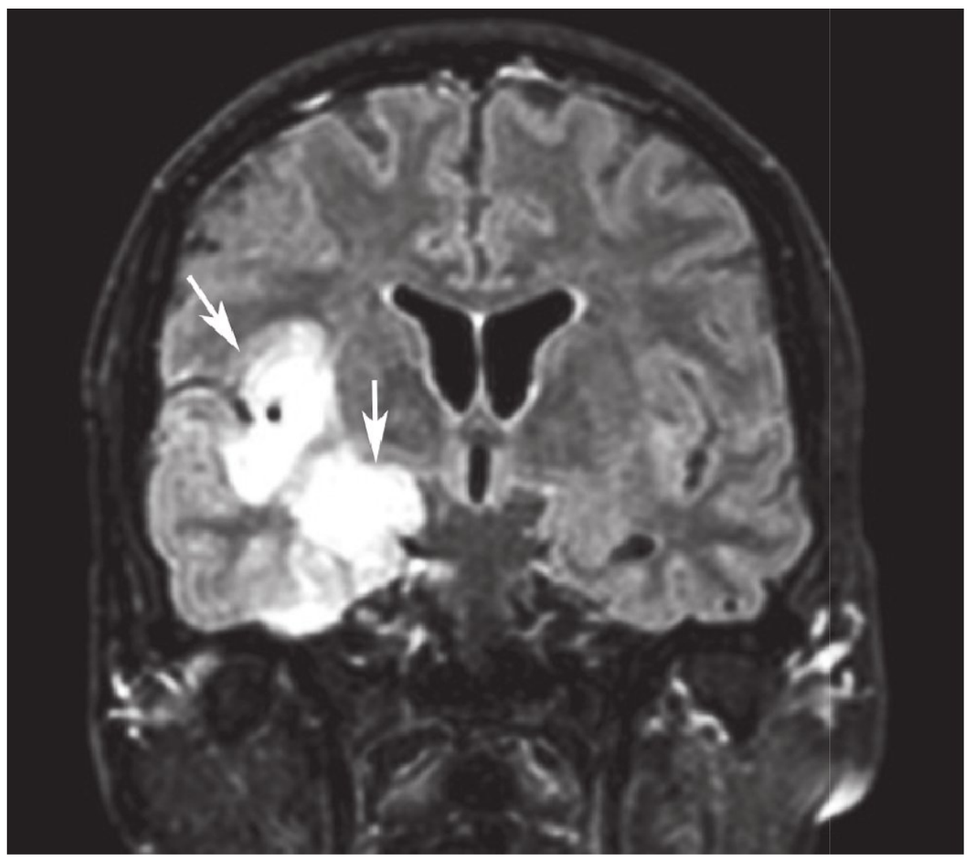


A B

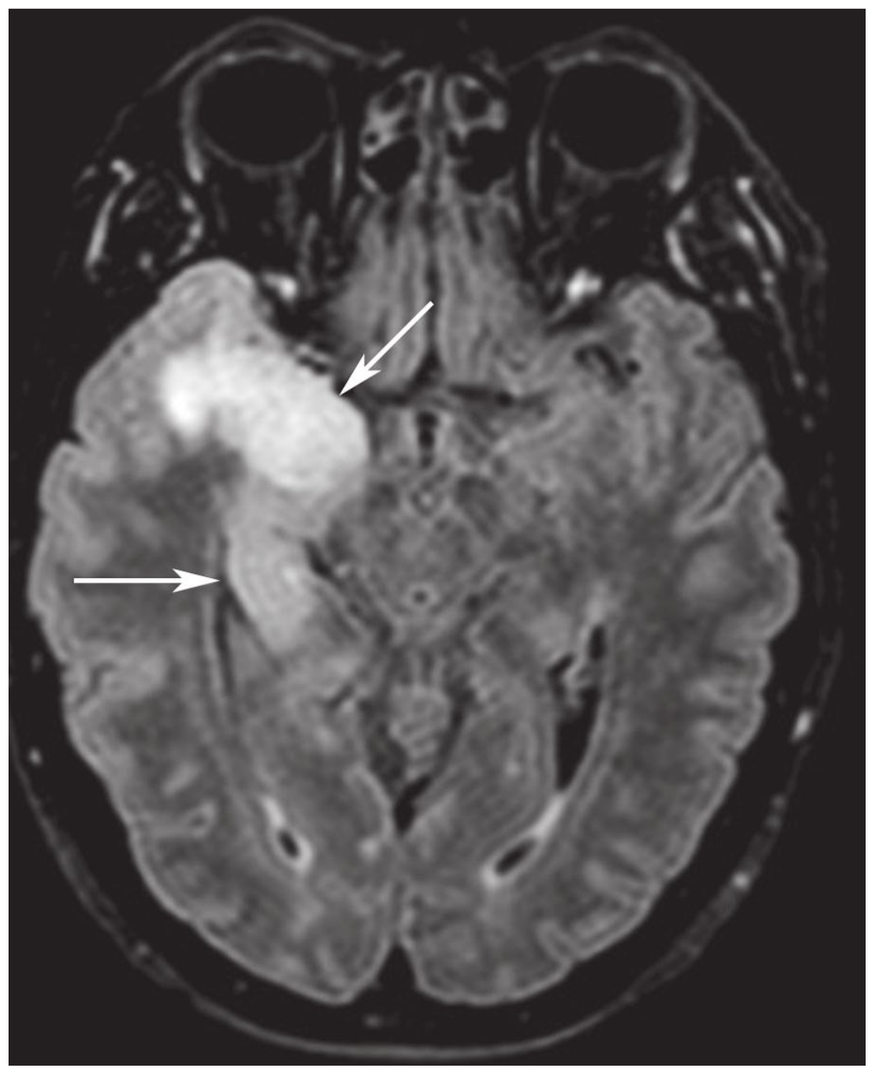
FIGURE 4-3

Cerebral abscess in a patient with fever and a right hemiparesis. A. Coronal postcontrast T1-weighted image demonstrates a ring-enhancing mass in the left frontal lobe. B. Axial diffusion-weighted image demonstrates restricted diffusion (high signal intensity) within the lesion, which in this setting is highly suggestive of cerebral abscess.

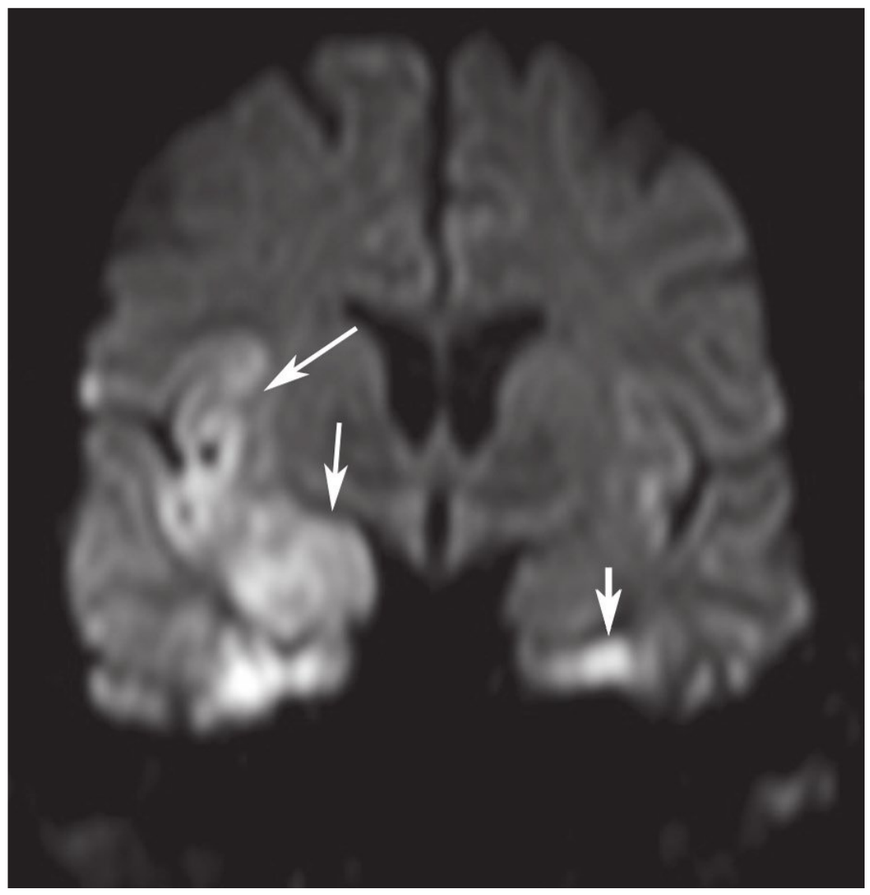
www.ketabpezeshki.com (021) 66485457 - 66485438



A



B



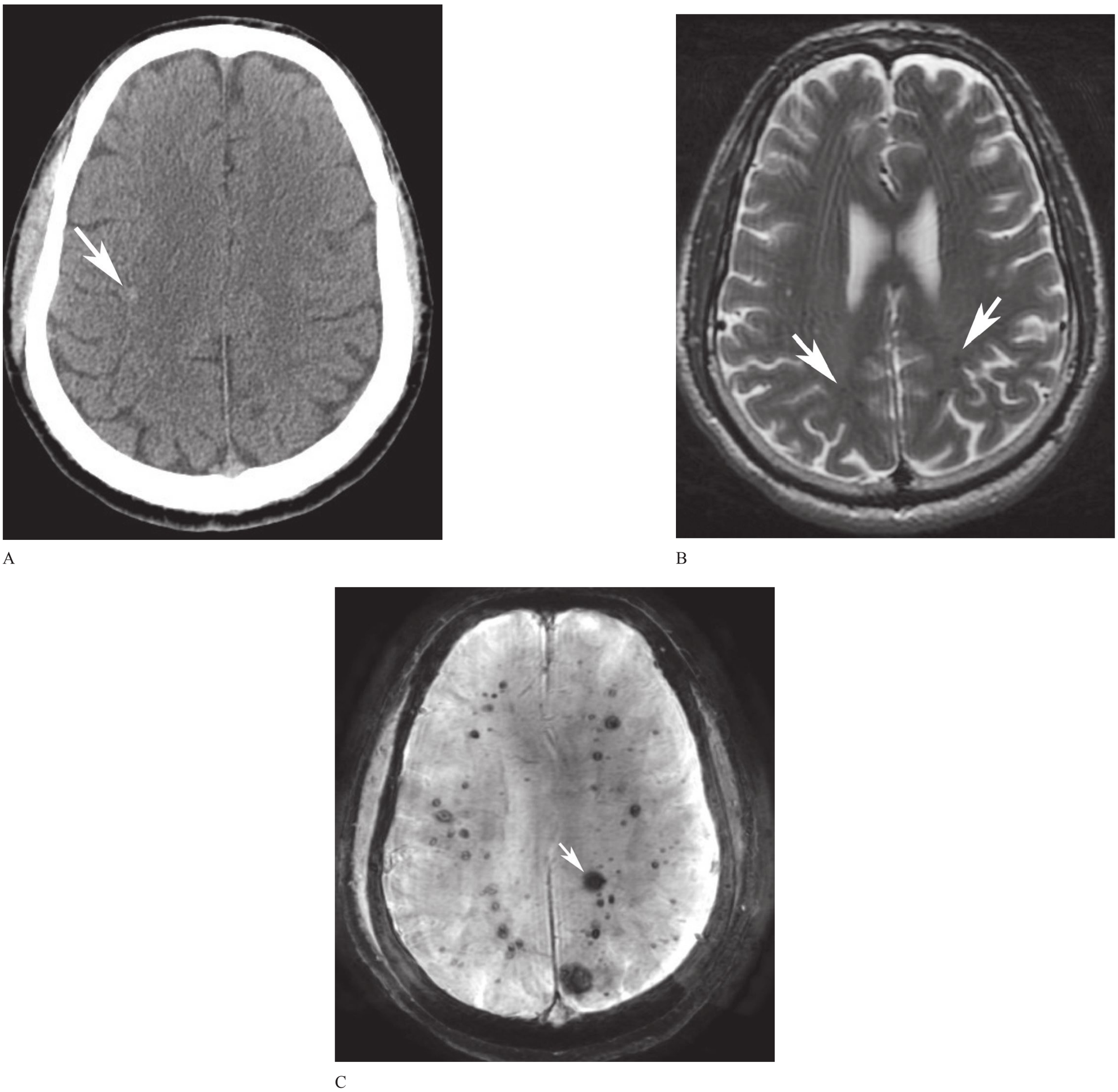
C

FIGURE 4-4

Herpes simplex encephalitis in a patient presenting with altered mental status and fever. A. and B. Coronal (A) and axial (B) T2-weighted fluid-attenuated inversion recovery images demonstrate expansion and high signal intensity involving the right medial temporal lobe and insular cortex (arrows). C. Coronal diffusion-weighted image demonstrates high signal intensity indicating restricted diffusion involving the right medial temporal lobe and hippocampus (arrows) as well as subtle involvement of the left inferior temporal lobe (arrowhead). This is most consistent with neuronal death and can be seen in acute infarction as well as encephalitis and other inflammatory conditions. The suspected diagnosis of herpes simplex encephalitis was confirmed by cerebrospinal fluid polymerase chain reaction analysis.

by blood, calcium, and air and routinely obtained in patients suspected of pathology that might result in microhemorrhages, such as amyloid, hemorrhagic metastases, and thrombotic states **(Fig. 4-5C)**. MR images can be generated in any plane without changing the patient's position. Each sequence, however, must be obtained separately and takes 1–10 min on average to complete. Three-dimensional volumetric imaging is also possible with MRI, resulting in a three-dimensional volume of data that can be reformatted in any orientation to highlight certain disease processes.

www.ketabpezeshki.com (021) 66485457 - 66485438



A

B

C

FIGURE 4-5

Susceptibility-weighted imaging in a patient with familial cavernous malformations. A. Noncontrast computed tomography scan shows one hyperdense lesion in the right hemisphere (arrow). B. T2-weighted fast spin echo image shows subtle low-intensity lesions (arrows). C. Susceptibility-weighted image shows numerous low-intensity lesions consistent with hemosiderin-laden cavernous malformations (arrow).

MR contrast material

The heavy-metal element gadolinium forms the basis of all currently approved intravenous MR contrast agents. Gadolinium is a paramagnetic substance, which means that it reduces the T1 and T2 relaxation times of nearby water protons, resulting in a high signal on T1W images and a low signal on T2W images (the latter requires a sufficient local concentration, usually in the form of an intravenous bolus). Unlike iodinated contrast agents, the effect of MR contrast agents depends on the presence of local hydrogen protons on which it must act to achieve the desired effect. There are nine different gadolinium agents approved in the United States for use with MRI. These differ according the attached chelated moiety, which also affects the strength of chelation

www.ketabpezeshki.com (021) 66485457 - 66485438

of the otherwise toxic gadolinium element. T e chelating carrier molecule for gadolinium can be classified by whether it is macrocyclic or has linear geometry and whether it is ionic or nonionic. Most of these are excreted by the renal system. Cyclical agents are less likely to release the gadolinium element, and thus are considered the safest category.

Allergic hypersensitivity

Gadolinium-DTPA (diethylenetriaminepentaacetic acid) does not normally cross the intact BBB immediately but will enhance lesions lacking a BBB (Fig. 4-3A) as well as areas of the brain that normally are devoid of the BBB (pituitary, dura, choroid plexus). However, gadolinium contrast has been noted to slowly cross an intact BBB over time and especially in the setting of reduced renal clearance or inf amed meninges. T e agents are generally well tolerated; overall adverse events after injection range from 0.07–2.4%. True allergic reactions are rare (0.004–0.7%) but have been reported. Severe life-threatening reactions are exceedingly rare; in one report, only 55 reactions out of 20 million doses occurred. However, the adverse reaction rate in patients with a prior history of reaction to gadolinium is eight times higher than normal. Other risk factors include atopy or asthma (3.7%); although there is no cross-reactivity to iodinated contrast material, those with a prior allergic response to iodine should be considered at higher risk. Gadolinium contrast material can be administered safely to children as well as adults, although these agents are generally avoided in those under 6 months of age.

Nephrotoxicity

Contrast-induced renal failure does not occur with gadolinium agents. A rare complication, nephrogenic systemic fibrosis (NSF), has occurred in patients with severe renal insufficiency who have been exposed to gadolinium contrast agents. T e onset of NSF has been reported between 5 and 75 days following exposure; histologic features include thickened collagen bundles with surrounding clefts, mucin deposition, and increased numbers of fibrocytes and elastic fibers in skin. In addition to dermatologic symptoms, other manifestations include widespread fibrosis of the skeletal muscle, bone, lungs, pleura, pericardium, myocardium, kidney, muscle, bone, testes, and dura. T e American College of Radiology recommends that a glomerular filtration rate (GFR) assessment be obtained within 6 weeks prior to elective gadolinium-based MR contrast agent administration in patients with:

1. A history of renal disease (including solitary kidney, renal transplant, renal tumor)
2. Age >60 years
3. History of hypertension
4. History of diabetes
5. History of severe hepatic disease, liver transplant, or pending liver transplant; for these patients, it is recommended that the patient's GFR assessment be nearly contemporaneous with the MR examination

T e incidence of NSF in patients with severe renal dysfunction (GFR <30) varies from 0.19 to 4%. Other risk factors for NSF include acute kidney injury, the use of nonmacrocyclic agents, and repeated or high-dose exposure to gadolinium. T e American College of Radiology Committee on Drugs and Contrast Media states that patients receiving any gadolinium-containing agent should be considered at risk of NSF if they are on dialysis (of any form); have severe or end-stage chronic renal disease (eGFR <30 mL/min/1.73 m^2) without dialysis; eGFR of 30–40 mL/min/1.73 m^2 without dialysis (as the GFR may f uctuate); or have acute renal insufficiency.

COMPLICATIONS AND CONTRAINDICATIONS

From the patient's perspective, an MRI examination can be intimidating, and a higher level of cooperation is required than with CT. T e patient lies on a table that is moved into a long, narrow gap within the magnet. Approximately 5% of the population experiences severe claustrophobia in the MR environment. T is can be reduced by mild sedation but remains a problem for some. Because it takes between 3 and 10 min per sequence, movement of the patient during an MR exam distorts all of the images; therefore, uncooperative patients should either be sedated for the MR study or scanned with CT. Generally, children under the age of 8 years usually require conscious sedation in order to complete the MR examination without motion degradation.

MRI is considered safe for patients, even at very high field strengths. Serious injuries have been caused, however, by attraction of ferromagnetic objects into the magnet, which act as missiles if brought too close to the magnet. Likewise, ferromagnetic implants, such as aneurysm clips, may torque within the magnet, causing damage to vessels and even death. Metallic foreign bodies in the eye have moved and caused intraocular hemorrhage; screening for ocular metallic fragments is indicated in those with a history of metal work or ocular metallic foreign bodies. Implanted cardiac pacemakers are generally a contraindication to MRI owing to the risk of induced arrhythmias; however, some newer pacemakers have been shown to be safe. All health care personnel and patients must be screened and educated thoroughly to prevent such disasters because the magnet is always "on." **Table 4-4** lists common contraindications for MRI.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 4-4

COMMON CONTRAINDICATIONS TO MAGNETIC RESONANCE IMAGING
Cardiac pacemaker or permanent pacemaker leads
Internal defibrillatory device
Cochlear prostheses
Bone growth stimulators
Spinal cord stimulators
Electronic infusion devices
Intracranial aneurysm clips (some but not all)
Ocular implants (some) or ocular metallic foreign body
McGee stapedectomy piston prosthesis
Duraphase penile implant
Swan-Ganz catheter
Magnetic stoma plugs
Magnetic dental implants
Magnetic sphincters
Ferromagnetic inferior vena cava filters, coils, stents—safe 6 weeks after implantation
Tattooed eyeliner (contains ferromagnetic material and may irritate eyes)

Note: See also http://www.mrisafety.com.

MAGNETIC RESONANCE ANGIOGRAPHY

MR angiography is a general term describing several MR techniques that result in vascular-weighted images. These provide a vascular flow map rather than the anatomic map shown by conventional angiography. On routine spin echo MR sequences, moving protons (e.g., flowing blood, CSF) exhibit complex MR signals that range from high- to low-signal intensity relative to background stationary tissue. Fast-flowing blood returns no signal (flow void) on routine T1W or T2W spin echo MR images. Slower-flowing blood, as occurs in veins or distal to arterial stenosis, may appear high in signal. However, using special pulse sequences called gradient echo sequences, it is possible to increase the signal intensity of moving protons in contrast to the low signal background intensity of stationary tissue. This creates angiography-like images, which can be manipulated in three dimensions to highlight vascular anatomy and relationships.

So called time-of-flight (TOF) MRA relies on the suppression of nonmoving tissue to provide a low-intensity background for the high signal intensity of flowing blood entering the section; arterial or venous structures may be highlighted. A typical TOF MRA sequence results in a series of contiguous, thin MR sections (0.6–0.9 mm thick), which can be viewed as a stack and manipulated to create an angiographic image data set that can be reformatted and viewed in various planes and angles, much like that seen with conventional angiography **(Fig. 4-2G)**.

Phase-contrast MRA has a longer acquisition time than TOF MRA, but in addition to providing anatomic information similar to that of TOF imaging, it can be used to reveal the velocity and direction of blood flow in a given vessel. Through the selection of different imaging parameters, differing blood velocities can be highlighted; selective venous and arterial MRA images can thus be obtained. One advantage of phase-contrast MRA is the excellent suppression of high-signal-intensity background structures.

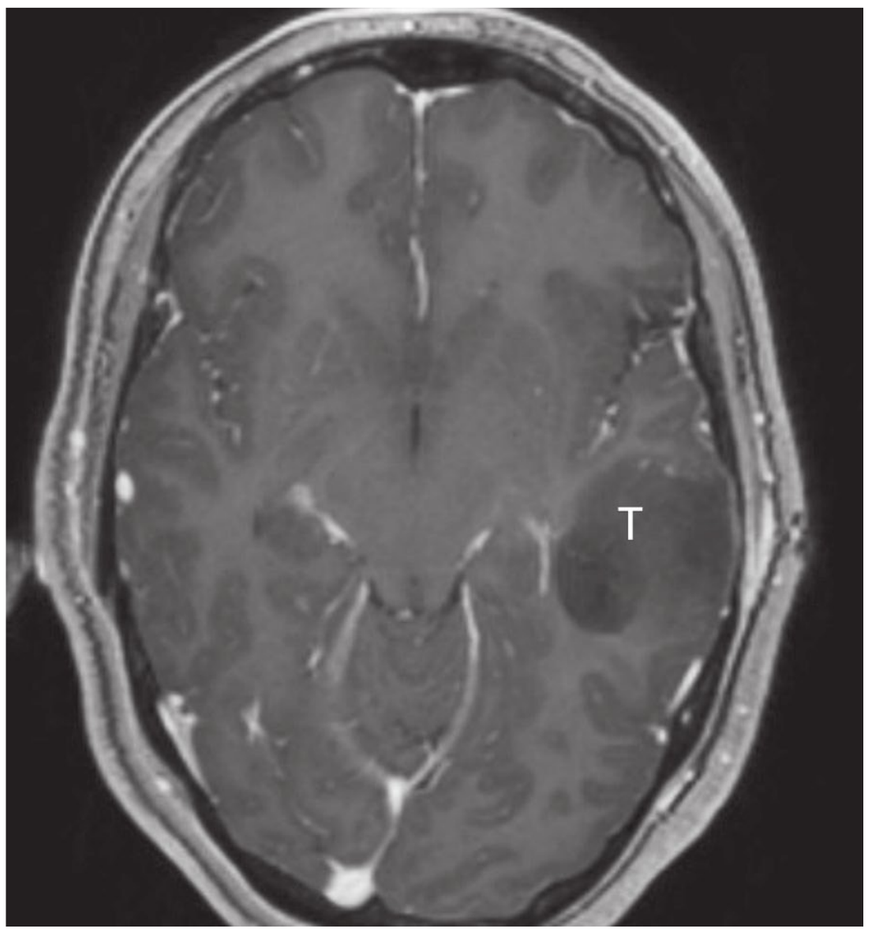
MRA can also be acquired during infusion of contrast material. Advantages include faster imaging times (1–2 min vs 10 min), fewer flow-related artifacts, and higher resolution images. Recently, contrast-enhanced MRA has become the standard for extracranial vascular MRA. This technique entails rapid imaging using coronal three-dimensional TOF sequences during a bolus infusion of gadolinium contrast agent. Proper technique and timing of acquisition relative to bolus arrival are critical for success.

MRA has lower spatial resolution compared with conventional film-based angiography, and therefore the detection of small-vessel abnormalities, such as vasculitis and distal vasospasm, is problematic. MRA is also less sensitive to slowly flowing blood and thus may not reliably differentiate complete from near-complete occlusions. Motion, either by the patient or by anatomic structures, may distort the MRA images, creating artifacts. These limitations notwithstanding, MRA has proved useful in evaluation of the extracranial carotid and vertebral circulation as well as of larger-caliber intracranial arteries and dural sinuses. It has also proved useful in the noninvasive detection of intracranial aneurysms and vascular malformations.

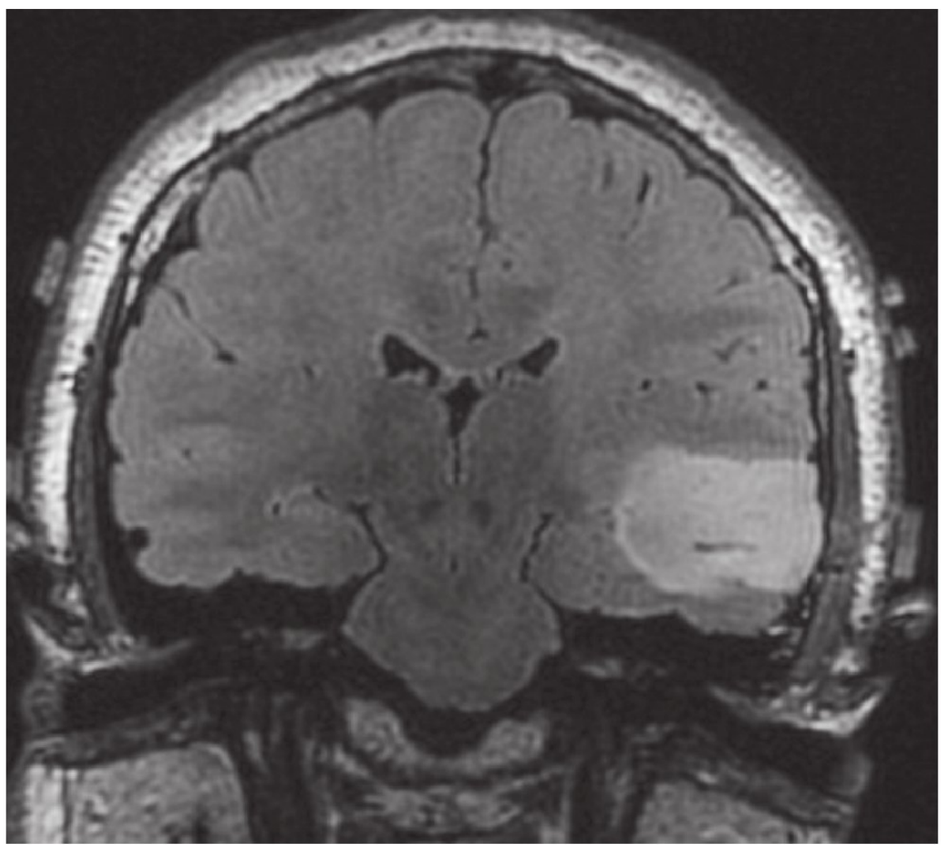
ECHO-PLANAR MRI

Recent improvements in gradients, software, and high-speed computer processors now permit extremely rapid MRI of the brain. With echo-planar MRI (EPI), fast gradients are switched on and off at high speeds to create the information used to form an image. In routine spin echo imaging, images of the brain can be obtained in 5–10 min. With EPI, all of the information required for processing an image is accumulated in milliseconds, and the information for the entire brain can be obtained in less than 1–2 min, depending on the degree of resolution required or desired. Fast MRI reduces patient and organ motion and is the basis of perfusion imaging during contrast infusion and kinematic motion studies. EPI is also the sequence used to obtain diffusion imaging and tractography, as well as fMRI and arterial spin-labeled studies **(Figs. 4-2H,** 4-3, **4-4C, and 4-6;** and see Fig. 32-16).

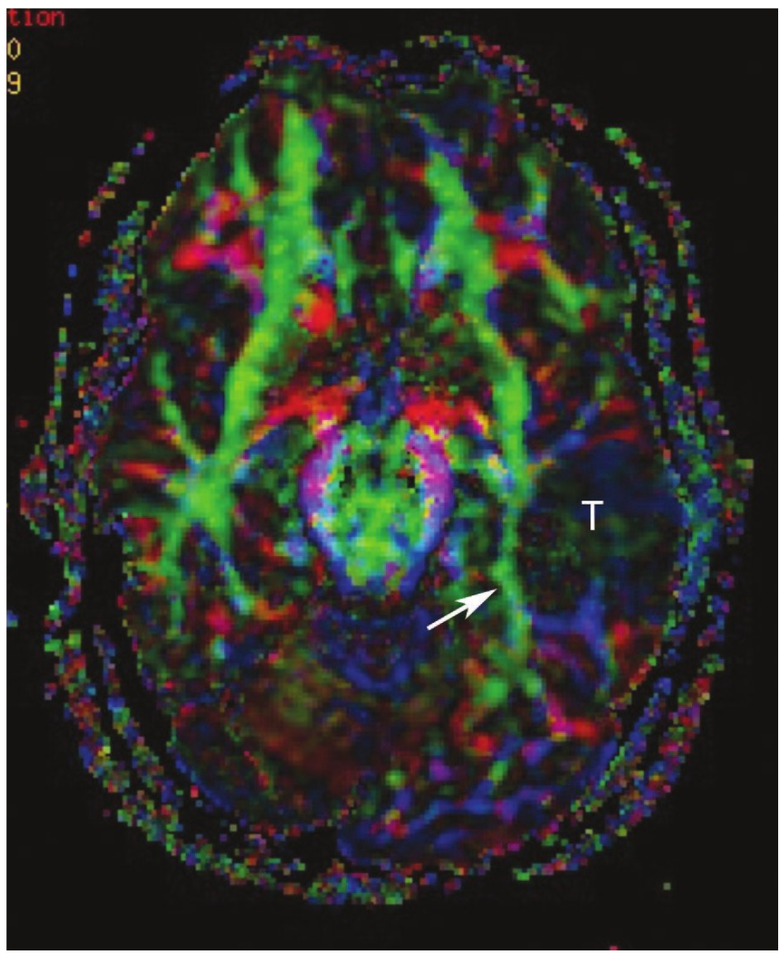
www.ketabpezeshki.com (021) 66485457 - 66485438



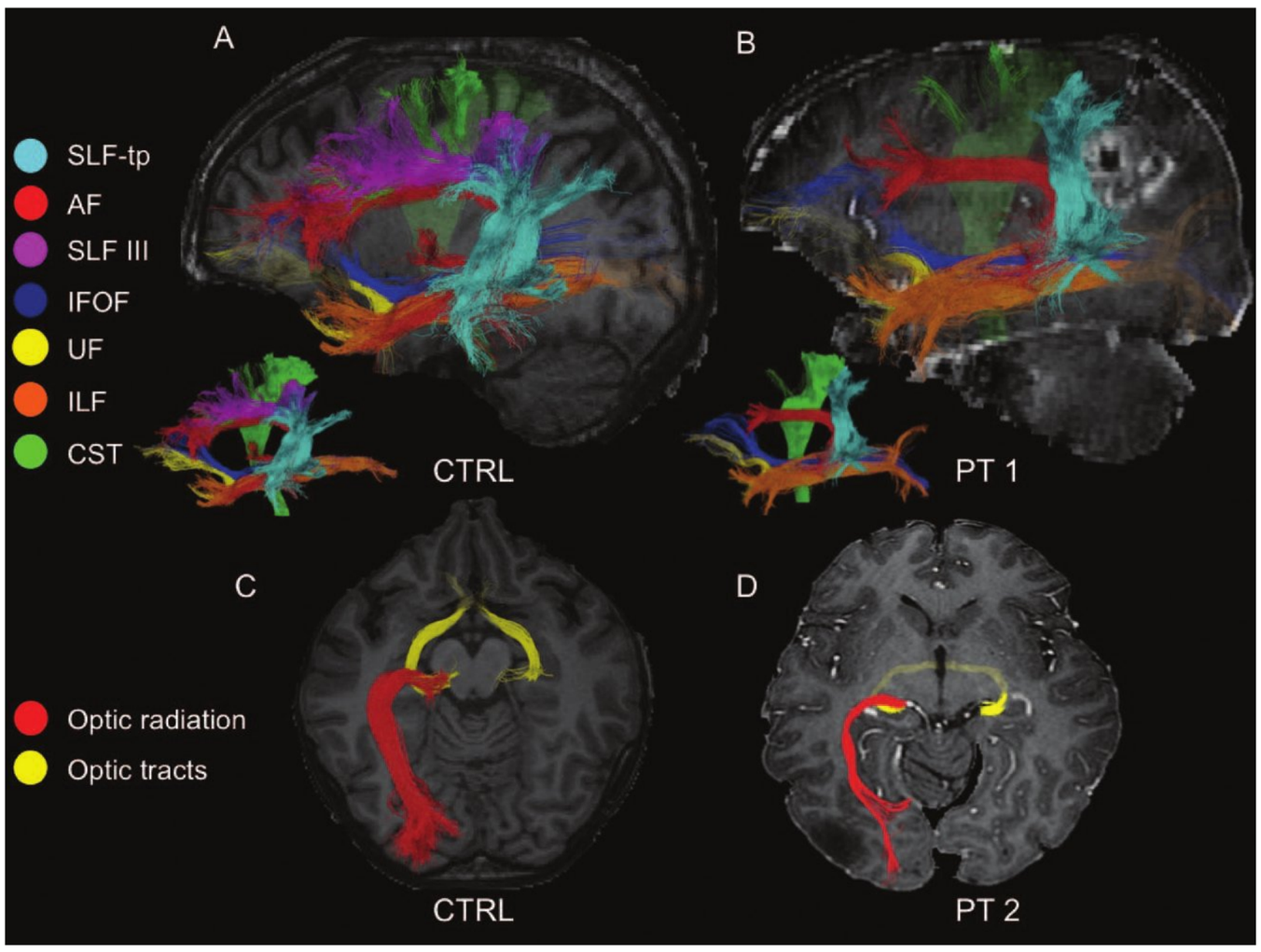
A



B



C



D

FIGURE 4-6

Diffusion tractography in cerebral glioma. Associative and descending pathways in a healthy subject (A) and in a patient with parietal lobe glioblastoma (B) presenting with a language deficit: the mass causes a disruption of the arcuate-SLF complex, in particular of its anterior portion (SLF III). Also shown are bilateral optic tract and left optic radiation pathways in a healthy subject (C) and in a patient with left occipital grade II oligoastrocytoma (D): the mass causes a disruption of the left optic radiation. Shown in neurologic orientation, i.e., the left brain appears on the left side of the image. AF, long segment of the arcuate fascicle; CST, corticospinal tract; IFOF: inferior fronto-occipital fascicle; ILF, inferior longitudinal fascicle; SLF III, superior longitudinal fascicle III or anterior segment of the arcuate fascicle; SLF-tp, temporo-parietal portion of the superior longitudinal fascicle or posterior segment of the arcuate fascicle; T, tumor; UF, uncinated fascicle. (Part D courtesy of Eduardo Caverzasi and Roland Henry.)

Perfusion and diffusion imaging are EPI techniques that are useful in early detection of ischemic injury of the brain and may be useful together to demonstrate infarcted tissue as well as ischemic but potentially viable tissue at risk of infarction (e.g., the ischemic penumbra). Diffusion-weighted imaging (DWI) assesses microscopic motion of water; abnormal restriction of motion appears as relative high-signal intensity on diffusion-weighted images. Infarcted tissue reduces the water motion within cells and in the interstitial tissues, resulting in high signal on DWI. DWI is the most sensitive technique for detection of acute cerebral infarction

www.ketabpezeshki.com (021) 66485457 - 66485438

of <7 days in duration (Fig. 4-2H). It is also quite sensitive for detecting dying or dead brain tissue secondary to encephalitis, as well as abscess formation (Fig. 4-3B).

Perfusion MRI involves the acquisition of fast echo planar gradient images during a rapid intravenous bolus of gadolinium contrast material. Relative cerebral blood volume, mean transit time, and cerebral blood f ow maps are then derived. Delay in mean transit time and reduction in cerebral blood volume and cerebral blood f ow are typical of infarction. In the setting of reduced blood f ow, a prolonged mean transit time of contrast but normal or elevated cerebral blood volume may indicate tissue supplied by collateral f ow that is at risk of infarction. Perfusion MRI imaging can also be used in the assessment of brain tumors to differentiate intraaxial primary tumors, whose BBB is relatively intact, from extraaxial tumors or metastases, which demonstrate a relatively more permeable BBB.

Diffusion tensor imaging is derived from diffusion MRI imaging sequences, which assesses the direction of microscopic motion of water along white matter tracts. T is technique has great potential in the assessment of brain maturation as well as disease entities that undermine the integrity of the white matter architecture. It has proven valuable in preoperative assessment of subcortical white matter tract anatomy prior to brain tumor surgery (Fig. 4-6).

fMRI of the brain is an EPI technique that localizes regions of activity in the brain following task activation. Neuronal activity elicits a slight increase in the delivery of oxygenated blood f ow to a specific region of activated brain. T is results in an alteration in the balance of oxyhemoglobin and deoxyhemoglobin, which yields a 2–3% increase in signal intensity within veins and local capillaries. Further studies will determine whether these techniques are cost effective or clinically useful, but currently, preoperative somatosensory and auditory cortex localization is possible. T is technique has proved useful to neuroscientists interested in interrogating the localization of certain brain functions.

ARTERIAL SPIN LABELING

ASL is a quantitative noninvasive MR technique that measures cerebral blood f ow. Blood traversing in the neck is labeled by an MR pulse and then imaged in the brain after a short delay. T e signal in the brain is ref ective of blood f ow. ASL is an especially important technique for patients with kidney failure and for pediatric patients in whom the use of radioactive tracers or exogenous contrast agents is contraindicated. Increased cerebral f ow is more easily identified than slow f ow, which can be sometimes difficult to quantify. T is technique has also been shown useful in detecting arterial venous shunting in arteriovenous malformations and arteriovenous fistulas.

MAGNETIC RESONANCE NEUROGRAPHY

MRN is a T2W MR technique that shows promise in detecting increased signal in irritated, inf amed, or infiltrated peripheral nerves. Images are obtained with fat-suppressed fast spin echo imaging or short inversion recovery sequences. Irritated or infiltrated nerves will demonstrate high signal on T2W imaging. T is is indicated in patients with radiculopathy whose conventional MR studies of the spine are normal, or in those suspected of peripheral nerve entrapment or trauma.

POSITRON EMISSION TOMOGRAPHY

PET relies on the detection of positrons emitted during the decay of a radionuclide that has been injected into a patient. T e most frequently used moiety is 2-[^{18}F]f uoro-2-deoxy-D-glucose (FDG), which is an analogue of glucose and is taken up by cells competitively with 2-deoxyglucose. Multiple images of glucose uptake activity are formed after 45–60 min. Images reveal differences in regional glucose activity among normal and pathologic brain structures. FDG-PET is used primarily for the detection of extracranial metastatic disease; however, a lower activity of FDG in the parietal lobes is associated with Alzheimer's disease, a finding that may simply ref ect atrophy that occurs in the later stages of the disease. Combination PET-CT scanners, in which both CT and PET are obtained at one sitting, have largely replaced PET scans alone for most clinical indications. MR-PET scanners have also been developed and may prove useful for imaging the brain and other organs without the radiation exposure of CT. More recent PET ligand developments include amyloid tracers, such as Pittsburgh compound B (PIB) and 18-F AV-45 (f orbetapir), and tau PET tracers, such as 18F-T807 and T808. Studies have shown an increased percentage of amyloid deposition in patients with Alzheimer's disease compared with mild cognitive impairment and healthy controls; however, up to 25% of cognitively "normal" patients show abnormalities on amyloid PET imaging. T is may either ref ect subclinical disease processes or variation of normal. Tau imaging may be more specific for Alzheimer's disease, and clinical studies are under way.

MYELOGRAPHY

TECHNIQUE

Myelography involves the intrathecal instillation of specially formulated water-soluble iodinated contrast medium into the lumbar or cervical subarachnoid space. CT scanning is typically performed after myelography (CT myelography) to better demonstrate

www.ketabpezeshki.com (021) 66485457 - 66485438

the spinal cord and roots, which appear as filling defects in the opacified subarachnoid space. Low-dose CT myelography, in which CT is performed after the subarachnoid injection of a small amount of relatively dilute contrast material, has replaced conventional myelography for many indications, thereby reducing exposure to radiation and contrast media. Newer multidetector scanners now obtain CT studies quickly so that reformations in sagittal and coronal planes, equivalent to traditional myelography projections, are now routine.

INDICATIONS

Myelography has been largely replaced by CT myelography and MRI for diagnosis of diseases of the spinal canal and cord (Table 4-1). Remaining indications for conventional plain-film myelography include the evaluation of suspected meningeal or arachnoid cysts and the localization of CSF fistulas. Conventional myelography and CT myelography provide the most precise information in patients with prior spinal fusion and spinal fixation hardware.

CONTRAINDICATIONS

Myelography is relatively safe; however, it should be performed with caution in any patient with elevated intracranial pressure, evidence of a spinal block, or a history of allergic reaction to intrathecal contrast media. In patients with a suspected spinal block, MR is the preferred technique. If myelography is necessary, only a small amount of contrast medium should be instilled below the lesion in order to minimize the risk of neurologic deterioration. Lumbar puncture is to be avoided in patients with bleeding disorders, including patients receiving anticoagulant therapy, as well as in those with infections of the overlying soft tissues **(Chap. 7)**.

COMPLICATIONS

Headache is the most frequent complication of myelography and is reported to occur in 5–30% of patients. Nausea and vomiting may also occur rarely. Postural headache (post–lumbar puncture headache) is generally due to leakage of CSF from the puncture site, resulting in CSF hypotension. A higher incidence is noted among younger women and with the use of larger gauge cutting-type spinal needles. If significant headache persists for longer than 48 h, placement of an epidural blood patch should be considered. **Management of lumbar puncture headache is discussed in Chap. 9**. Vasovagal syncope may occur during lumbar puncture; it is accentuated by the upright position used during lumbar myelography. Adequate hydration before and after myelography will reduce the incidence of this complication.

Hearing loss is a rare complication of myelography. It may result from a direct toxic effect of the contrast medium or from an alteration of the pressure equilibrium between CSF and perilymph in the inner ear. Puncture of the spinal cord is a rare but serious complication of cervical (C1–2) or high lumbar puncture. T e risk of cord puncture is greatest in patients with spinal stenosis, Chiari malformations, or conditions that reduce CSF volume. In these settings, a low-dose lumbar injection followed by thin-section CT or MRI is a safer alternative to cervical puncture. Intrathecal contrast reactions are rare, but aseptic meningitis and encephalopathy are reported complications. T e latter is usually dose related and associated with contrast entering the intracranial subarachnoid space. Seizures occur following myelography in 0.1–0.3% of patients. Risk factors include a preexisting seizure disorder and the use of a total iodine dose of >4500 mg. Other reported complications include hyperthermia, hallucinations, depression, and anxiety states. T ese side effects have been reduced by the development of nonionic, water-soluble contrast agents as well as by head elevation and generous hydration following myelography.

SPINE INTERVENTIONS

DISKOGRAPHY

T e evaluation of back pain and radiculopathy may require diagnostic procedures that attempt either to reproduce the patient's pain or relieve it, indicating its correct source prior to lumbar fusion. Diskography is performed by fuoroscopic placement of a 22- to 25-gauge needle into the intervertebral disk and subsequent injection of 1–3 mL of contrast media. T e intradiskal pressure is recorded, as is an assessment of the patient's response to the injection of contrast material. Typically little or no pain is felt during injection of a normal disk, which does not accept much more than 1 mL of contrast material, even at pressures as high as 415–690 kPa (60–100 lb/in^2). CT and plain films are obtained following the procedure. Concerns have been raised that diskography may contribute to an accelerated rate of disk degeneration.

SELECTIVE NERVE ROOT AND EPIDURAL SPINAL INJECTIONS

Percutaneous selective nerve root and epidural blocks with glucocorticoid and anesthetic mixtures may be both therapeutic and diagnostic, especially if a patient's pain is relieved. Typically, 1–2 mL of an equal mixture of a long-acting glucocorticoid such as betamethasone and a long-acting anesthetic such as bupivacaine 0.75%

www.ketabpezeshki.com (021) 66485457 - 66485438

is instilled under CT or fluoroscopic guidance in the intraspinal epidural space or adjacent to an existing nerve root.

ANGIOGRAPHY

Catheter angiography is indicated for evaluating intracranial small-vessel pathology (such as vasculitis), for assessing vascular malformations and aneurysms, and in endovascular therapeutic procedures (Table 4-1). Angiography has been replaced for many indications by CT/CTA or MRI/MRA.

Angiography carries the greatest risk of morbidity of all diagnostic imaging procedures, owing to the necessity of inserting a catheter into a blood vessel, directing the catheter to the required location, injecting contrast material to visualize the vessel, and removing the catheter while maintaining hemostasis. Therapeutic transcatheter procedures (see below) have become important options for the treatment of some cerebrovascular diseases. The decision to undertake a diagnostic or therapeutic angiographic procedure requires careful assessment of the goals of the investigation and its attendant risks.

To improve tolerance to contrast agents, patients undergoing angiography should be well hydrated before and after the procedure. Because the femoral route is used most commonly, the femoral artery must be compressed after the procedure to prevent a hematoma from developing. The puncture site and distal pulses should be evaluated carefully after the procedure; complications can include thigh hematoma or lower extremity emboli.

COMPLICATIONS

A common femoral arterial puncture provides retrograde access via the aorta to the aortic arch and great vessels. The most feared complication of cerebral angiography is stroke. Thrombus can form on or inside the tip of the catheter, and atherosclerotic thrombus or plaque can be dislodged by the catheter or guide wire or by the force of injection and can embolize distally in the cerebral circulation. Risk factors for ischemic complications include limited experience on the part of the angiographer, atherosclerosis, vasospasm, low cardiac output, decreased oxygen-carrying capacity, advanced age, and prior history of migraine. The risk of a neurologic complication varies but is ~4% for transient ischemic attack and stroke, 1% for permanent deficit, and <0.1% for death.

Ionic contrast material injected into the cerebral vasculature can be neurotoxic if the BBB is breached, either by an underlying disease or by the injection of hyperosmolar contrast agent. Ionic contrast media are less well tolerated than nonionic media, probably because they can induce changes in cell membrane electrical potentials. Patients with dolichoectasia of the basilar artery can suffer reversible brainstem dysfunction and acute short-term memory loss during angiography, owing to the slow percolation of the contrast material and the consequent prolonged exposure of the brain. Rarely, an intracranial aneurysm ruptures during an angiographic contrast injection, causing subarachnoid hemorrhage, perhaps as a result of injection under high pressure.

SPINAL ANGIOGRAPHY

Spinal angiography may be indicated to evaluate vascular malformations and tumors and to identify the artery of Adamkiewicz **(Chap. 43)** prior to aortic aneurysm repair. The procedure is lengthy and requires the use of relatively large volumes of contrast; the incidence of serious complications, including paraparesis, subjective visual blurring, and altered speech, is ~2%. Gadolinium-enhanced MRA has been used successfully in this setting, as has iodinated contrast CTA, which has promise for replacing diagnostic spinal angiography for some indications.

INTERVENTIONAL NEURORADIOLOGY

This rapidly developing field is providing new therapeutic options for patients with challenging neurovascular problems. Available procedures include detachable coil therapy for aneurysms, particulate or liquid adhesive embolization of arteriovenous malformations, stent retrieval systems for embolectomy, balloon angioplasty and stenting of arterial stenosis or vasospasm, transarterial or transvenous embolization of dural arteriovenous fistulas, balloon occlusion of carotid-cavernous and vertebral fistulas, endovascular treatment of vein-of-Galen malformations, preoperative embolization of tumors, and thrombolysis of acute arterial or venous thrombosis. Many of these disorders place the patient at high risk of cerebral hemorrhage, stroke, or death.

The highest complication rates are found with the therapies designed to treat the highest risk diseases. The advent of electrolytically detachable coils has ushered in a new era in the treatment of cerebral aneurysms. Two randomized trials found reductions of morbidity and mortality at 1 year among those treated for aneurysm with detachable coils compared with neurosurgical clipping. It remains to be determined what the role of coils will be relative to surgical options, but in many centers, coiling has become standard therapy for many aneurysms.

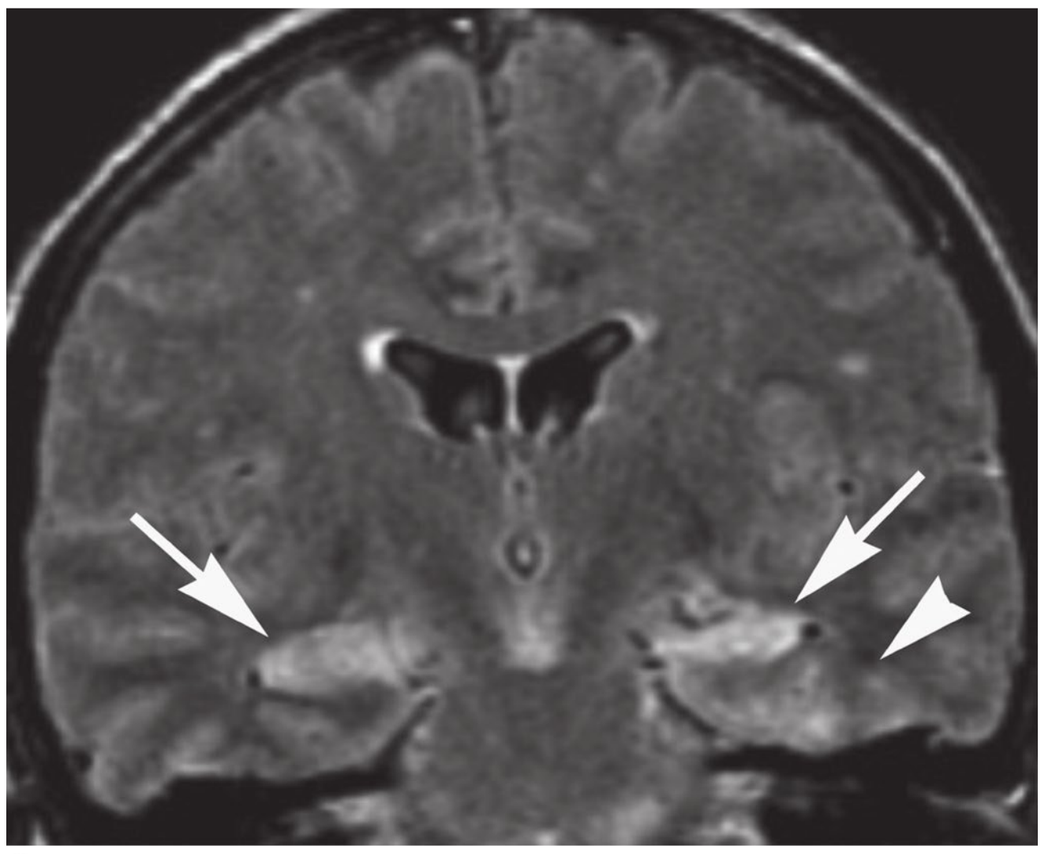
www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 5

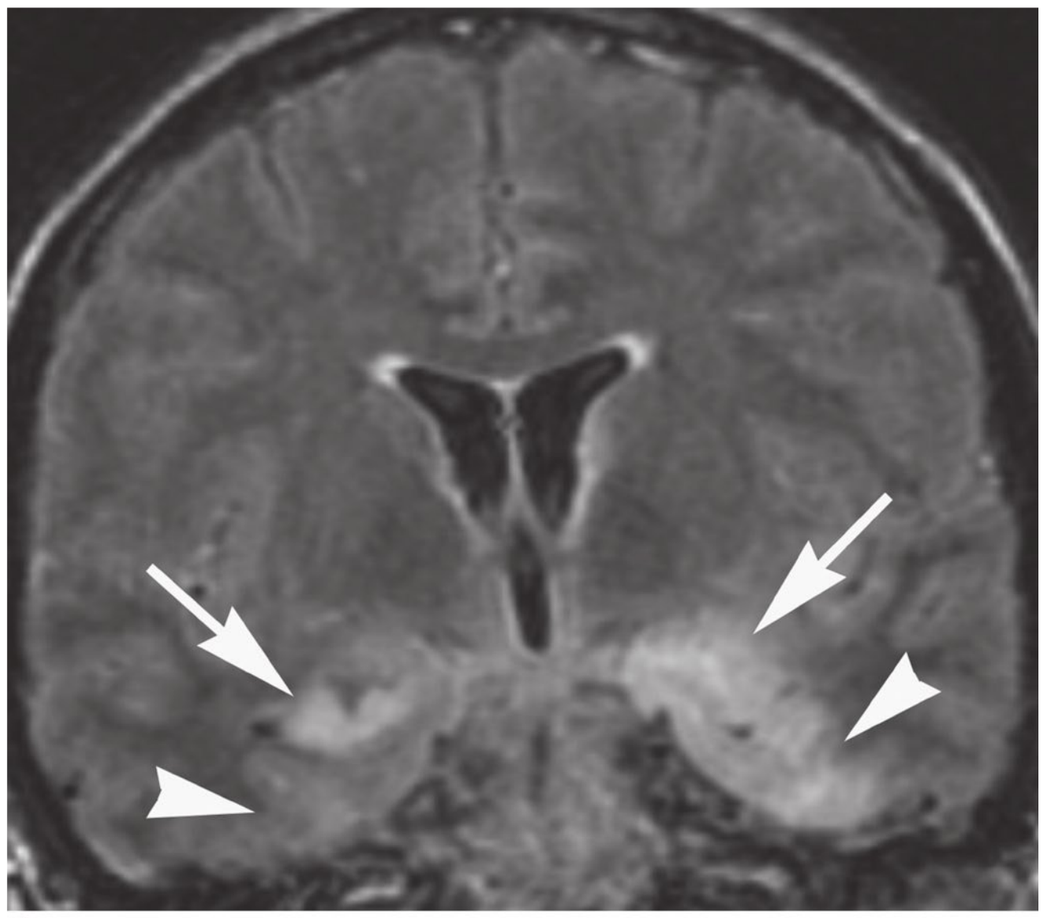
ATLAS OF NEUROIMAGING

Andre D. Furtado ■ William P. Dillon

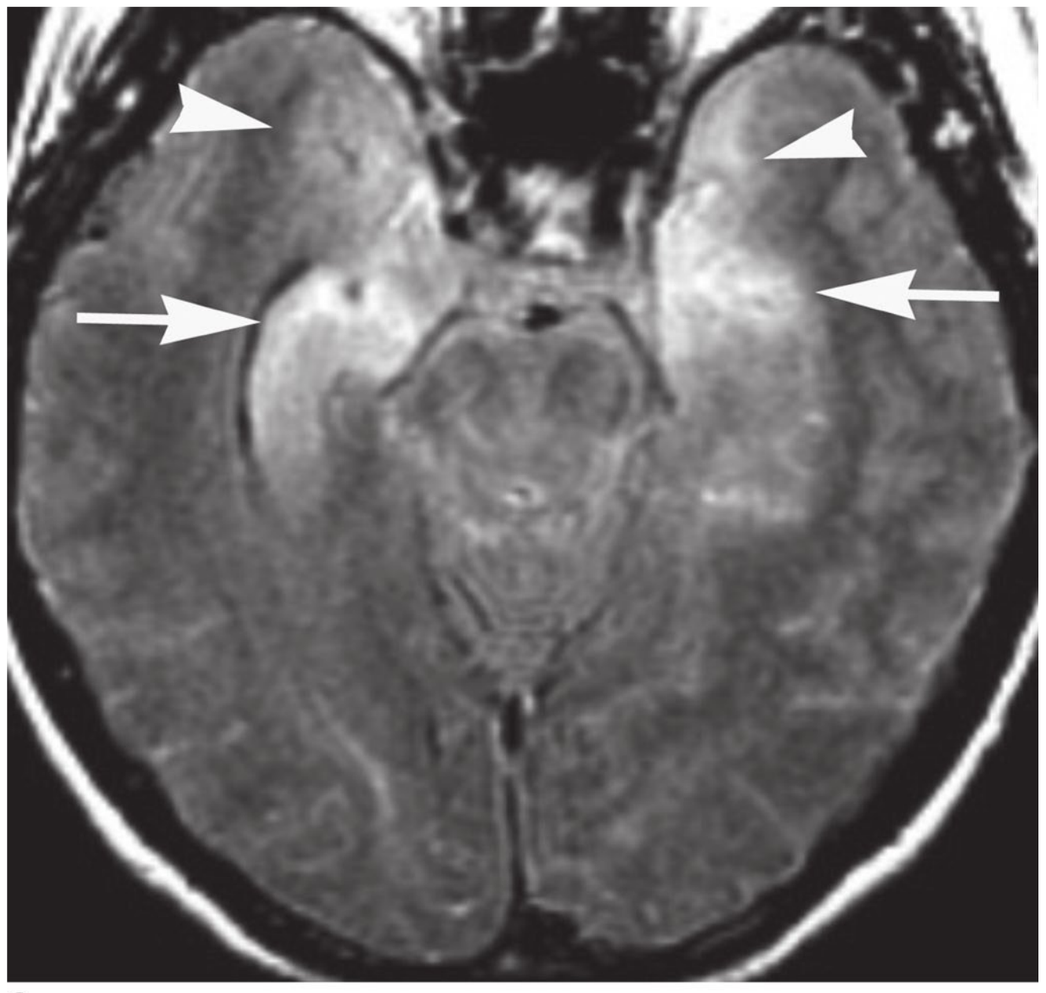
T is atlas comprises 48 cases to assist the clinician caring for patients with neurologic symptoms. T e majority of the images shown are magnetic resonance imaging (MRI) scans; other techniques illustrated include magnetic resonance (MR) and conventional angiography and computed tomography (CT) scans. Many different categories of neurologic disease are illustrated, including numerous examples of ischemic, inf ammatory, inherited, vascular, and neoplastic etiologies.



A



B

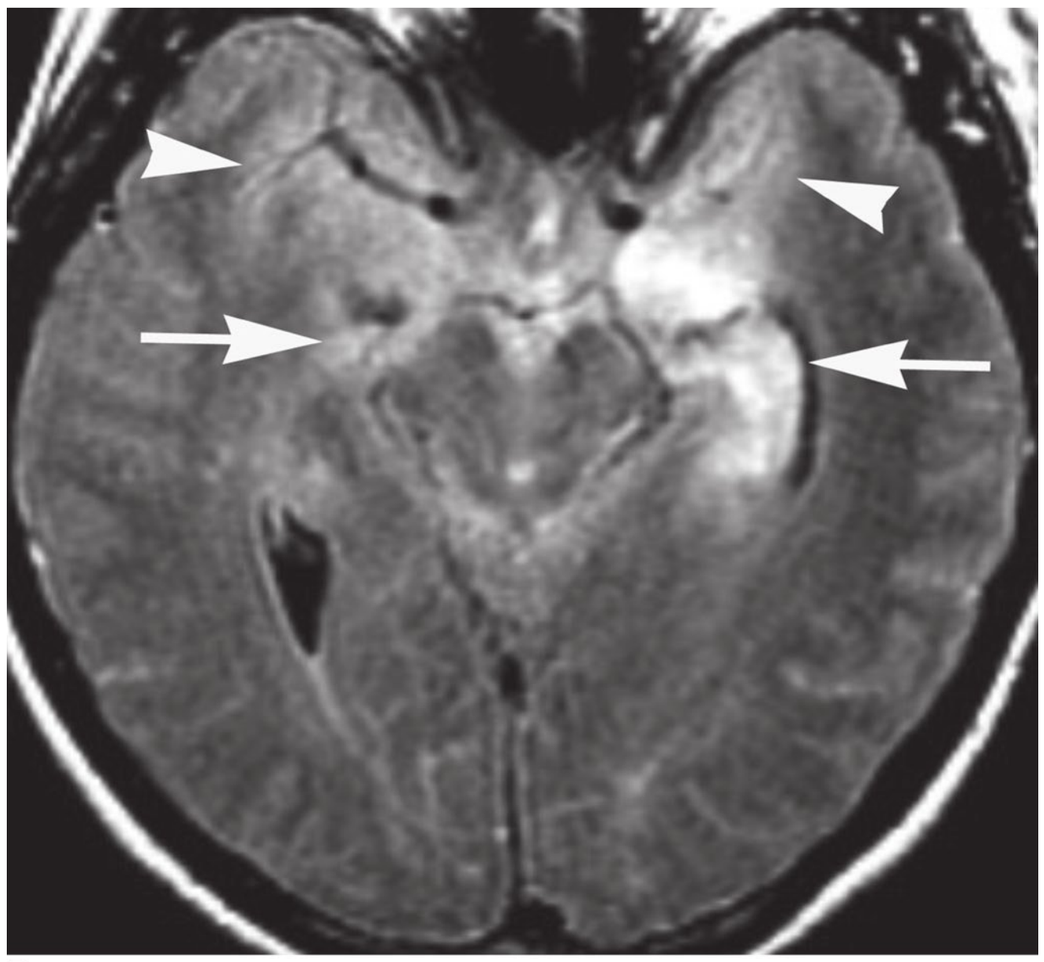


C

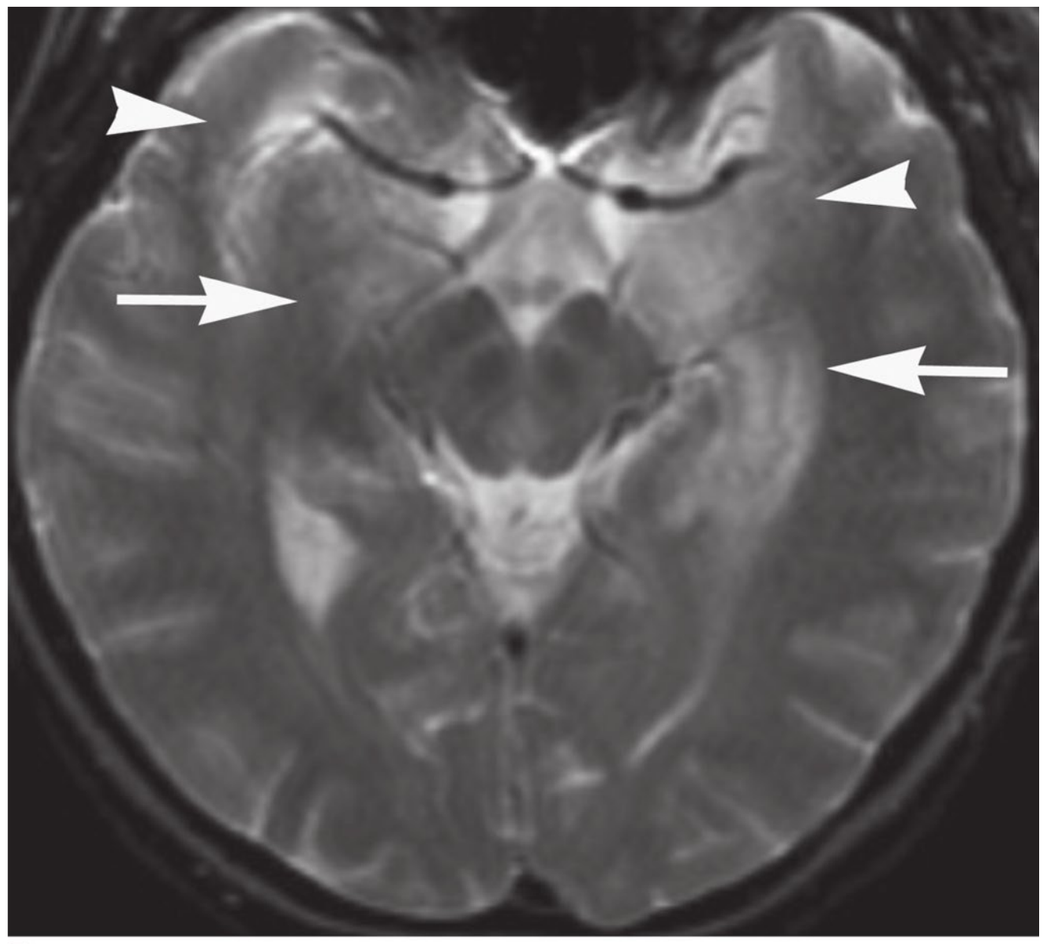
FIGURE 5-1

Limbic encephalitis (Chap. 50). Coronal (A, B), axial fluid-attenuated inversion recovery (FLAIR) (C, D), and axial T2-weighted (E) MR images demonstrate abnormal high signal involving the bilateral mesial temporal lobes (arrowheads) including the hippocampi (left greater than right) without significant mass effect (arrows). There was no enhancement on postgadolinium images (not shown).

www.ketabpezeshki.com (021) 66485457 - 66485438

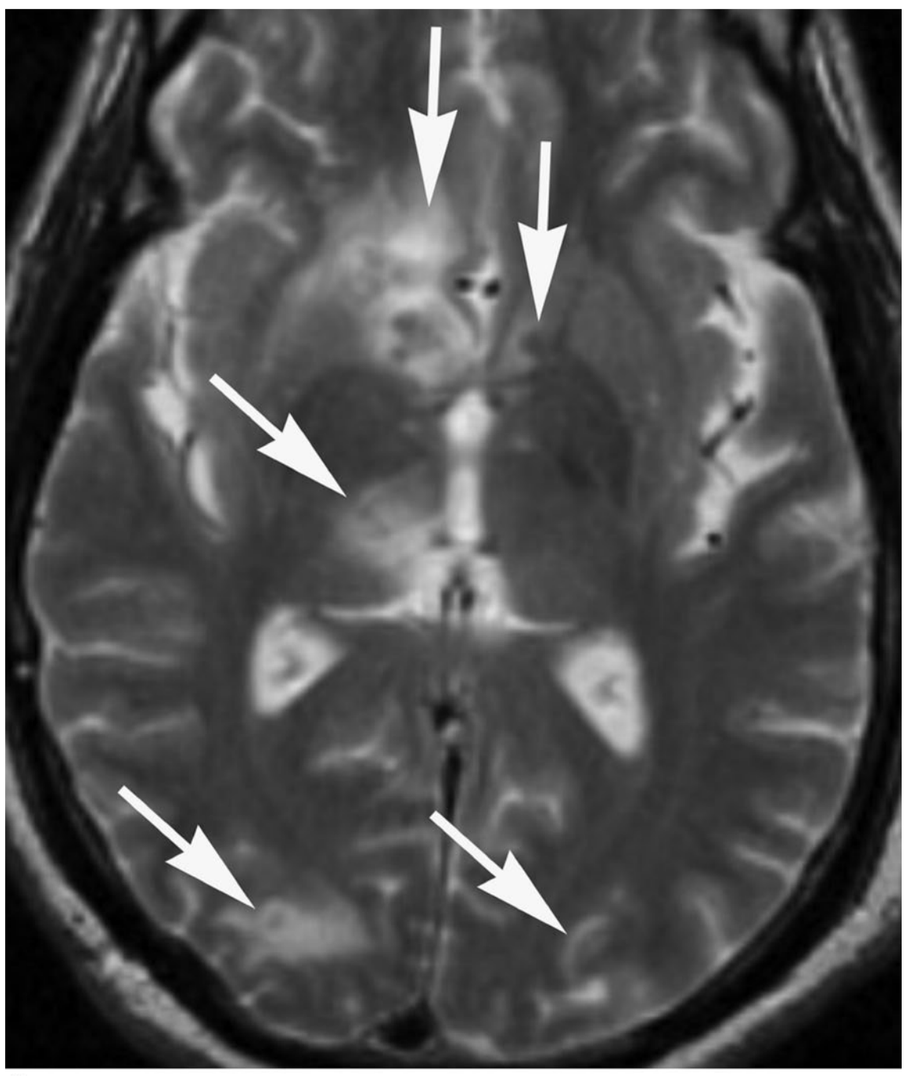


D

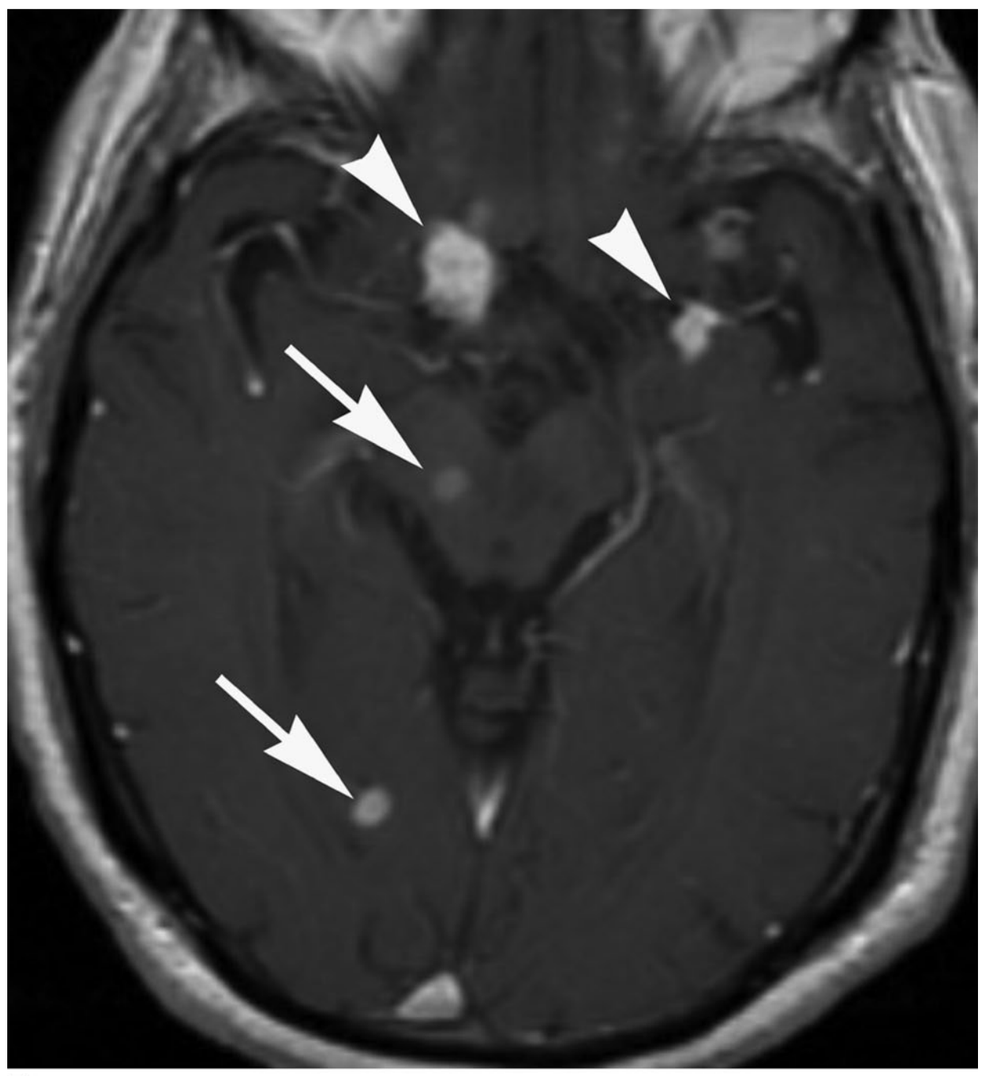


E

FIGURE 5-1
(continued)



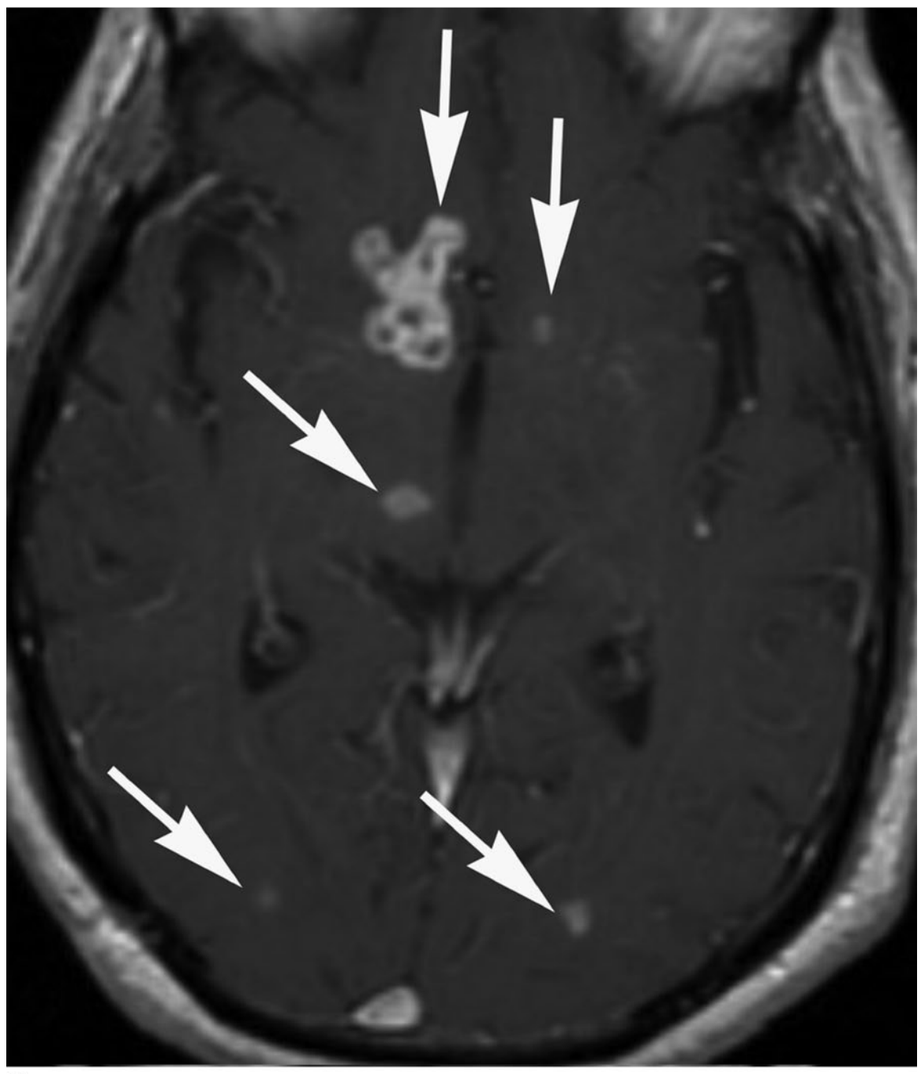
A



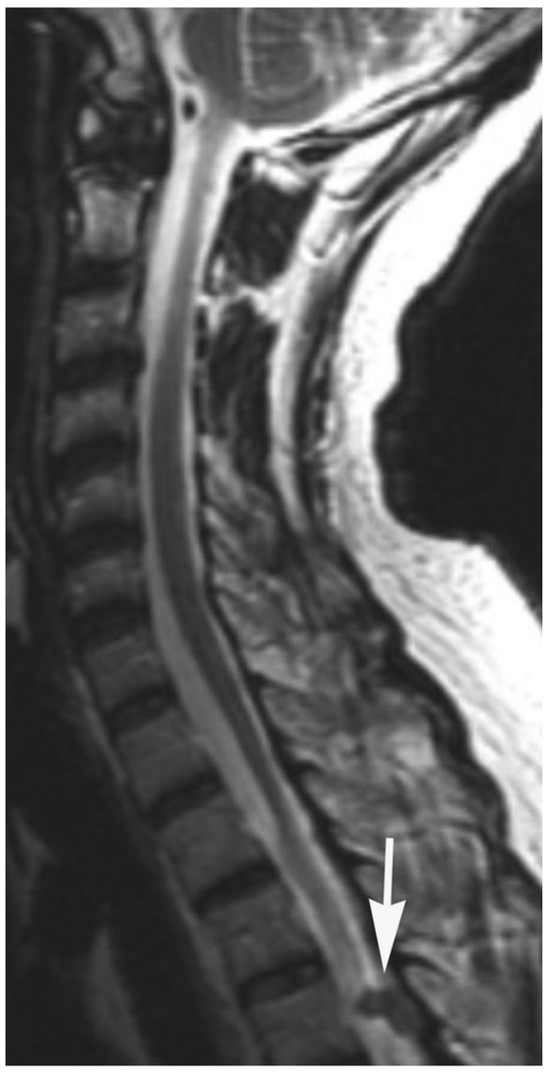
B

FIGURE 5-2
Central nervous system tuberculosis. Axial T2-weighted MRI (A) demonstrates multiple lesions (arrows) with peripheral high signal and central low signal, located predominantly in the cortex and subcortical white matter, as well as in the basal ganglia. Axial T1-weighted MR images postgadolinium (B, C) demonstrate ring enhancement of the lesions (arrows) and additional lesions in the subarachnoid space (arrowheads). Sagittal T2-weighted MR image of the cervical spine (D) demonstrates a hypointense lesion in the subarachnoid space at the level of T5 (arrow). Sagittal T1-weighted postgadolinium MRI of the cervical spine (E) demonstrates enhancement of the lesion in the subarachnoid space at the level of T5 (arrow).

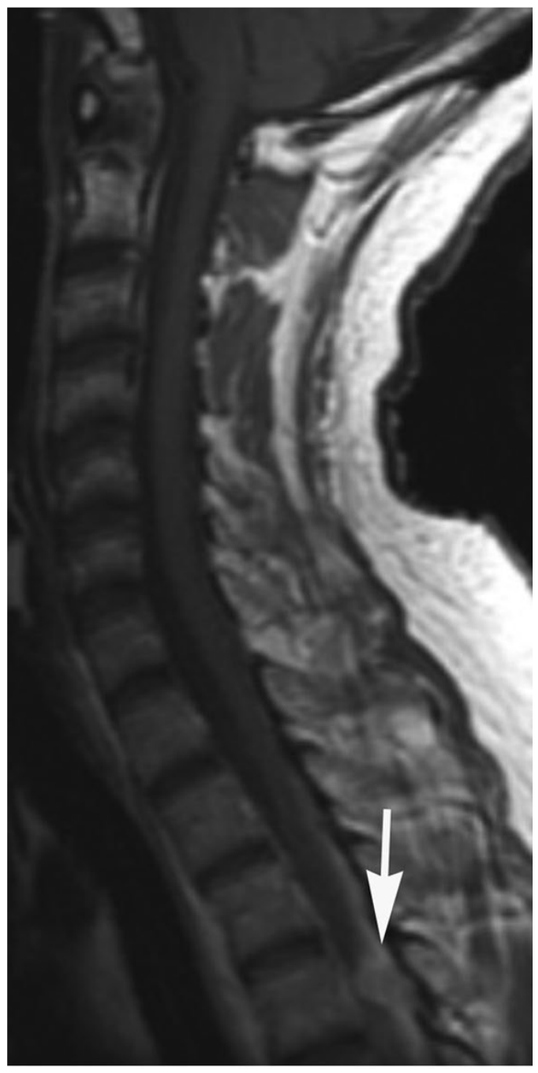
www.ketabpezeshki.com (021) 66485457 - 66485438



C

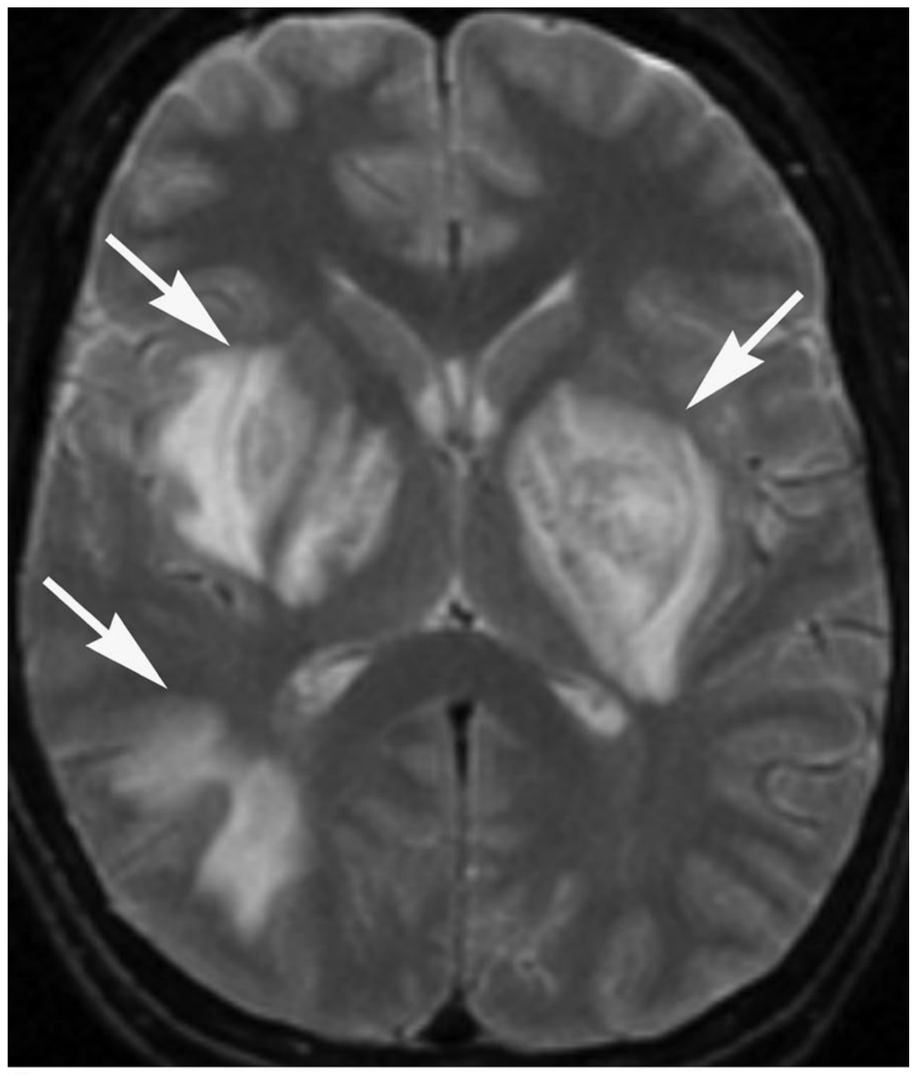


D

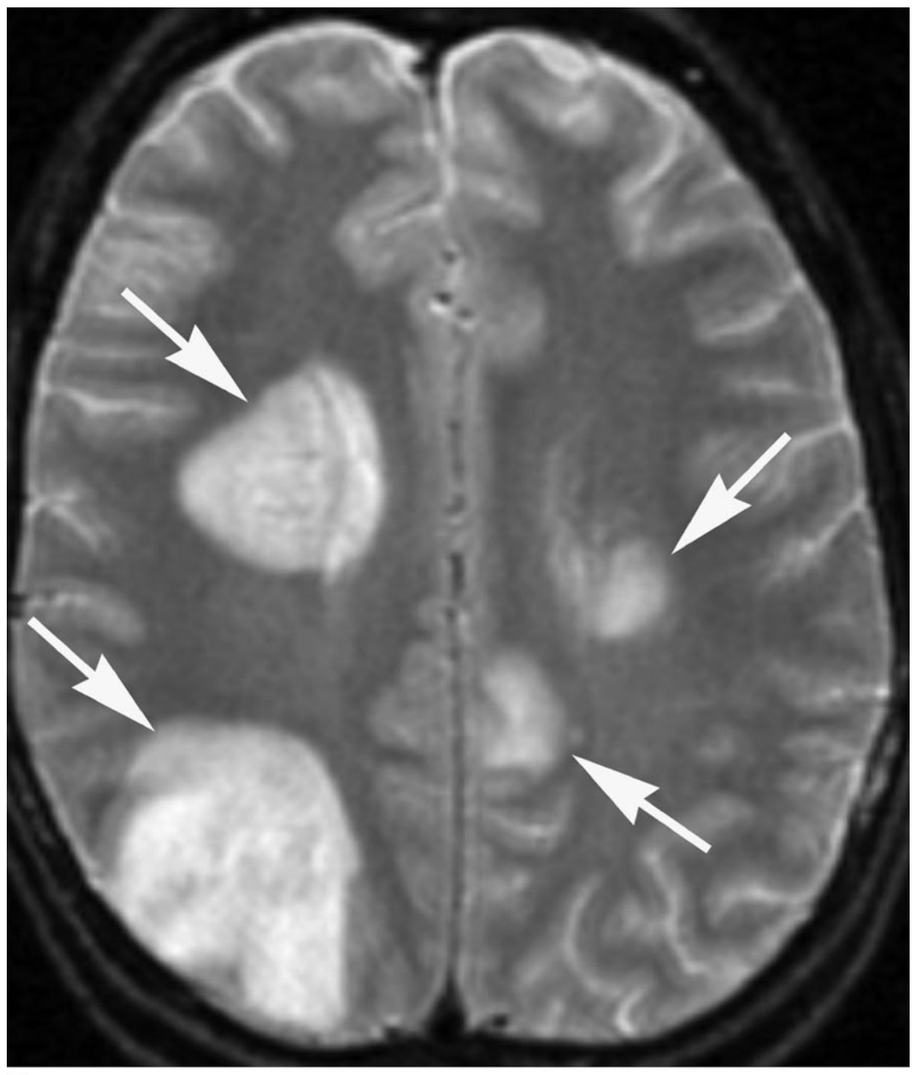


E

FIGURE 5-2
(continued)



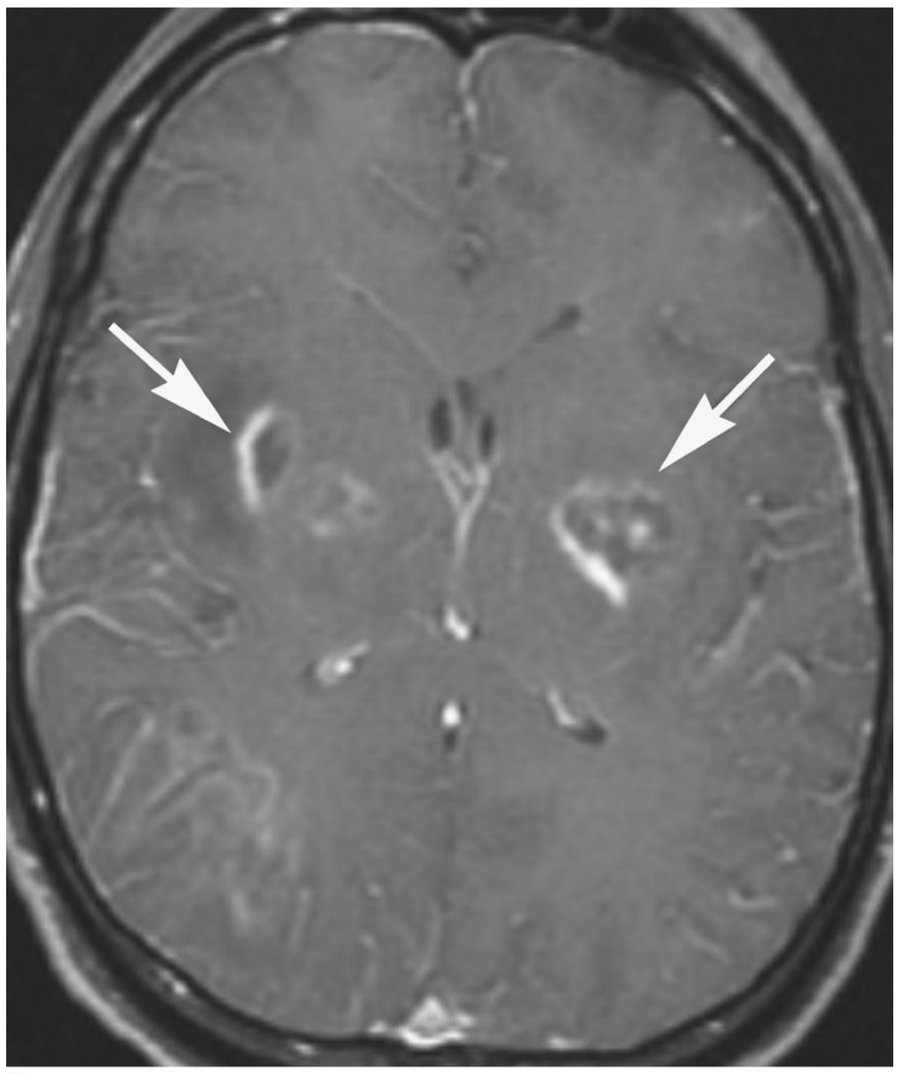
A



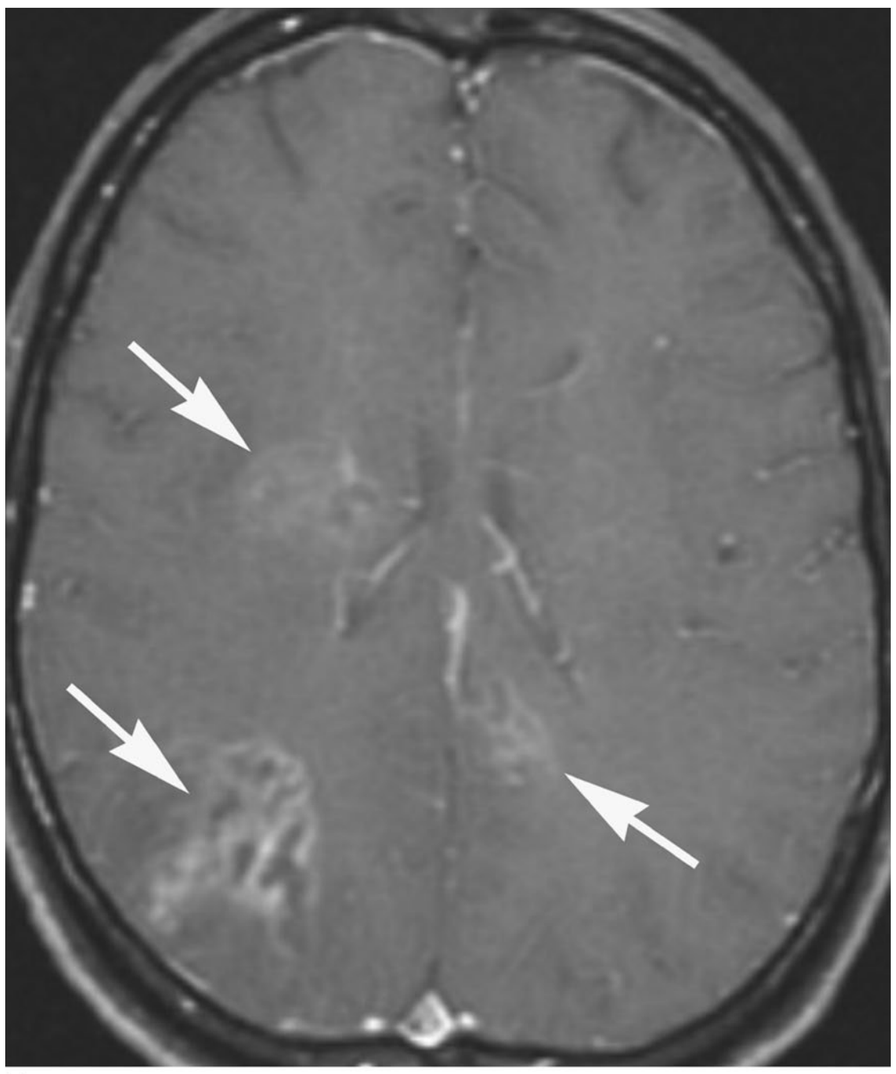
B

FIGURE 5-3
Neurosyphilis: Case I. Axial T2-weighted MRIs (A, B) demonstrate well-defined areas of abnormal high signal in the basal ganglia bilaterally and in a wedge-shaped distribution in the right parietal lobe (arrows). Axial (C, D) T1-weighted images postgadolinium. Coronal (E, F) T1-weighted images postgadolinium demonstrate irregular ring enhancement of the lesions (arrows).

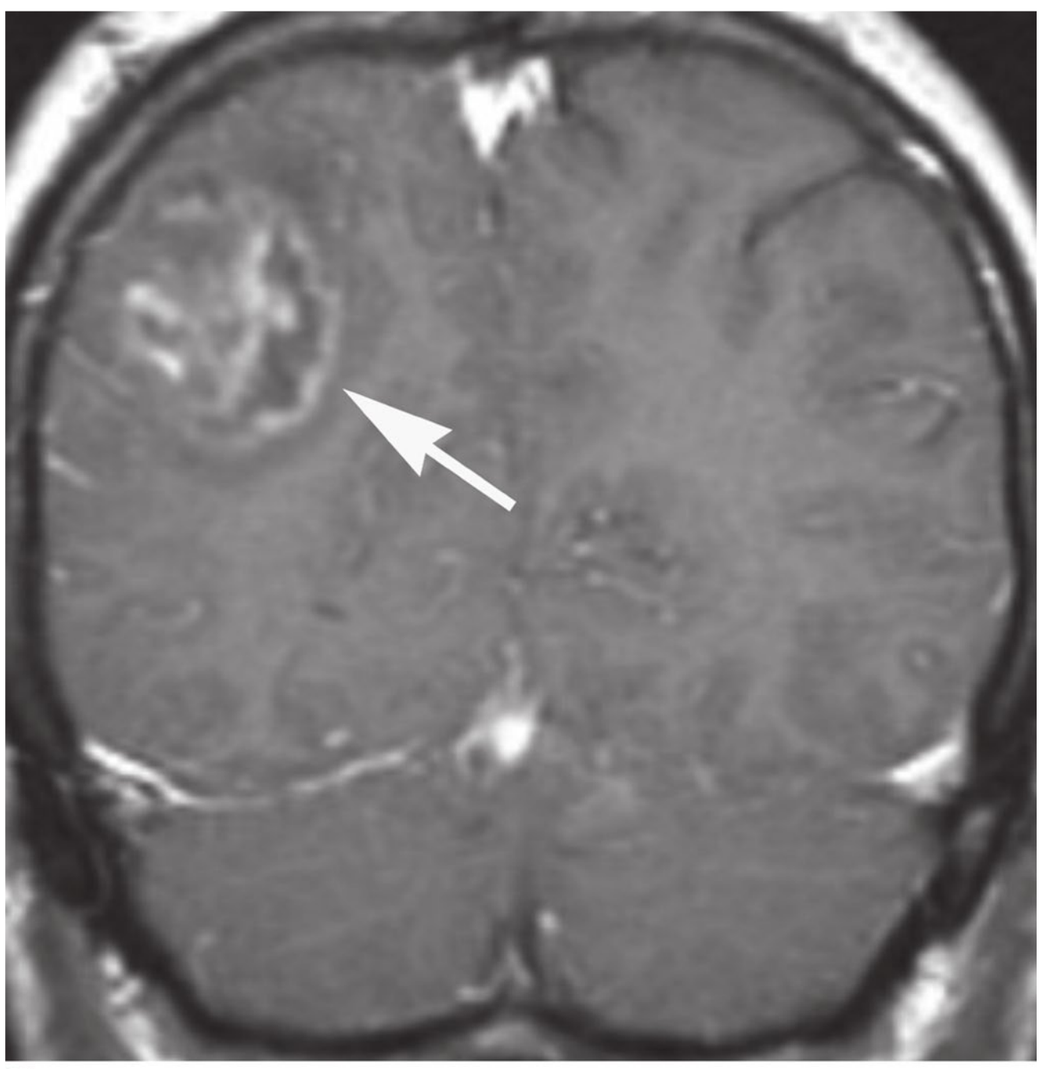
www.ketabpezeshki.com (021) 66485457 - 66485438



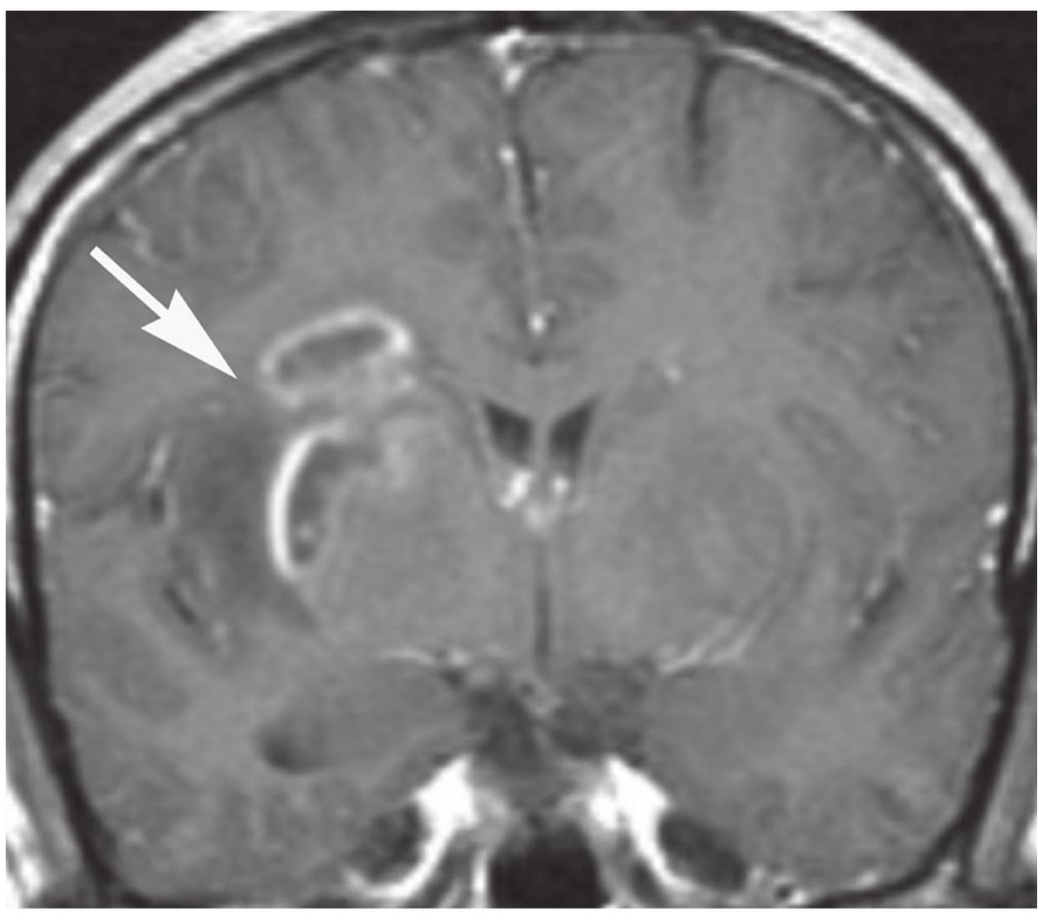
C



D



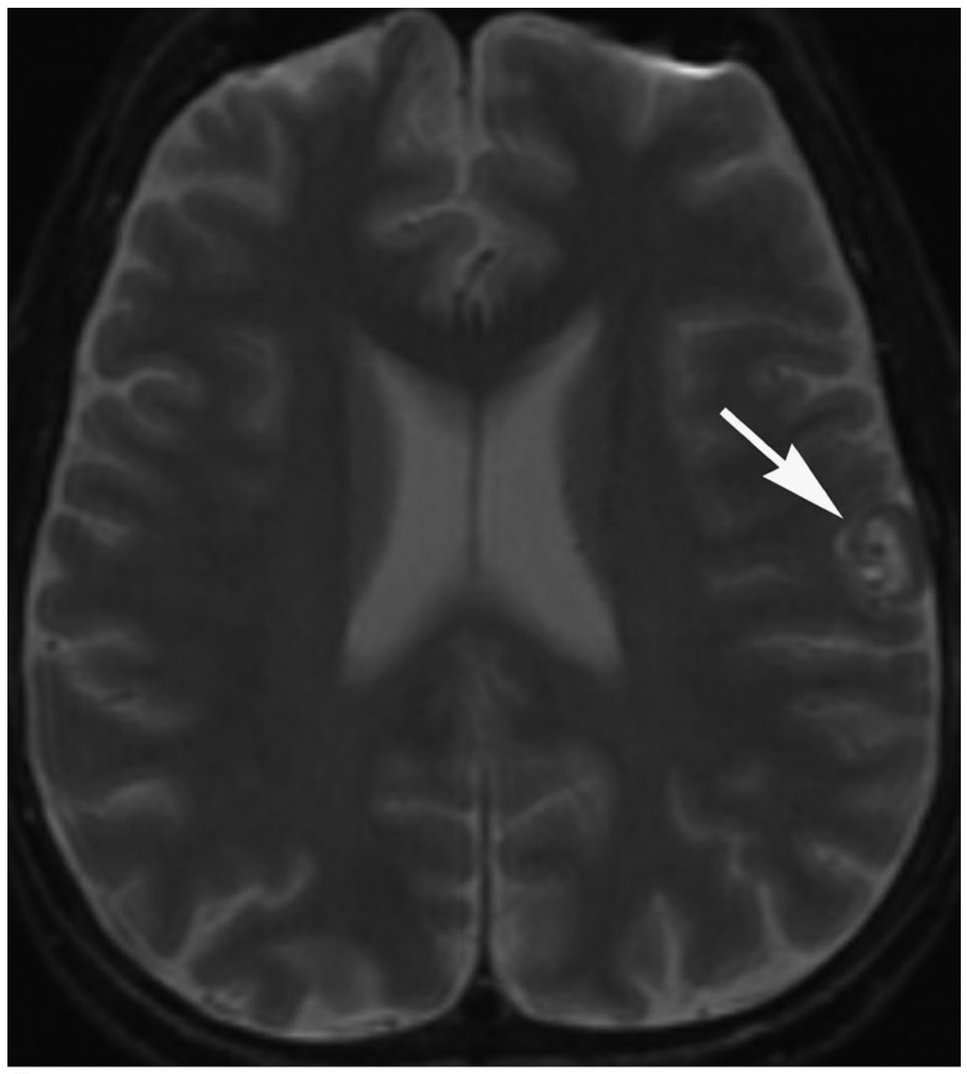
E



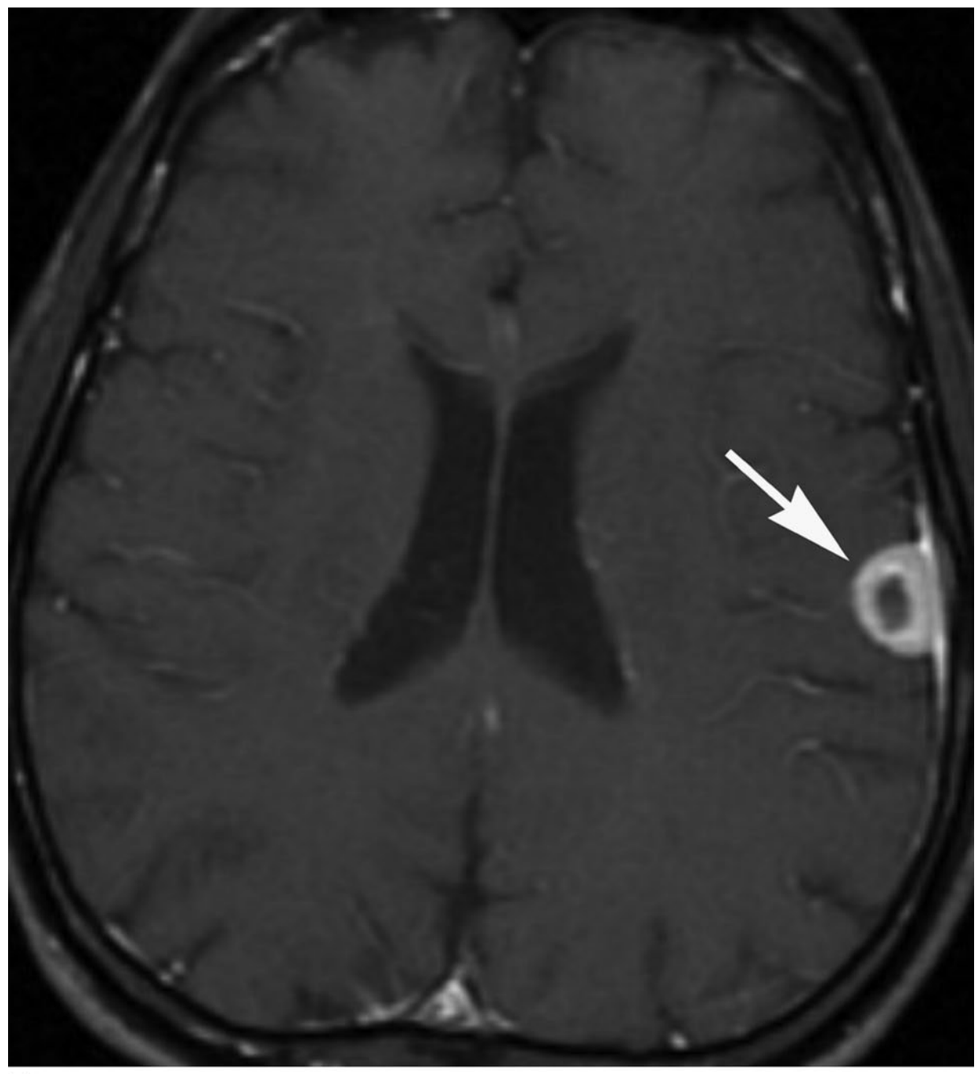
F

FIGURE 5-3
(continued)

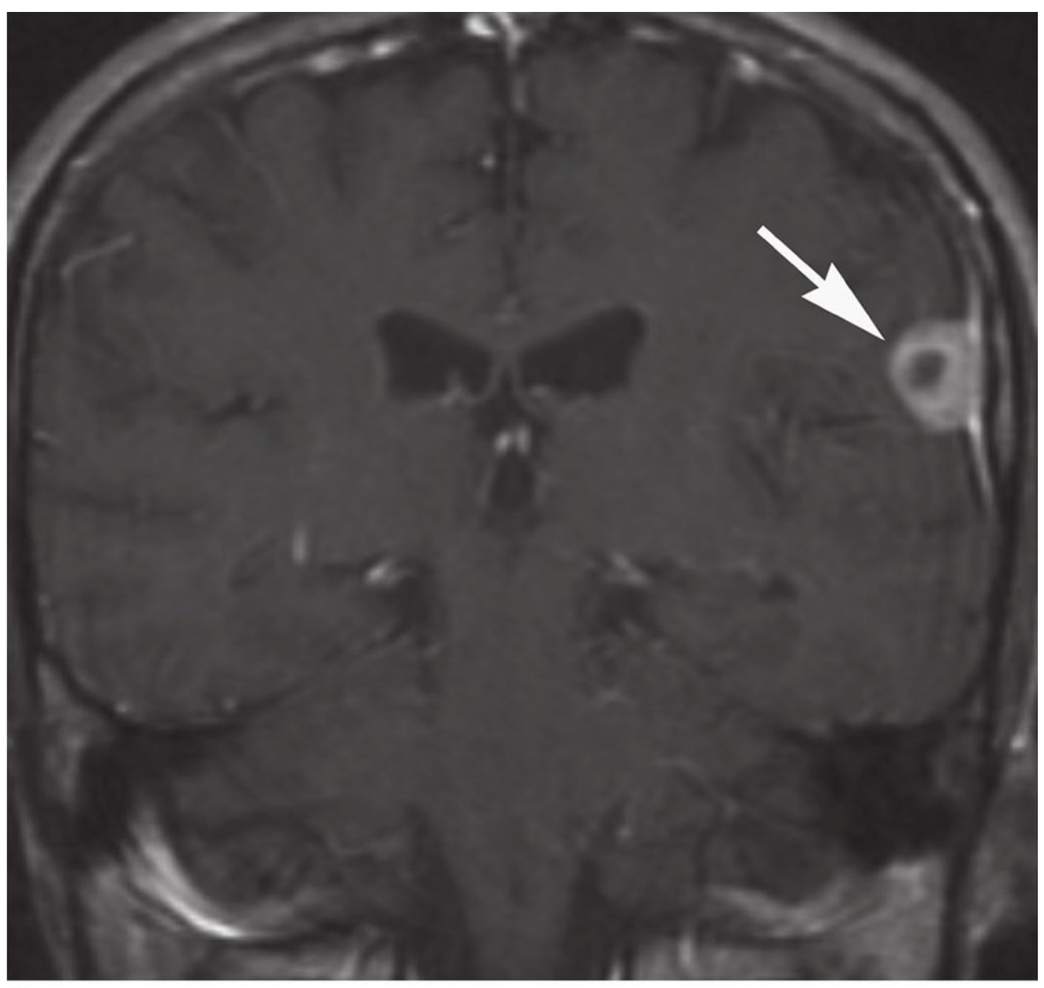
www.ketabpezeshki.com (021) 66485457 - 66485438



A



B



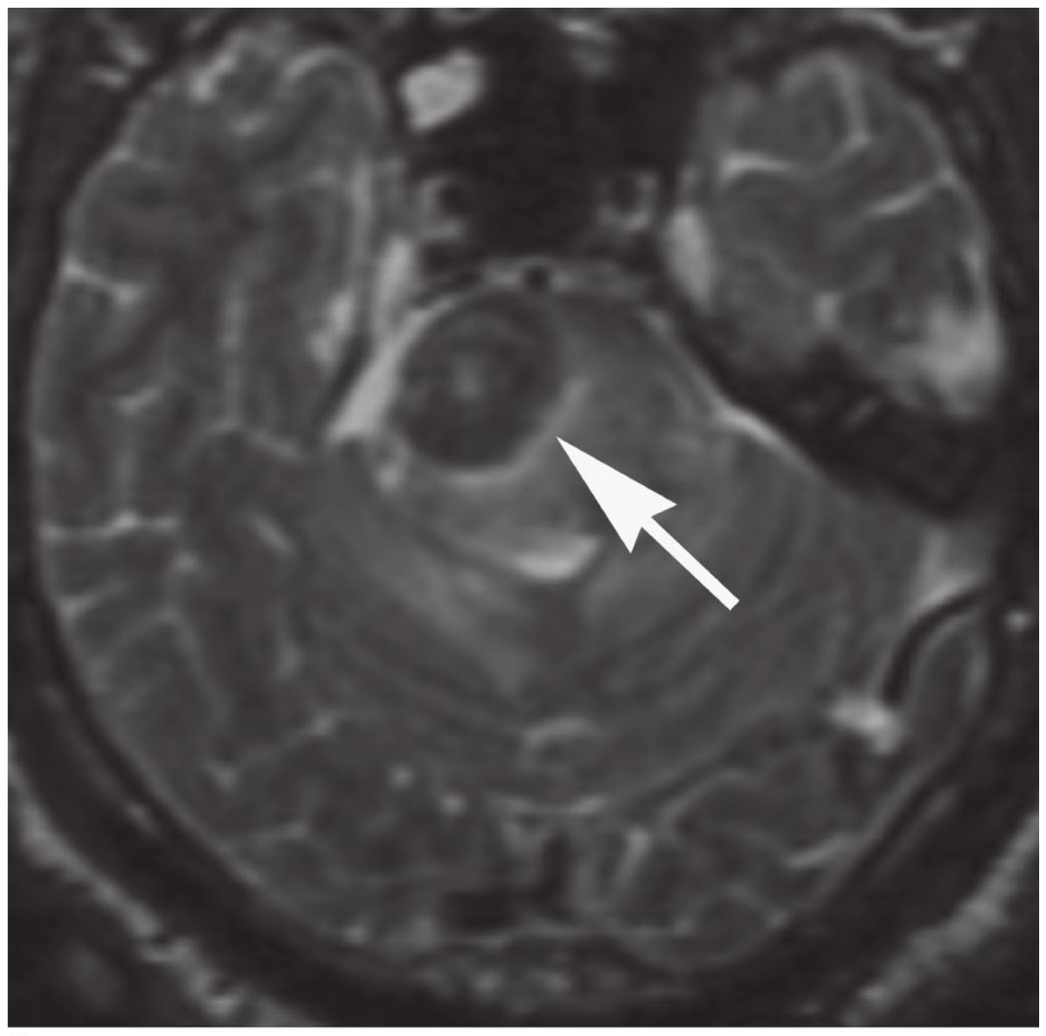
C

FIGURE 5-4

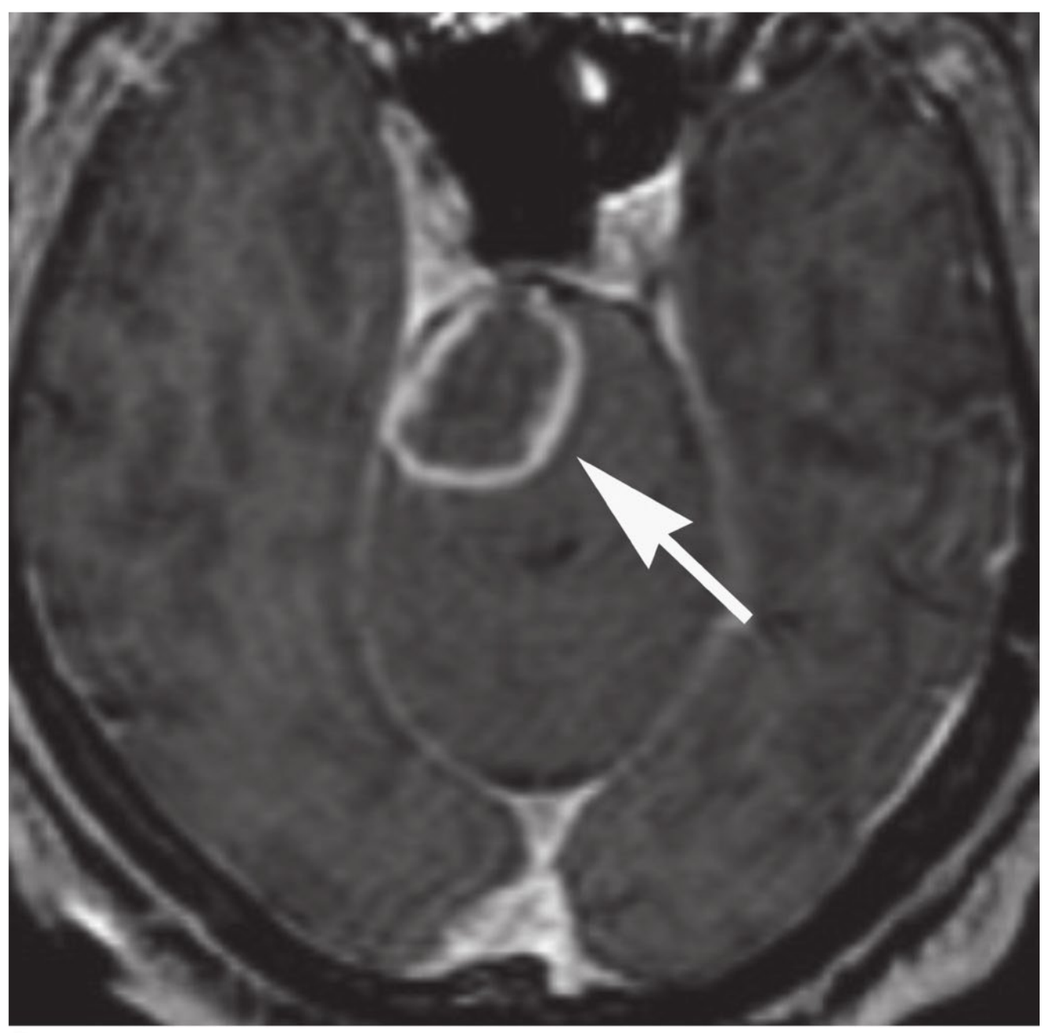
Neurosyphilis: Case II. Axial T2-weighted MRI (A) demonstrates a dural-based, peripherally hyperintense and centrally hypointense lesion located lateral to the left frontal lobe (arrow). Axial (B) and coronal (C) T1-weighted MRIs postgadolinium demonstrate peripheral enhancement of the lesion (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

A



B

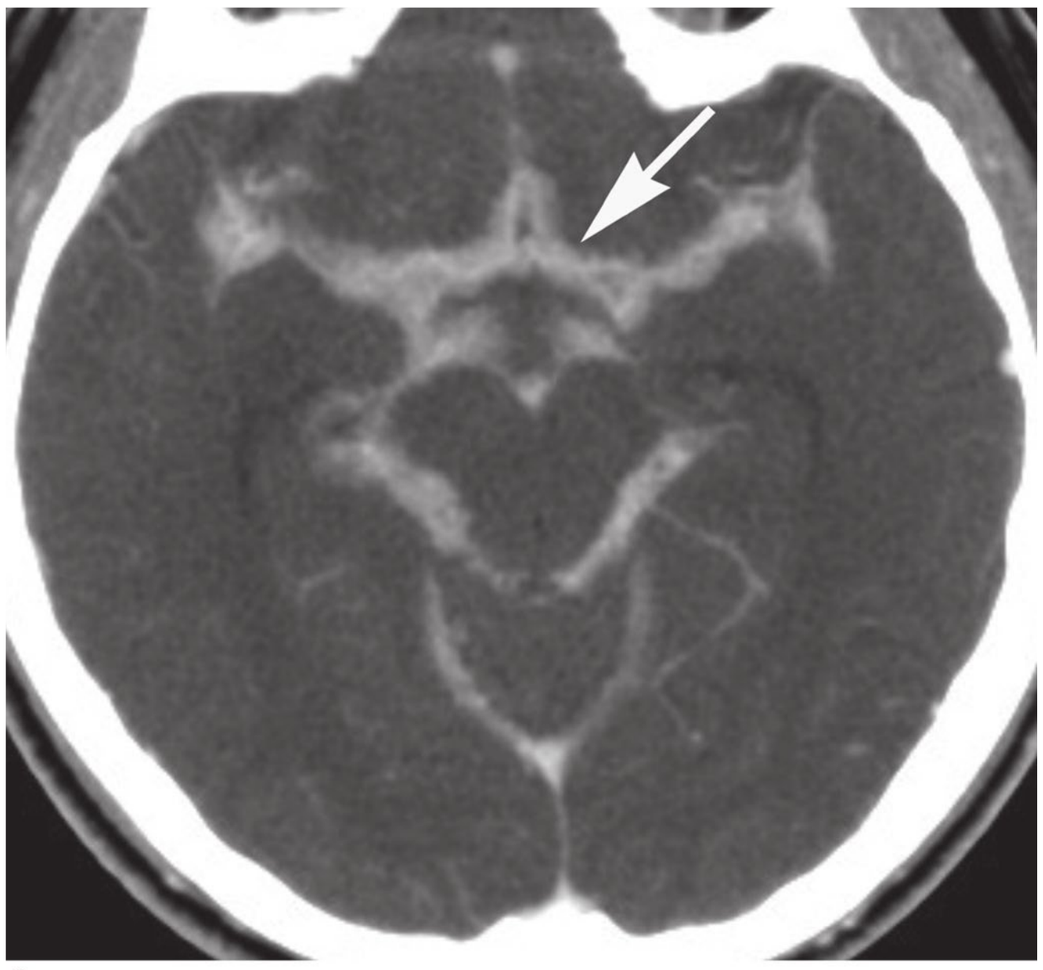


C

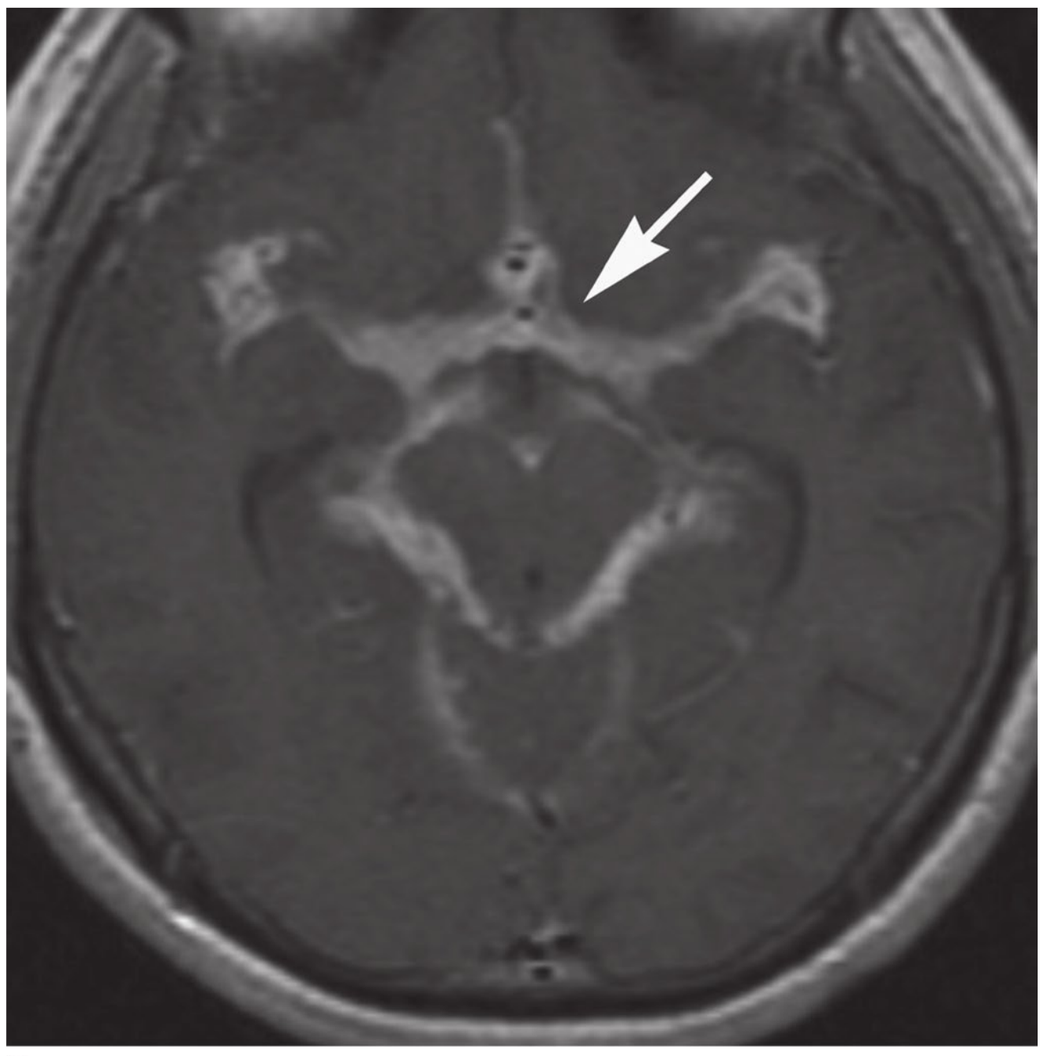
FIGURE 5-5

Histoplasmosis of the pons. Axial FLAIR (A) and T2-weighted (B) MRIs demonstrate a low signal mass in the right pons (arrows) with surrounding vasogenic edema. Axial T1-weighted MRI postgadolinium (C) demonstrates ring enhancement of the lesion in the right pons (arrow). Of note, there was no evidence of restricted diffusion (not shown).

www.ketabpezeshki.com (021) 66485457 - 66485438



A



B

C

FIGURE 5-6

Coccidiomycosis meningitis. Axial postcontrast CT (A) and axial (B) and coronal (C) T1-weighted MRIs postgadolinium demonstrate enhancement of the perimesencephalic cisterns (arrows), as well as the sylvian and interhemispheric fissures.

www.ketabpezeshki.com (021) 66485457 - 66485438

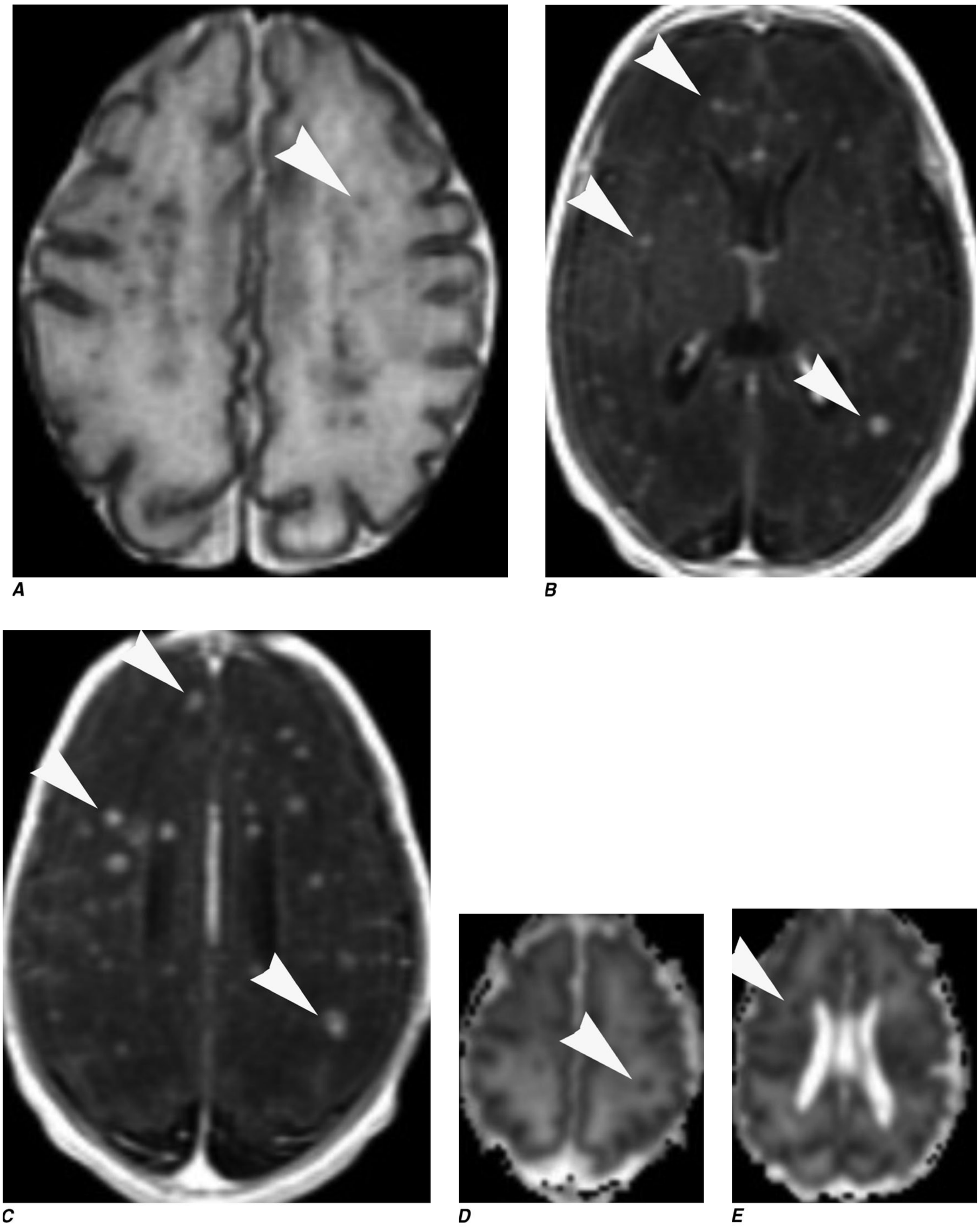


FIGURE 5-7

Candidiasis in a newborn. Axial T2-weighted MRI (A) demonstrates multiple punctate foci of low signal diffusely distributed in the brain parenchyma (arrowhead). Axial T1-weighted MRIs postgadolinium (B, C) demonstrate marked enhancement of the lesions (arrowheads). Apparent diffusion coef cient (ADC) map (D, E) demonstrates restricted diffusion of water molecules in the lesions (arrowheads).

www.ketabpezeshki.com (021) 66485457 - 66485438

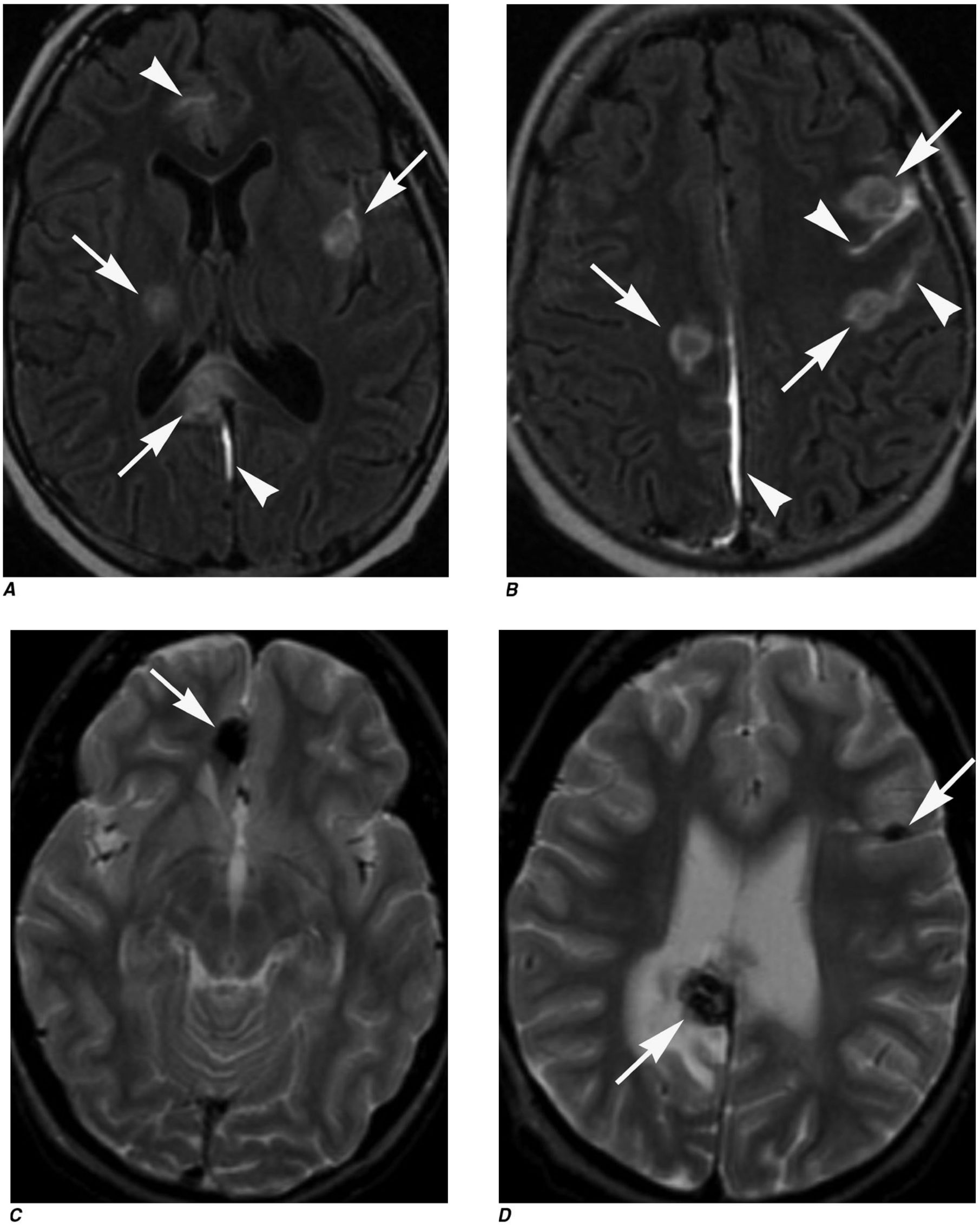
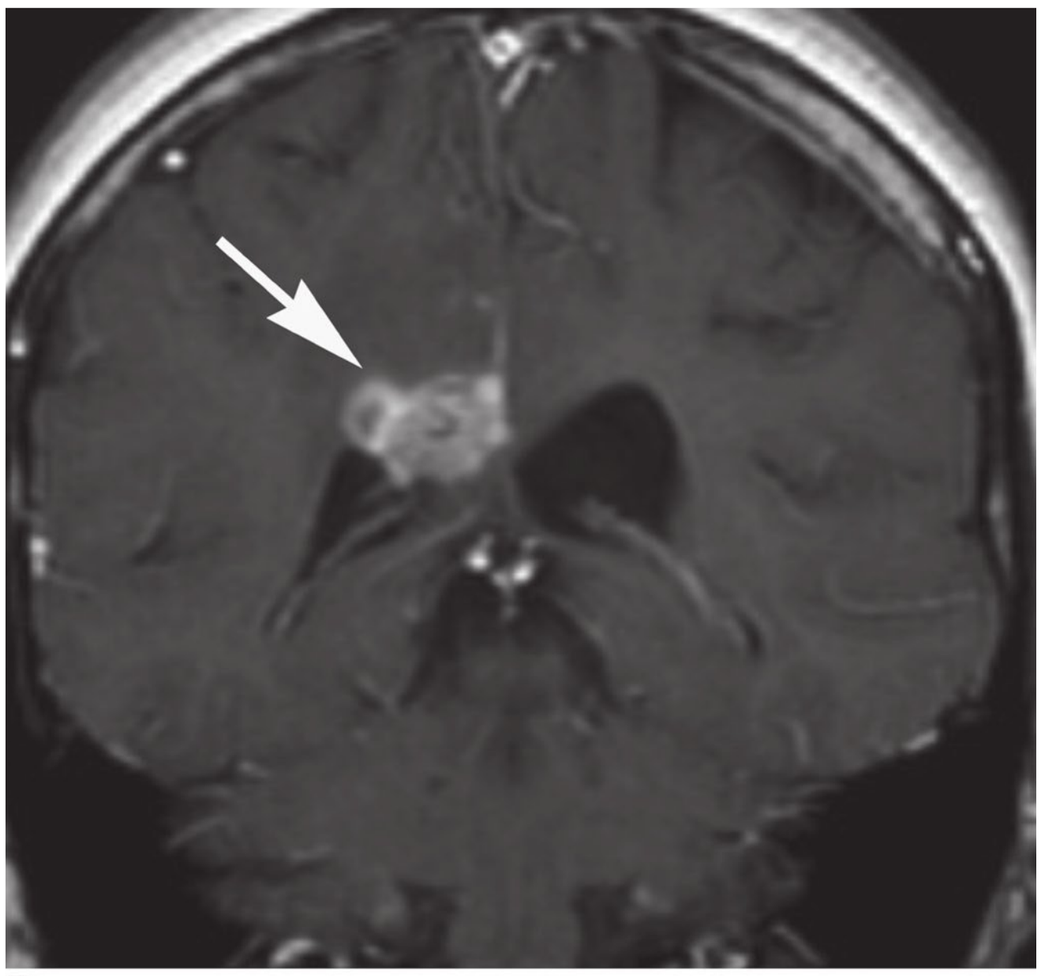


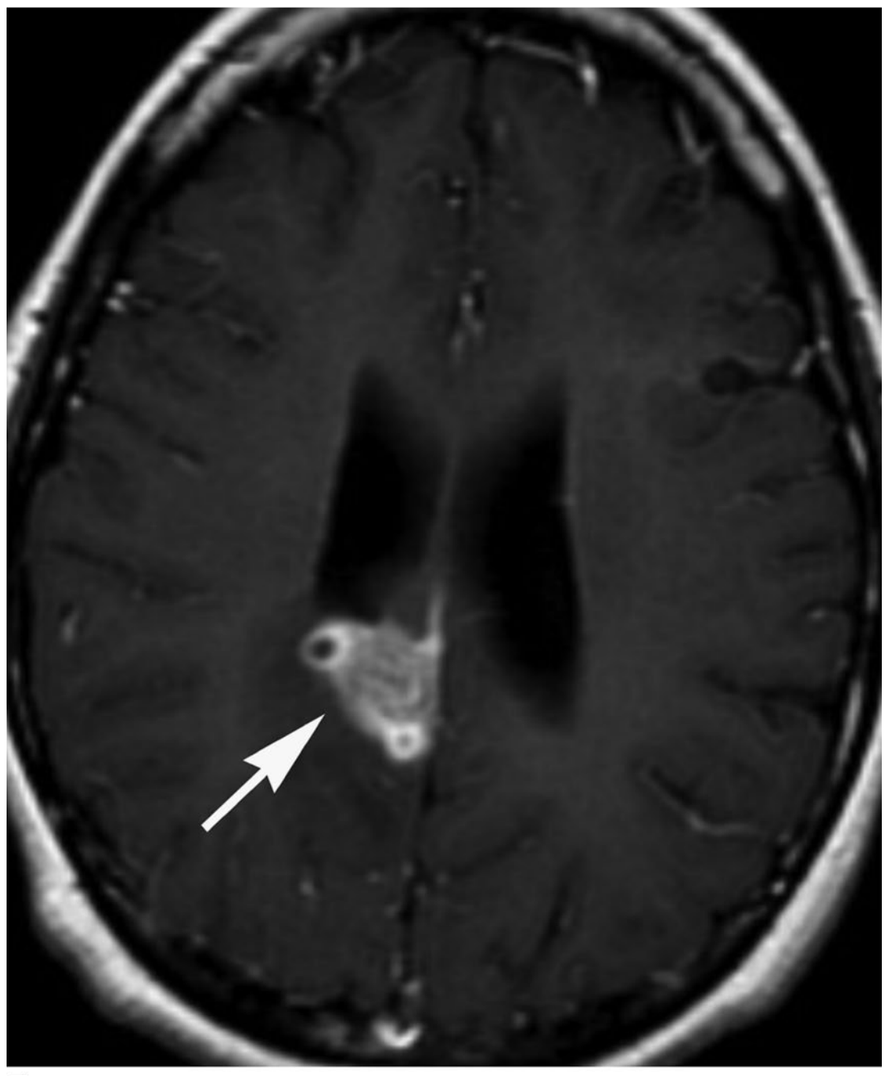
FIGURE 5-8

Central nervous system (CNS) aspergillosis. Axial FLAIR MRIs (A, B) demonstrate multiple areas of abnormal high signal in the basal ganglia as well as cortex and subcortical white matter (arrows). There is also abnormal high signal in the subarachnoid space adjacent to the lesions (arrowheads) that can correspond to blood or high protein content. Axial T2-weighted MRIs (C, D) demonstrate intrinsic low signal in the lesions (arrows), suggesting the presence of blood products. Some of the lesions also show vasogenic edema. Coronal (E) and axial (F) T1-weighted MRIs postgadolinium demonstrate peripheral enhancement of the lesions (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

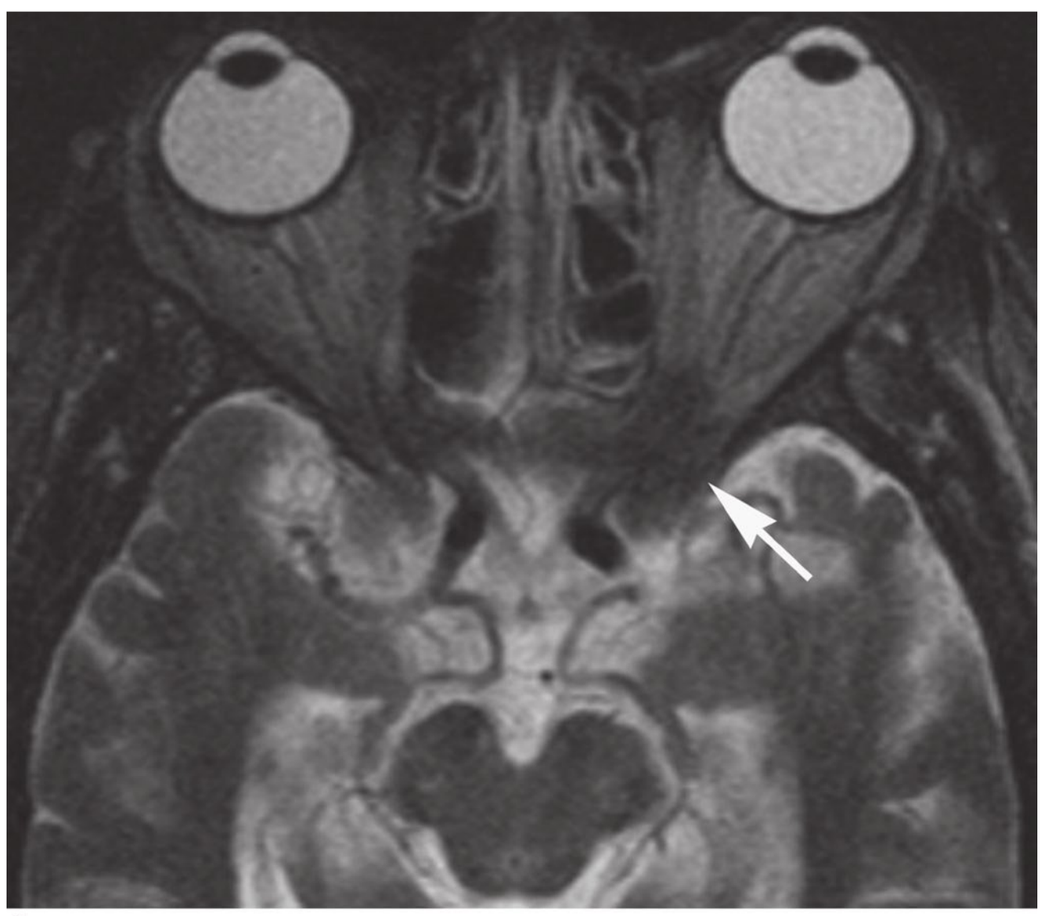


E

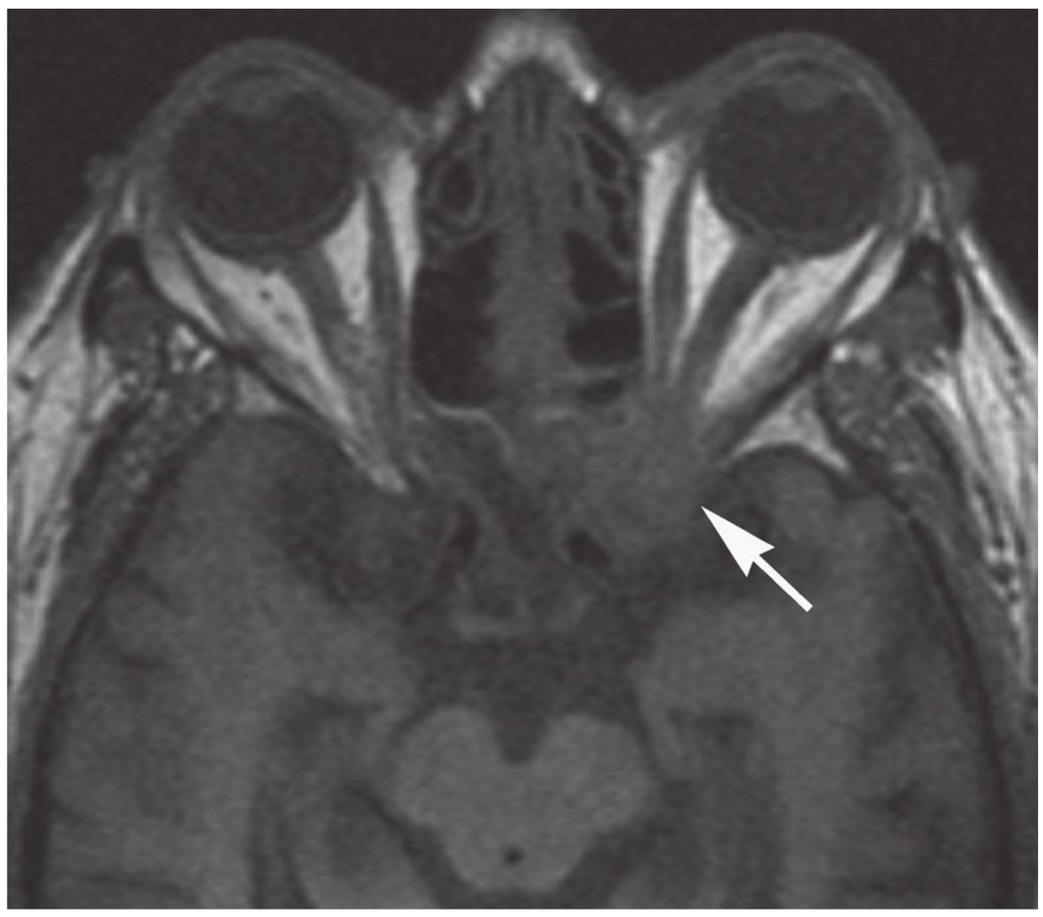


F

FIGURE 5-8
(continued)



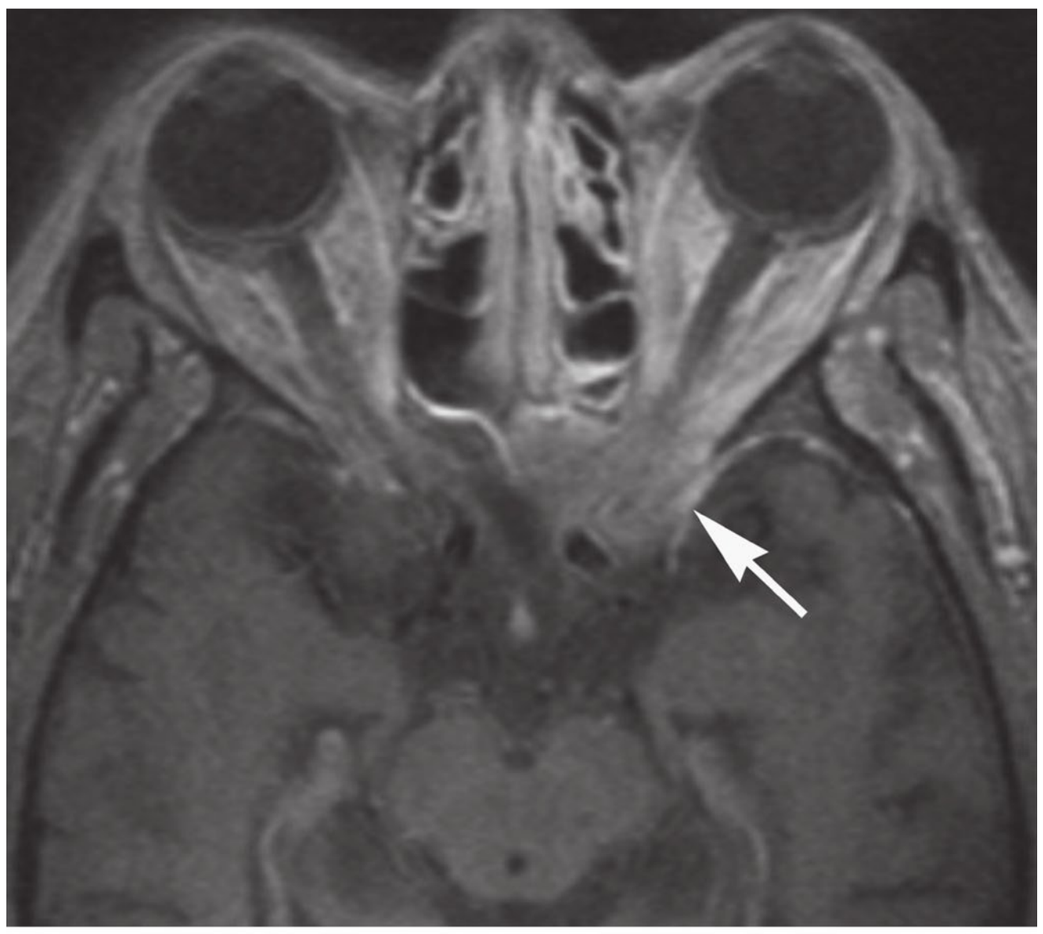
A



B

FIGURE 5-9
Invasive sinonasal aspergillosis. Axial T2-weighted MRI (A) demonstrates an irregularly shaped low signal lesion involving the left orbital apex (arrow). B. T1-weighted image pregadolinium demonstrates low signal in left anterior clinoid process (arrow). C. T1-weighted image postgadolinium demonstrates enhancement of lesion (arrow).

www.ketabpezeshki.com (021) 66485457 - 66485438



C

FIGURE 5-9
(continued)

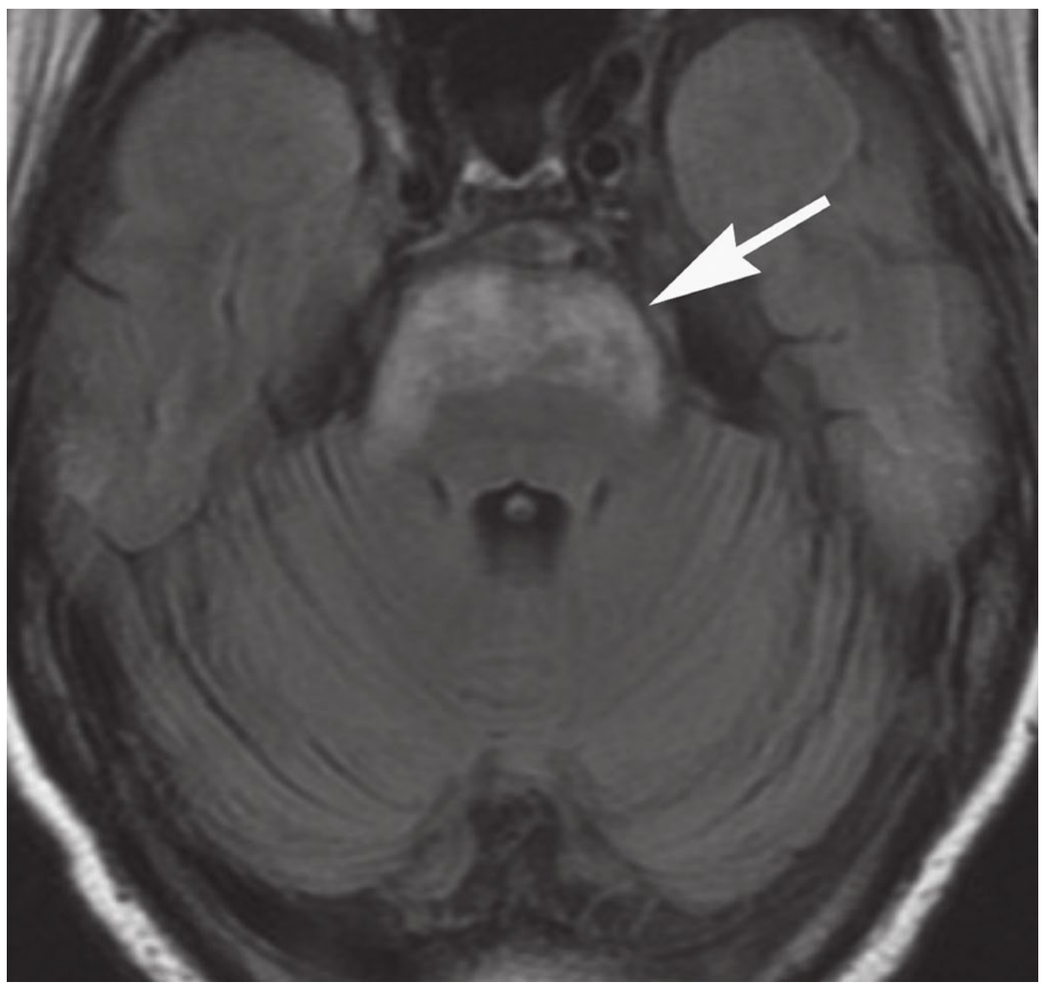
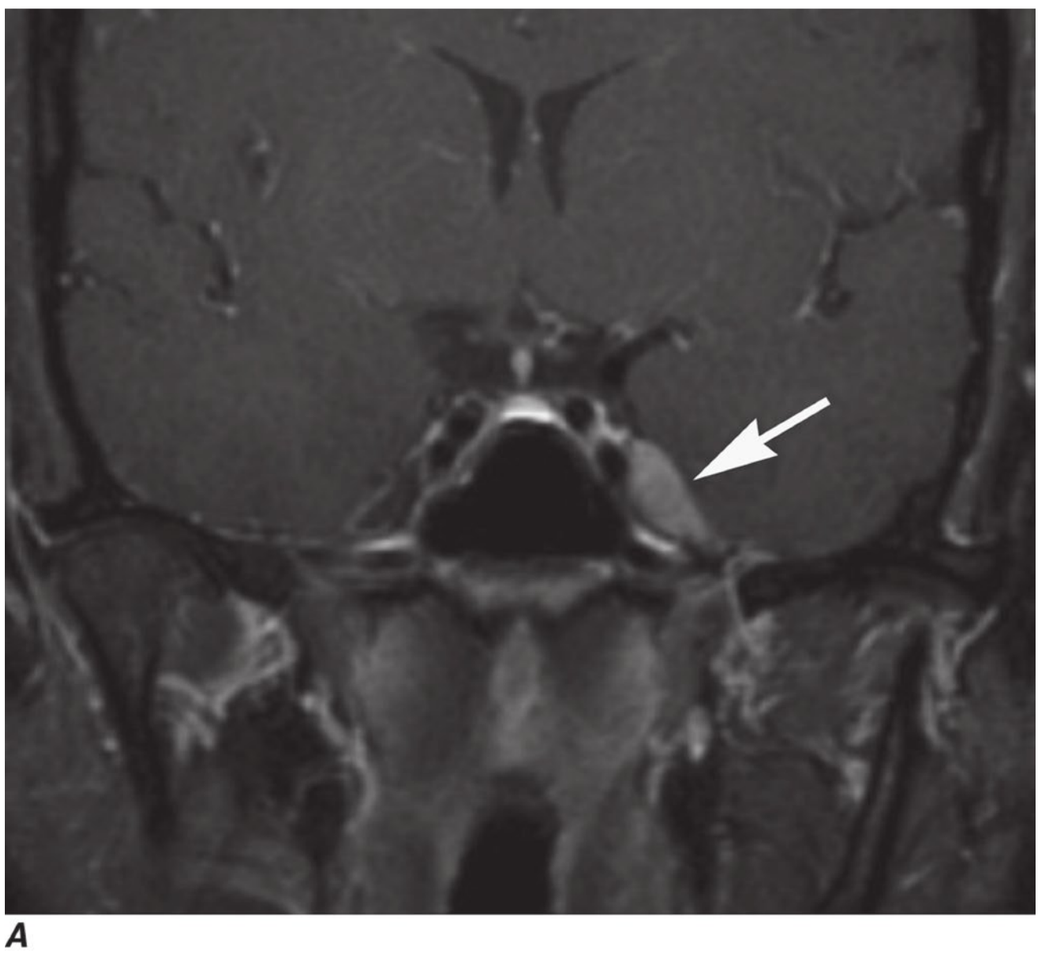
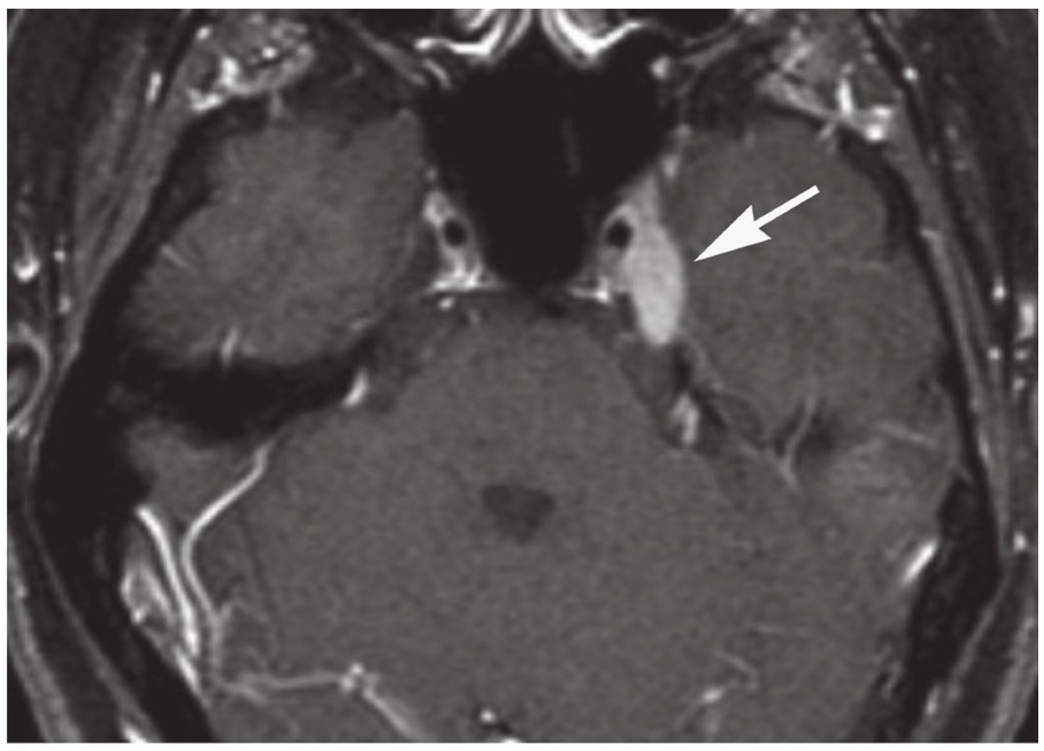


FIGURE 5-10
Behçet's disease. Axial FLAIR MRI demonstrates abnormal high signal involving the anterior pons (arrow); following gadolinium administration, the lesion was nonenhancing (not shown). Brainstem lesions are typical of Behçet's disease, caused primarily by vasculitis and in some cases demyelinating lesions.



A



B

FIGURE 5-11
Neurosarcoid: Case I. Coronal (A) and axial (B) T1-weighted images postgadolinium with fat suppression demonstrate a homogeneously enhancing well-circumscribed mass centered in the left Meckel's cave (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

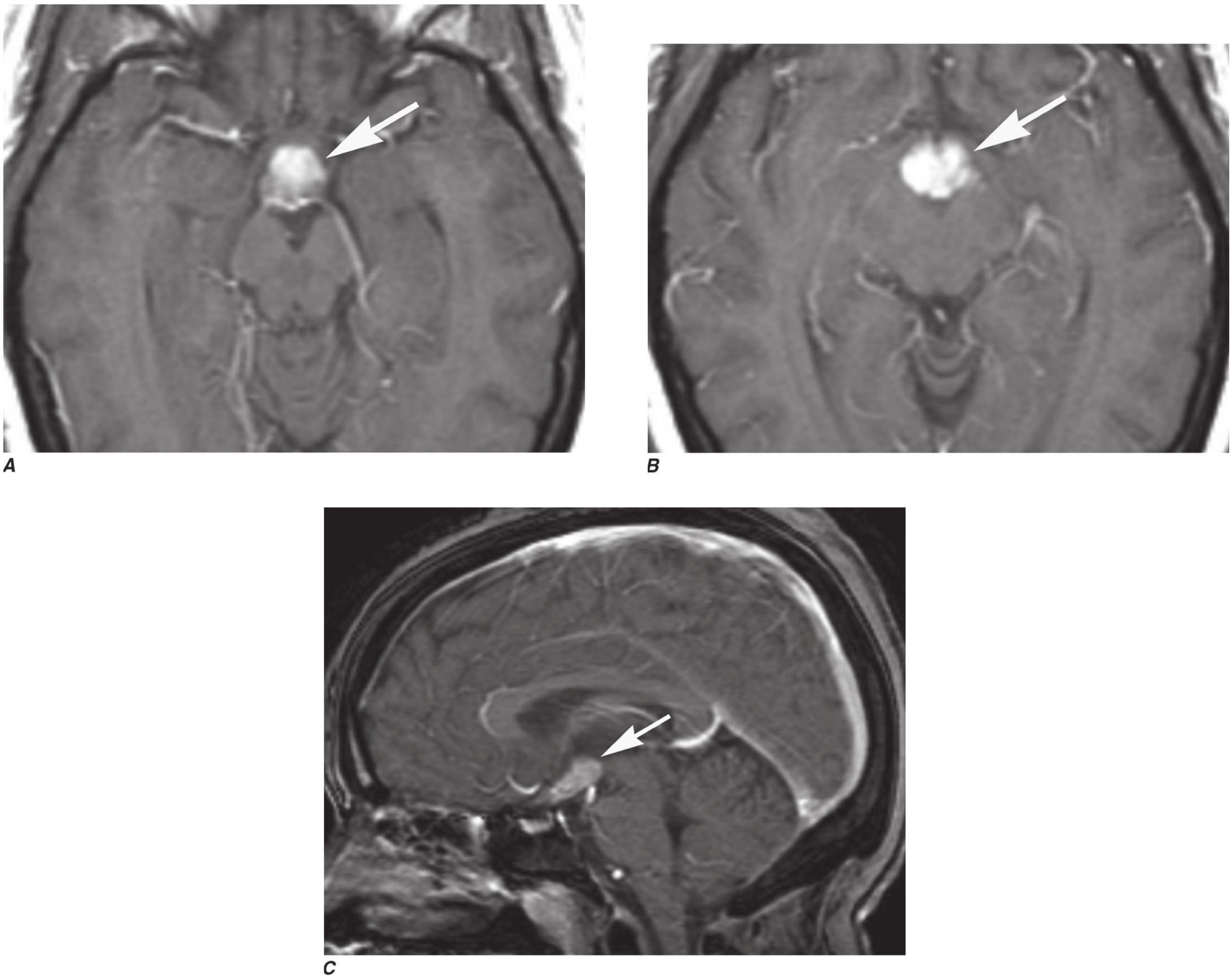
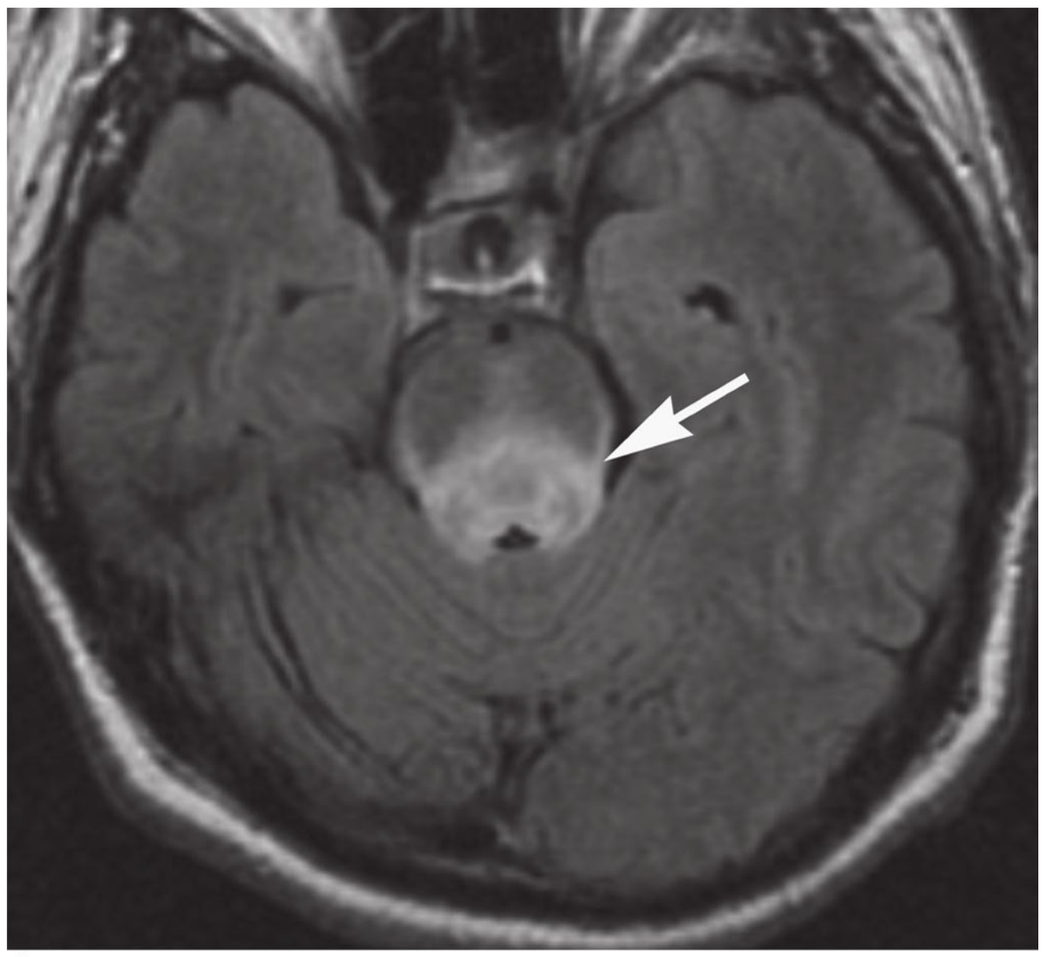


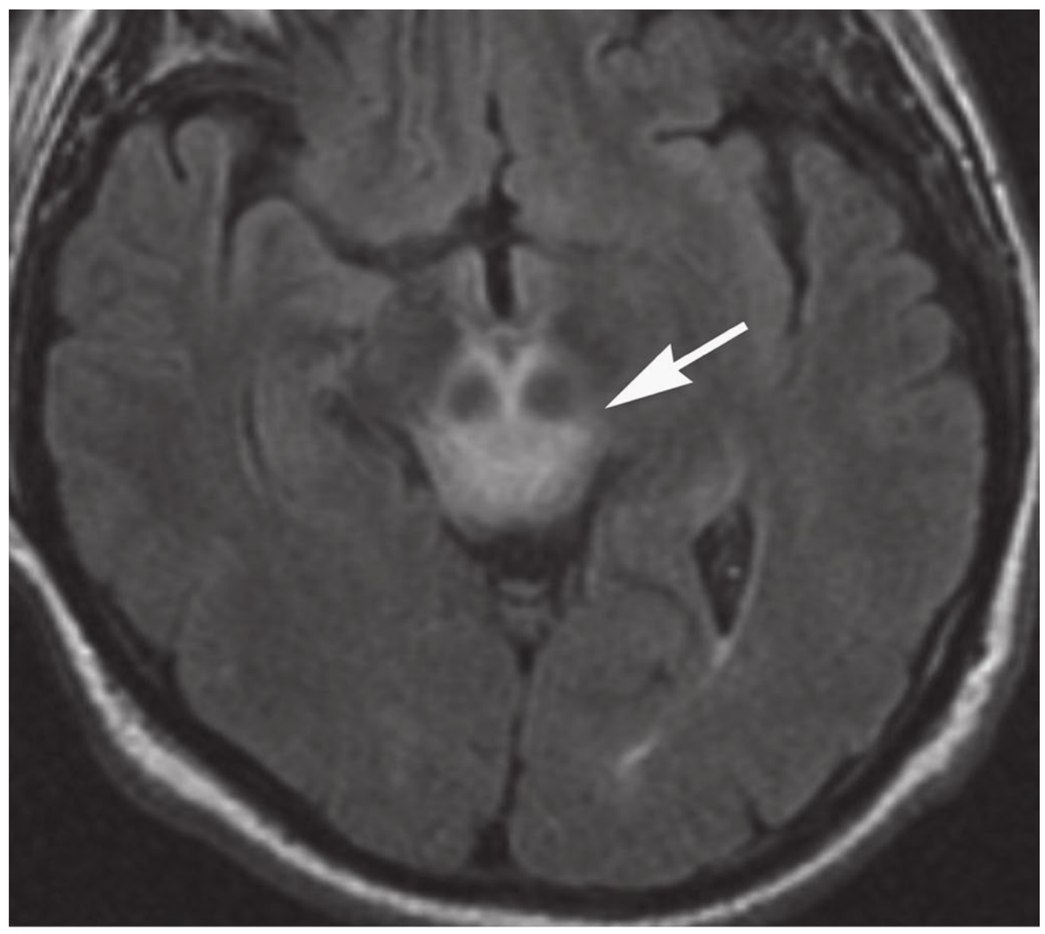
FIGURE 5-12

Neurosarcoid: Case II. Axial (A, B) and sagittal (C) T1-weighted images postgadolinium with fat suppression demonstrate a homogeneously enhancing mass involving the hypothalamus and the pituitary stalk (arrows).

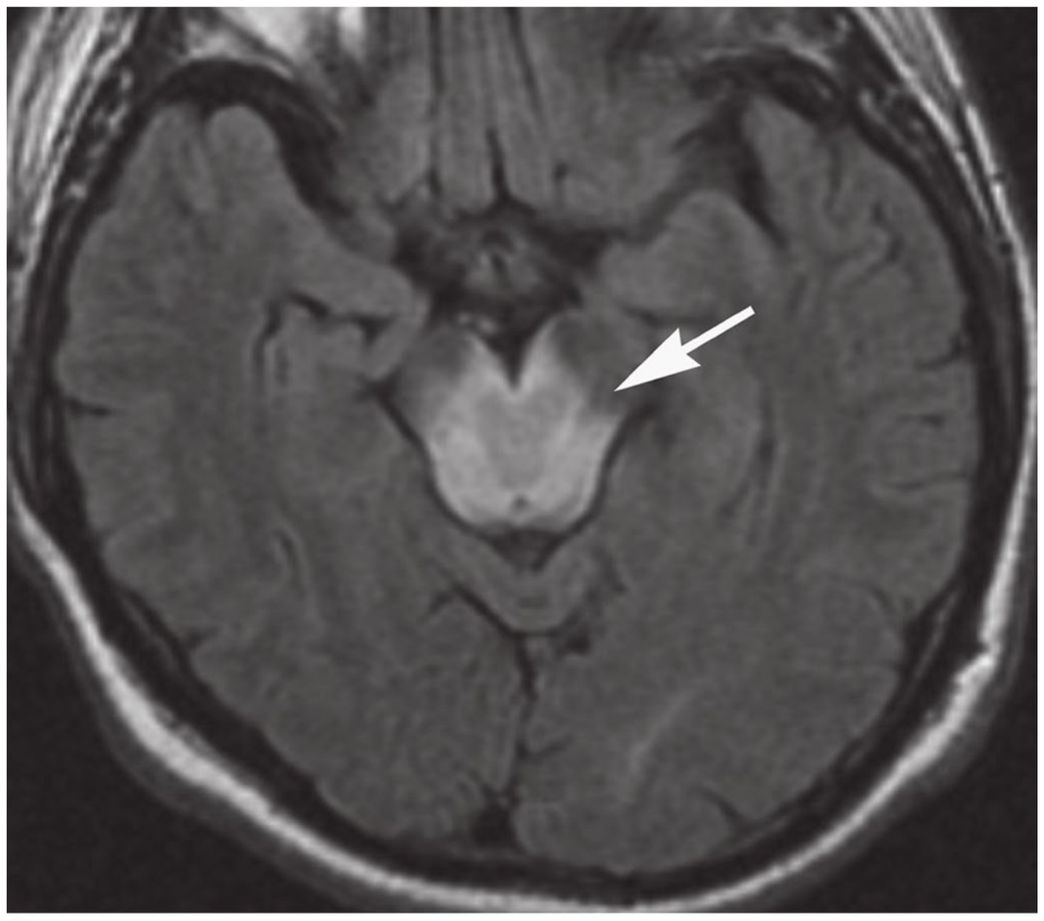
www.ketabpezeshki.com (021) 66485457 - 66485438



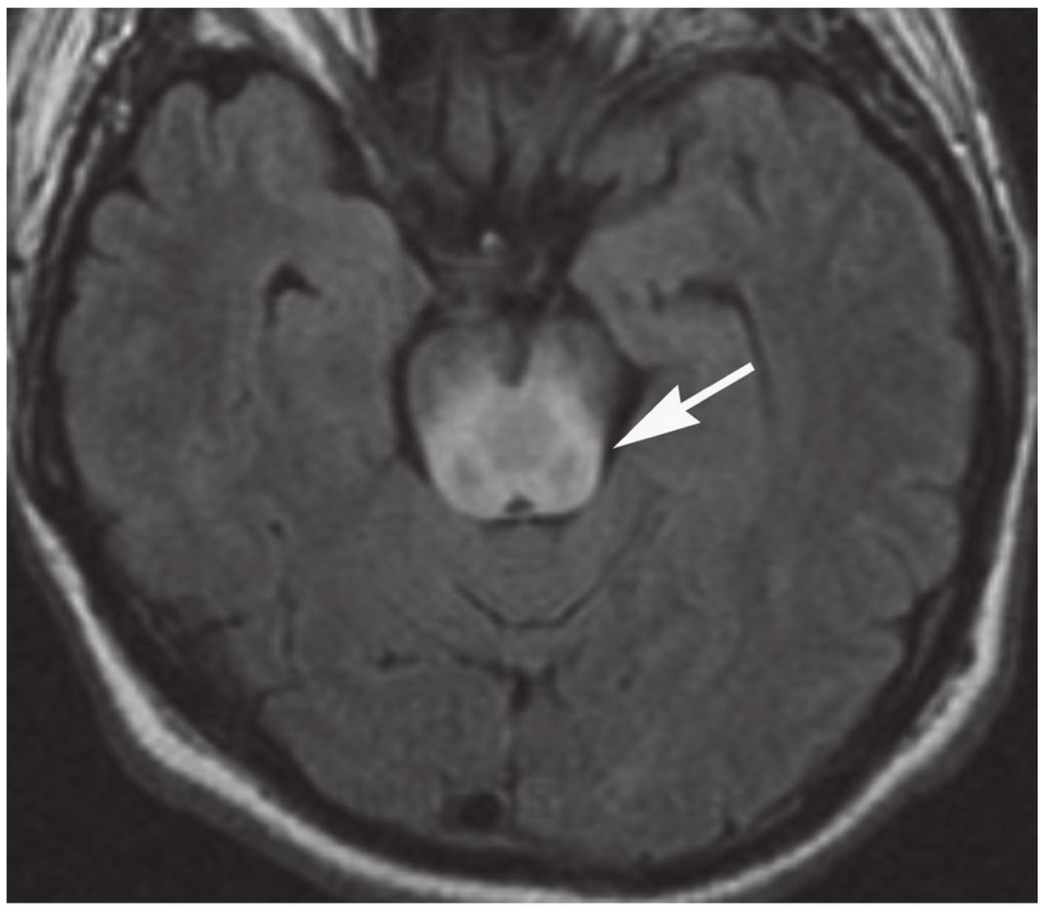
A



B



C

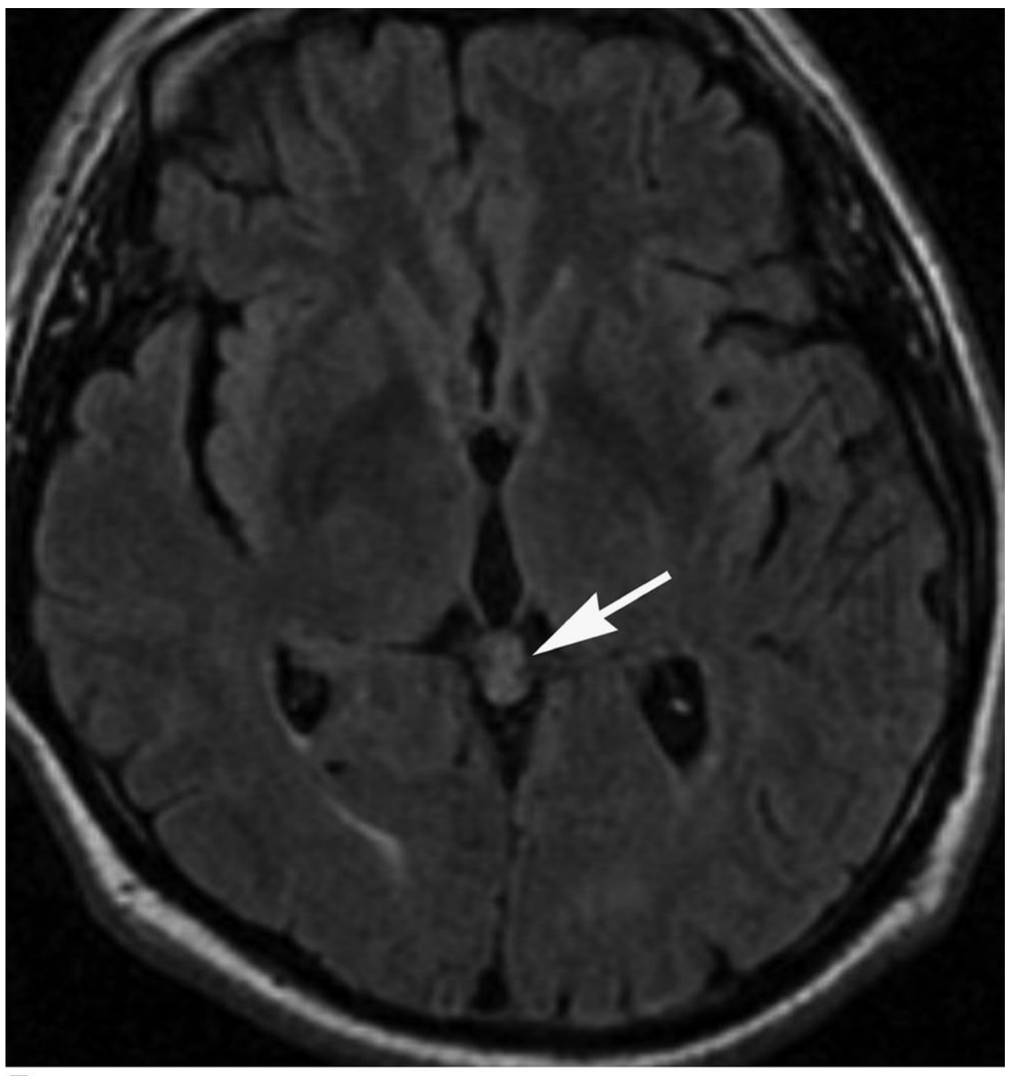


D

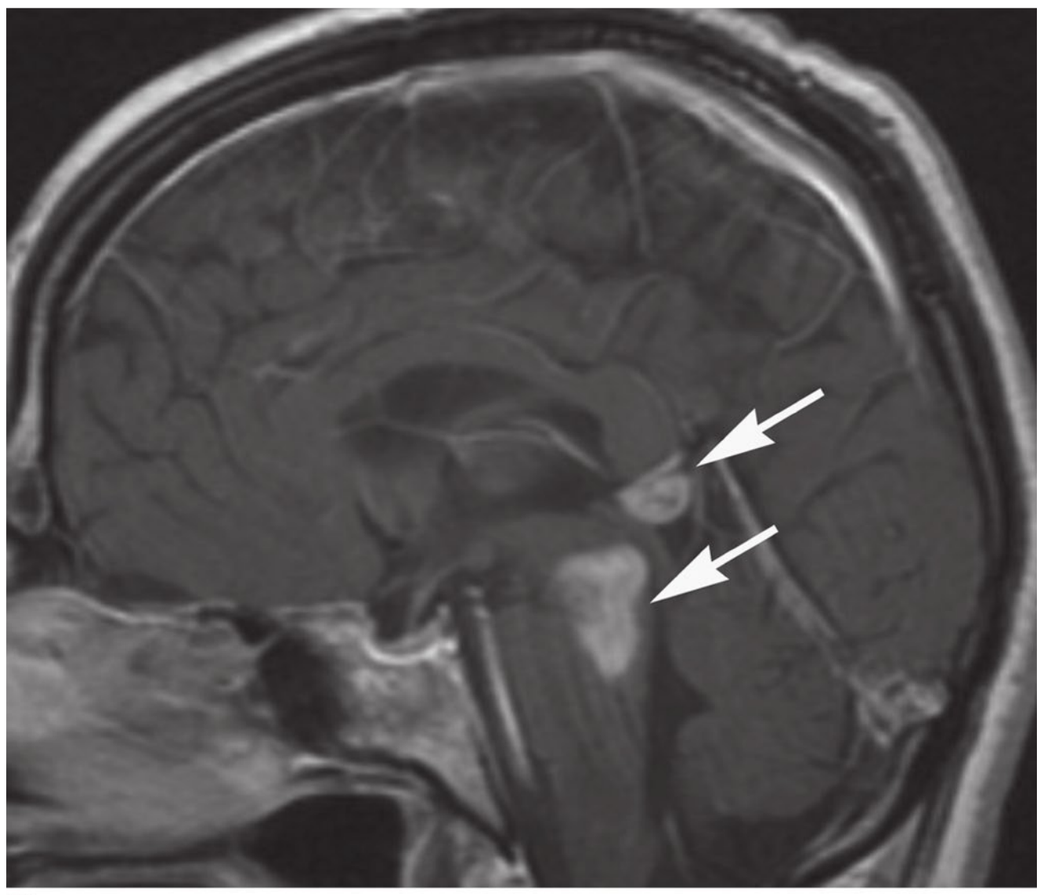
FIGURE 5-13

Neurosarcoid: Case III. Axial FLAIR images (A–E) demonstrate abnormal high signal and slight expansion in the midbrain, dorsal pons, and pineal region (arrows) without significant mass effect. Sagittal T1-weighted images postgadolinium (F) with fat suppression demonstrate abnormal enhancement in the midbrain, dorsal pons, and pineal region (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

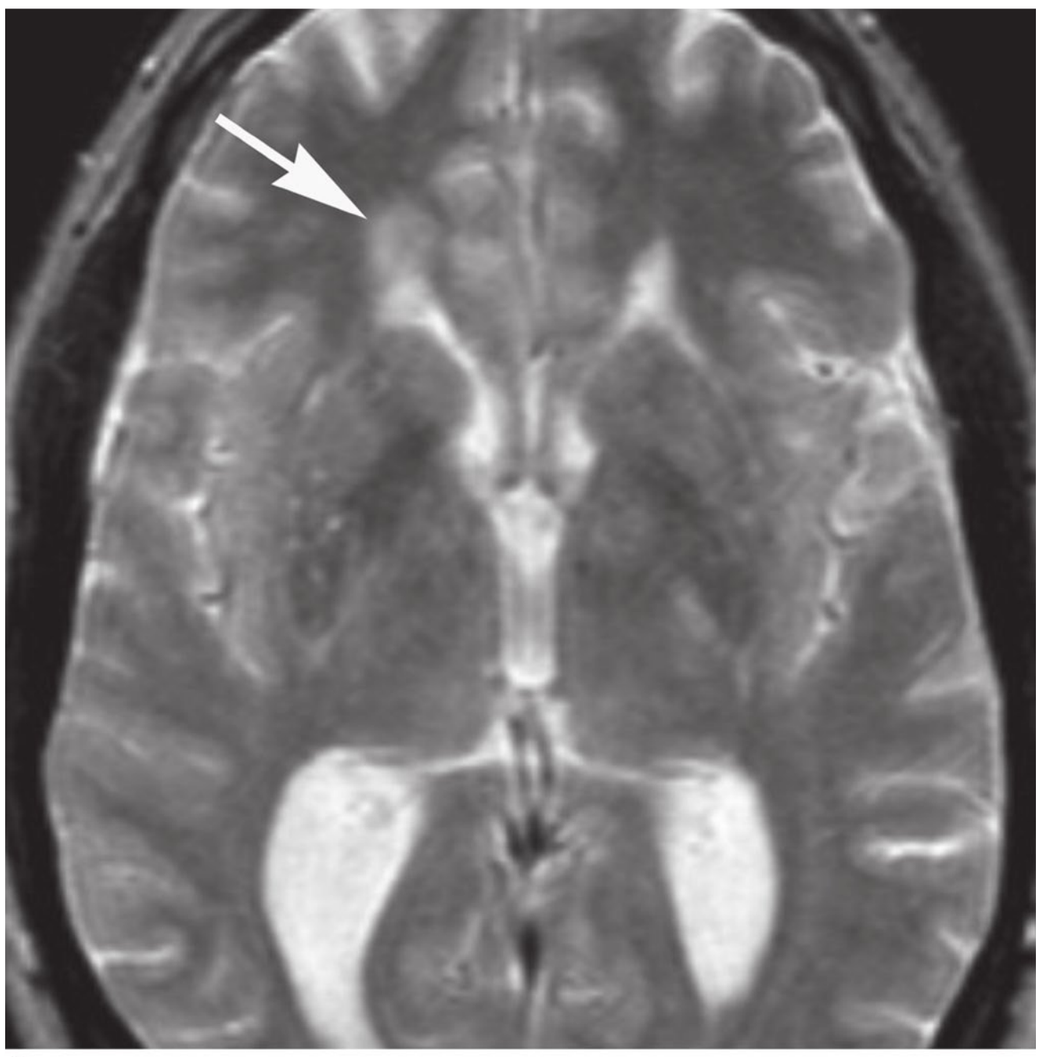


E

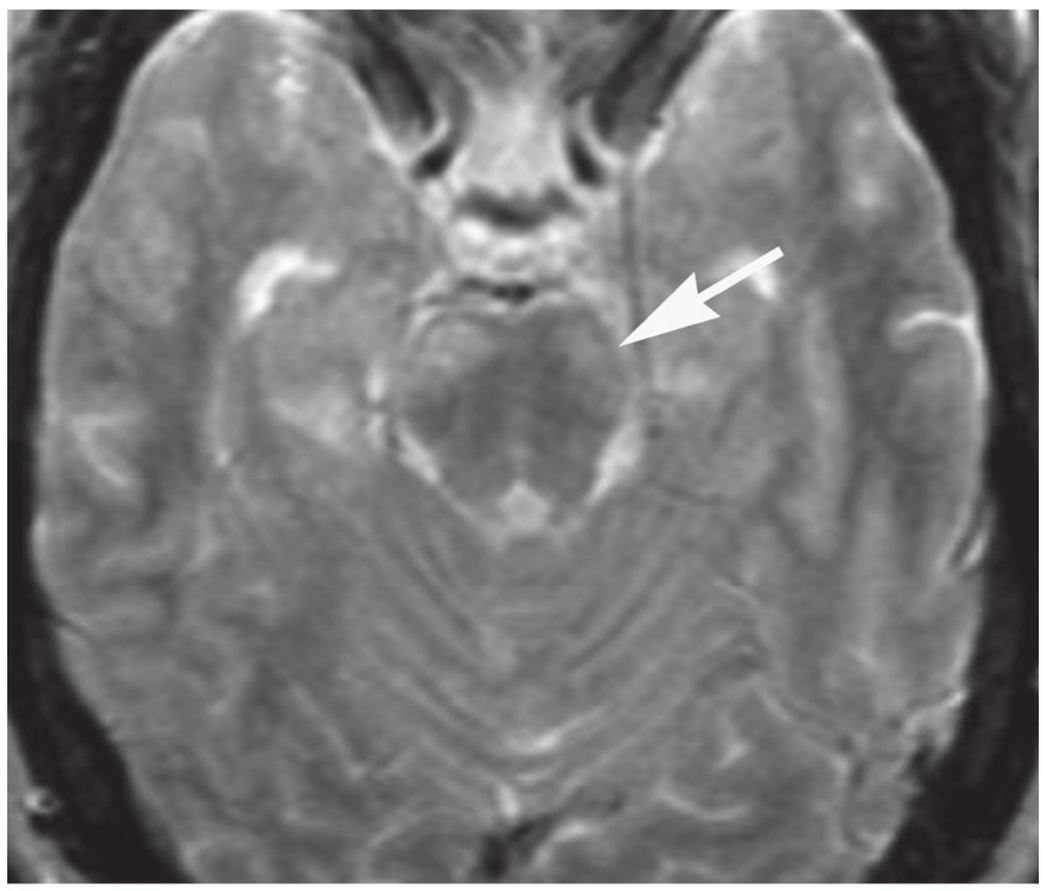


F

FIGURE 5-13
(continued)



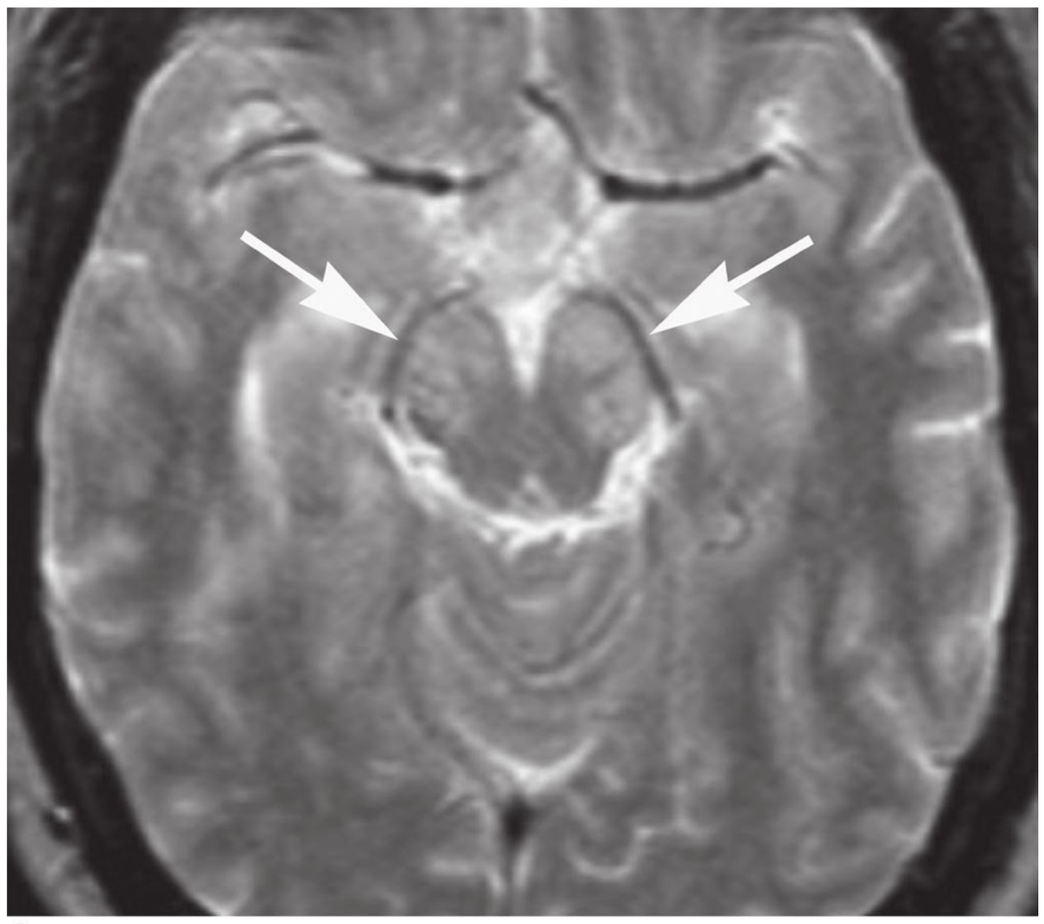
A



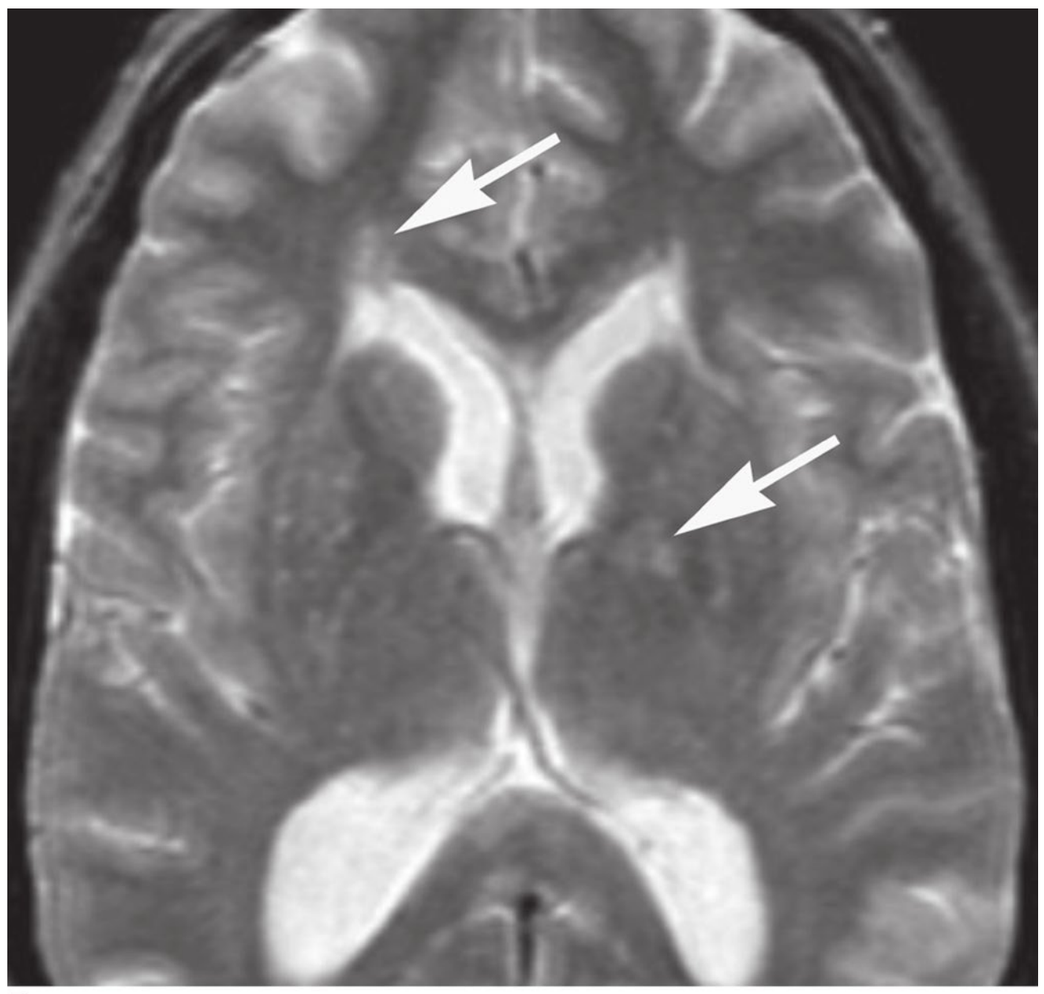
B

FIGURE 5-14
Neurosarcoid: Case IV. Axial T2-weighted images (A–D) demonstrate numerous areas of abnormal hyperintensity involving the corpus callosum, left internal capsule and globus pallidus, bilateral cerebral peduncles, bilateral gyrus rectus, right frontal lobe periventricular white matter, and patchy areas in bilateral temporal lobes. T1-weighted images postgadolinium (E–H) demonstrate abnormal enhancement of those areas with high T2 signal.

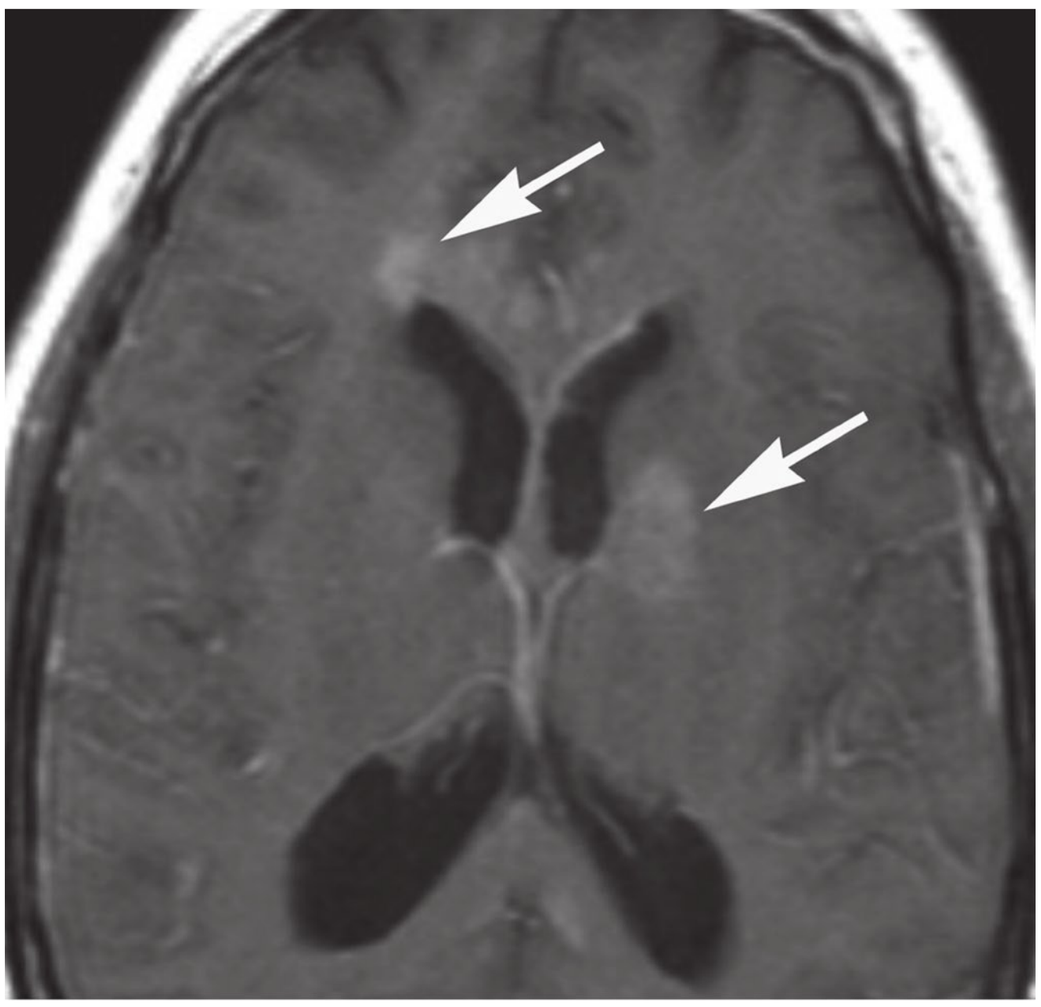
www.ketabpezeshki.com (021) 66485457 - 66485438



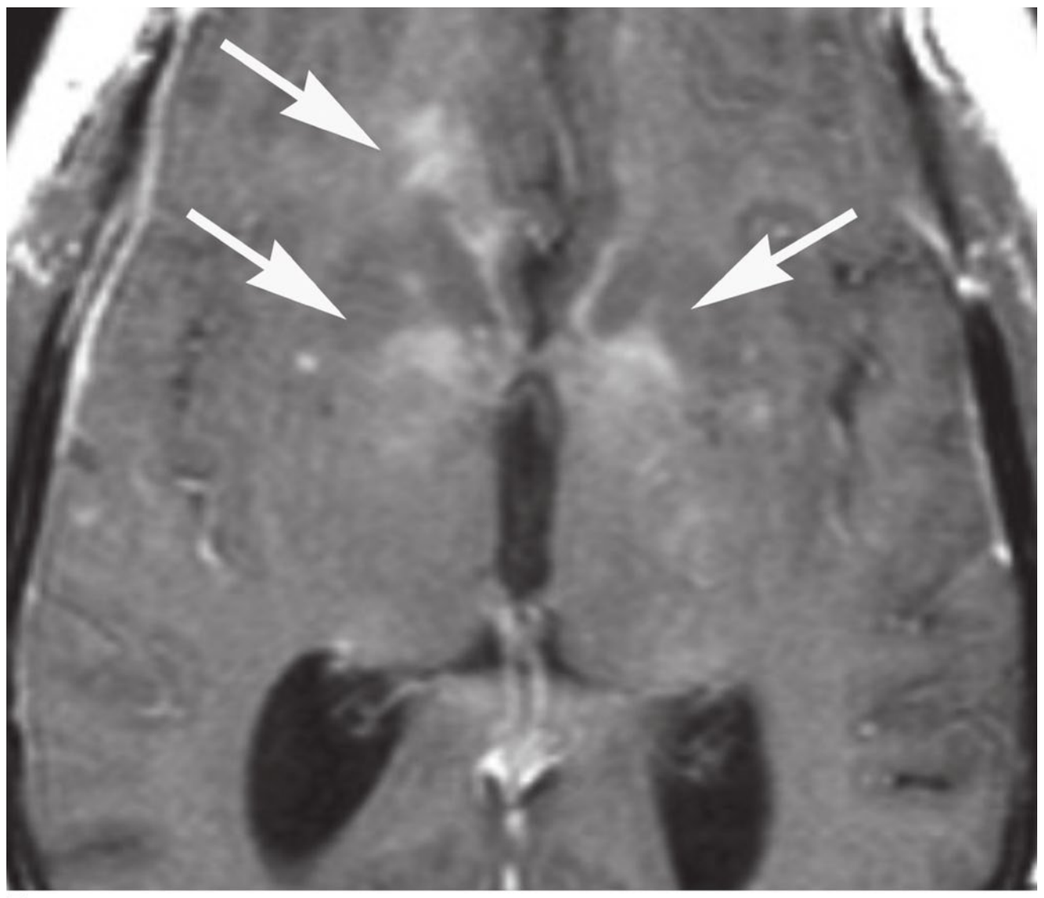
C



D



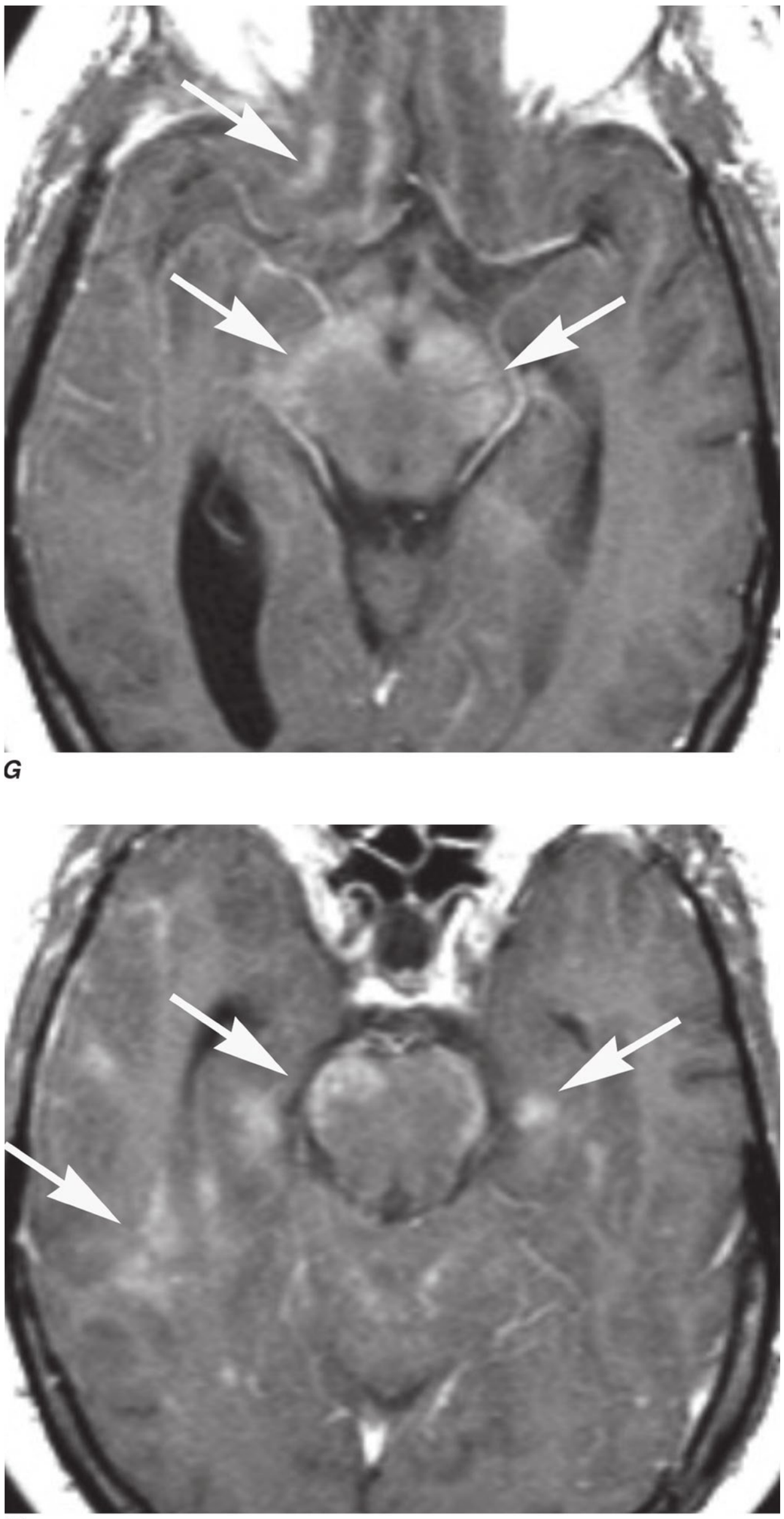
E



F

FIGURE 5-14
(continued)

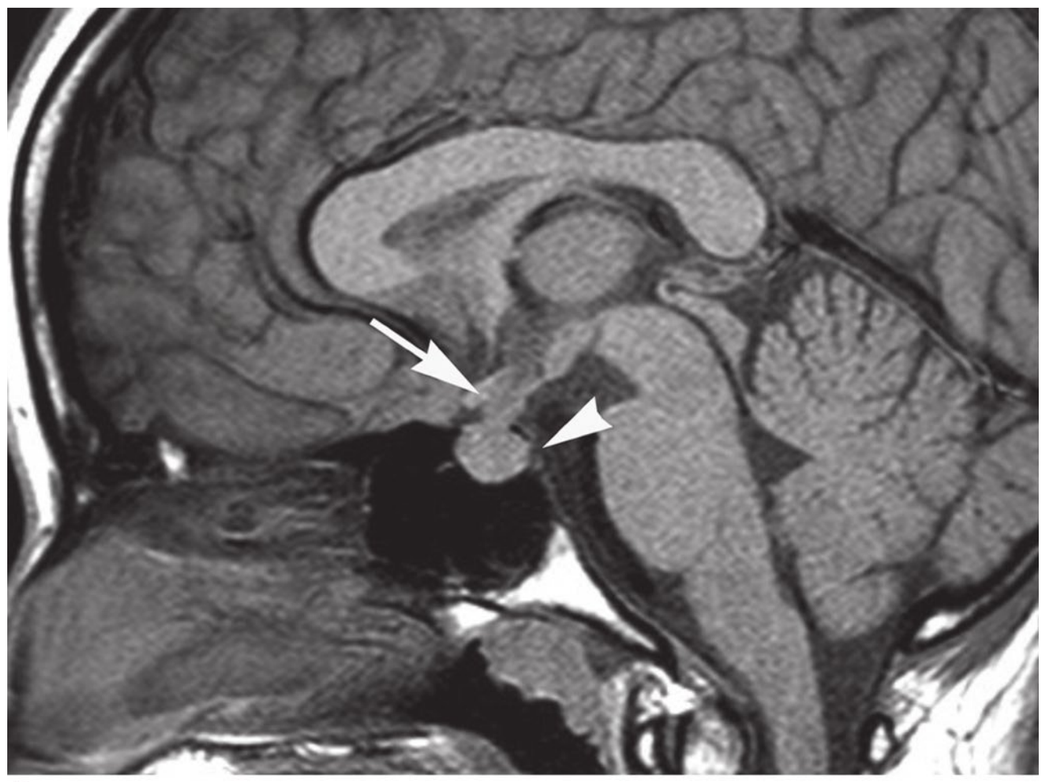
www.ketabpezeshki.com (021) 66485457 - 66485438



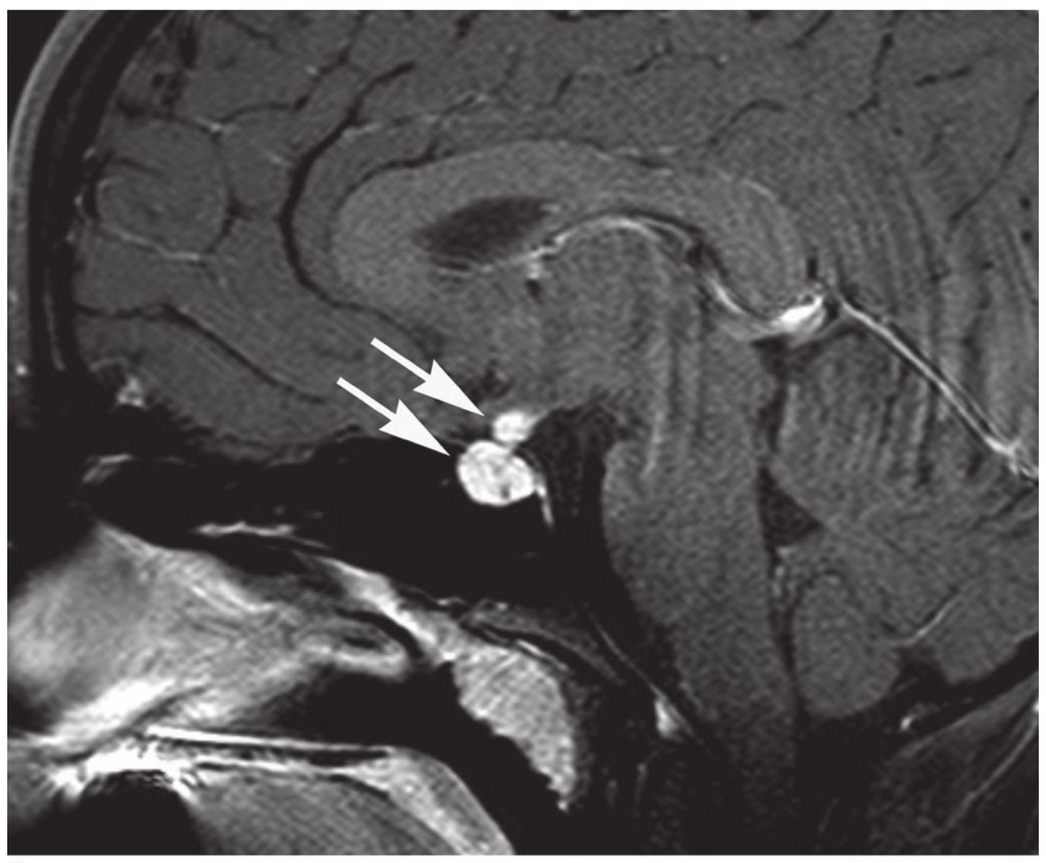
G

H

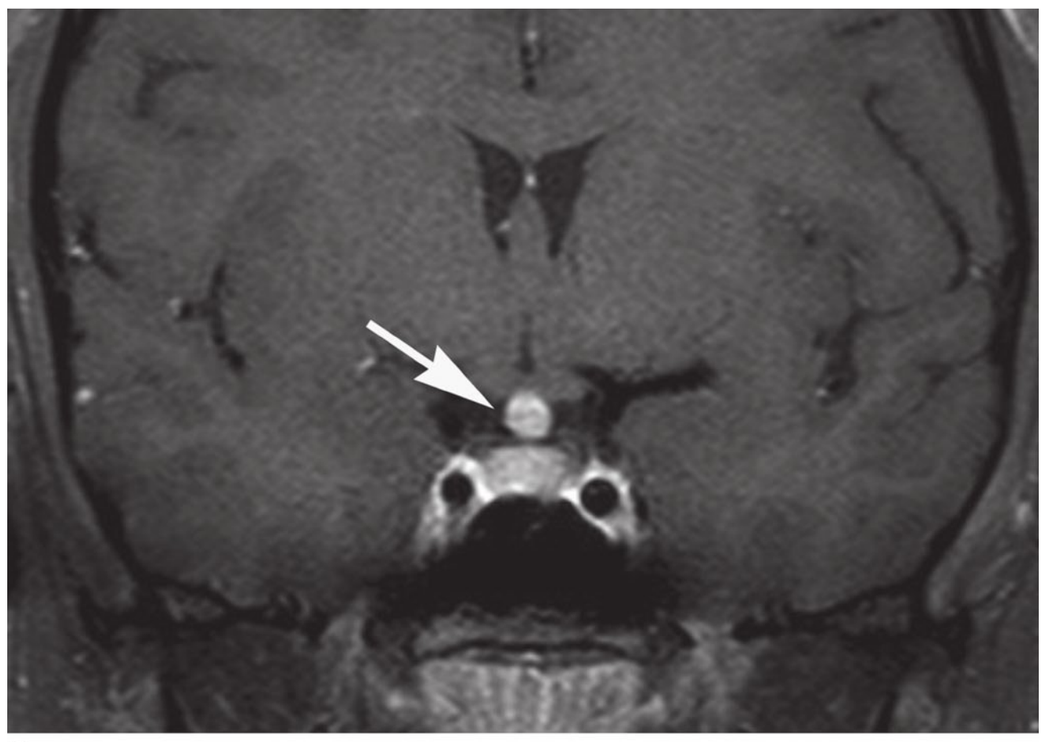
FIGURE 5-14
(continued)



A



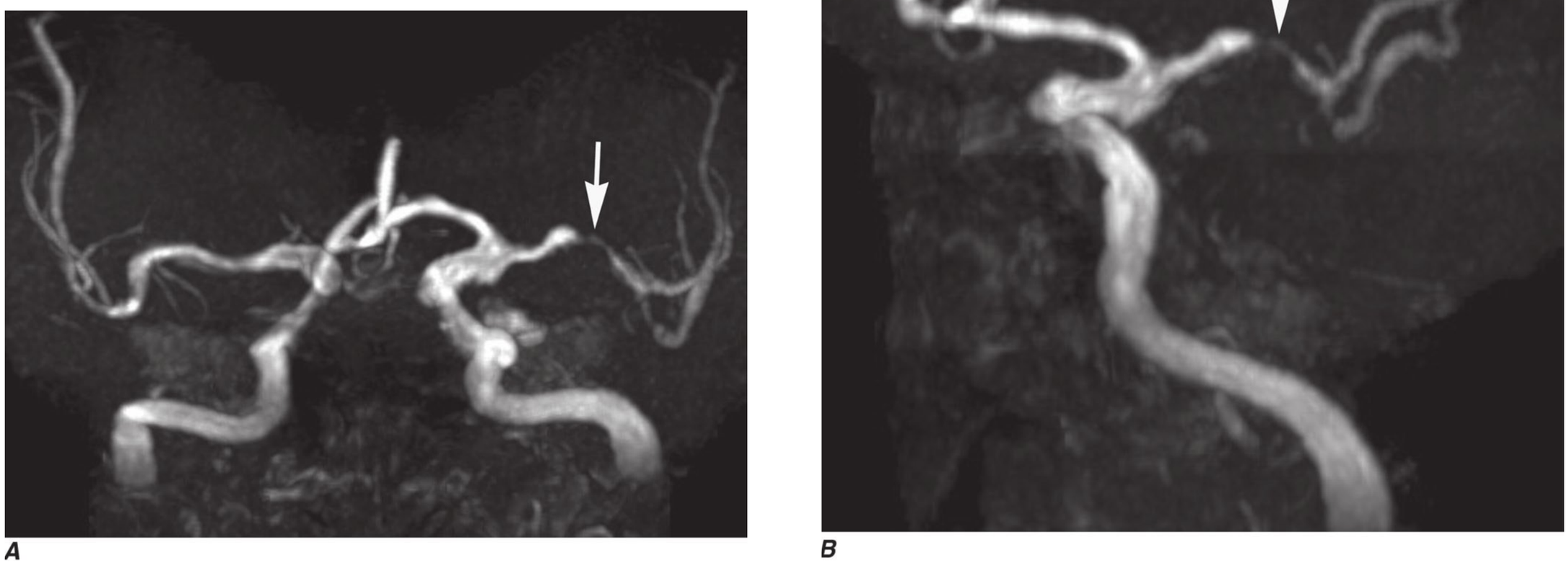
B



C

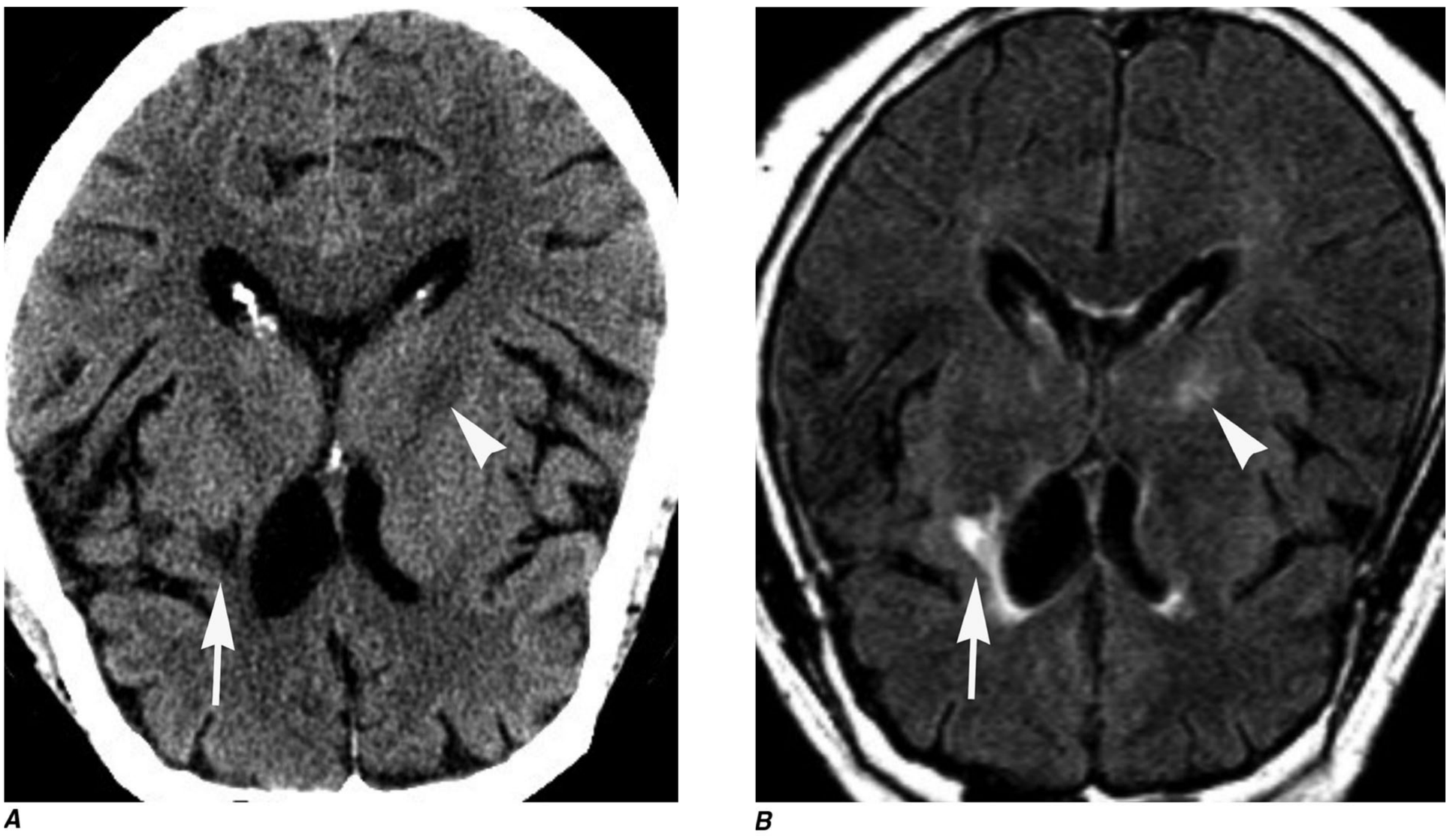
FIGURE 5-15
Histiocytosis (Chap. 52). Sagittal T1-weighted image (A) demonstrates enlargement of the pituitary stalk (arrow) and absence of the posterior pituitary intrinsic T1 hyperintensity (arrowhead). Sagittal and coronal T1-weighted images postgadolinium (B, C) demonstrate enhancement of the pituitary stalk and infundibulum (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

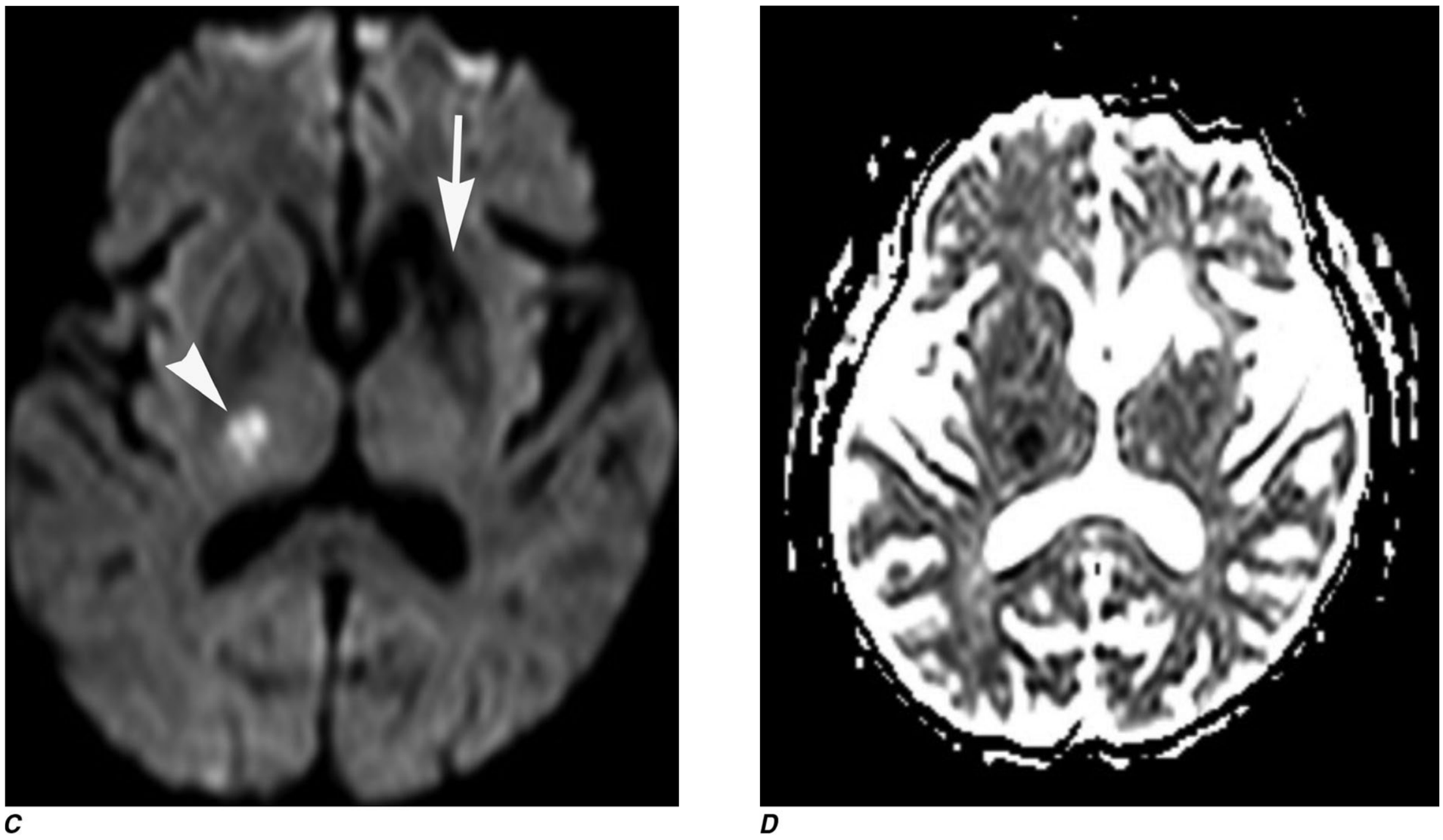
FIGURE 5-16
Middle cerebral artery stenosis (Chap. 32). Time-of-flight (TOF) MR angiography (MRA) (A, B) reveals narrowing within the left M1 segment that is likely secondary to atherosclerosis (arrows).



A B

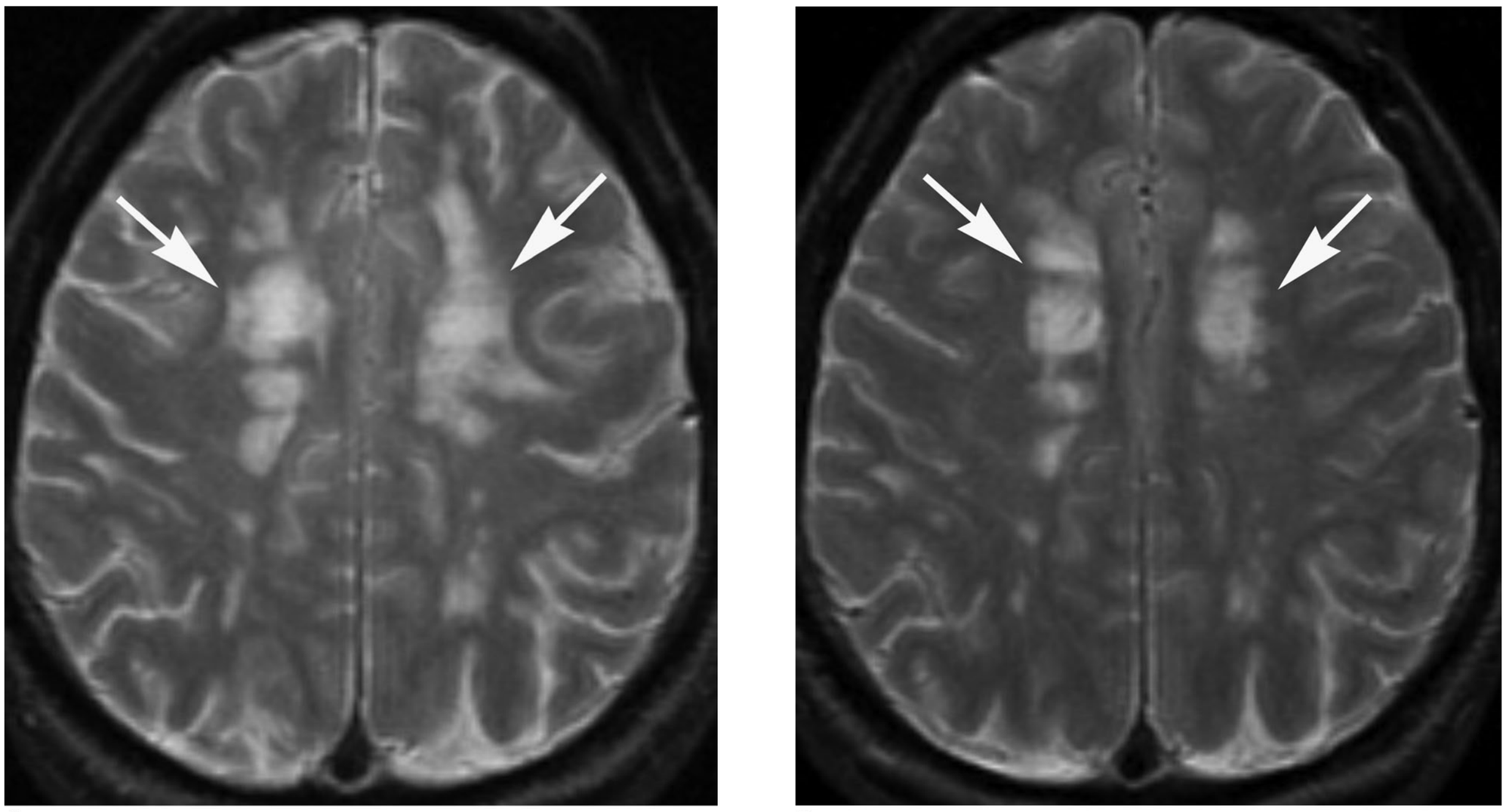
FIGURE 5-17
Lacunar infarction (Chap. 32). Axial noncontrast CT (A) demonstrates abnormal hypodensity involving the left anterior putamen and anterior limb of internal capsule with ex-vacuo dilatation of the adjacent frontal horn of the left lateral ventricle, suggestive of an old infarction (arrow). A small area of slight hypodensity is also seen in the posterior limb of the right internal capsule that can correspond to an acute infarct (arrowhead). Axial FLAIR MRI (B) demonstrates abnormal high signal involving the left anterior putamen and anterior limb of internal capsule with ex-vacuo dilatation of the adjacent frontal horn of the left lateral ventricle, suggestive of an old infarction (arrow). A small area of slight hyperintensity is also seen in the posterior limb of the right internal capsule that can correspond to an acute lacunar infarct (arrowhead). Diffusion-weighted image (C) and apparent diffusion coef cient (ADC) map (D) demonstrate restricted water motion in the lesion of the posterior limb of the right internal capsule, strongly suggestive for an acute lacunar infarct (arrowhead). There is no evidence of restricted diffusion in the old infarct (arrow).

www.ketabpezeshki.com (021) 66485457 - 66485438



C D

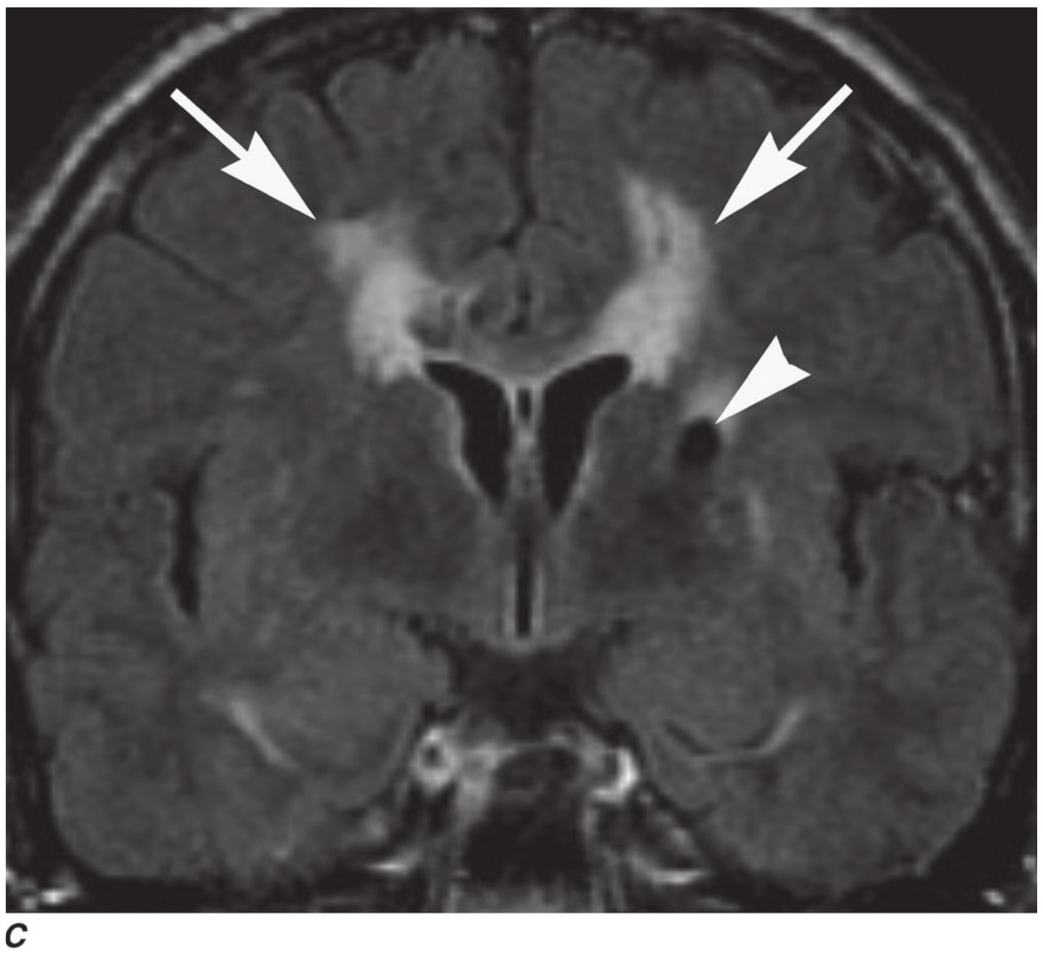
FIGURE 5-17
(continued)



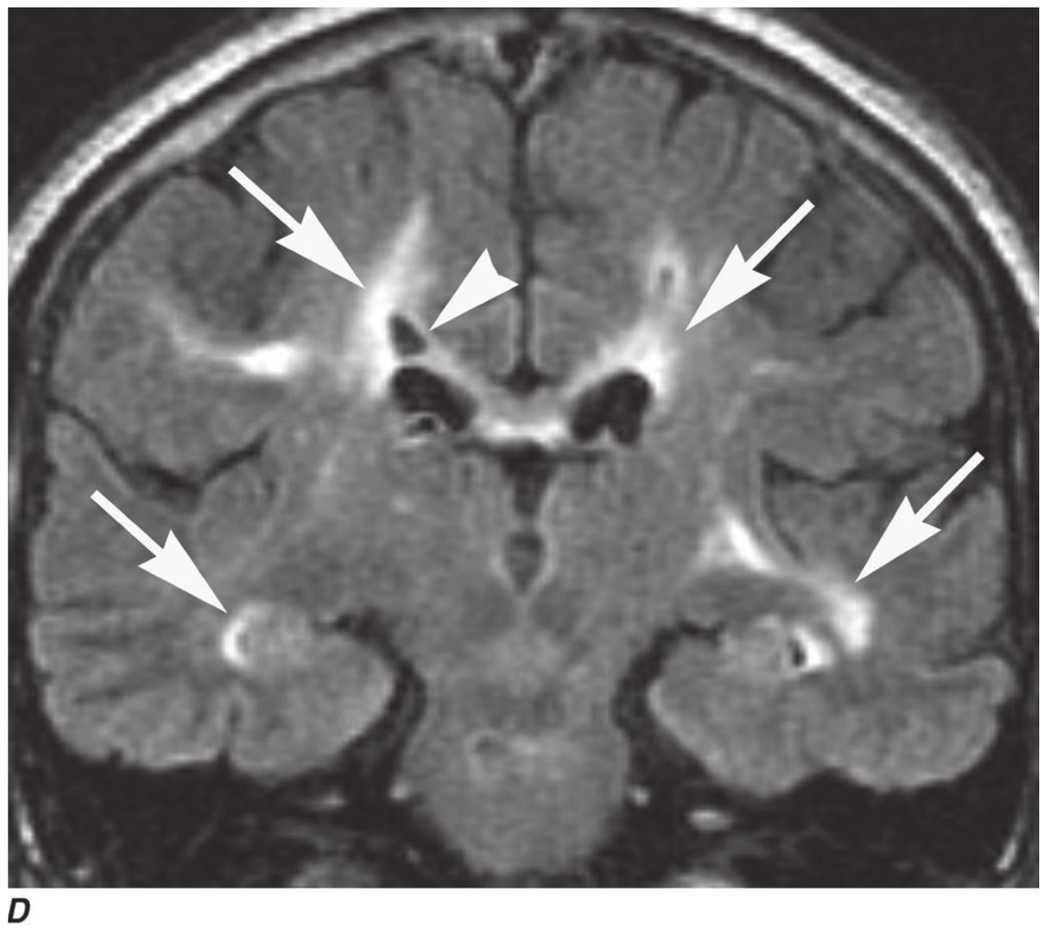
A B

FIGURE 5-18
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chap. 32). Axial T2-weighted MRIs (A, B) demonstrate multiple patchy areas of abnormal high signal in the periventricular white matter (arrows). Coronal FLAIR MRI (C, D) demonstrates multiple patchy areas of abnormal high signal in the periventricular white matter bilaterally, including the temporal lobes (arrows). In some of these areas, there are small areas of tissue loss (encephalomalacia) (arrowheads).

www.ketabpezeshki.com (021) 66485457 - 66485438



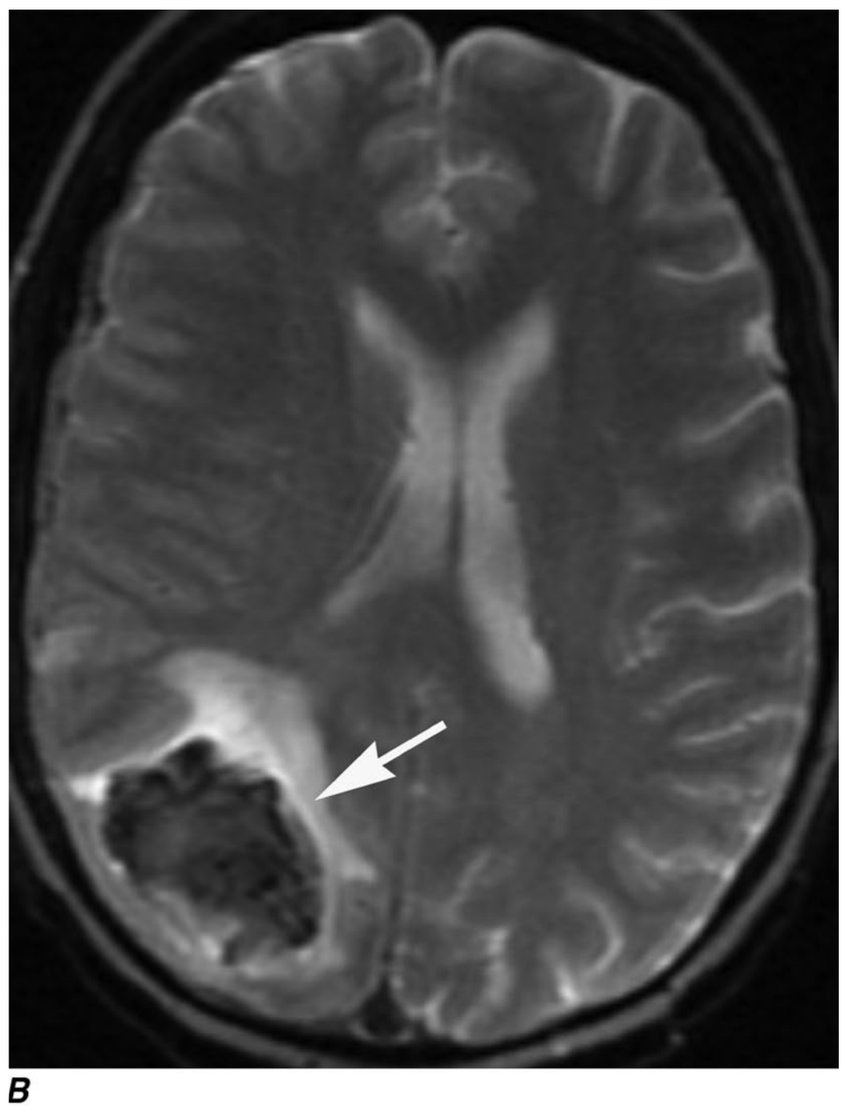
C



D

FIGURE 5-18
(continued)

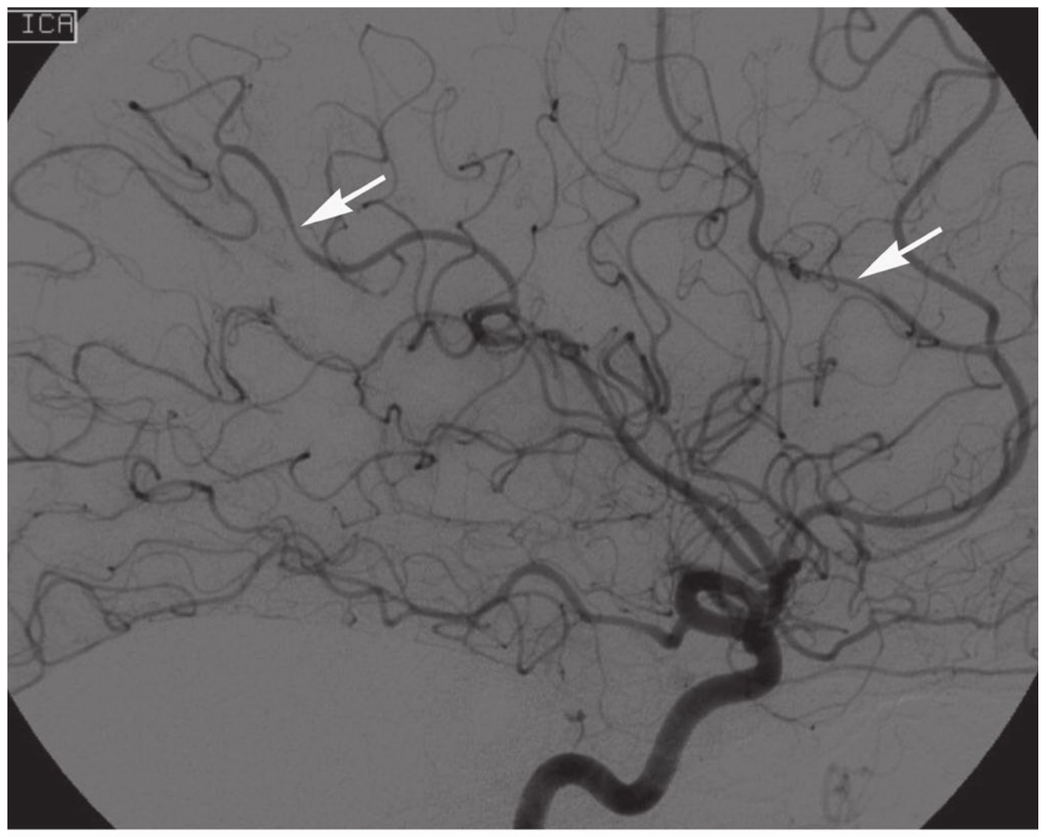
A



B

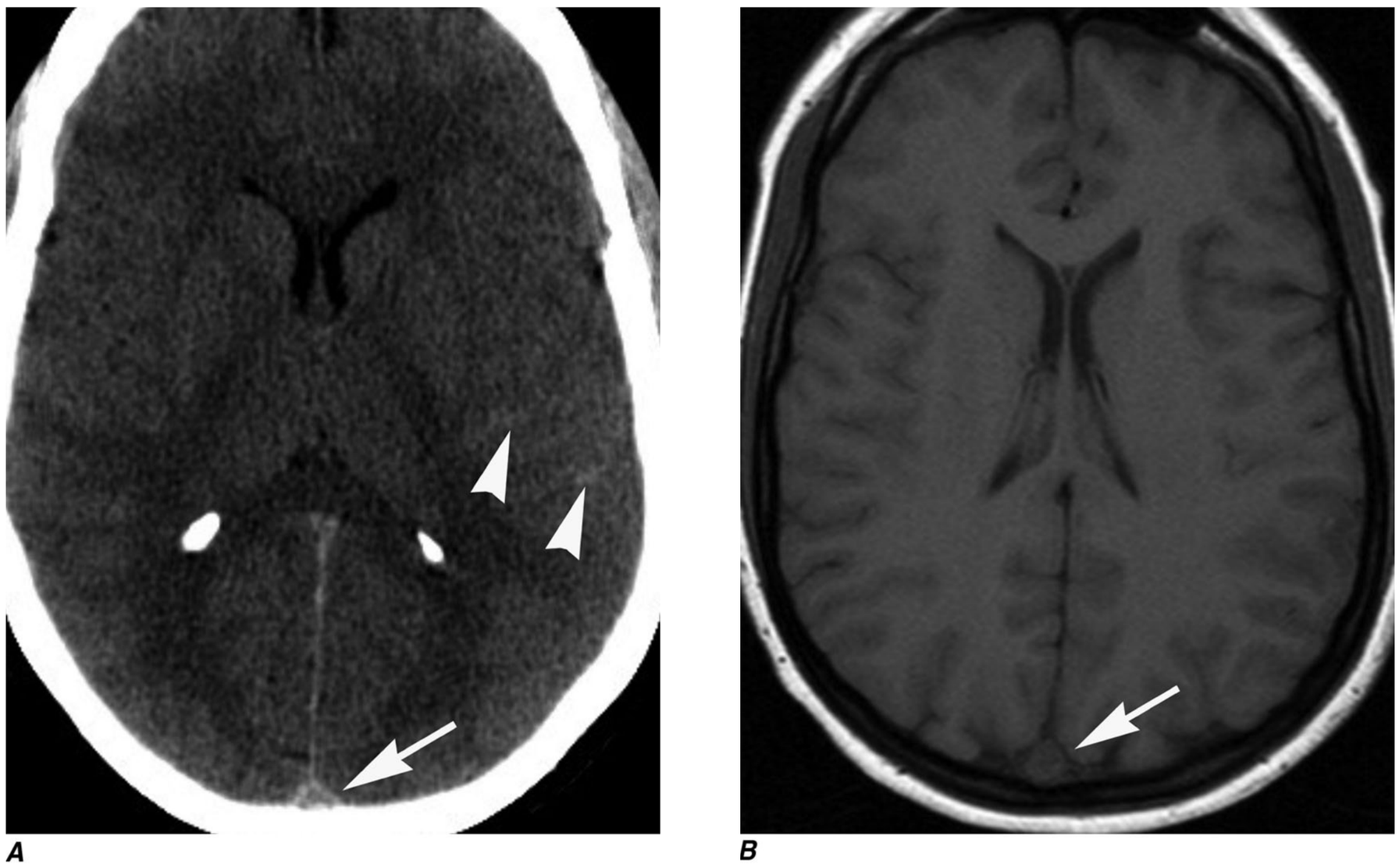
FIGURE 5-19
CNS vasculitis (Chap. 32). Axial noncontrast CT (A) demonstrates a large hyperdense intraparenchymal hematoma surrounded by hypodense vasogenic edema in the right parietal lobe. Axial T2-weighted MRI (B) demonstrates a large hypointense intraparenchymal hematoma surrounded by hyperintense vasogenic edema in the right parietal lobe. Conventional angiography (C) demonstrates multiple segments of intracranial arterial narrowing, some of which have associated adjacent areas of focal arterial dilatation. These abnormalities are suggestive of vasculitis.

www.ketabpezeshki.com (021) 66485457 - 66485438



C

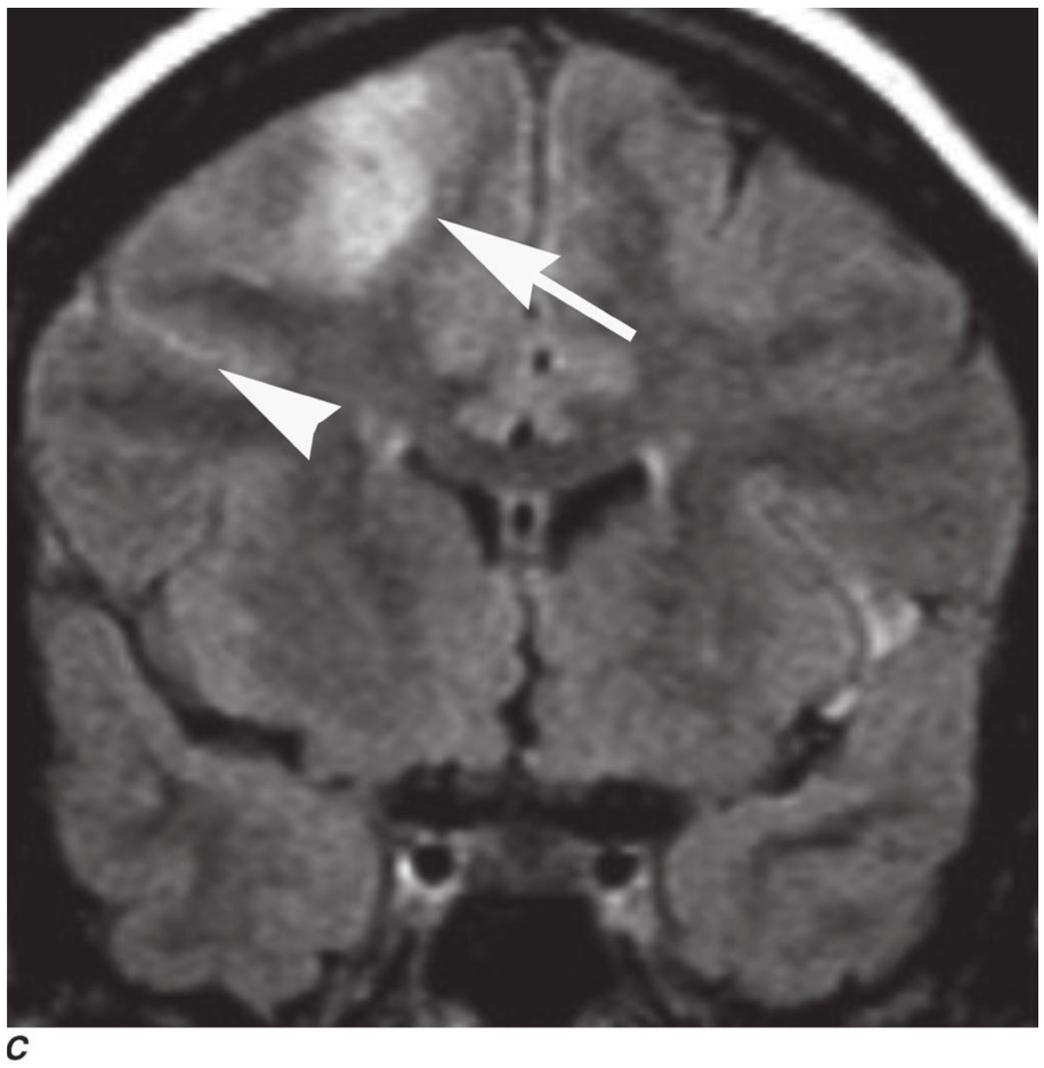
FIGURE 5-19
(continued)



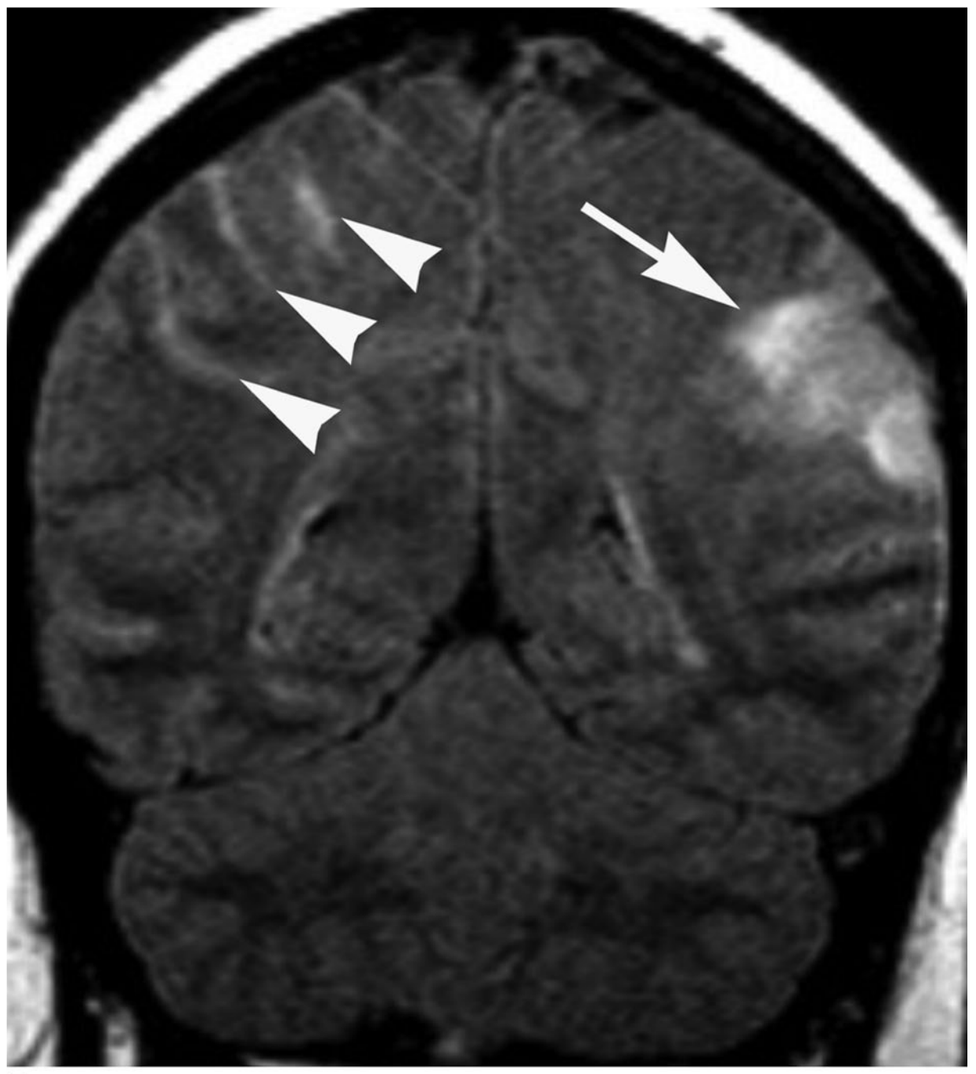
A B

FIGURE 5-20
Superior sagittal sinus thrombosis (Chap. 32). Noncontrast CT of the head (A) demonstrates increased density in the superior sagittal sinus, suggestive of thrombosis (arrow), and small linear hyperdensities in some temporal lobe sulci, suggestive of subarachnoid hemorrhage (arrowheads). Axial T1-weighted MRI (B) demonstrates absence of flow void in the superior sagittal sinus, suggestive of thrombosis. Coronal FLAIR images (C, D) demonstrate areas of abnormal high signal involving the gray and the subcortical white matter of the right frontal and left parietal lobes, as well as the adjacent sulci. These findings are suggestive of vasogenic edema with subarachnoid hemorrhage (arrowheads). Diffusion-weighted images (E, F) and ADC maps (G, H) demonstrate restricted diffusion of the abnormal areas on FLAIR, suggestive of infarct. Phase-contrast venography of the brain (I) demonstrates absence of signal in the superior sagittal sinus down to the torcular herophili, and left transverse sinus and jugular vein. Axial (J) and coronal (K) T1-weighted images postgadolinium demonstrate a filling defect in the superior sagittal sinus, suggestive of thrombosis.

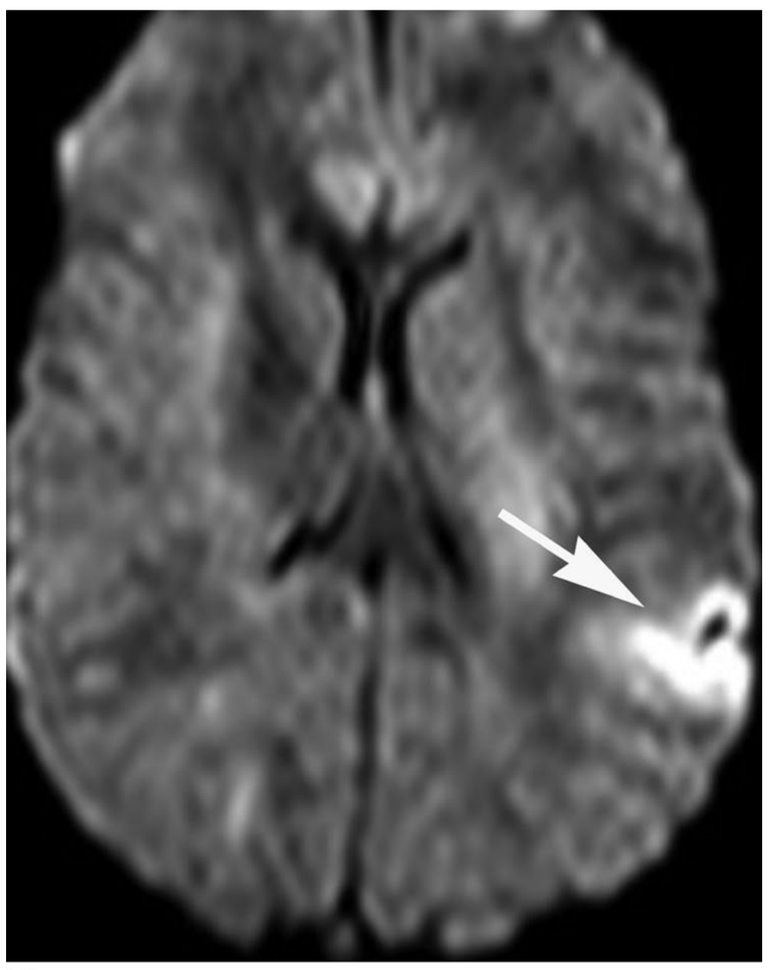
www.ketabpezeshki.com (021) 66485457 - 66485438



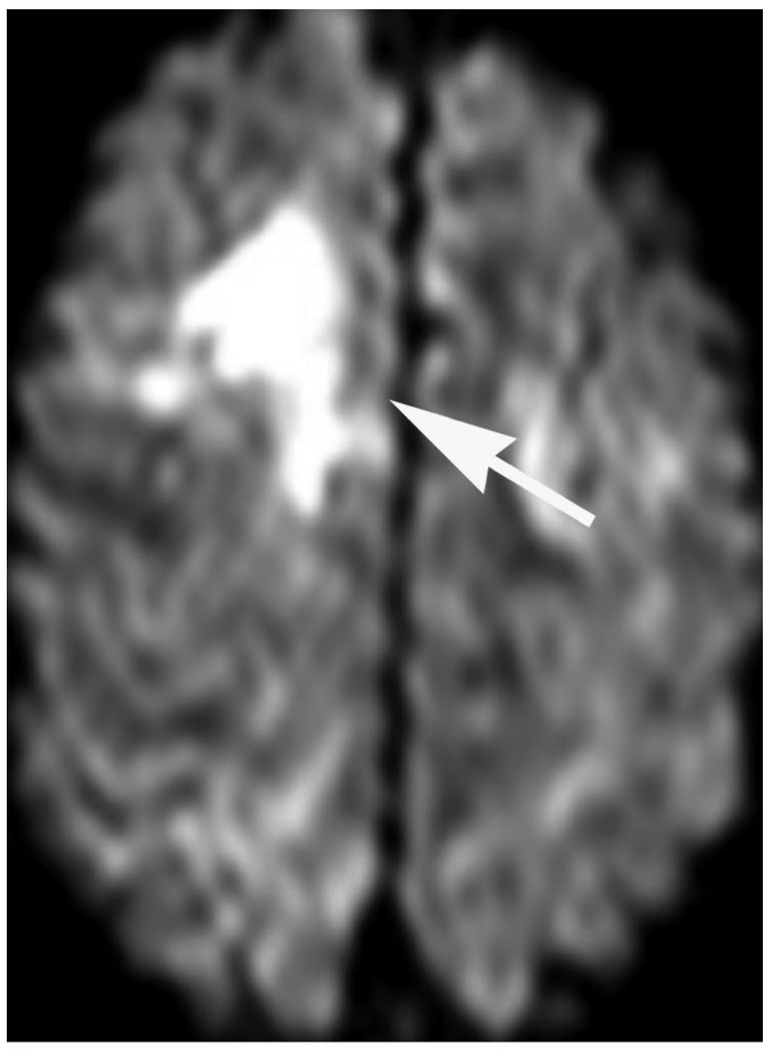
C



D



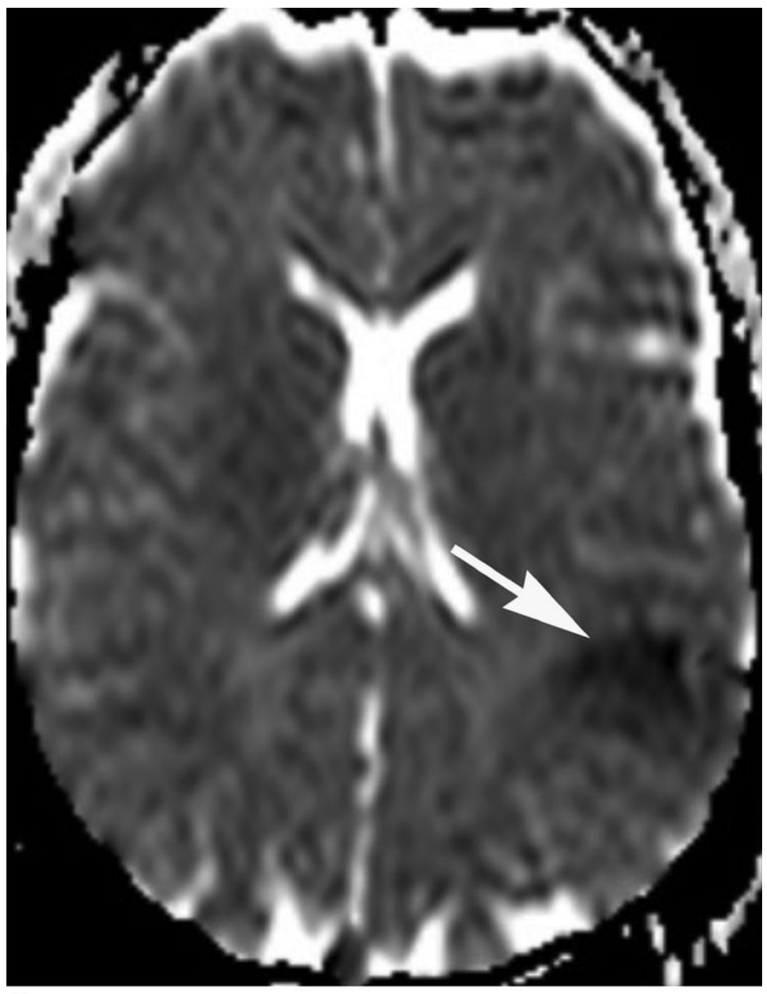
E



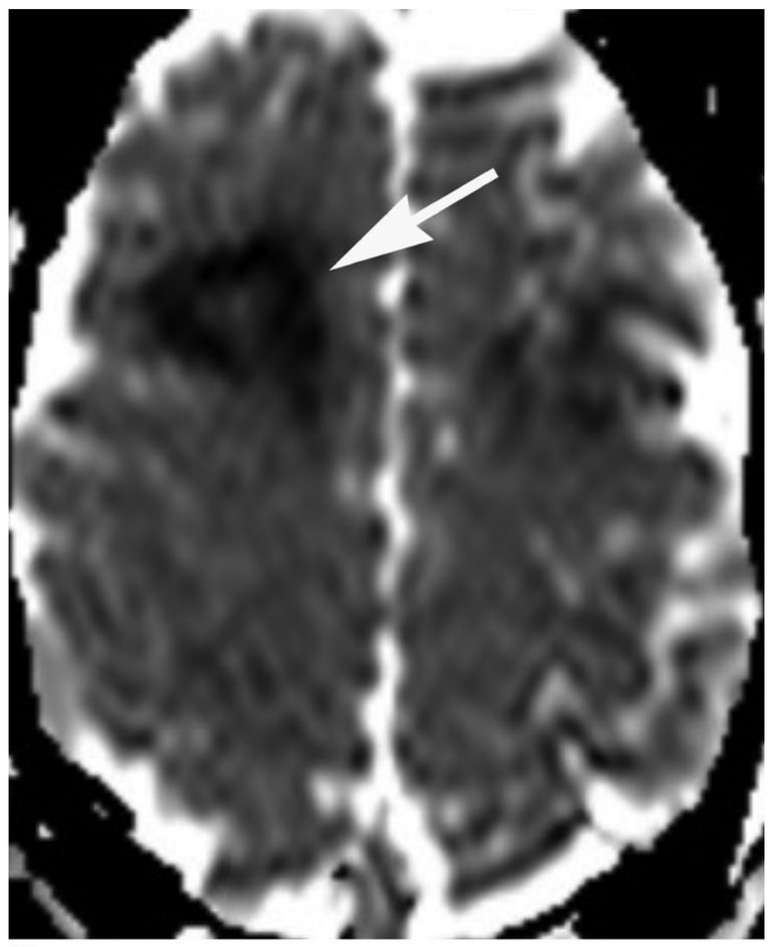
F

FIGURE 5-20
(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

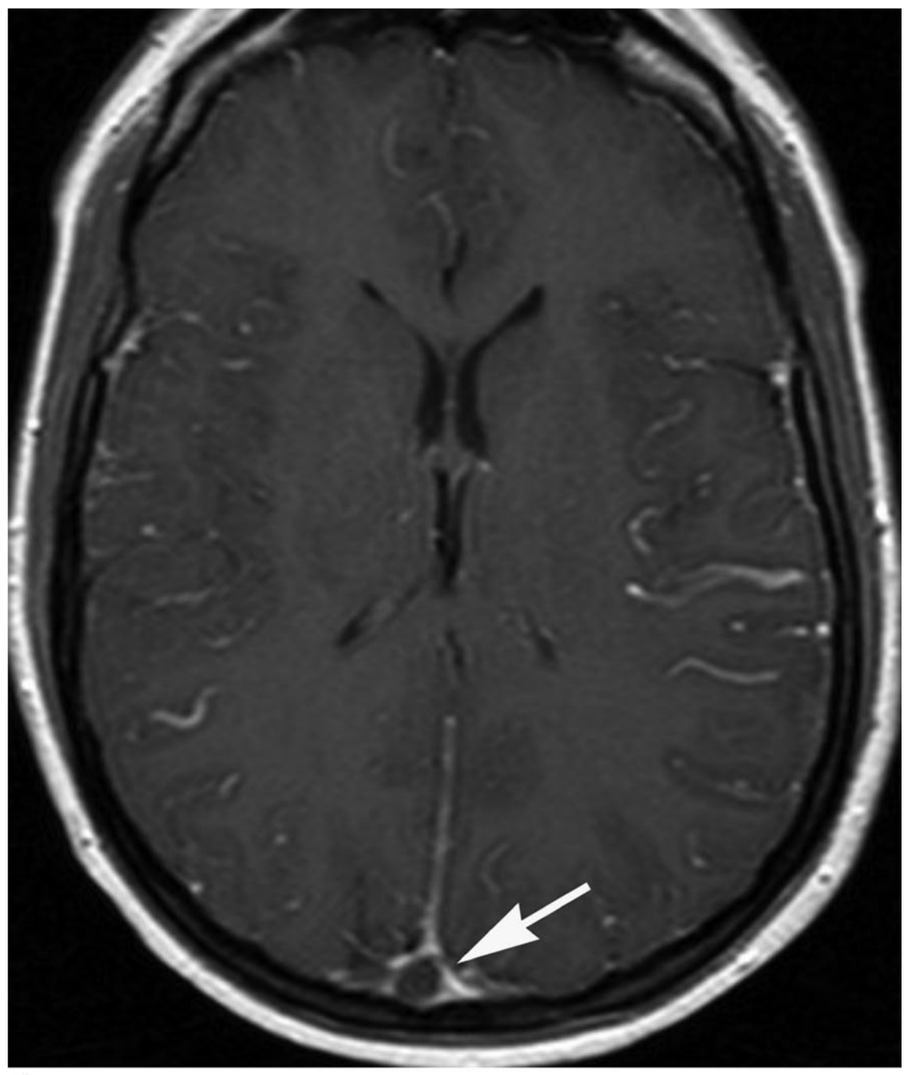


G



H

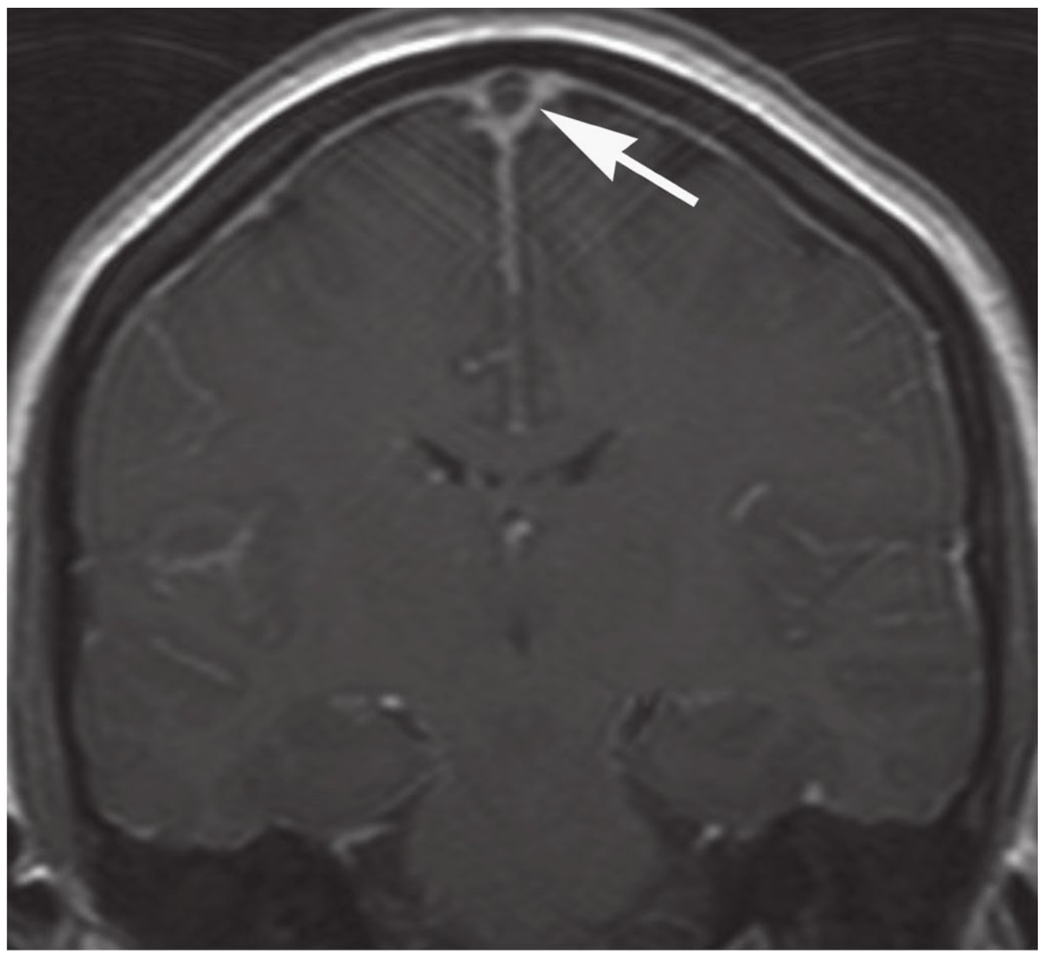
I



J

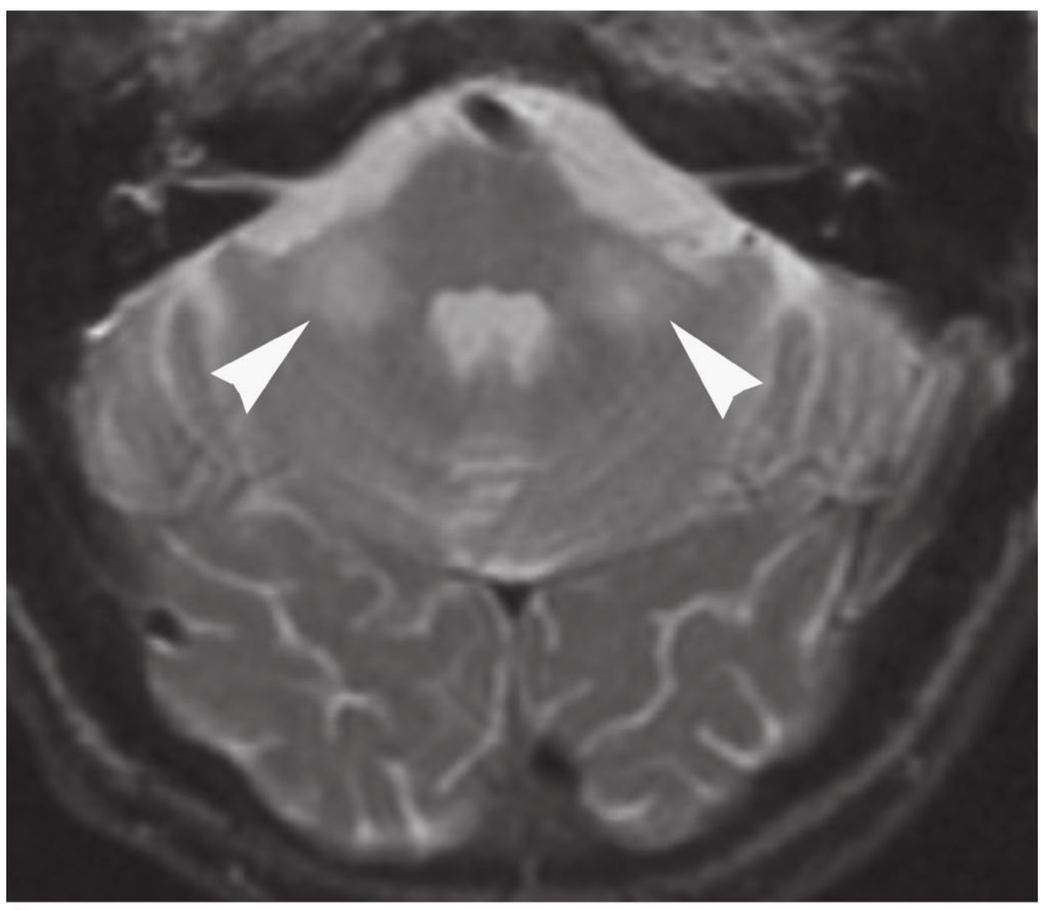
FIGURE 5-20
(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

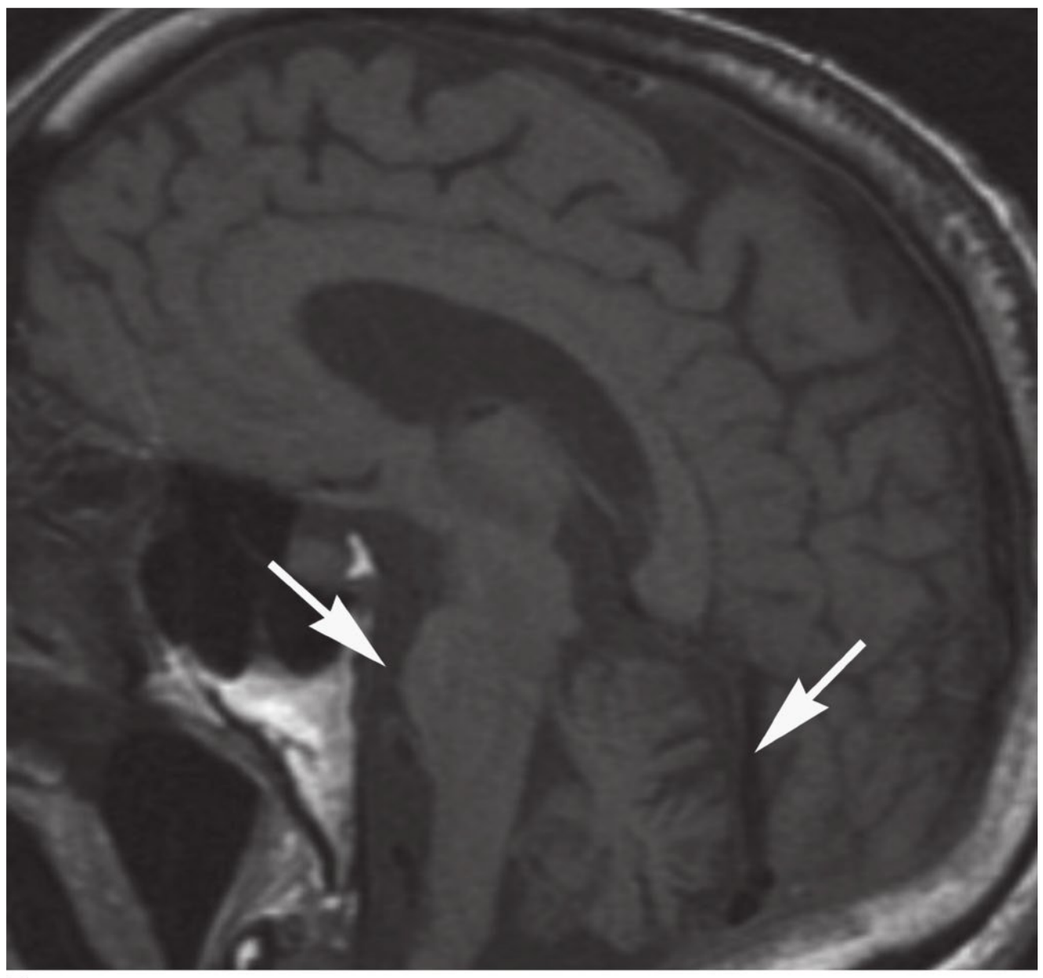


K

FIGURE 5-20
(continued)



A

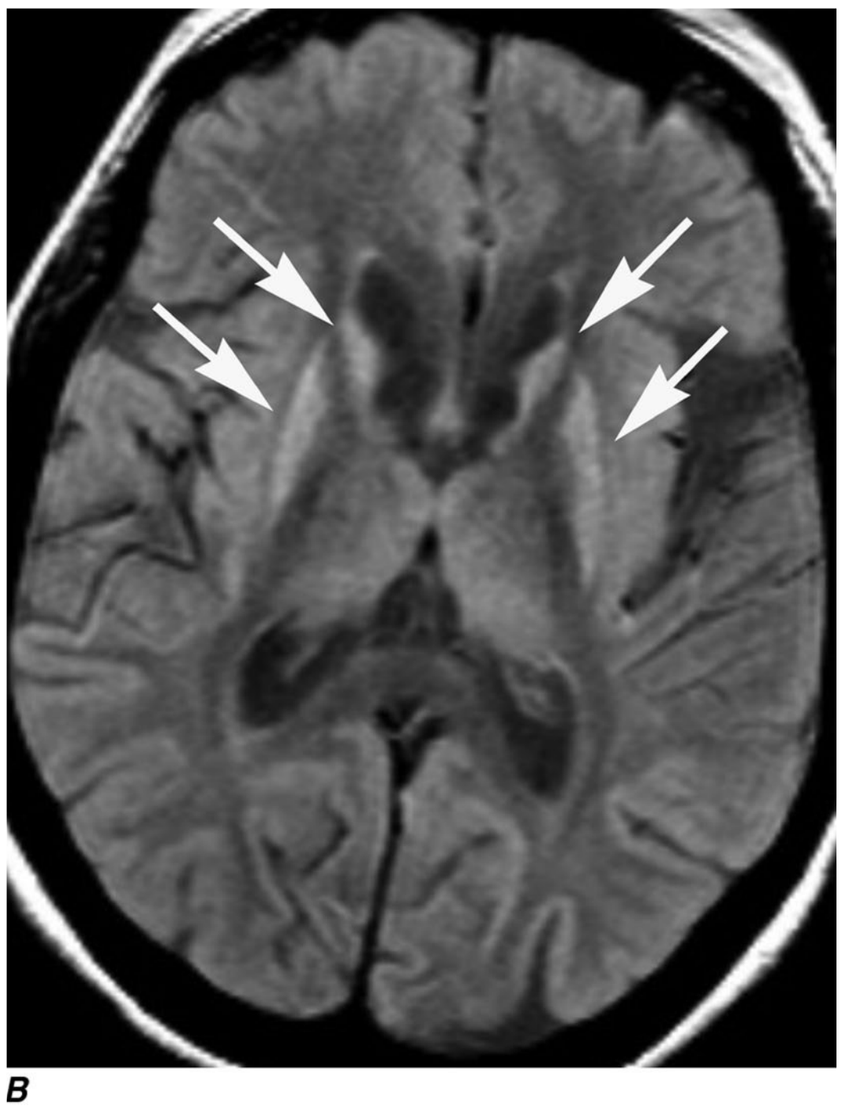


B

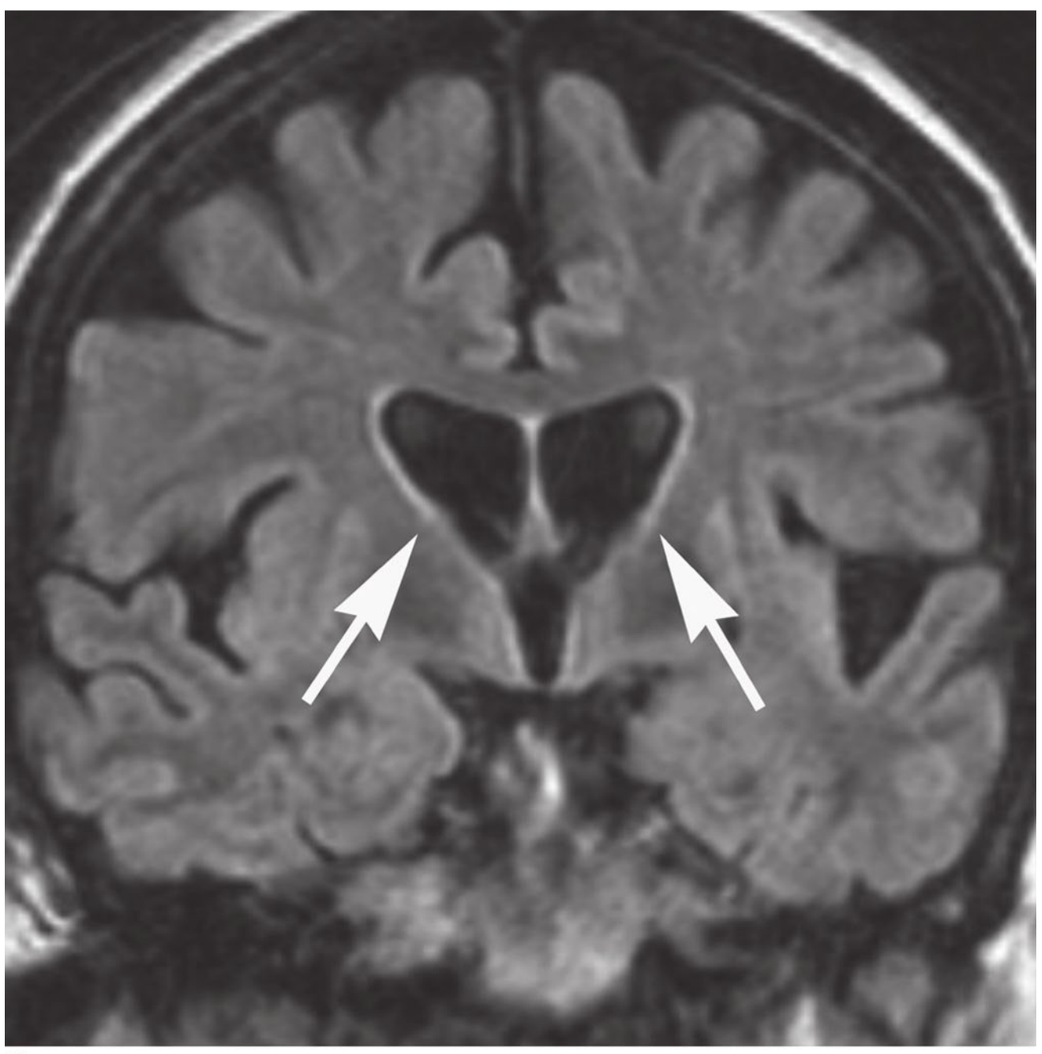
FIGURE 5-21
Multiple system atrophy (Chap. 36). Axial T2-weighted MRI (A) reveals symmetric poorly circumscribed abnormal high signal in the middle cerebellar peduncles bilaterally (arrowheads). Sagittal T1-weighted MRI (B) demonstrates pontine atrophy and enlarged cerebellar fissures as a result of cerebellar atrophy (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

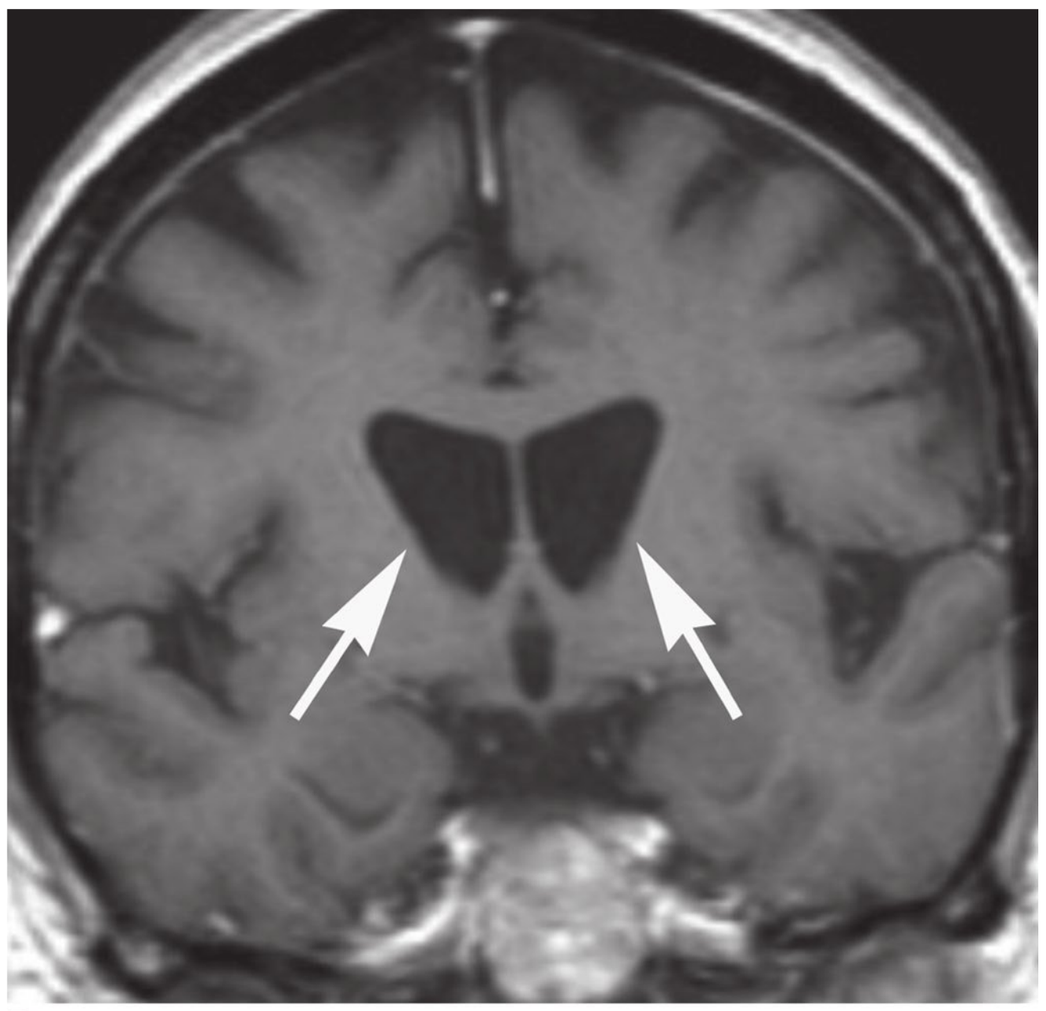
A



B



C

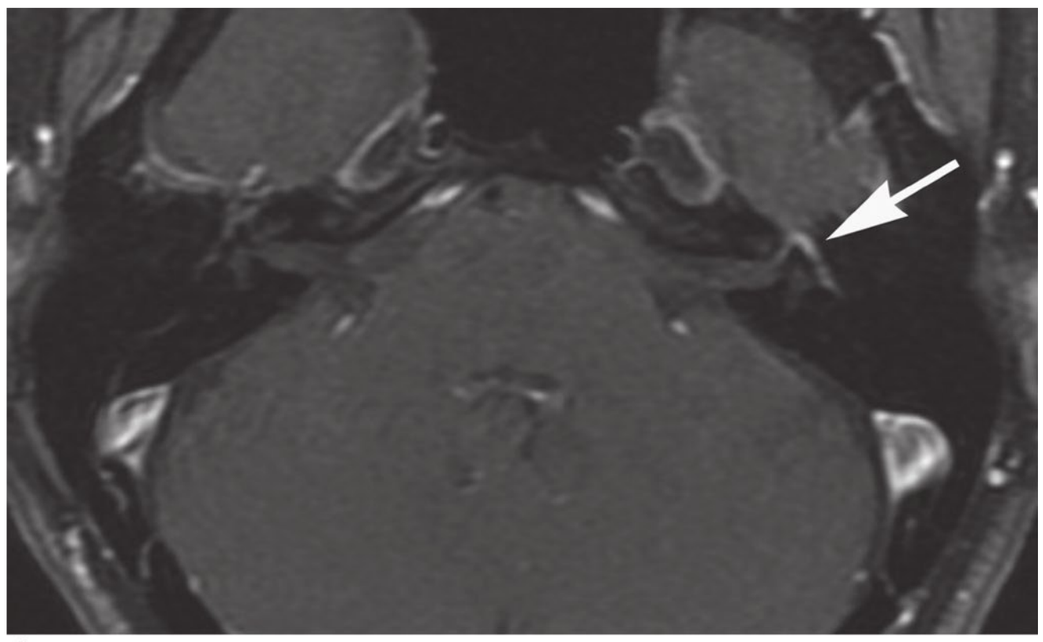


D

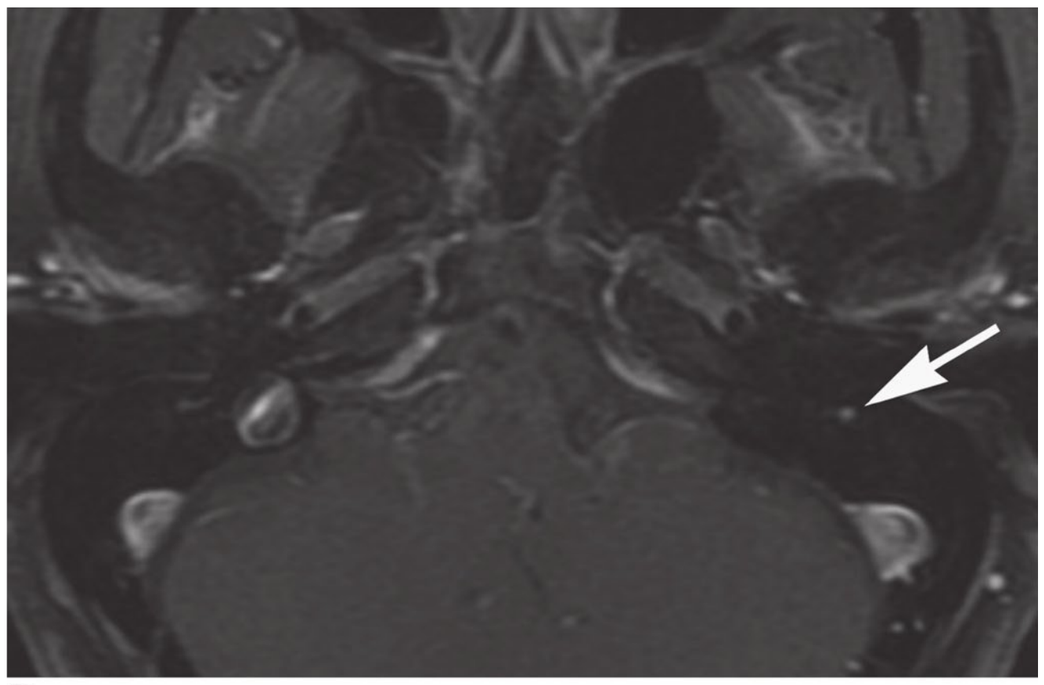
FIGURE 5-22

Huntington's disease (Chap. 36). Axial noncontrast CT (A) demonstrates symmetric bilateral severe atrophy involving the caudate nuclei, putamen, and globus pallidi bilaterally with consequent enlargement of the frontal horns of the lateral ventricles (arrows). There is also diffuse prominence of the sulci indicating generalized cortical atrophy. Axial (B) and coronal (C) FLAIR images demonstrate bilateral symmetric abnormal high signal in the caudate and putamen. Coronal T1-weighted image (D) demonstrates enlarged frontal horns with abnormal configuration. Also note diffusely decreased marrow signal, which could represent anemia or myeloproliferative disease.

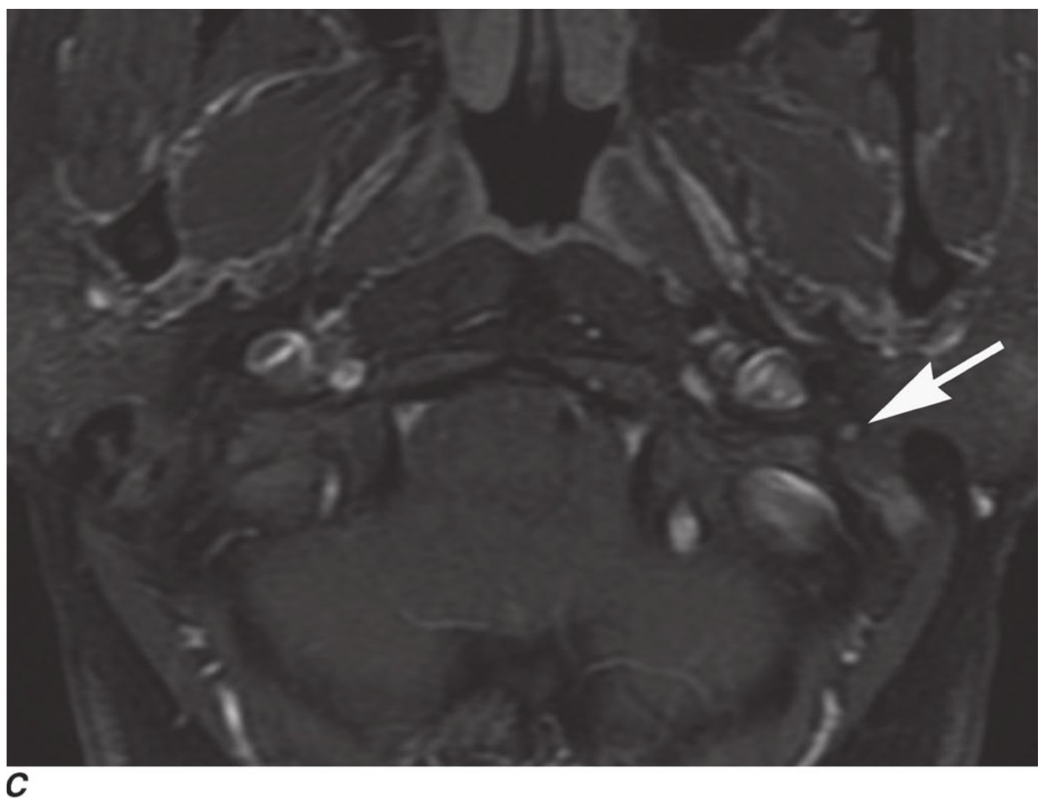
www.ketabpezeshki.com (021) 66485457 - 66485438



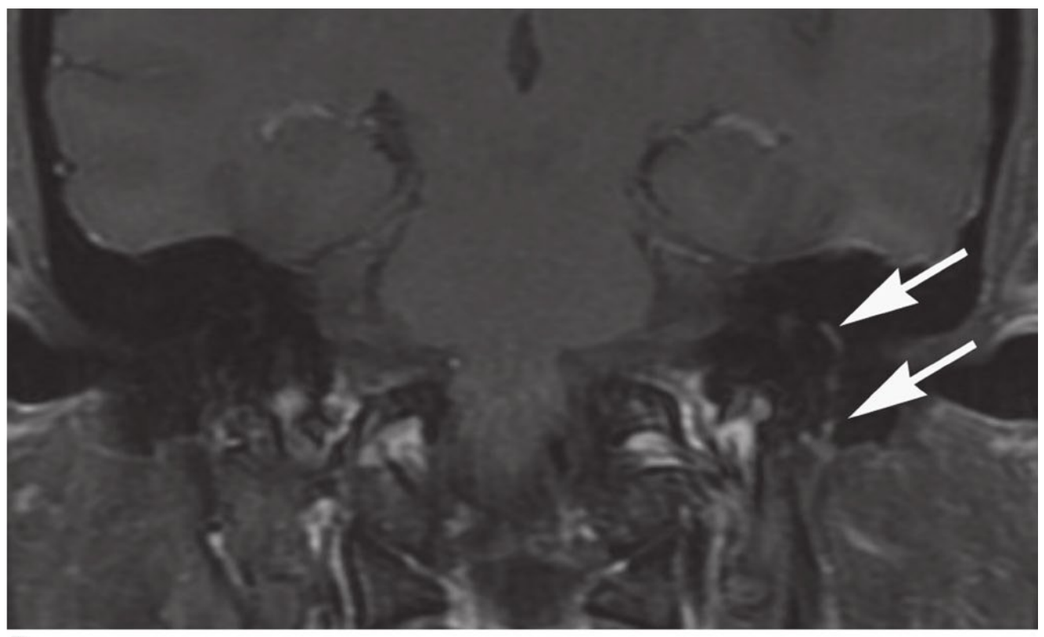
A



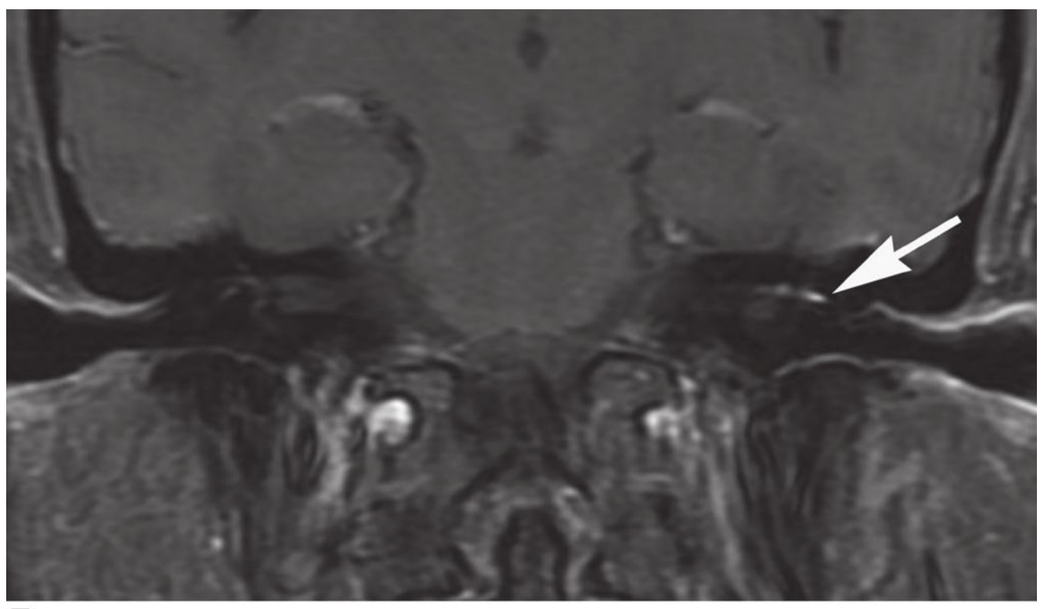
B



C



D



E

FIGURE 5-23

Bell's palsy (Chap. 42). Axial T1-weighted images postgadolinium with fat suppression (A–C) demonstrate diffuse smooth linear enhancement along the left facial nerve, involving the second and third segments (genu, tympanic, and mastoid) within the temporal bone (arrows). Note that there is no evidence of a mass lesion. A potential pitfall for facial nerve enhancement in the stylomastoid foramen is the enhancement of the stylomastoid artery that enters the foramen and supplies the tympanic cavity, the tympanic antrum, mastoid cells, and the semicircular canals. Coronal T1-weighted images postgadolinium with fat suppression (D, E) demonstrate the course of the enhancing facial nerve (arrows). Although these findings are highly suggestive of Bell's palsy, the diagnosis is established on clinical grounds.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 5-24

Spinal cord infarction (Chap. 43). Sagittal T2-weighted MRI of the lumbar spine (A) demonstrates poorly defined areas of abnormal high signal in the conus medullaris and mild cord expansion (arrow). T1-weighted MRI of the lumbar spine postgadolinium (B) demonstrates mild enhancement (arrow). Sagittal diffusion-weighted MRI of the lumbar spine (C) demonstrates restricted diffusion (arrow) in the areas of abnormal high signal on the T2-weighted image (A).

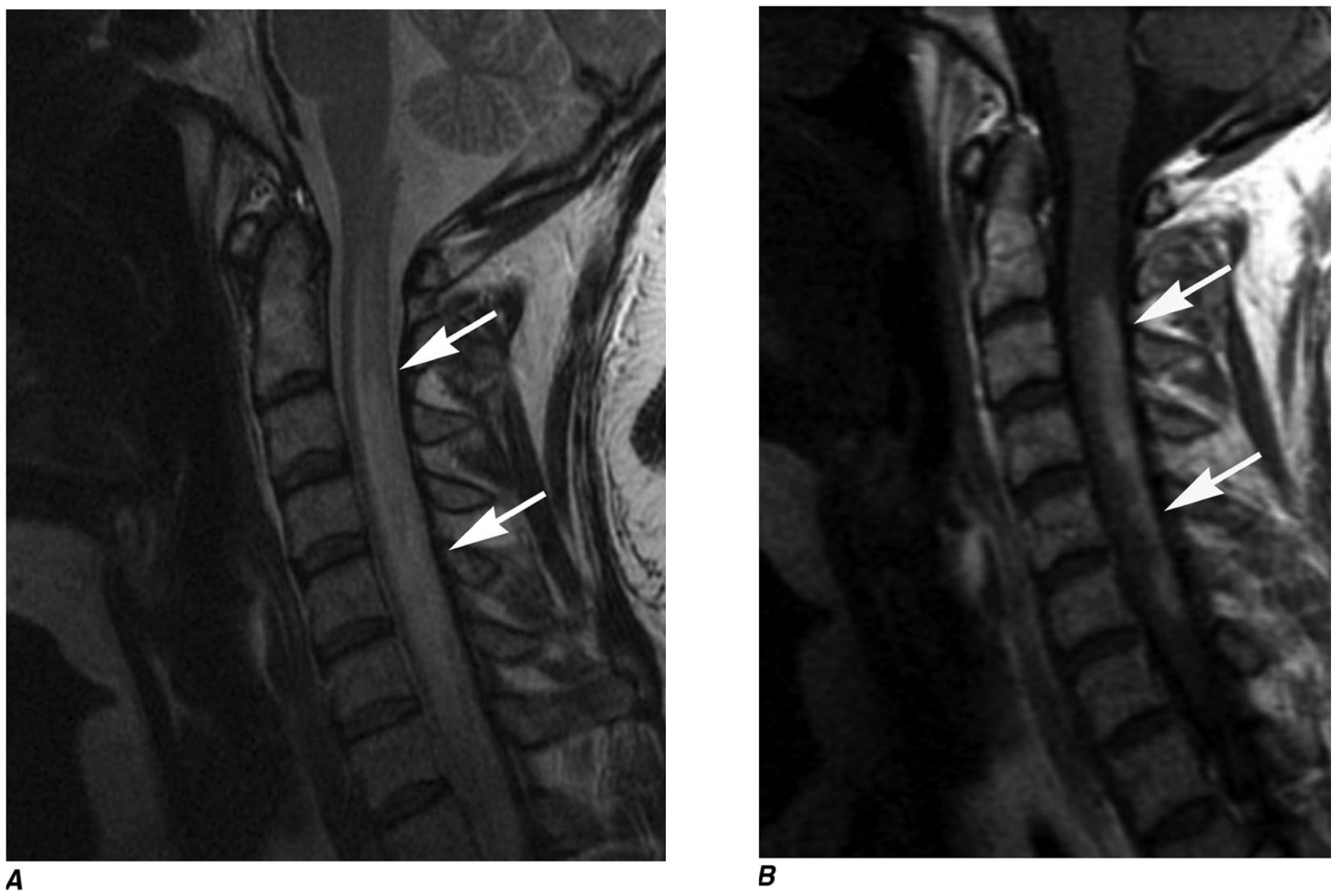
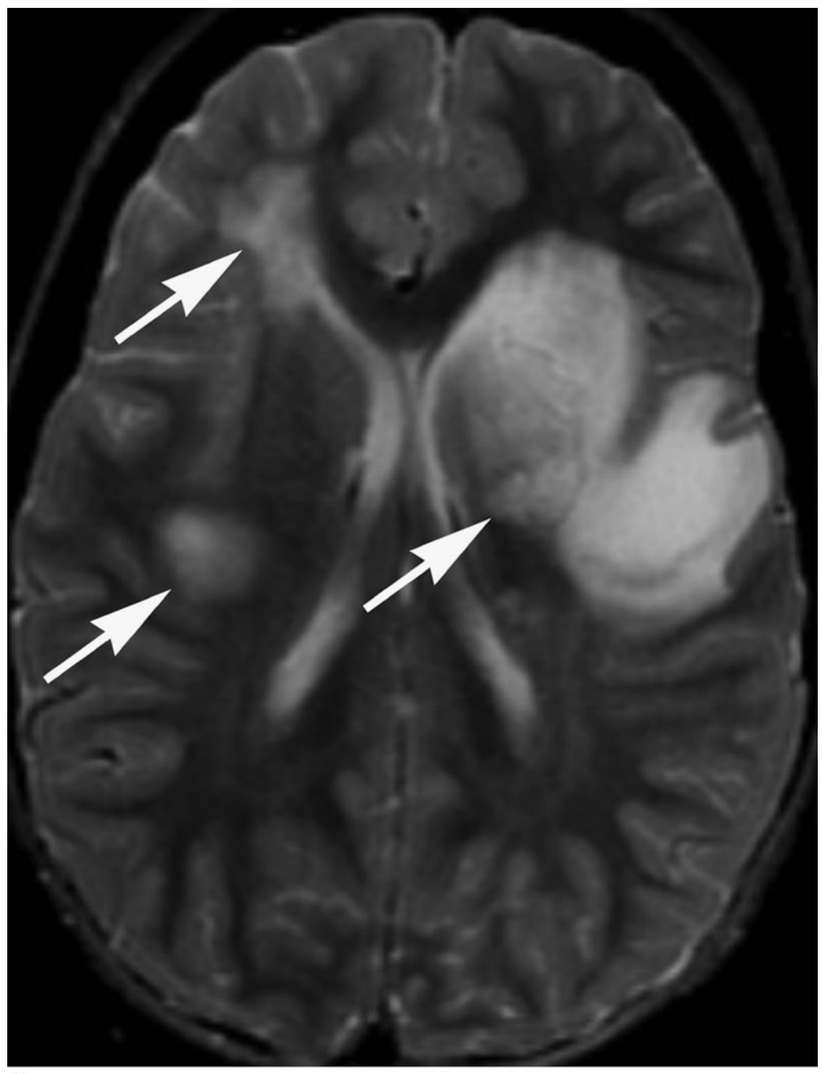


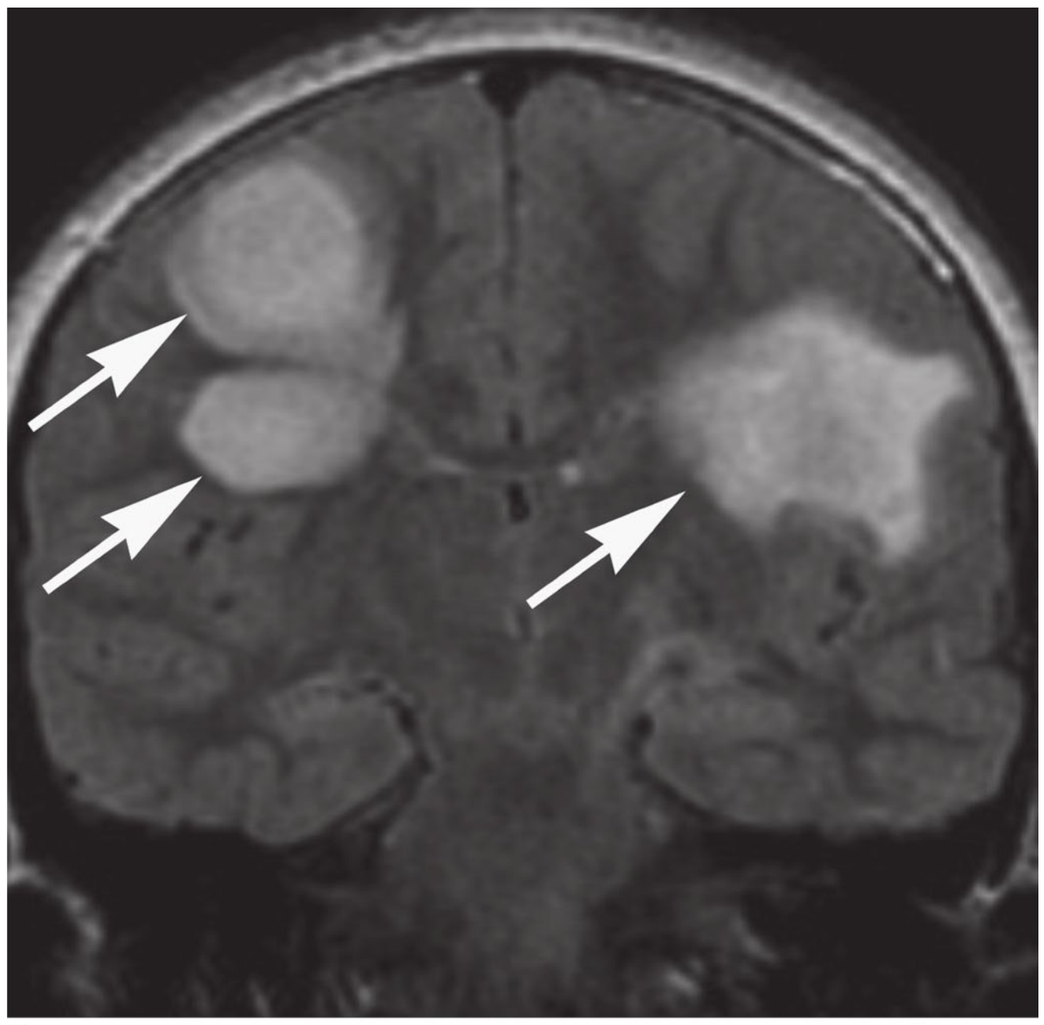
FIGURE 5-25

Acute transverse myelitis (Chap. 43). Sagittal T2-weighted MRI (A) demonstrates abnormal high signal in the cervical cord extending from C1 to T1 with associated cord expansion (arrows). Sagittal T1-weighted MRI postgadolinium (B) demonstrates abnormal enhancement in the posterior half of the cord from C2 to T1 (arrows).

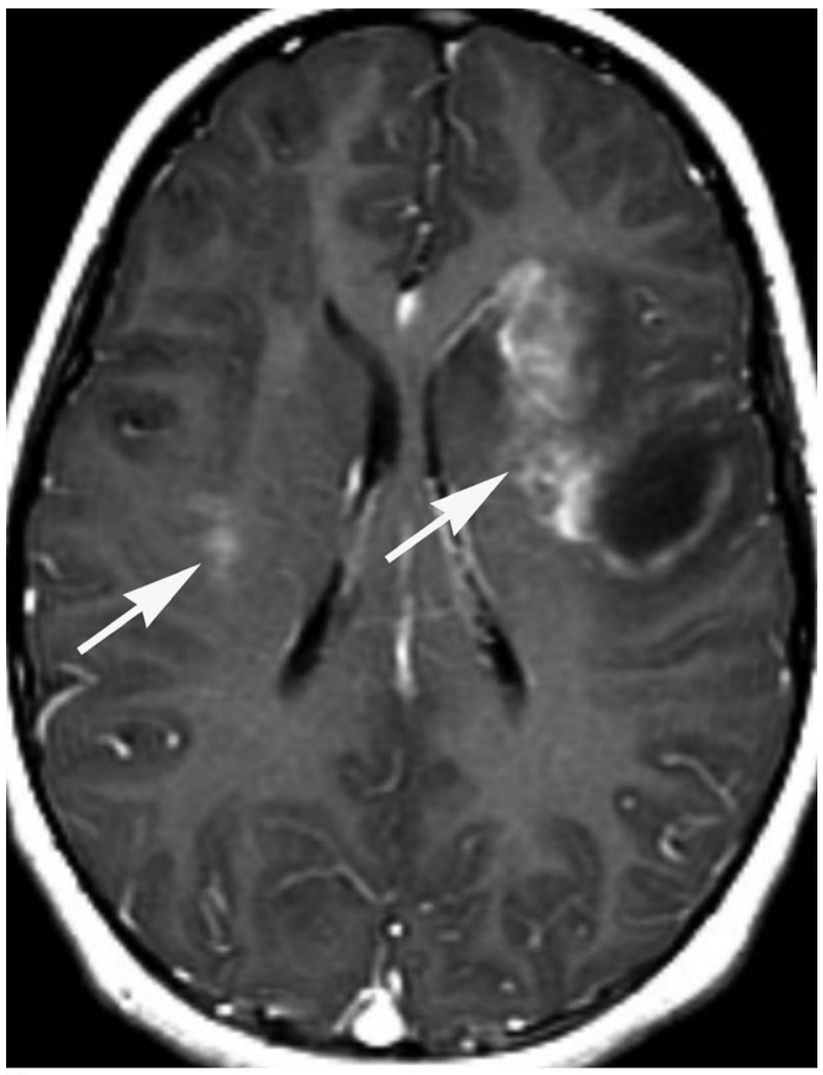
www.ketabpezeshki.com (021) 66485457 - 66485438



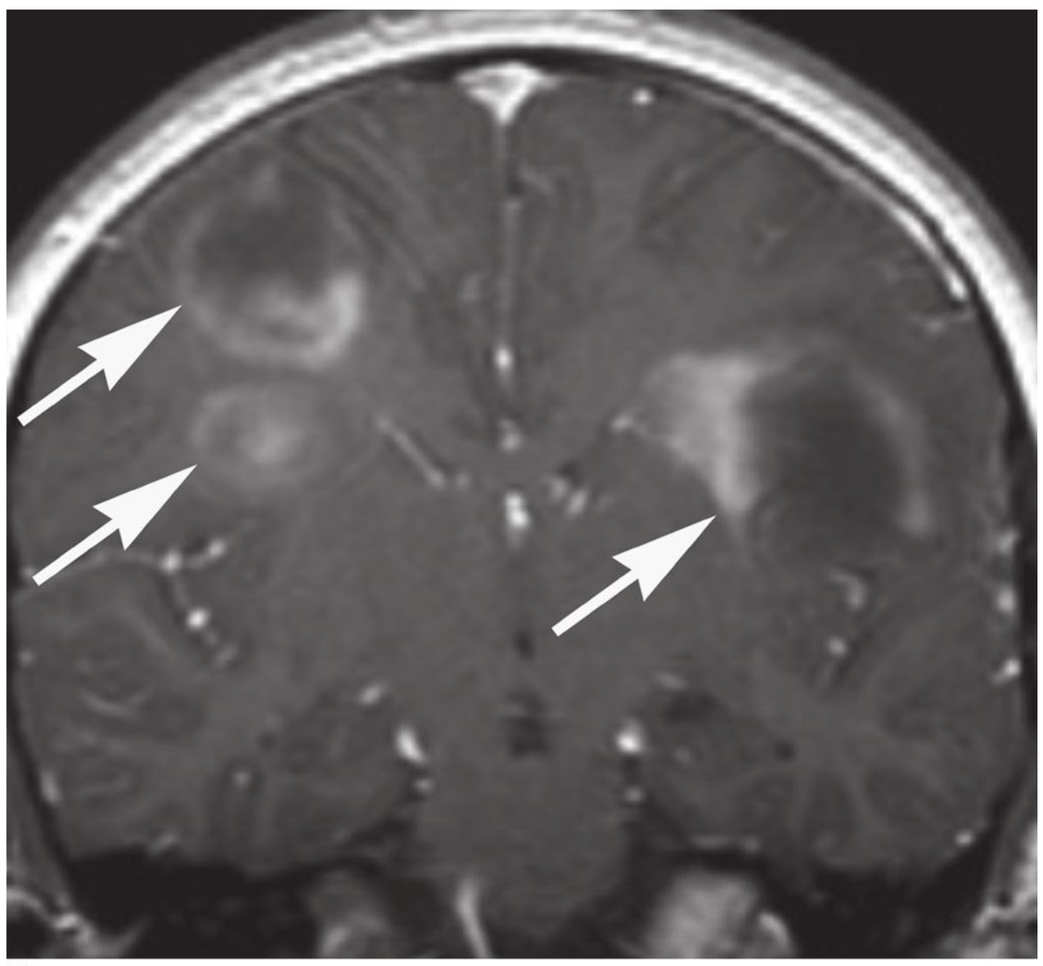
A



B



C

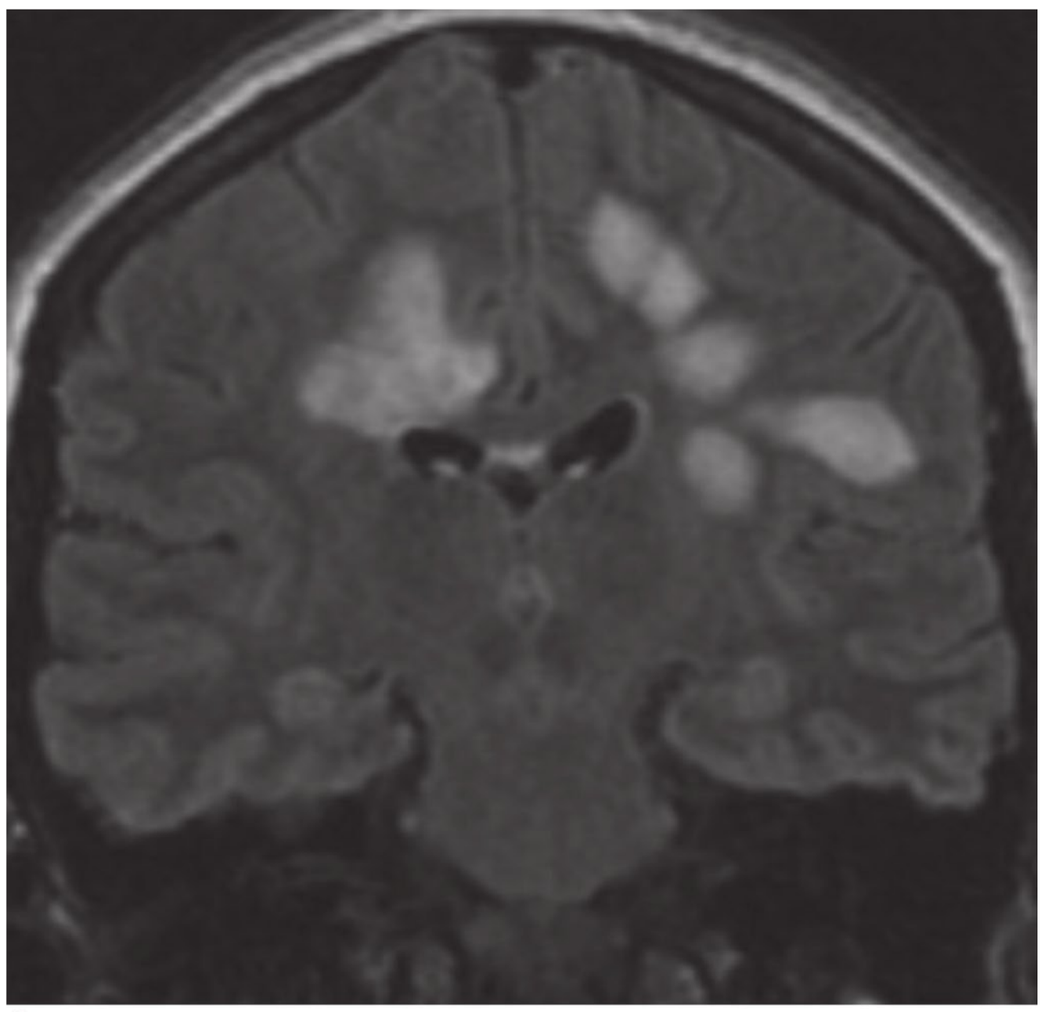


D

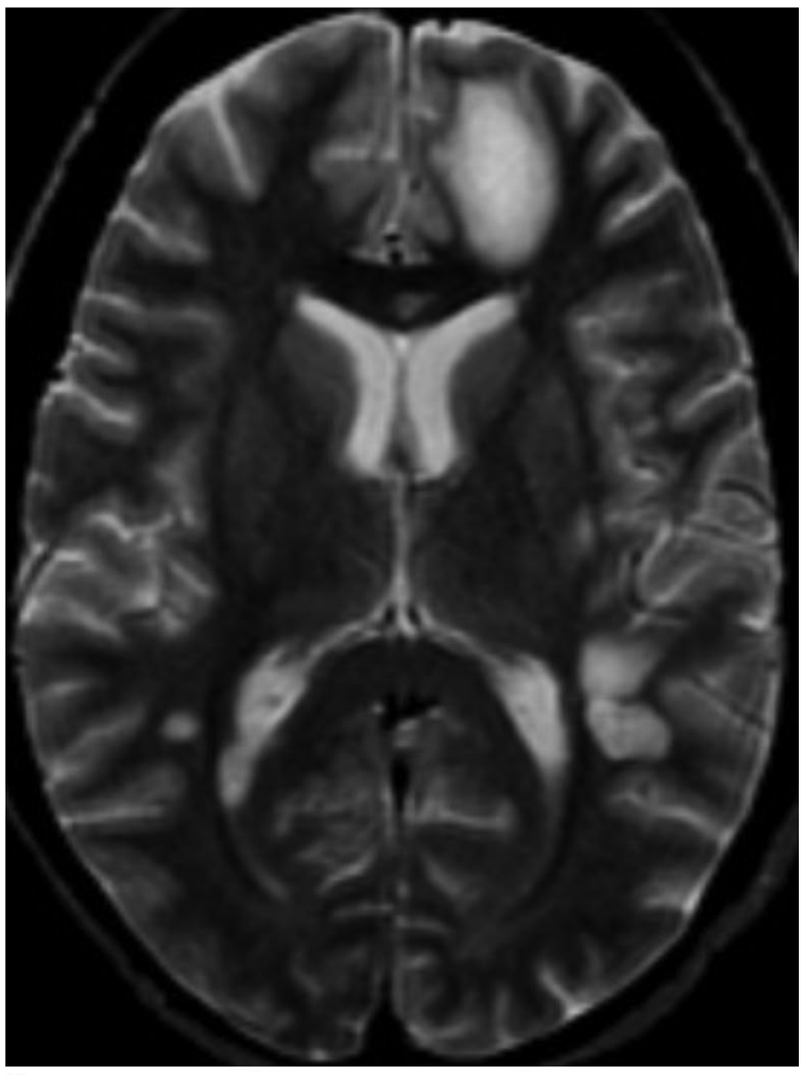
FIGURE 5-26

Acute disseminated encephalomyelitis (ADEM) (Chap. 45). Axial T2-weighted (A) and coronal FLAIR (B) images demonstrate abnormal areas of high signal involving predominantly the subcortical white matter of the frontal lobe bilaterally and left caudate head. Following administration of gadolinium, corresponding axial (C) and coronal (D) T1-weighted images demonstrate irregular enhancement consistent with blood-brain barrier breakdown and inflammation; some lesions show incomplete rim enhancement, typical for demyelination.

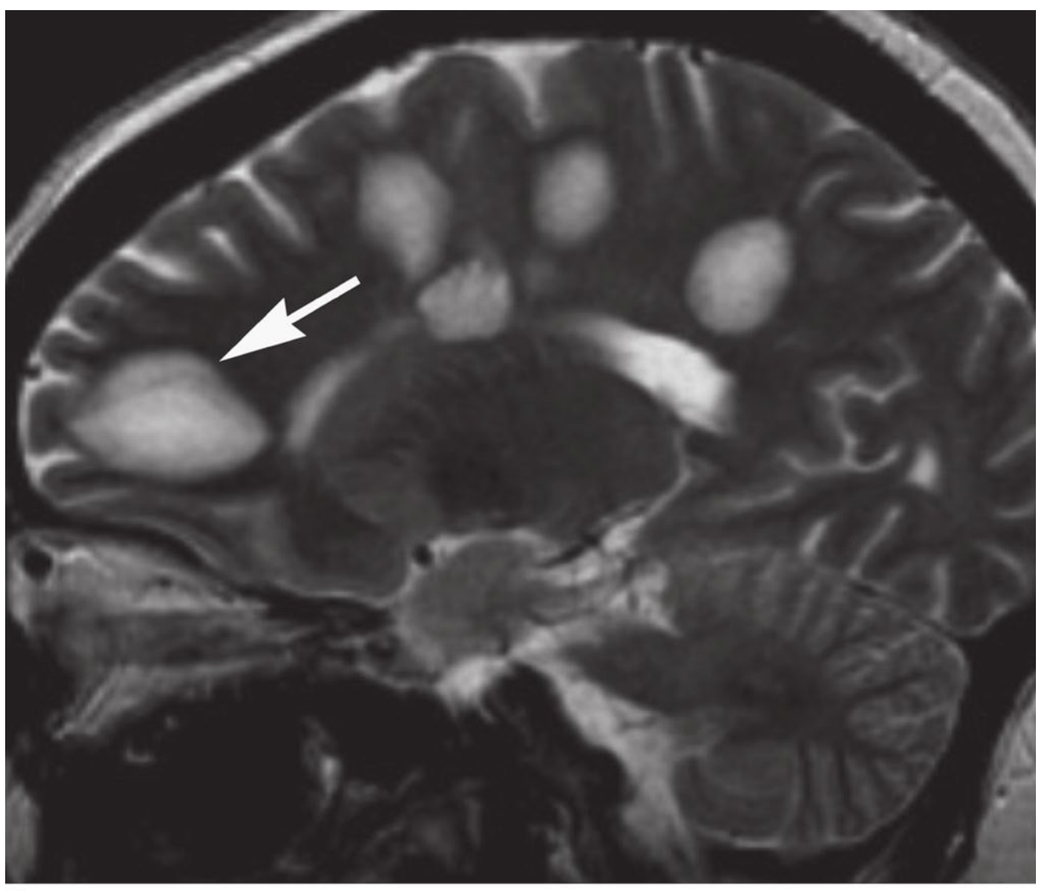
www.ketabpezeshki.com (021) 66485457 - 66485438



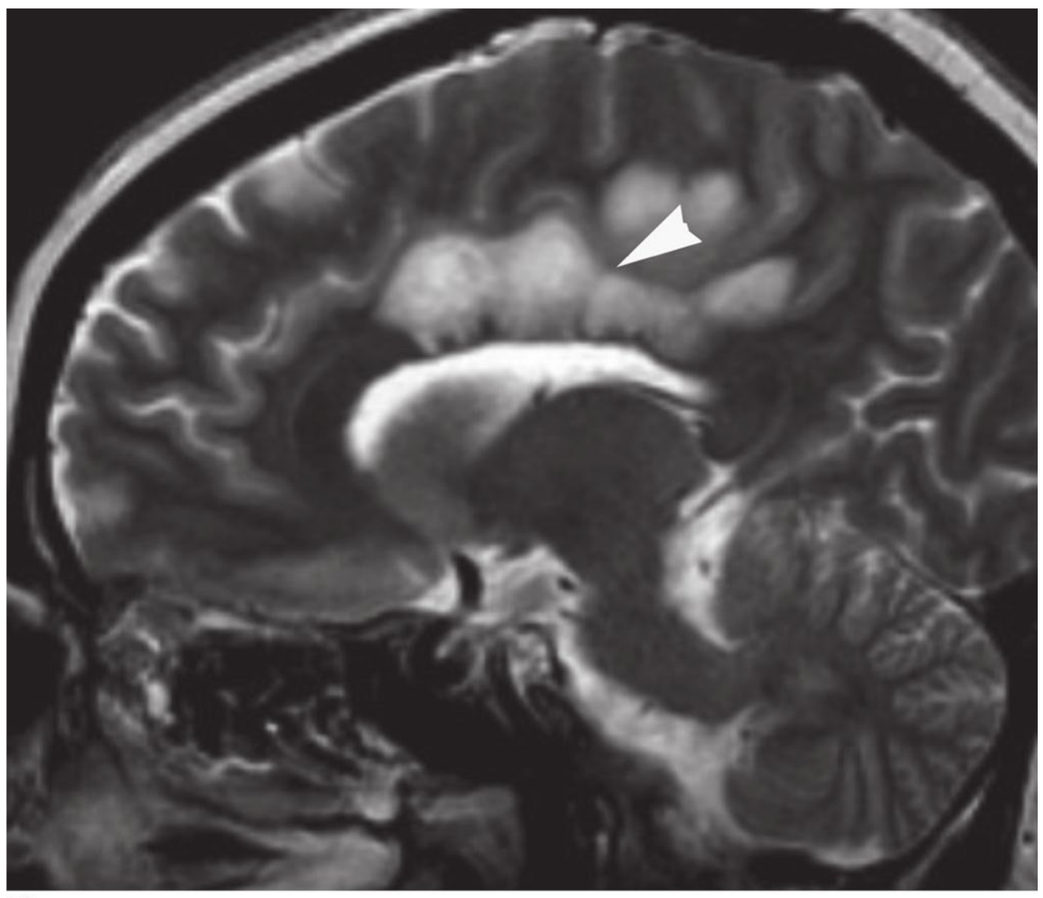
A



B



C

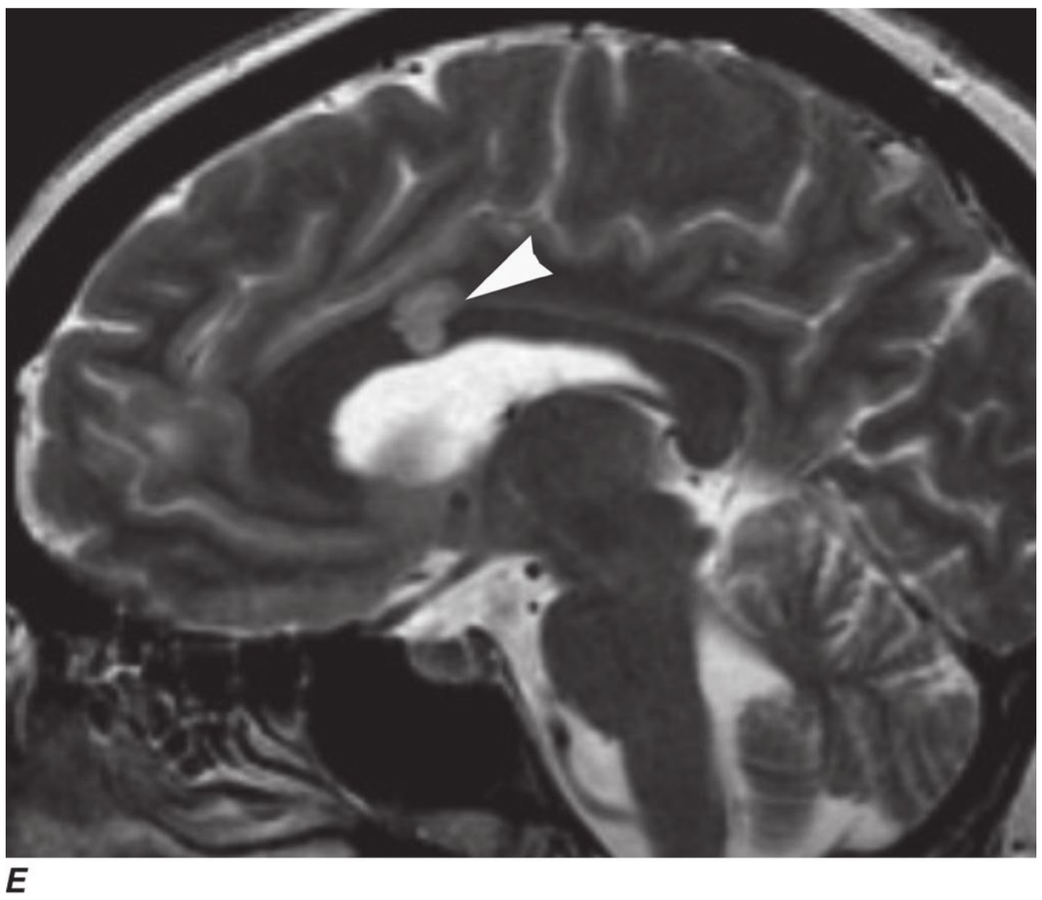


D

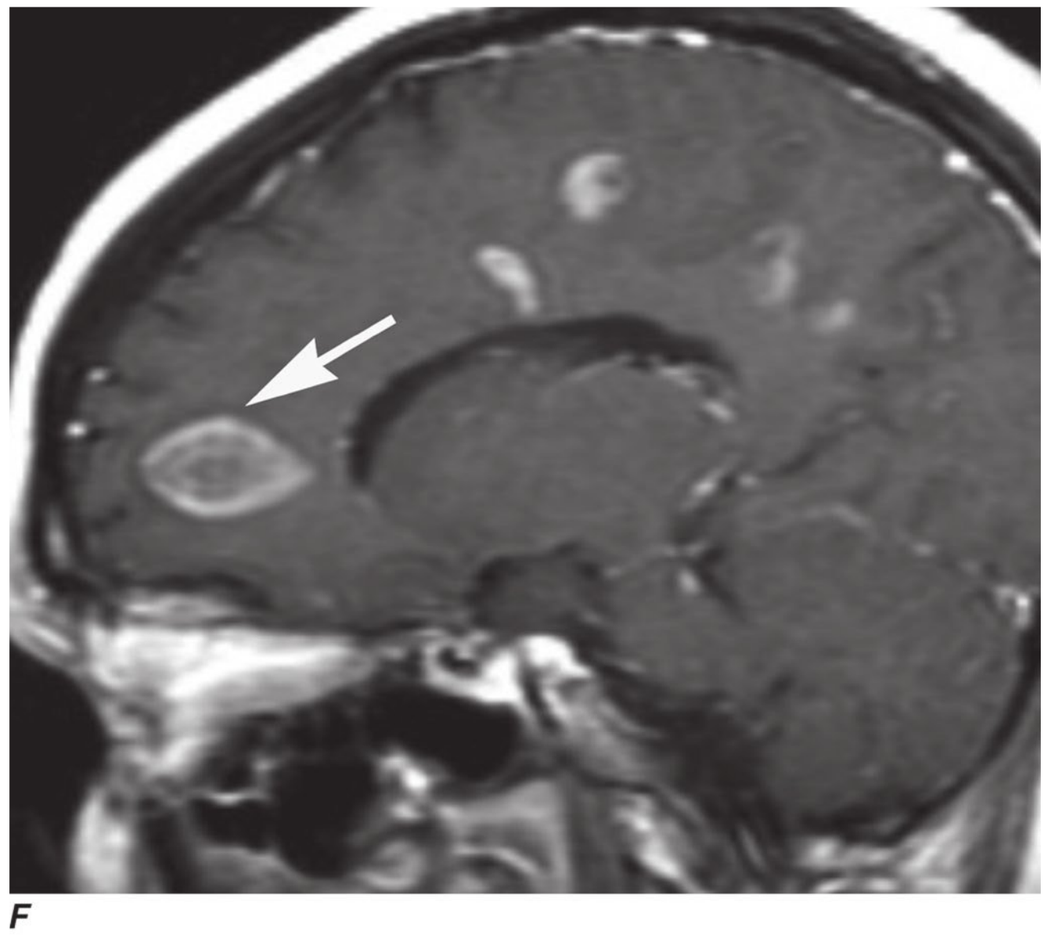
FIGURE 5-27

Baló's concentric sclerosis (a variant of multiple sclerosis) (Chap. 45). Coronal FLAIR MRI (A) demonstrates multiple areas of abnormal high signal in the supratentorial white matter bilaterally. The lesions are ovoid in shape, perpendicular to the orientation of the lateral ventricles, and with little mass effect. Axial (B) and sagittal (C–E) T2-weighted MRIs demonstrate multiple areas of abnormal high signal in the supratentorial white matter bilaterally, as well as the involvement of the body and splenium of the corpus callosum and the callosal-septal interface (arrowhead). Some of the lesions reveal concentric layers, typical of Baló's concentric sclerosis (arrows). Sagittal (F) and axial (G, H) T1-weighted MRIs postgadolinium demonstrate abnormal enhancement of all lesions with some of the lesions demonstrating concentric ring enhancement (arrows).

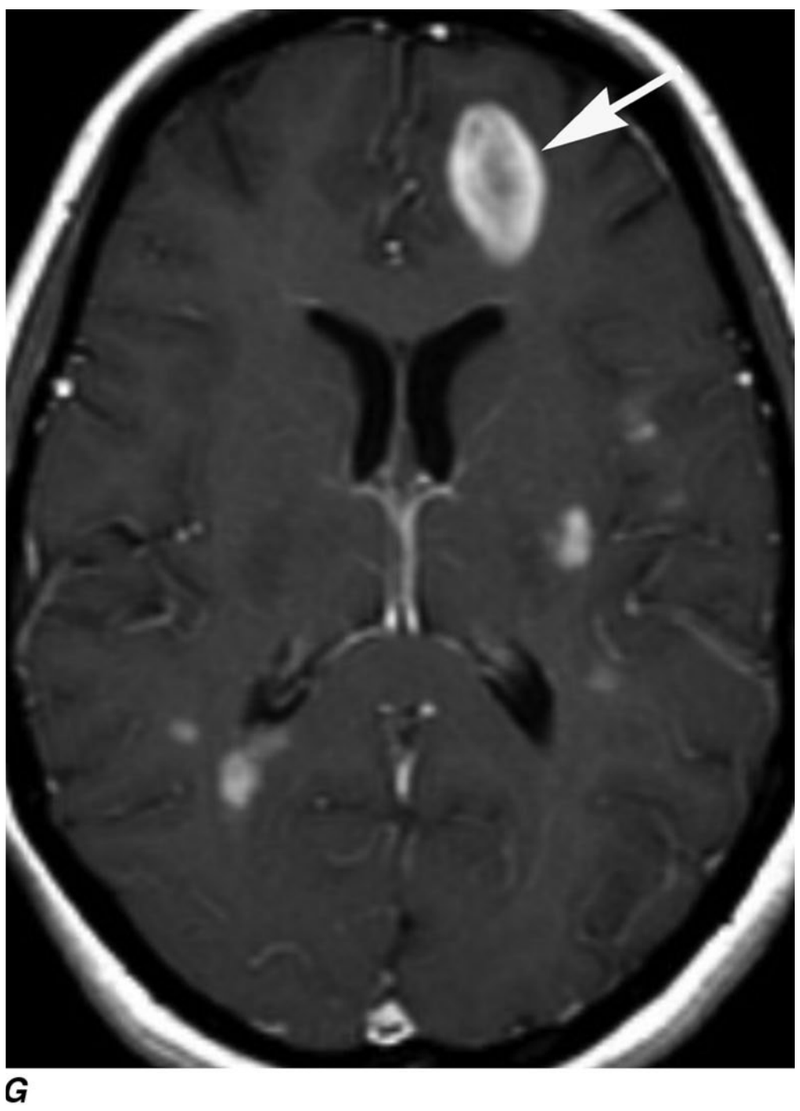
www.ketabpezeshki.com (021) 66485457 - 66485438



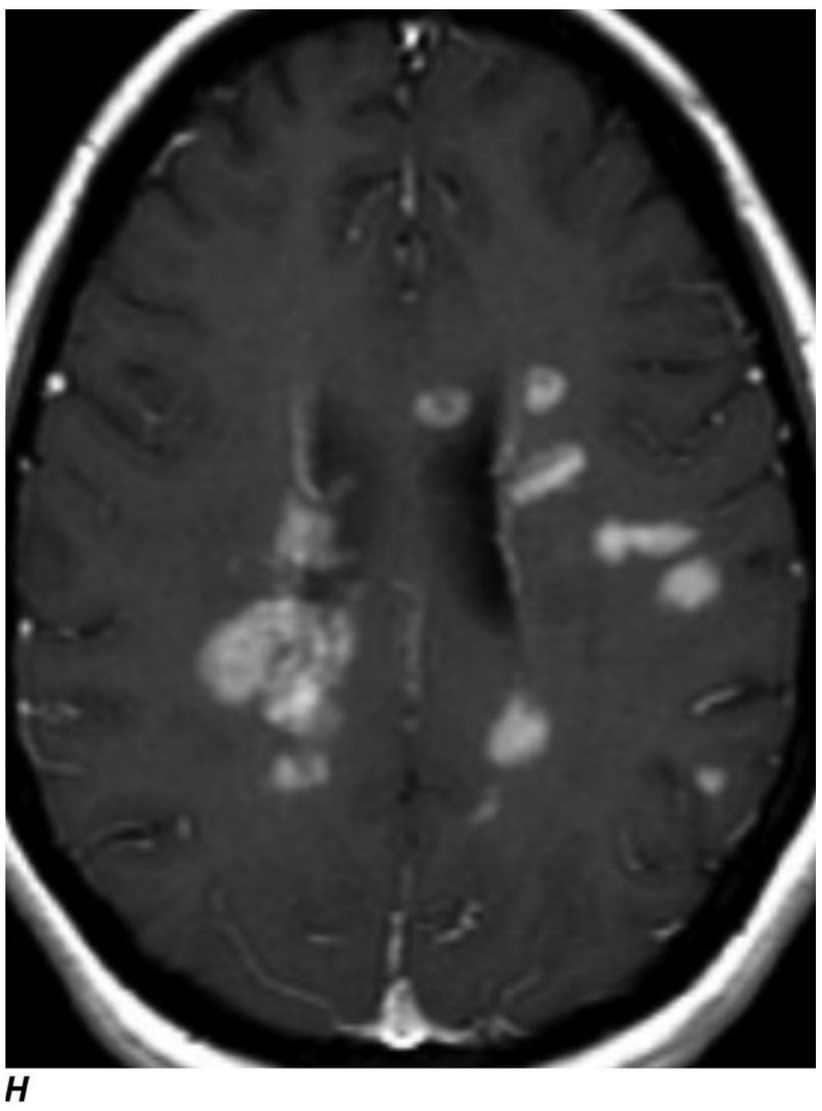
E



F



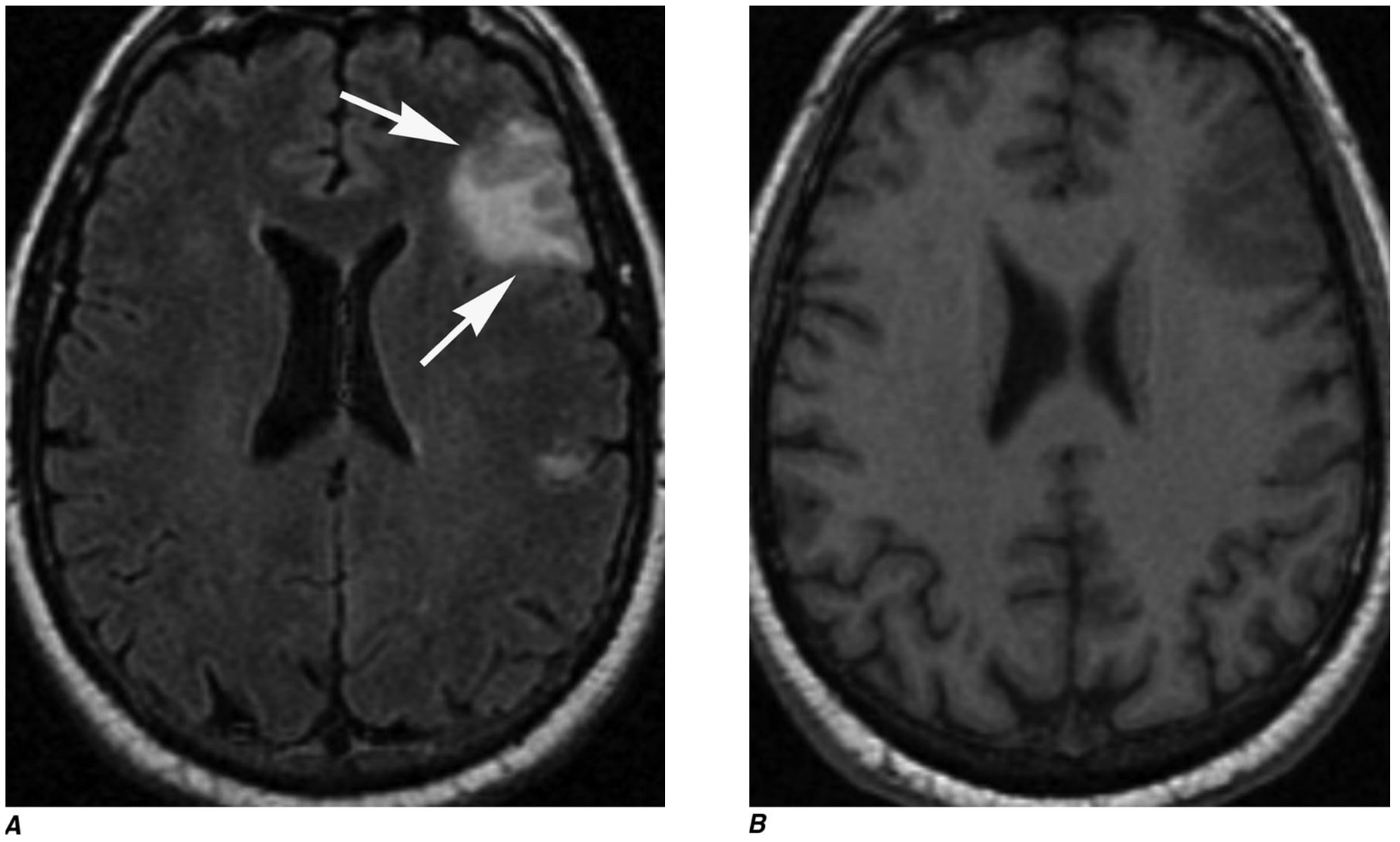
G



H

FIGURE 5-27
(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438



A

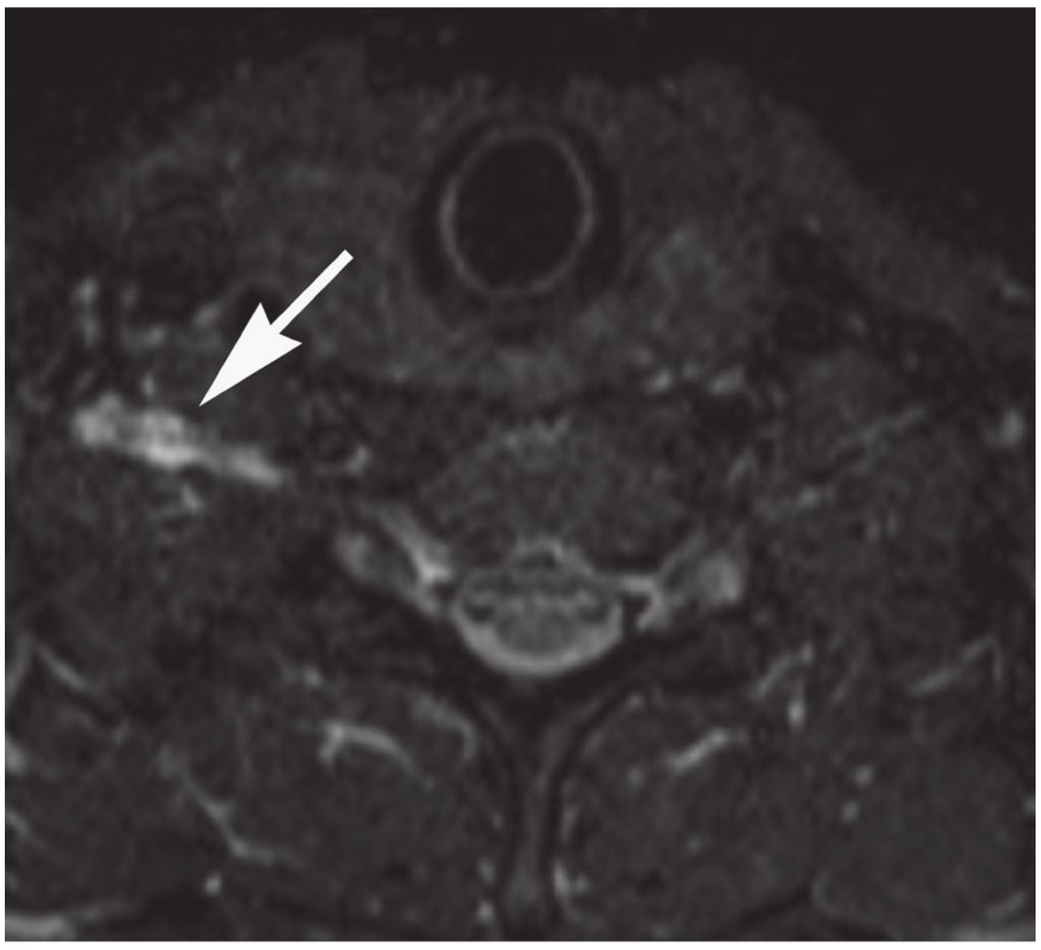
B

C

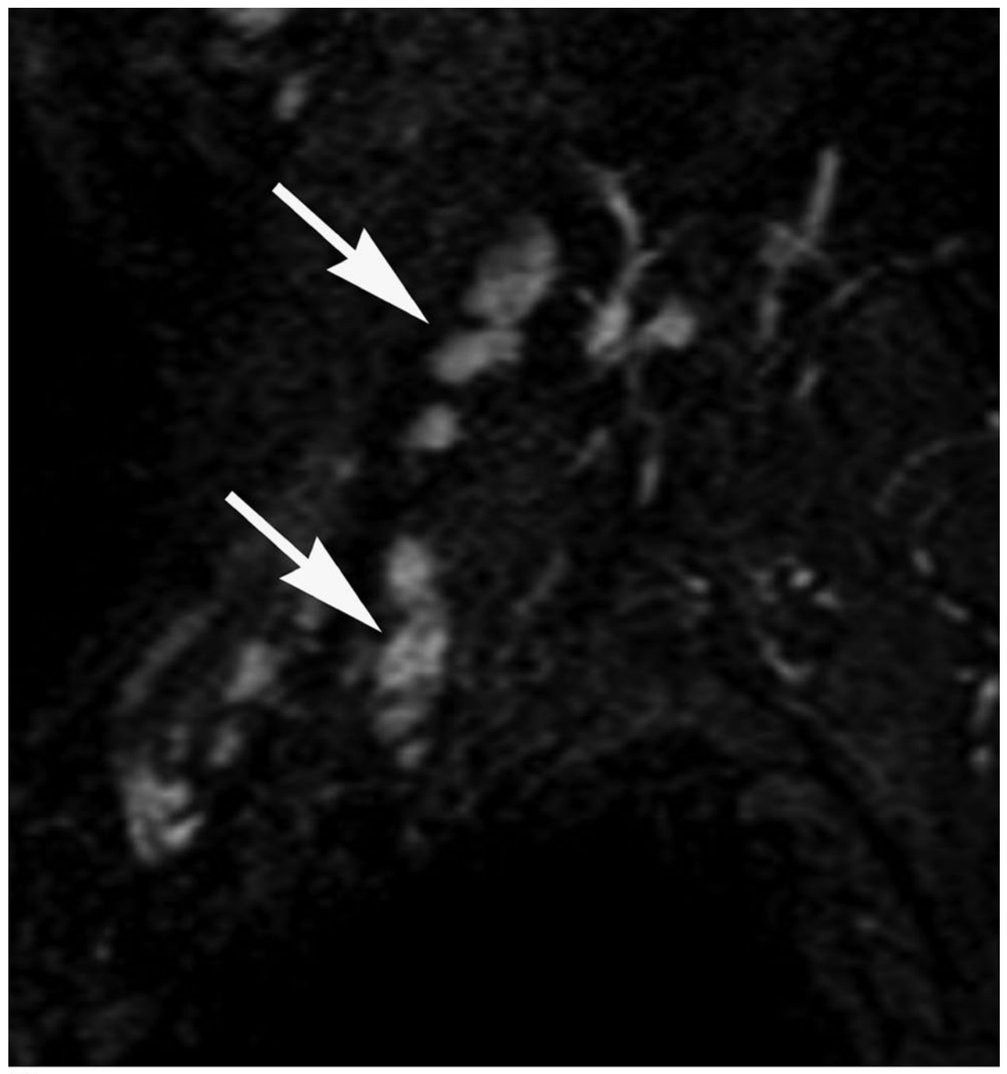
FIGURE 5-28

Hashimoto's encephalopathy (Chap. 46). Axial FLAIR (A) demonstrates focal area of abnormal high signal involving the gray and white matter in the left frontal lobe. There is also a small area of abnormal high signal in the precentral gyrus. Axial T1-weighted images (B, C) pre and postgadolinium demonstrate cortical/pial enhancement in the region of high signal on FLAIR.

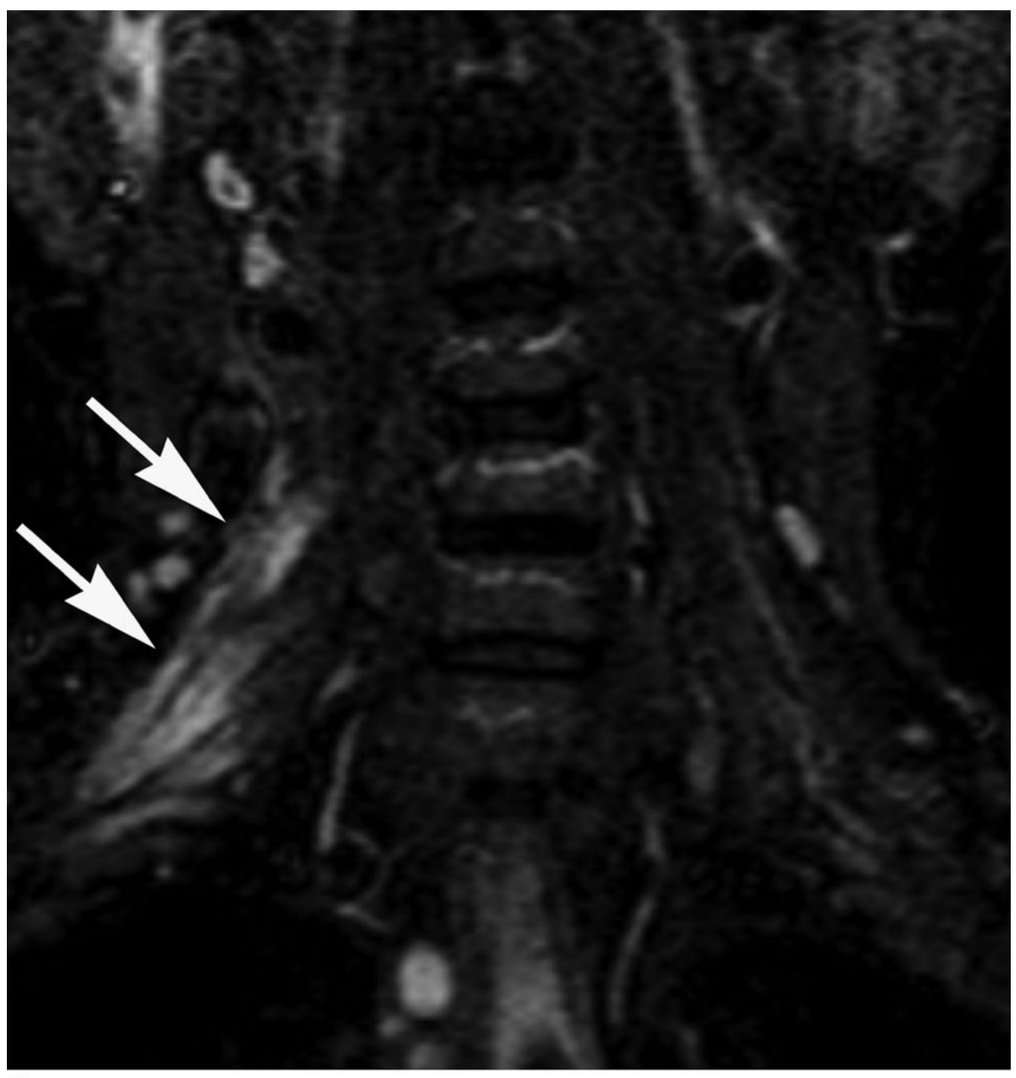
www.ketabpezeshki.com (021) 66485457 - 66485438



A



B



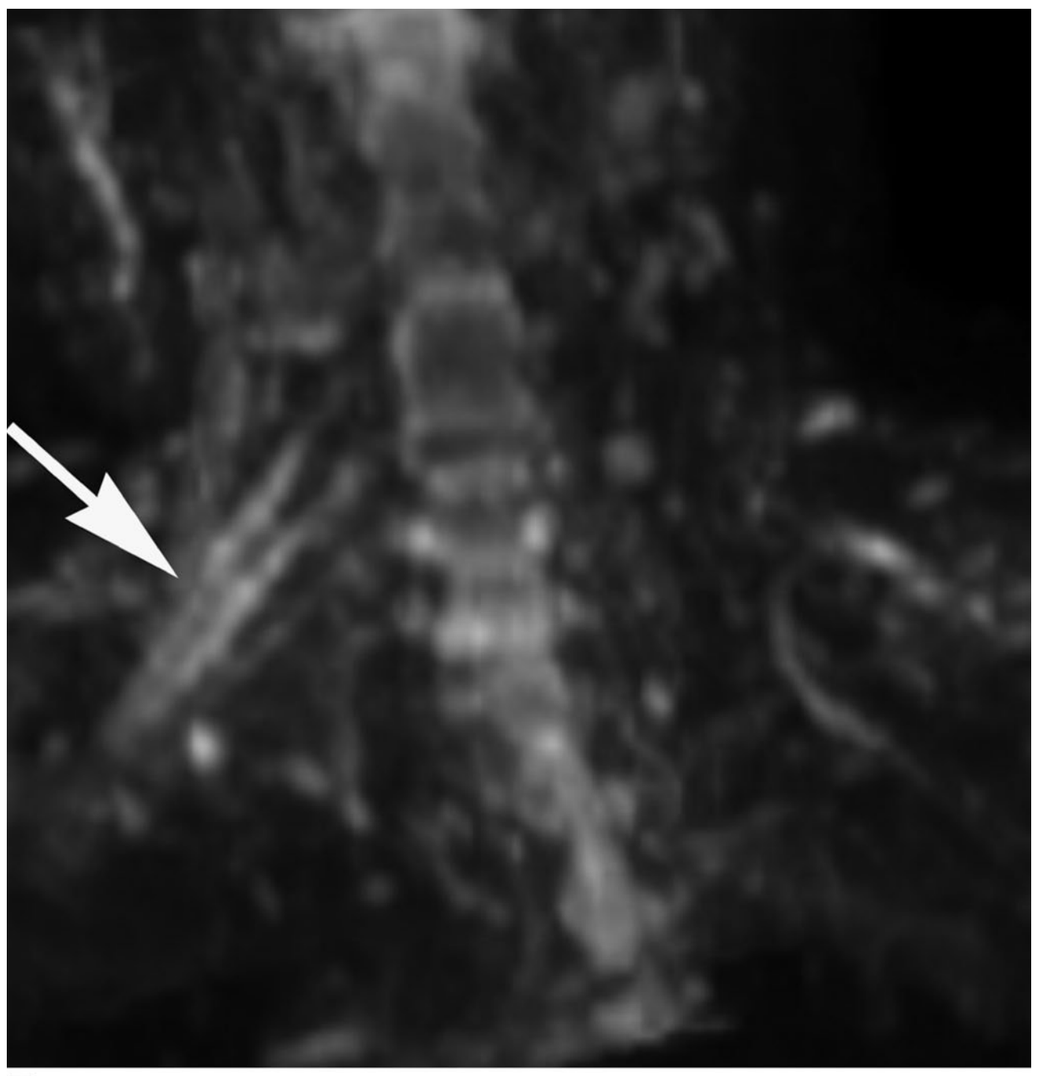
C

D

FIGURE 5-29

Brachial plexopathy (Chap. 53). Axial (A), sagittal (B), and coronal (C, D) short tau inversion recovery (STIR) MRIs demonstrate abnormal enlargement and abnormal high signal involving the right C6, C7, and C8 nerve roots, and the trunks and divisions that originate from these roots (arrows). Diffusion-weighted MRI (E) demonstrates abnormal reduced diffusion within the right C6, C7, and C8 nerve roots and their corresponding trunks and divisions (arrow). These findings are compatible with radiation-induced brachial plexopathy.

www.ketabpezeshki.com (021) 66485457 - 66485438



E

FIGURE 5-29
(continued)

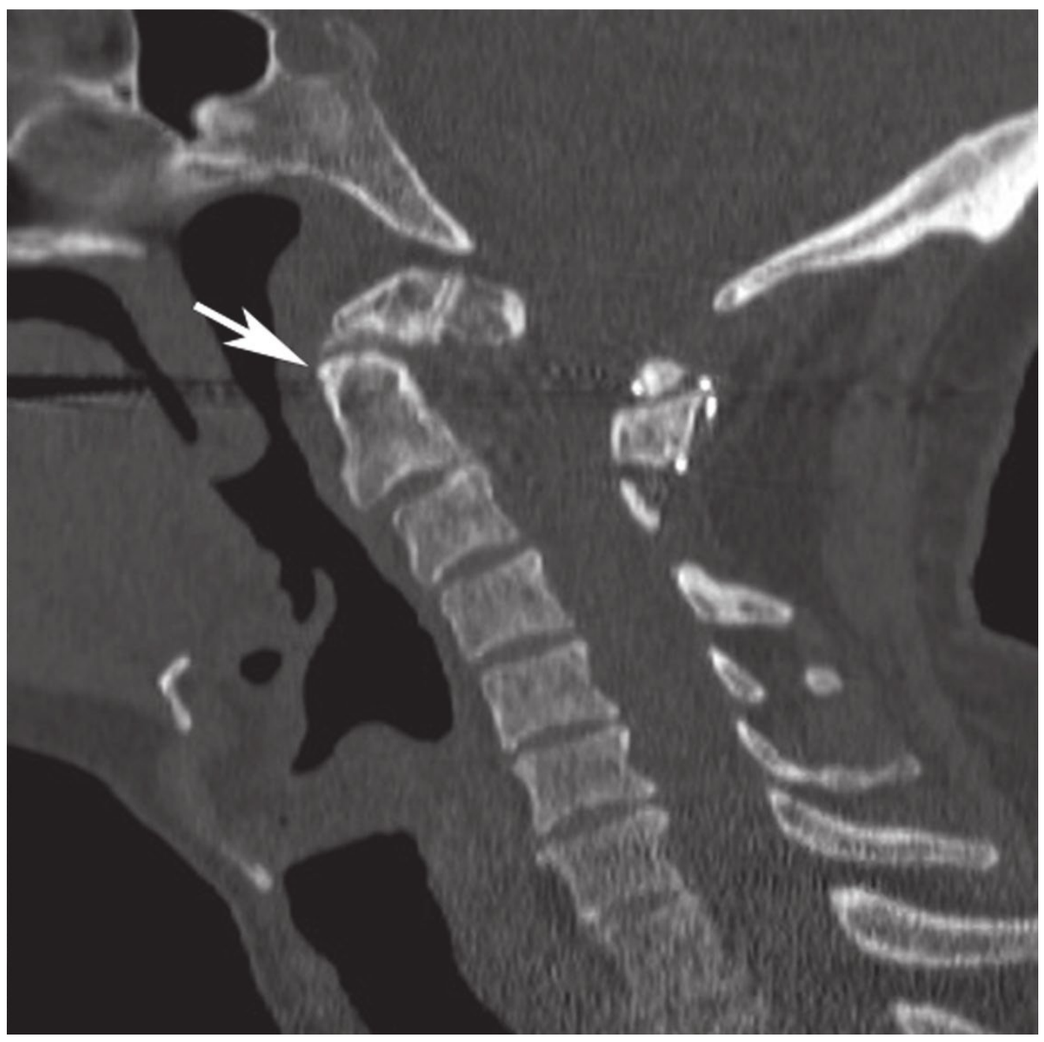


FIGURE 5-30
Anterior dens dislocation. Sagittal CT demonstrates the tip of the dens below the anterior arch of C2 (arrow), indicating anterior dislocation.

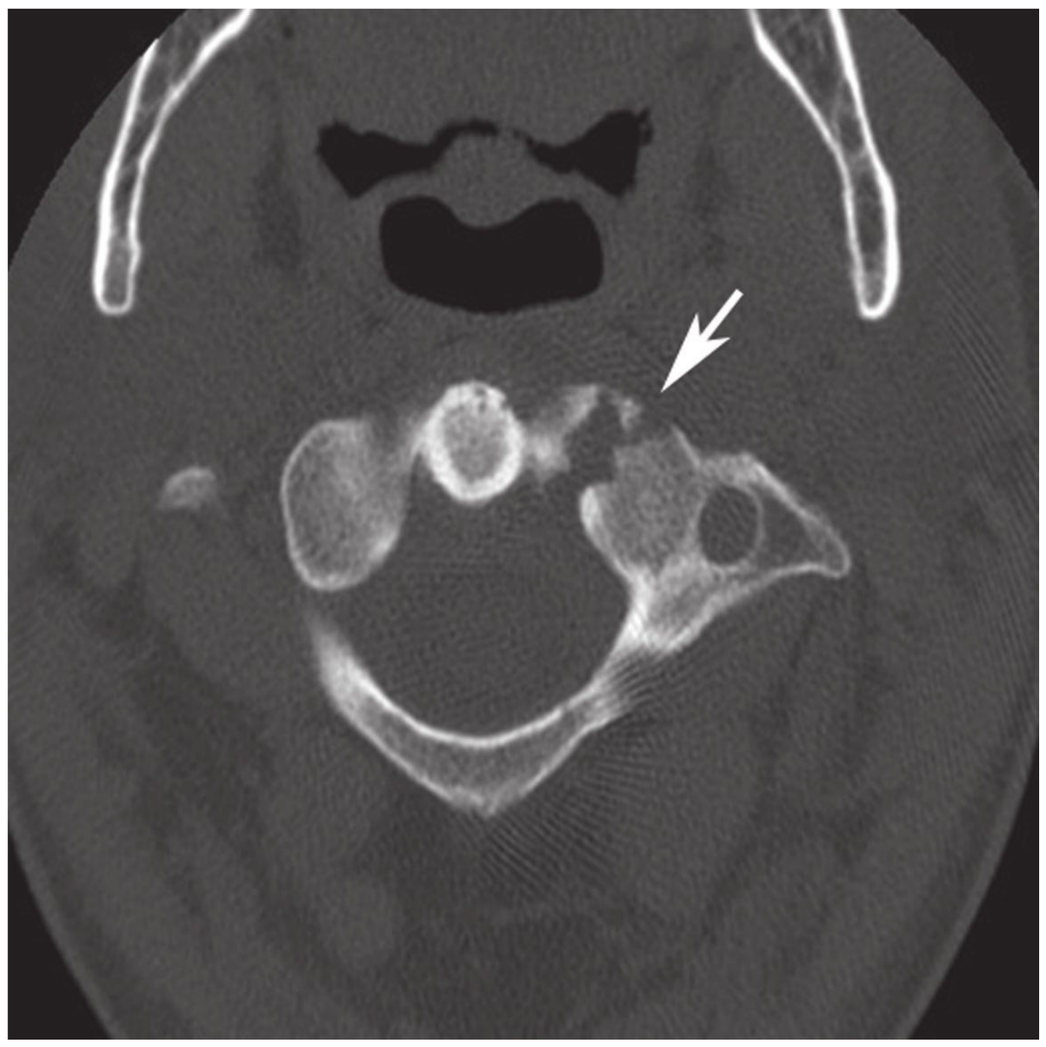


FIGURE 5-31
CT facet fracture. Axial CT demonstrates fracture line along the C2 facet (arrow).

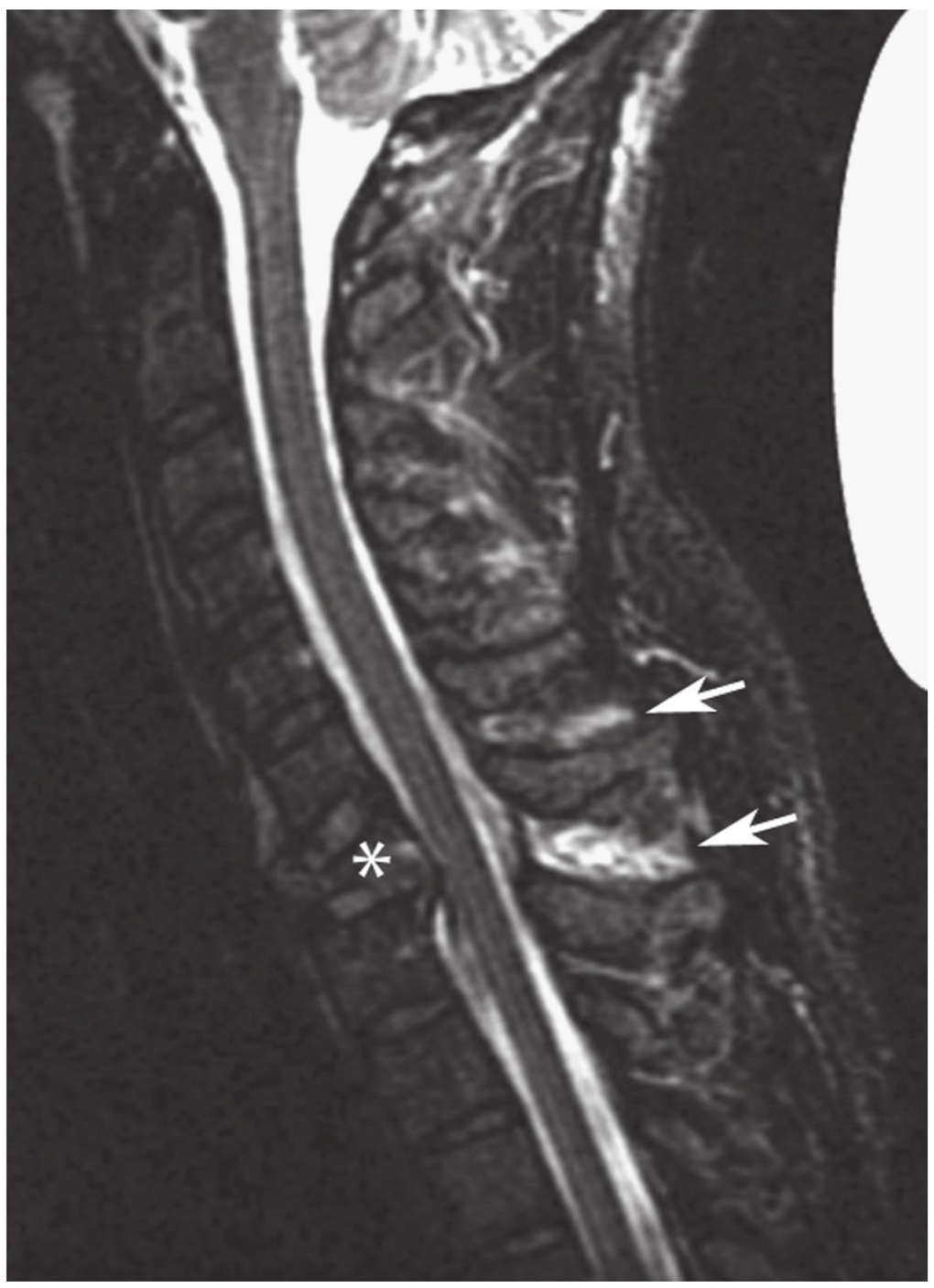
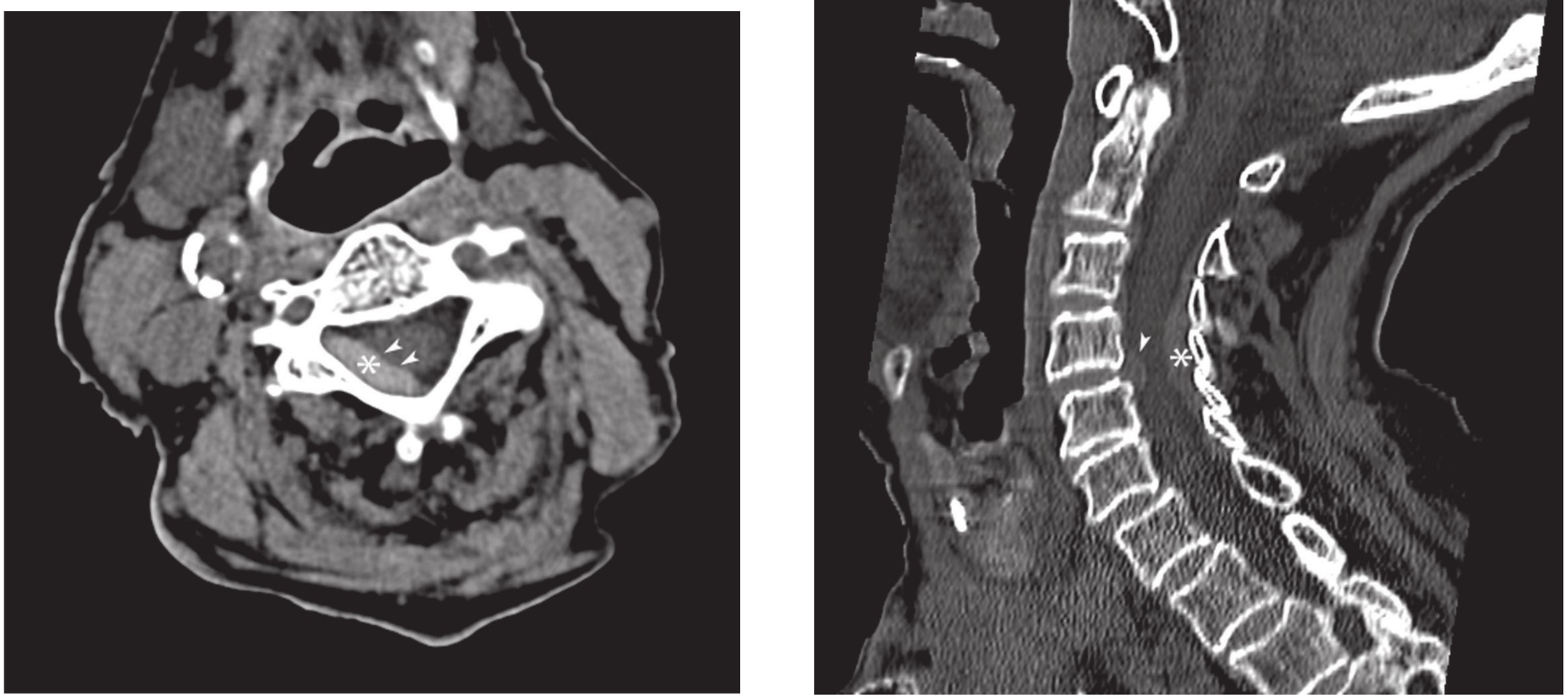


FIGURE 5-32
Compression fracture. Sagittal T2-weighted MRI demonstrates compression fracture of C7 (*) and high signal within the spinous processes of C6-C7 (arrows) and to lesser degree C5-C6. This is suggestive of interspinous ligament injury. Note the pad under the patient's neck to maintain neck alignment during the scanning time.

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 5-33
Epidural hematoma. Axial noncontrast CT (A) demonstrates a high-density epidural collection in the cervical spine (*), which is consistent with acute hemorrhage. Also noted is mass effect on the spinal cord (arrowheads). Sagittal reformatted CT image (B) demonstrates the extension of the acute epidural hematoma (*) and a disk bulge (arrowhead), which further contributes to spinal canal narrowing. CT is the imaging procedure of choice to detect acute hematoma.

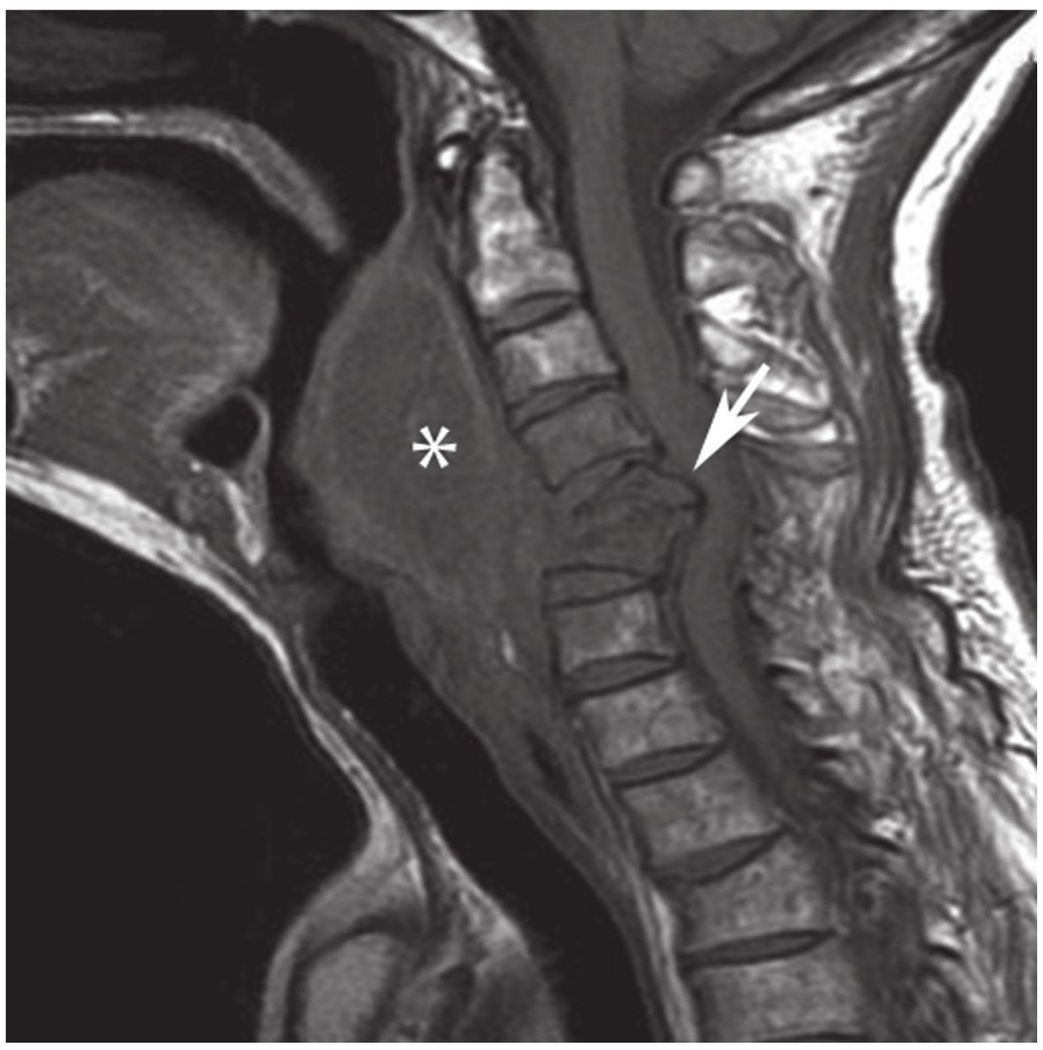


FIGURE 5-34
Retropharyngeal soft tissue mass. Sagittal T1-weighted MRI demonstrates a hyperflexion fracture with retropulsion of the posterior wall in the canal at C5 and C6 (arrow). There is also a large retropharyngeal hematoma (*). The distance from the posterior wall of the airway to the anterior wall of the vertebral body should not measure more than 6 mm at C2 or more than 20 mm at C6 (mnemonic "6 at 2 and 20 at 6").

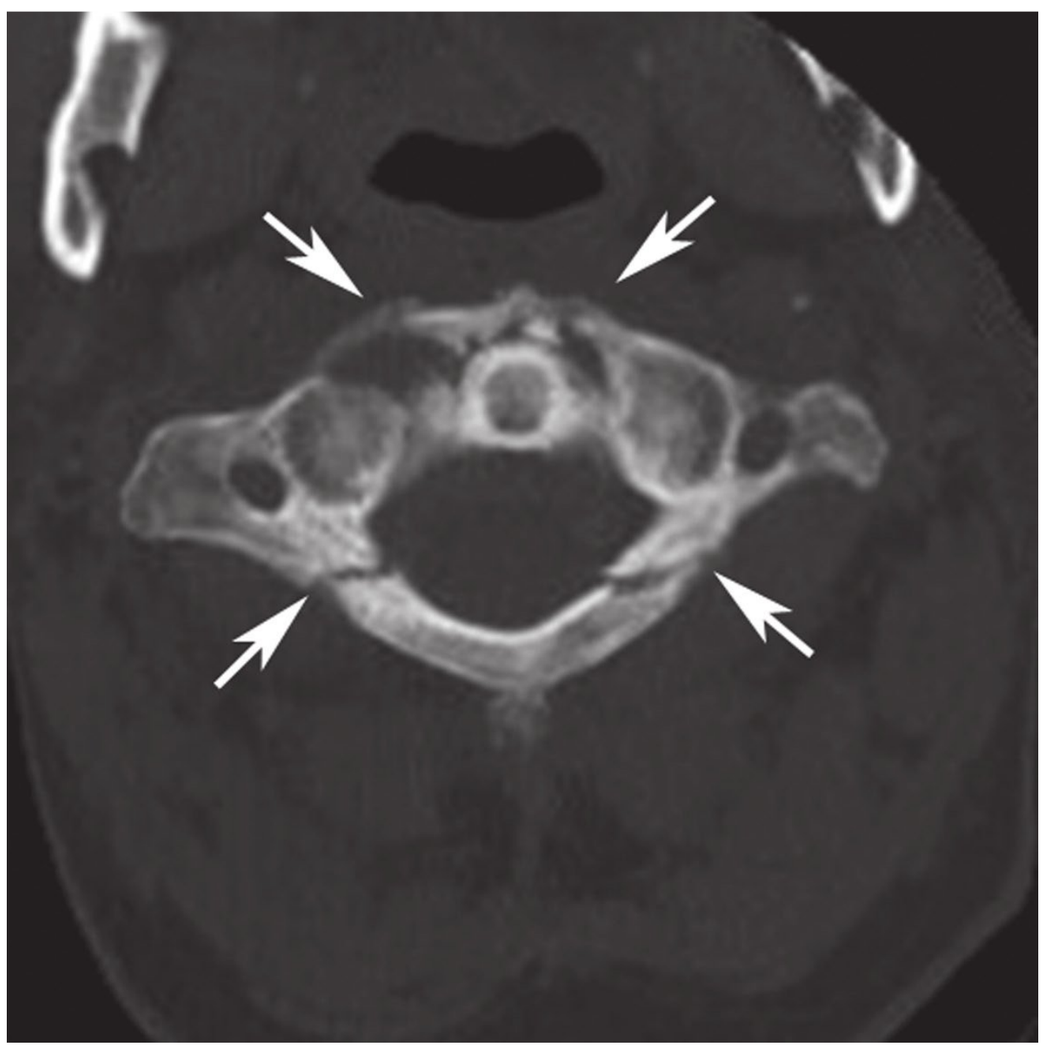


FIGURE 5-35
Jefferson fracture. Axial CT demonstrates four fracture lines (arrows) separating C1 in four parts. Jefferson fracture is usually caused by axial impact to the head such as diving in shallow water.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 5-36
Ligament injury after trauma. Coronal CT reconstruction demonstrates abnormal asymmetry between the dens and the lateral masses of C1 indicating transverse ligament rupture.

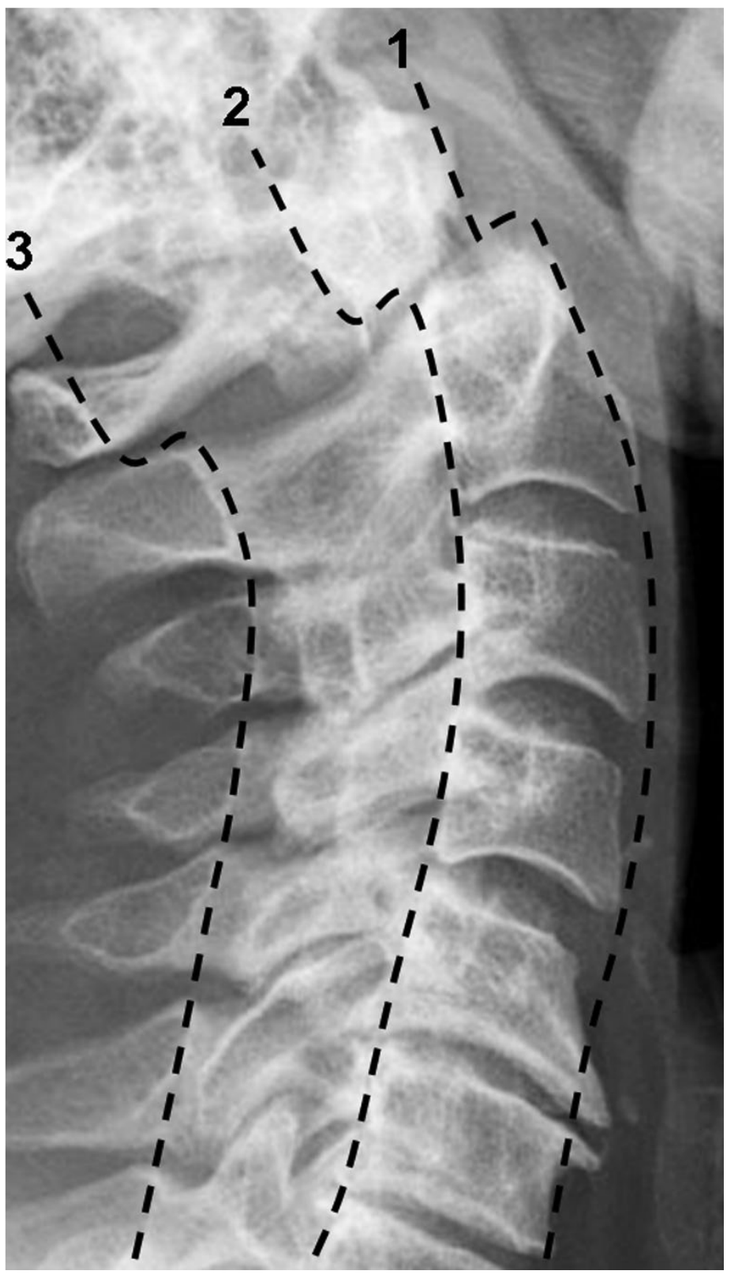
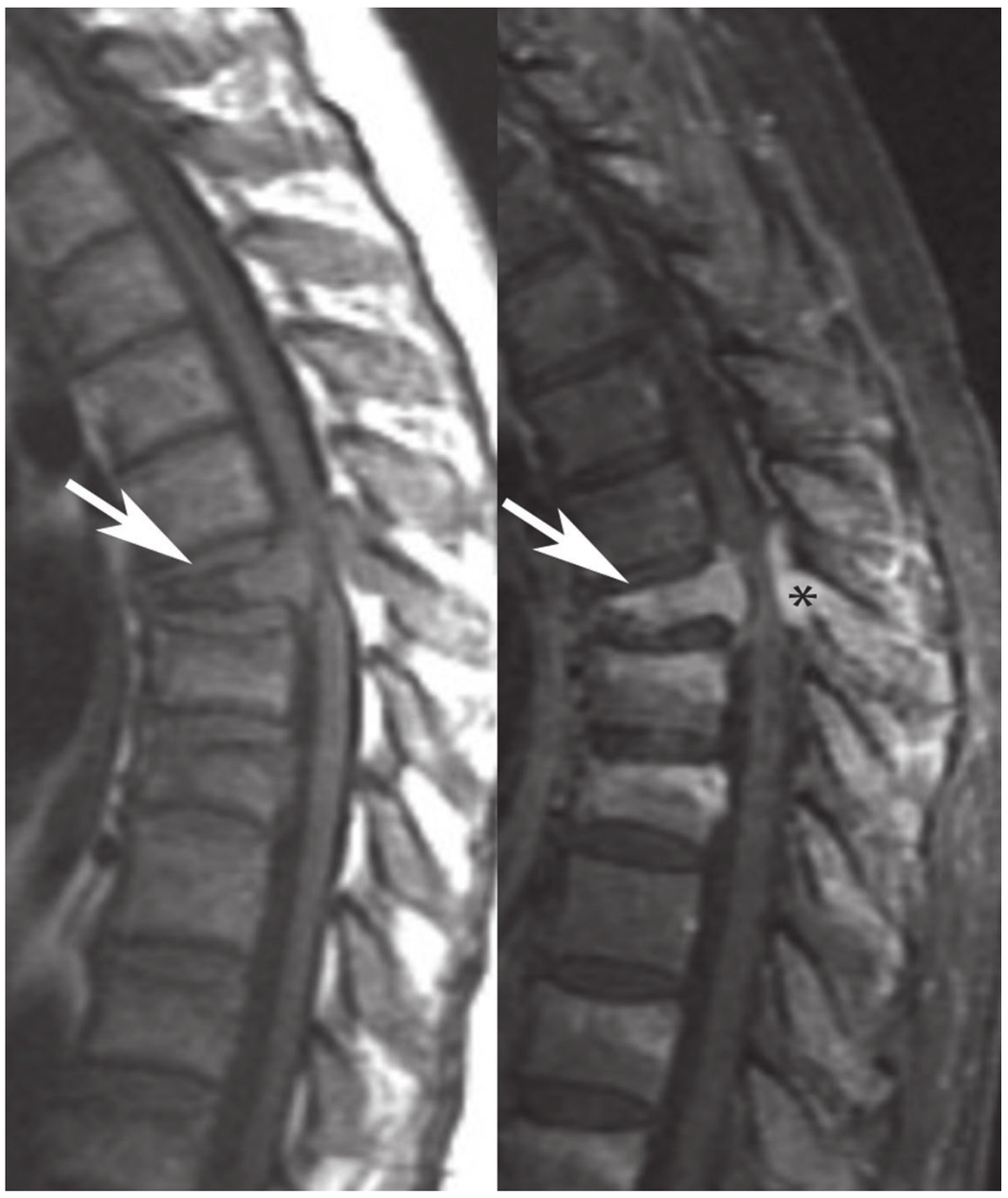
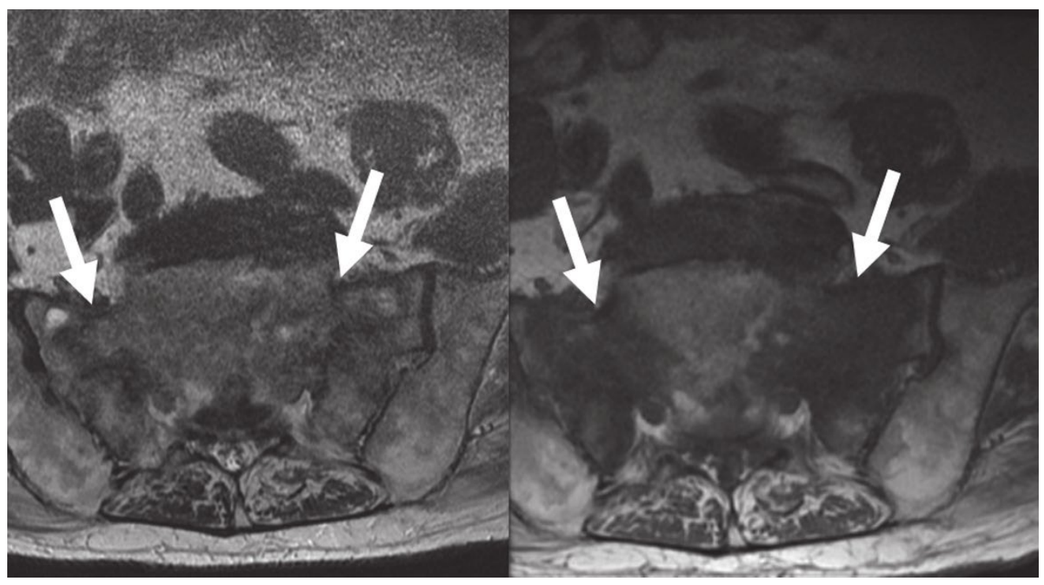


FIGURE 5-37
Odontoid fracture. Sagittal CT demonstrates disruption of the main reference cervical lines. 1: Anterior vertebral body line; 2: Posterior vertebral body line; 3: Spinolaminar line.



A B

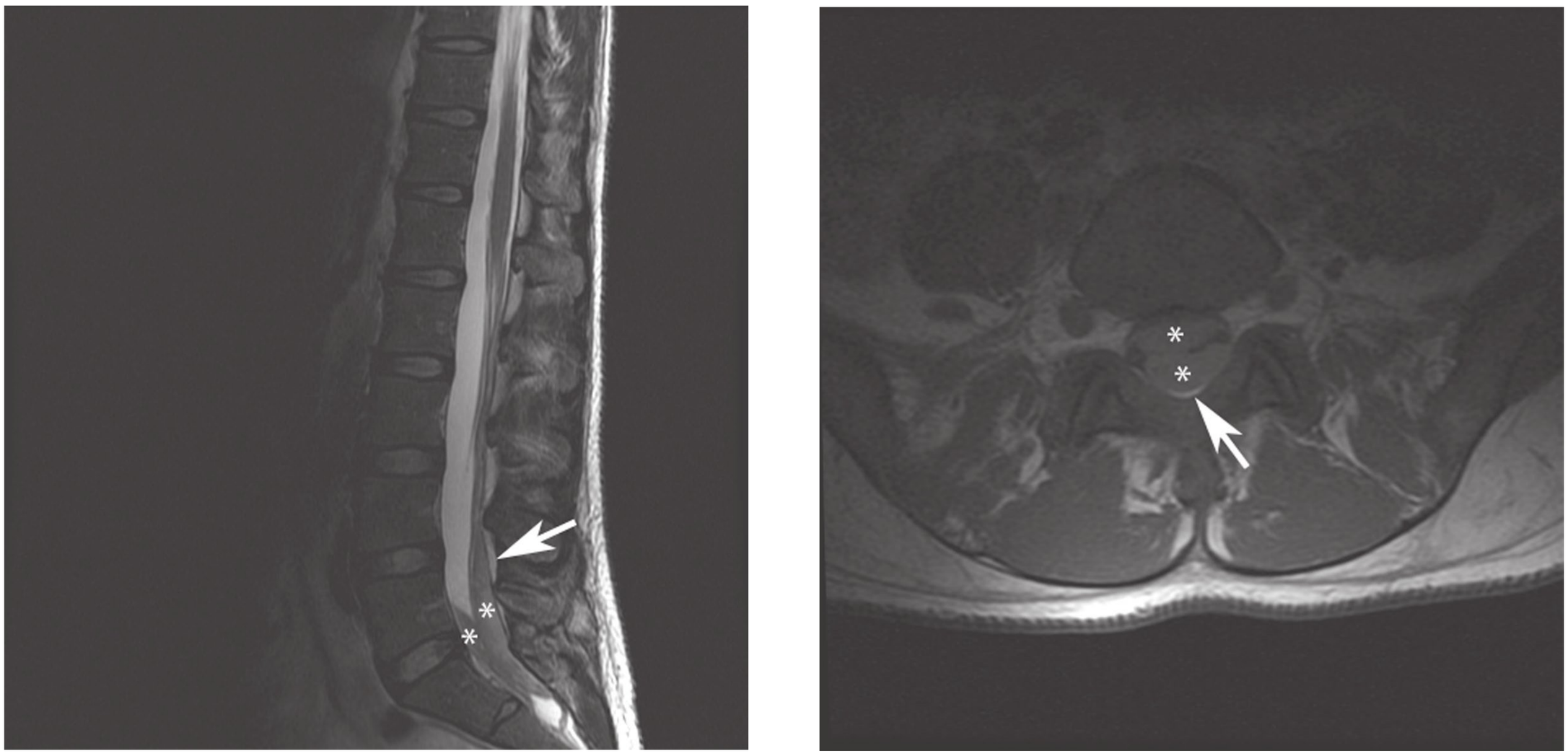
FIGURE 5-38
Pathologic fracture. Sagittal T1-weighted MRI (A) demonstrates wedge-shaped T6 vertebral body (arrow). Sagittal post-contrast T1-weighted MRI (B) depicts tumor extension into the epidural space and the involvement of the posterior arch (*), which are highly suggestive of metastatic or primary bone tumor.



A B

FIGURE 5-39
Sacral insufficiency fracture. Axial T2-weighted MRI (A) and T1-weighted MRI (B) demonstrate symmetric high T2 and low T1 signal involving the sacral alae longitudinally (arrows).

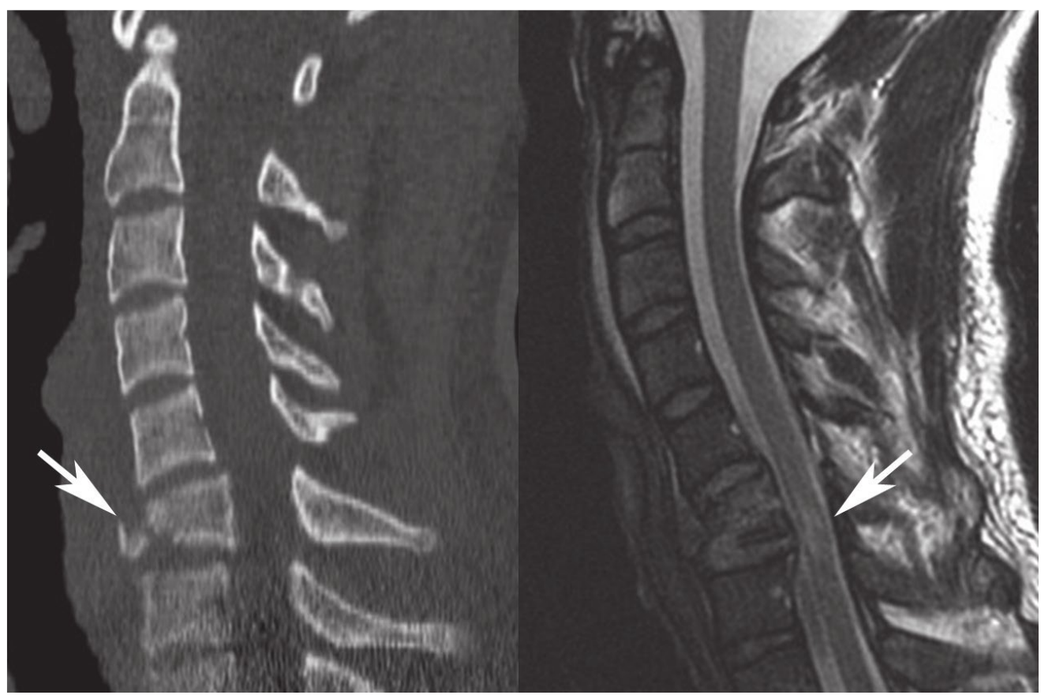
www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 5-40

Subdural hematoma. Sagittal T2-weighted MRI (A) and axial noncontrast T1-weighted MRI (B) demonstrate subdural collection in the lumbosacral region (**). Note that the epidural fat is compressed but not involved (arrow).



A B

FIGURE 5-41

Teardrop fracture. Sagittal CT (A) demonstrates fracture line separating the anteroinferior corner of C6 (arrow). Sagittal T2-weighted MRI (B) displays cord injury (arrow).

www.ketabpezeshki.com (021) 66485457 - 66485438

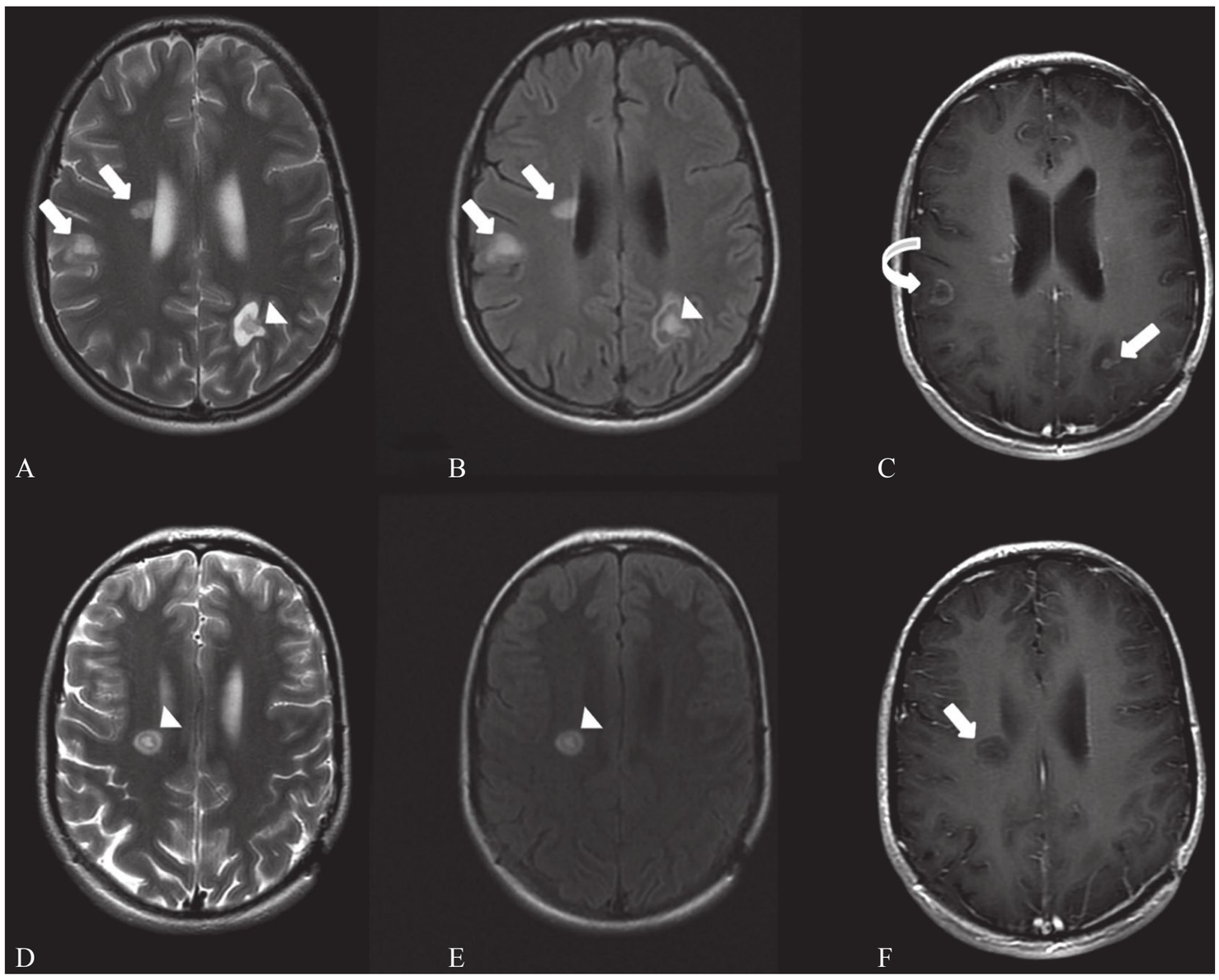


FIGURE 5-42

Demyelinating disease (multiple sclerosis, Chap. 45). Axial T2-weighted MRI (A, D) and axial T2 FLAIR MRI (B, E) demonstrate multiple hyperintense lesions involving the periventricular and subcortical white matter (arrows). Although not always present, the appearance of a "lesion within and lesion" (arrowheads) is typical of demyelinating disease. Axial T1-weighted postcontrast MRI (C, F) shows partial enhancement of the lesion (arrows), which is often peripheral, incomplete, and "C-shaped" (curved arrow).

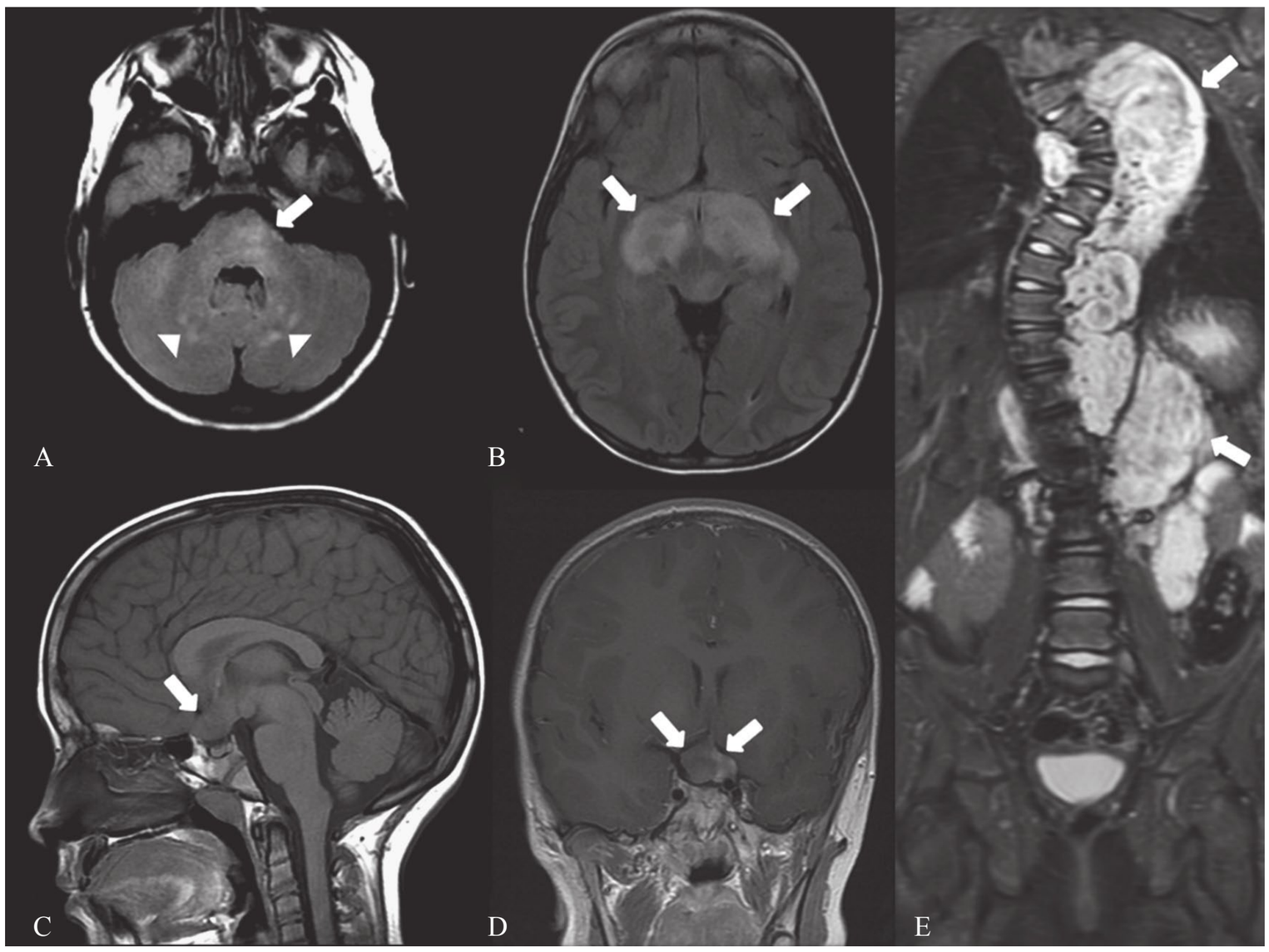


FIGURE 5-43

Neurofibromatosis type 1 (Chap. 49). Axial T2 FLAIR MRI (A, B) demonstrates multiple hyperintense lesions involving the brainstem and basal ganglia (arrows) as well as deep cerebellar hemispheres (arrowheads). Sagittal and corona T1-weighted postcontrast MRI (C, D) shows enlargement of the optic chiasm with an area of enhancement on the left, representing an optic pathway glioma (arrows). Coronal STIR MRI (E) shows thoracolumbar scoliosis and a large paravertebral plexiform neurofibroma (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

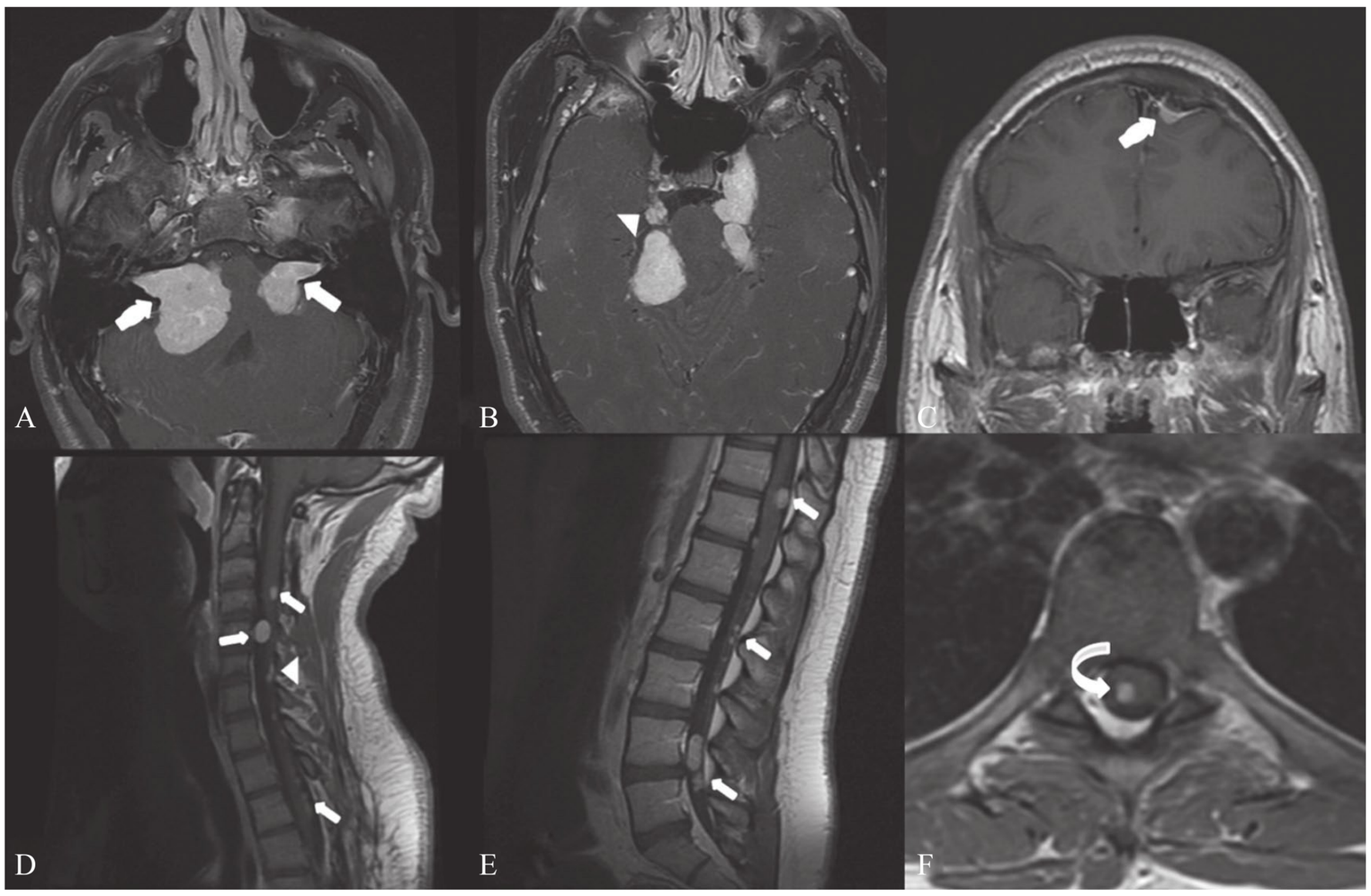


FIGURE 5-44

Neurofbromatosis type 2 (Chap. 49). Axial T1-weighted postcontrast MRI (A, B) shows enhancing expansible lesions in the bilateral cerebellopontine cisterns extending in the internal auditory canals, consistent with vestibular schwannomas (arrows), as well as in the bilateral prepontine cistern, consistent with trigeminal schwannomas (arrowheads). Coronal axial T1-weighted image postgadolinium (C) demonstrates an intensely enhancing dural-based lesion typical for a small meningioma (arrows). Sagittal (D, E) T1-weighted images postgadolinium show intradural, extramedullary lesions, suggestive of multiple spinal schwannomas (small arrows). The flat dural-based lesion may represent a spinal meningioma (arrowhead). Axial T1-weighted image postgadolinium (F) shows an enhancing intramedullary lesion, most consistent with an ependymoma. (curved arrow).

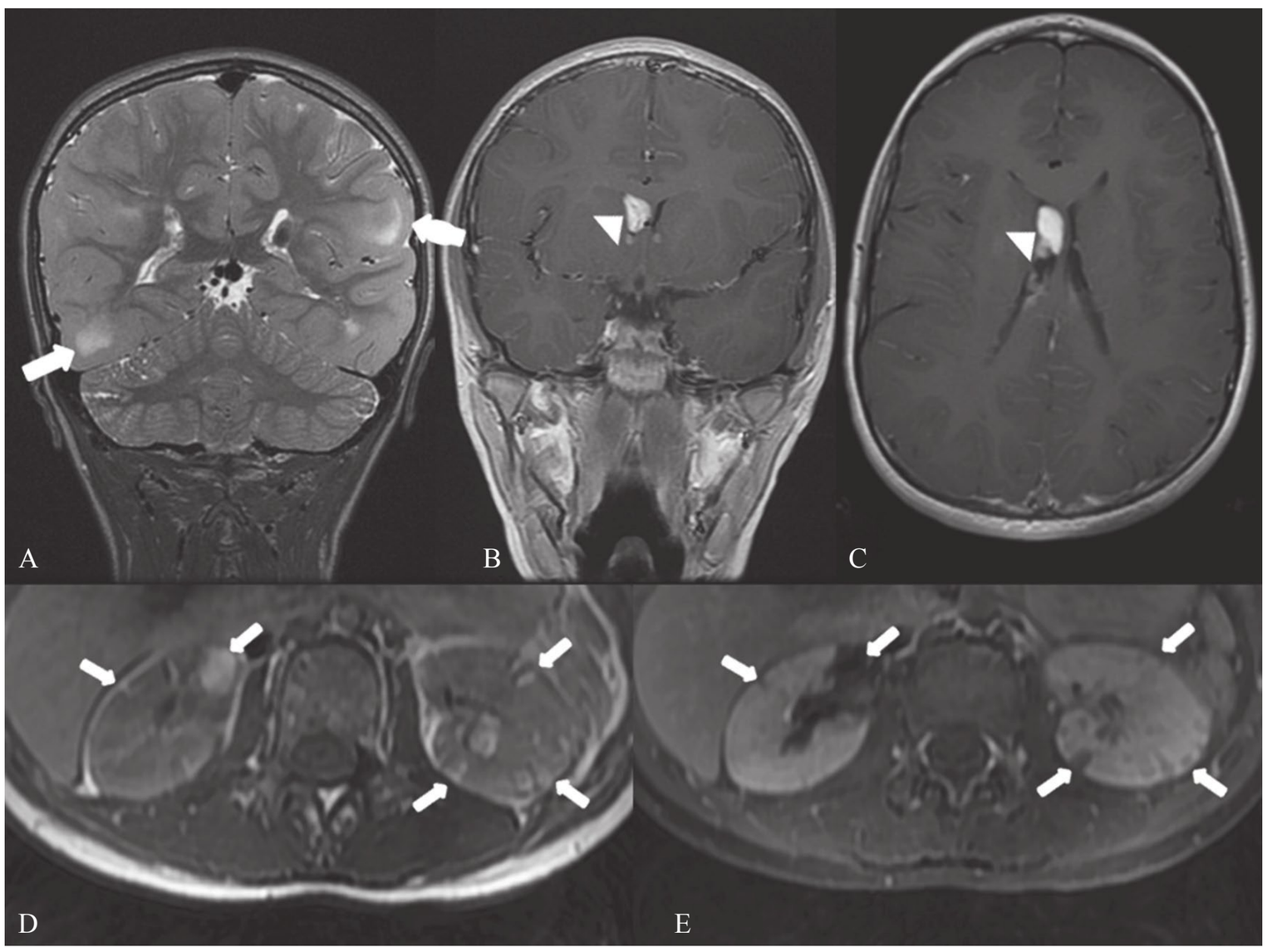


FIGURE 5-45

Tuberous sclerosis (Chap. 49). Coronal T2-weighted MRI (A) shows multiple T2 hyperintense lesions in a cortical and subcortical distribution (arrows). Coronal and axial postcontrast T1-weighted image (B, C) demonstrates an expanding nodule with intense enhancement in the proximity of the right foramen of Monro, consistent with a subependymal giant-cell astrocytoma (SEGA) (arrowheads). Surveillance T1-weighted image (D) and postcontrast T1-weighted image with fat saturation (E) show multiple bilateral renal lesions with signal intensity of fat, consistent with angiomyolipomas (small arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

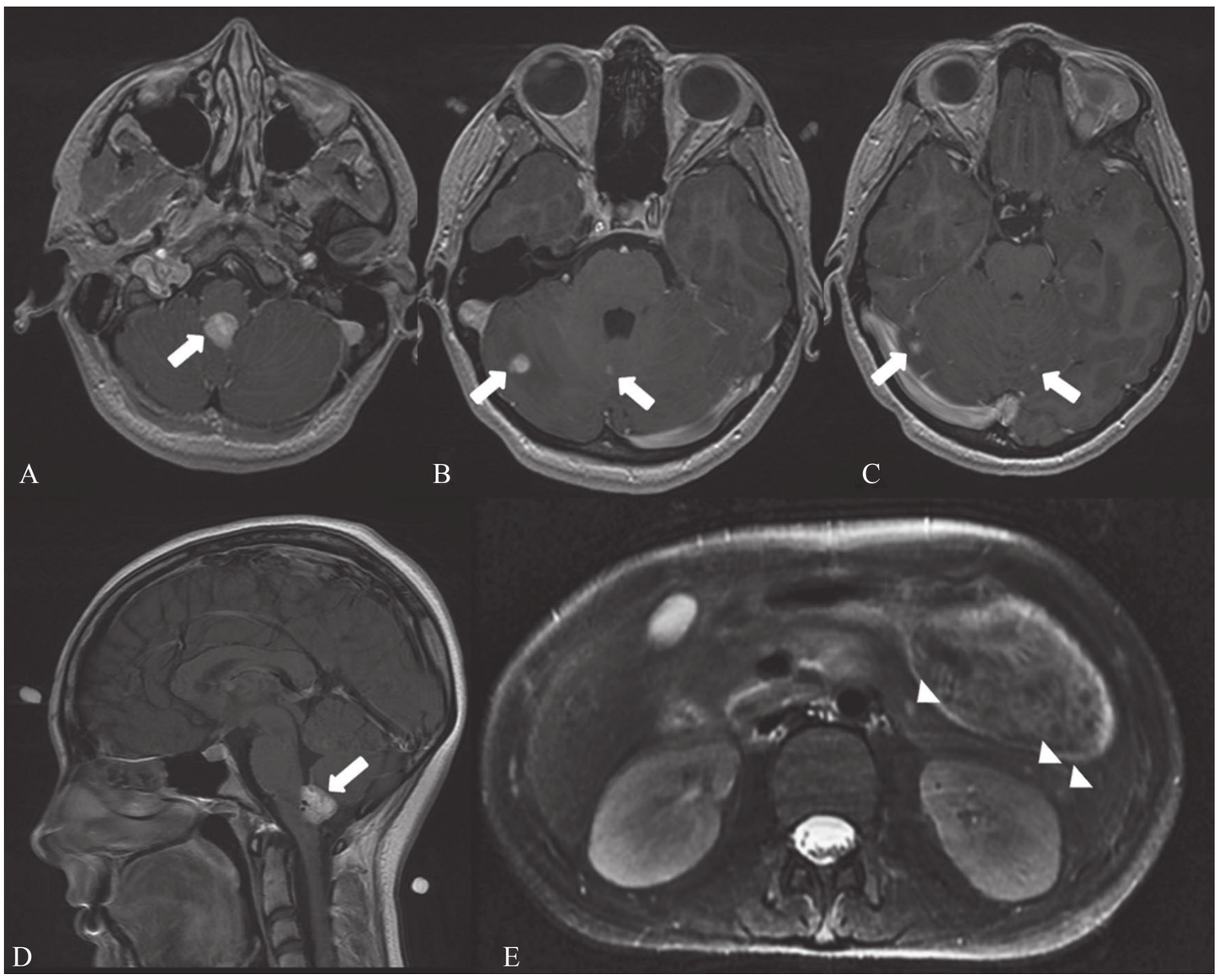


FIGURE 5-46
Von Hippel–Lindau (VHL). Axial postcontrast T1 weighted images (A–C) demonstrates multiple enhancing nodules in the posterior fossa (arrows). Sagittal postcontrast T1-weighted image (D) shows vascular flow voids within the enhancing nodule in the region of the foramen of Magendie (arrow), indicating increased vascularity. Surveillance axial T2-weighted MRI of the abdomen (E) shows multiple small pancreatic cysts (arrowheads). This patient did not have an endolymphatic sac tumor, renal cell carcinoma, neuroendocrine pancreatic tumor, or pheochromocytoma, all of which may also occur in von Hippel–Lindau disease.

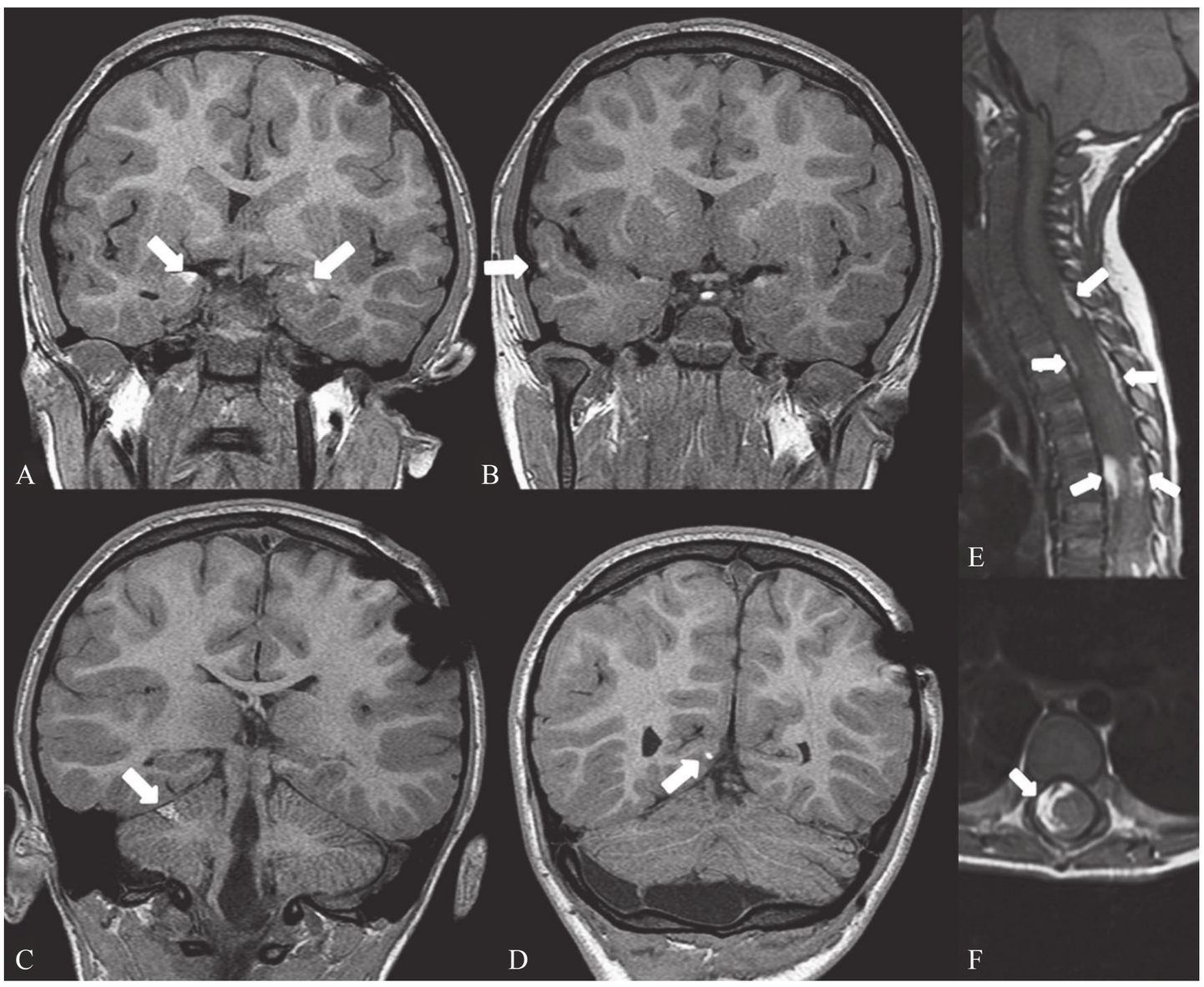


FIGURE 5-47
Neurocutaneous melanosis. Coronal T1 weighted MRI (A–D) shows multiple lesions with intrinsic increased T1 signal in the bilateral amygdalae, right superior temporal gyrus, right cerebellar hemisphere, and right medial occipital cortex (arrows). Sagittal and axial T1-weighted images of the spine (E, F) show intradural, extramedullary lesions, also with intrinsic increased T1 signal, due to malignant melanoma (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

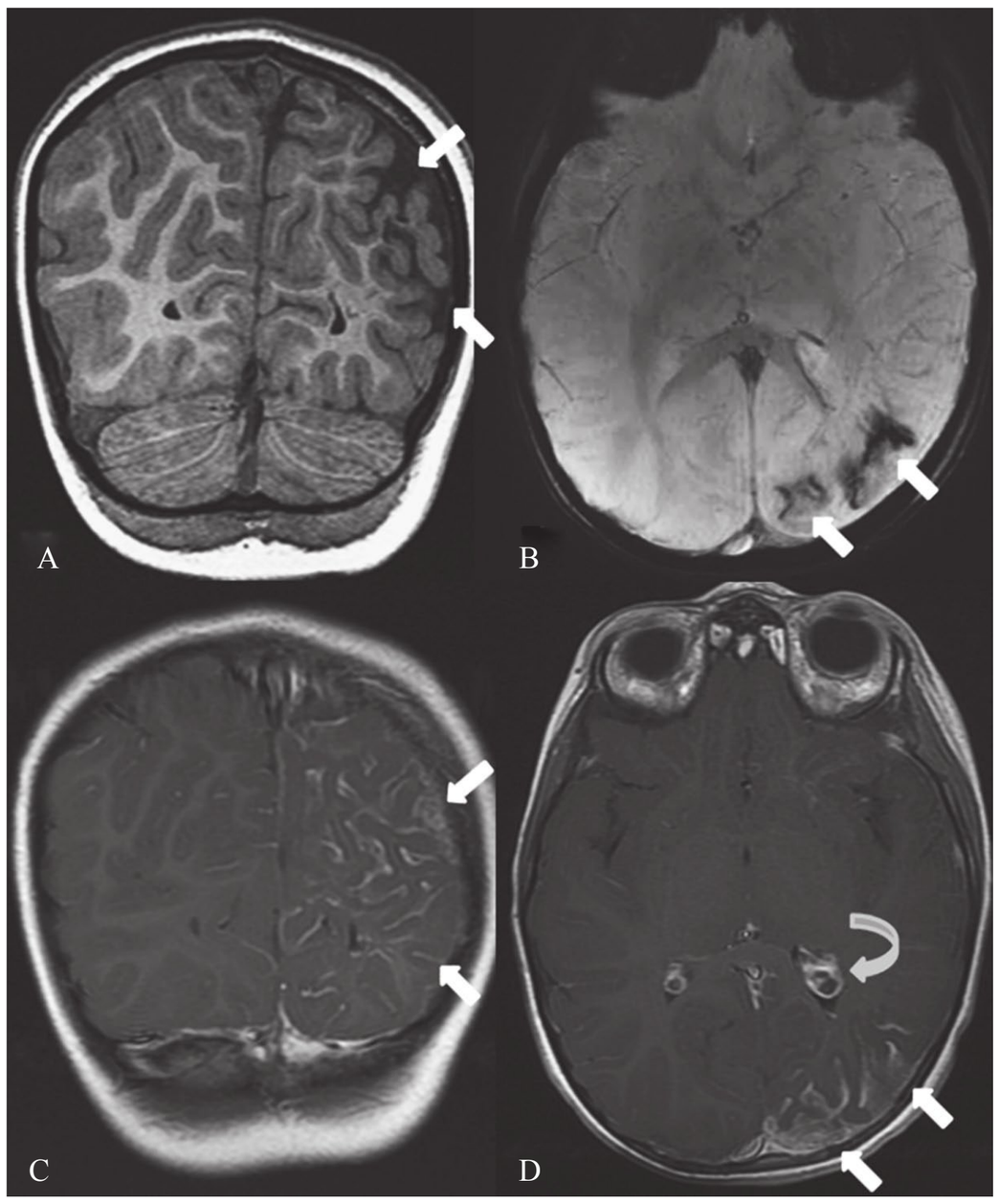


FIGURE 5-48

Sturge-Weber syndrome. Coronal T1-weighted MRI (A) shows enlargement of the sulci in the left parietal lobe, consistent with brain parenchymal volume loss (arrows). Axial susceptibility weighted imaging shows susceptibility effect in this region, consistent with calcifications (arrows). Coronal and axial T1-weighted images postgadolinium (C, D) show increased leptomeningeal enhancement (arrows) and enlargement of the left choroid plexus (curved arrow).

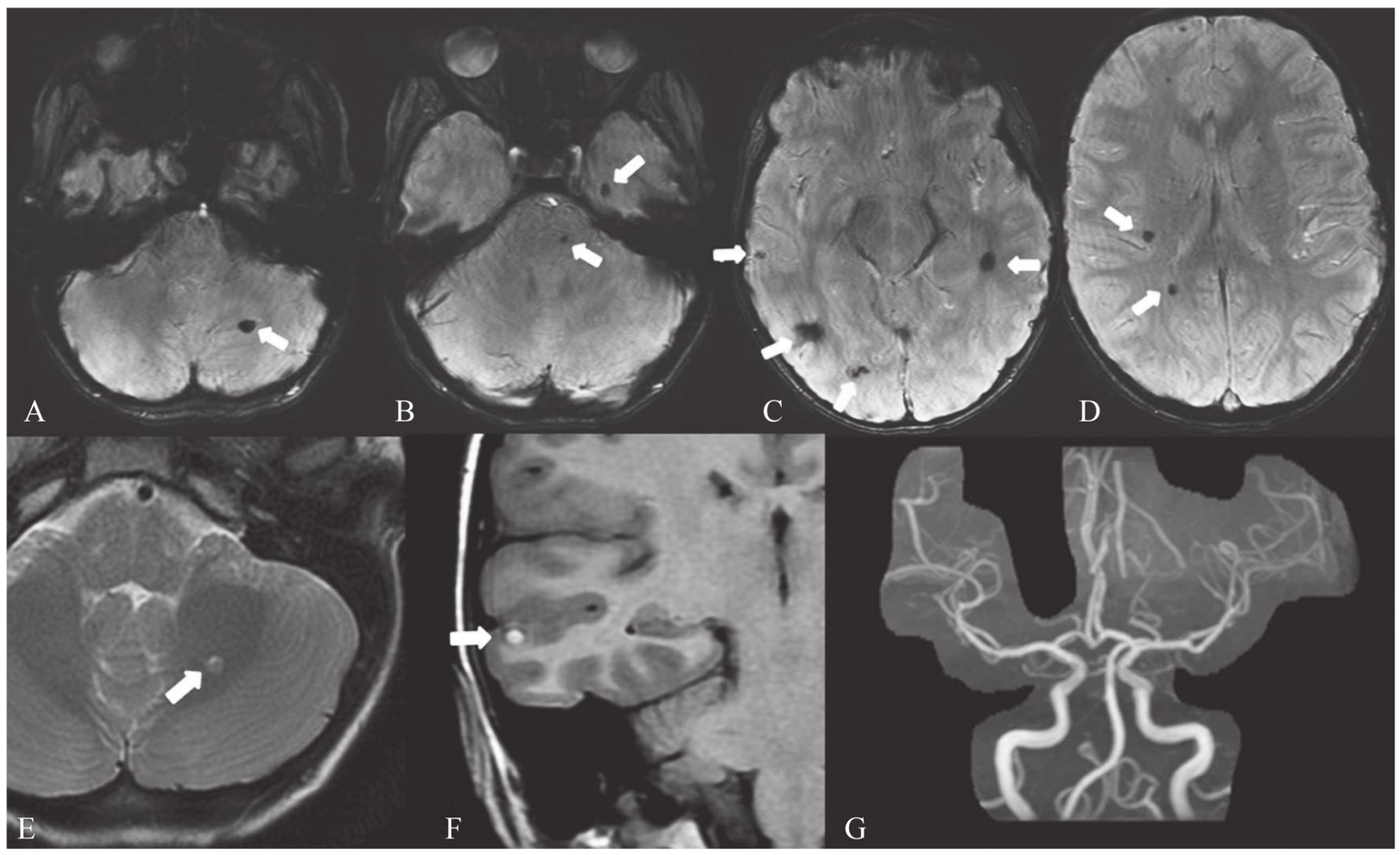
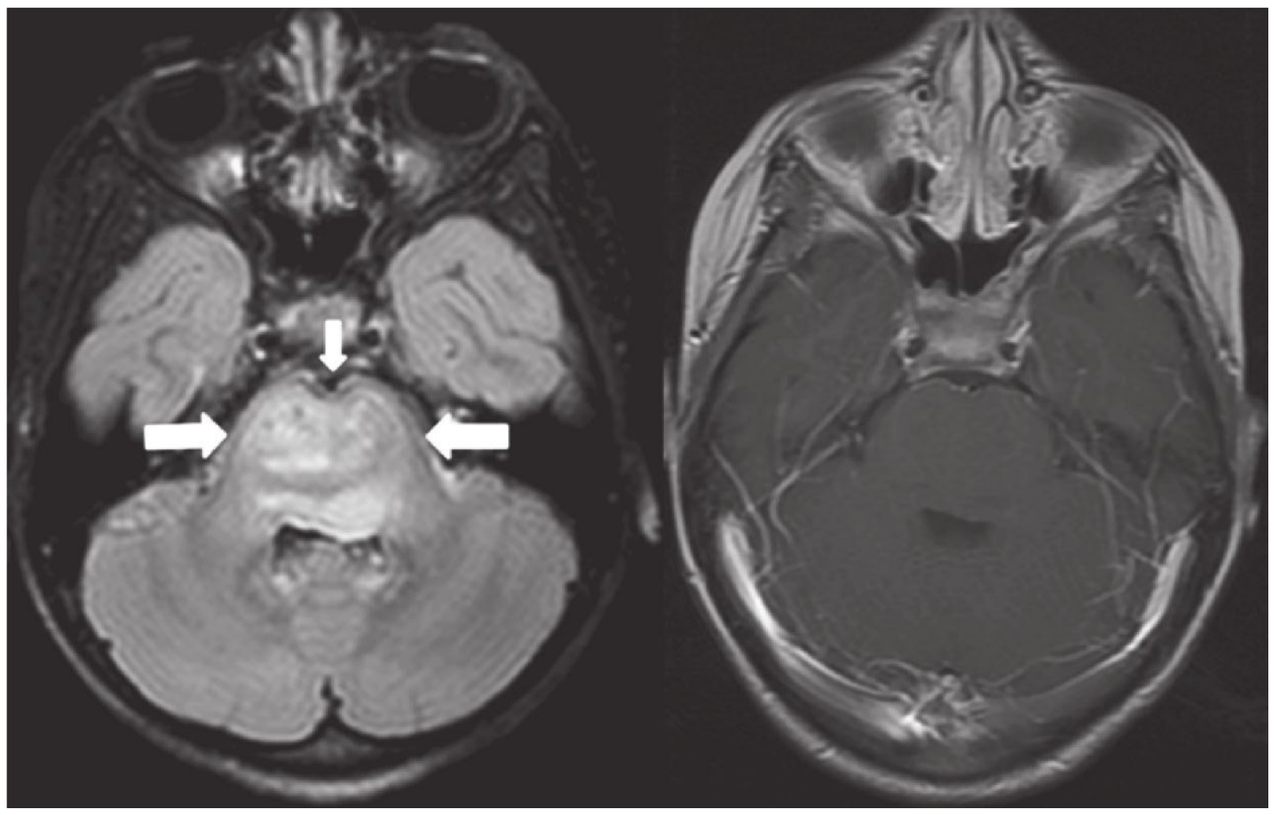


FIGURE 5-49

Multiple cavernomas (Chap. 32). Axial susceptibility weighted images (A–D) show multiple foci of susceptibility involving the bilateral cerebral hemispheres, pons, and left cerebellum, which in a young patient most likely represents multiple cavernomas (arrows). These lesions have variable signal intensity on T2-weighted (E) and T1-weighted MRI (F), related to the different stages of hemoglobin degradation (arrows). Cavernomas are not seen on the time-of-flight MR angiography (G); thus these are designated as angiographically occult vascular malformations. Of note, in elderly patients, amyloid angiopathy may have a similar appearance.

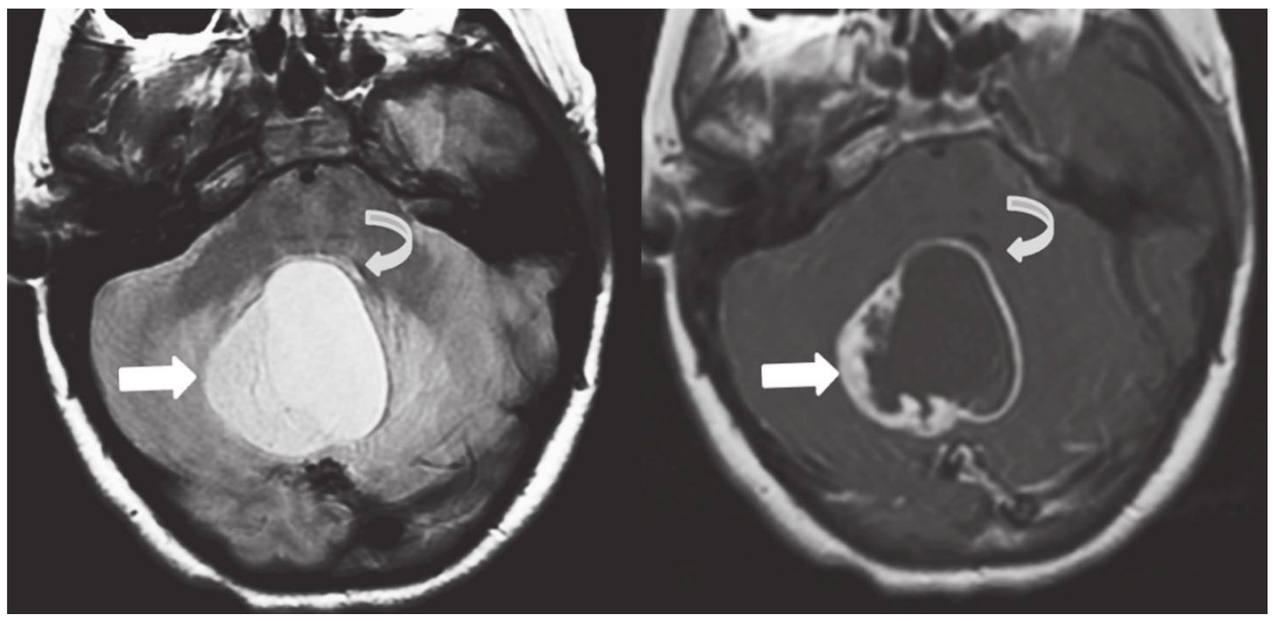
www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 5-50

Brainstem glioma (Chap. 49). Axial T2 FLAIR MRI (A) demonstrates increased T2 signal and marked enlargement of the pons (large arrows), which engulfs the basilar artery (small arrow). These findings are characteristic of brainstem glioma. At the time of diagnosis, these lesions are typically low grade without abnormal enhancement, as shown by axial postcontrast T1-weighted image (B).

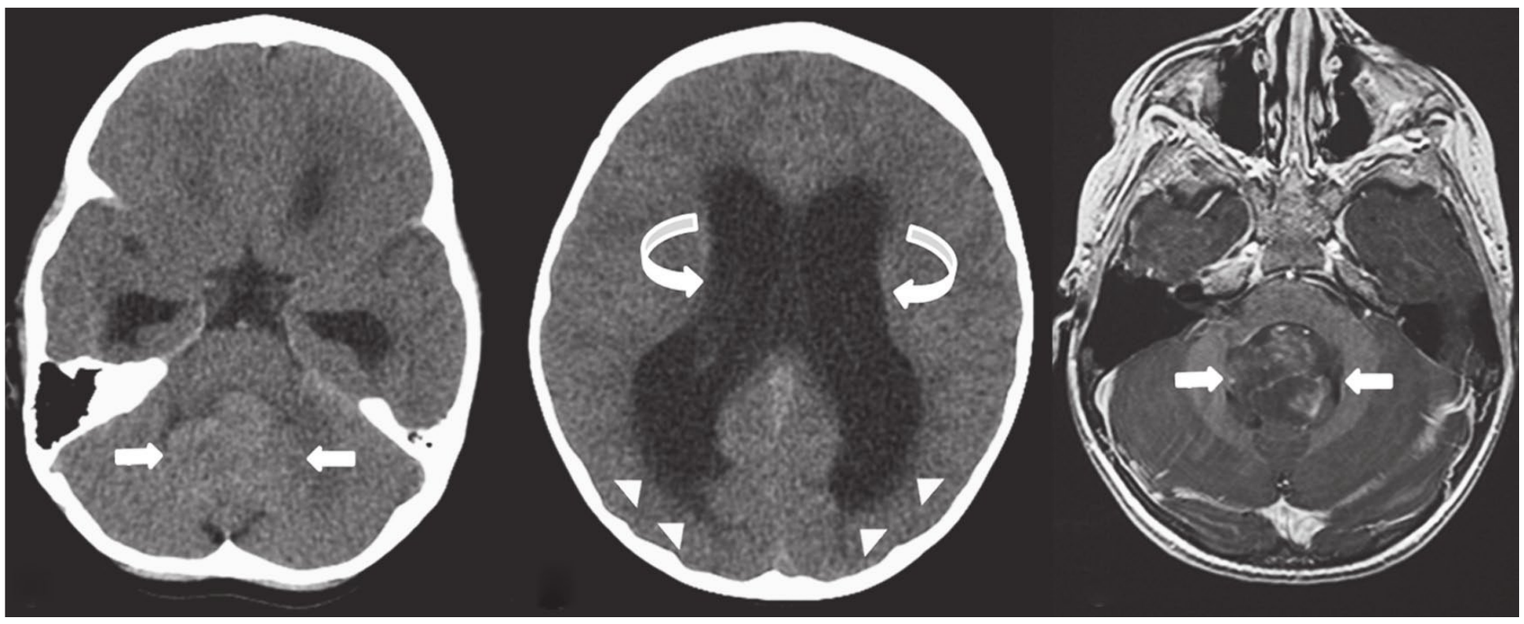


A B

FIGURE 5-51

Pilocytic astrocytoma (Chap. 49). Axial T2-weighted and T1-weighted postgadolinium images (A, B) show a cystic lesion with peripheral enhancement and an enhancing solid component located in the posterior fossa (arrows). These findings are suggestive of a pilocytic astrocytoma. Note that the lesion exerts mass effect on the fourth ventricle, which is compressed (curved arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438



A B C

FIGURE 5-52

Fourth ventricle ependymoma causing hydrocephalus (Chap. 49). Unenhanced axial CT images (A, B) demonstrate an expansile mass lesion, isodense with brain parenchyma, filling the fourth ventricle (arrows) and causing obstruction of cerebrospinal fluid flow, dilation of the lateral ventricles, and hydrocephalus (curved arrows). The hypoattenuation within periventricular white matter bilaterally represents transependymal flow (arrowheads). Axial T1-weighted postgadolinium MRI confirms the presence of a heterogeneously enhancing mass filling the fourth ventricle (arrow), which is suggestive of ependymoma.

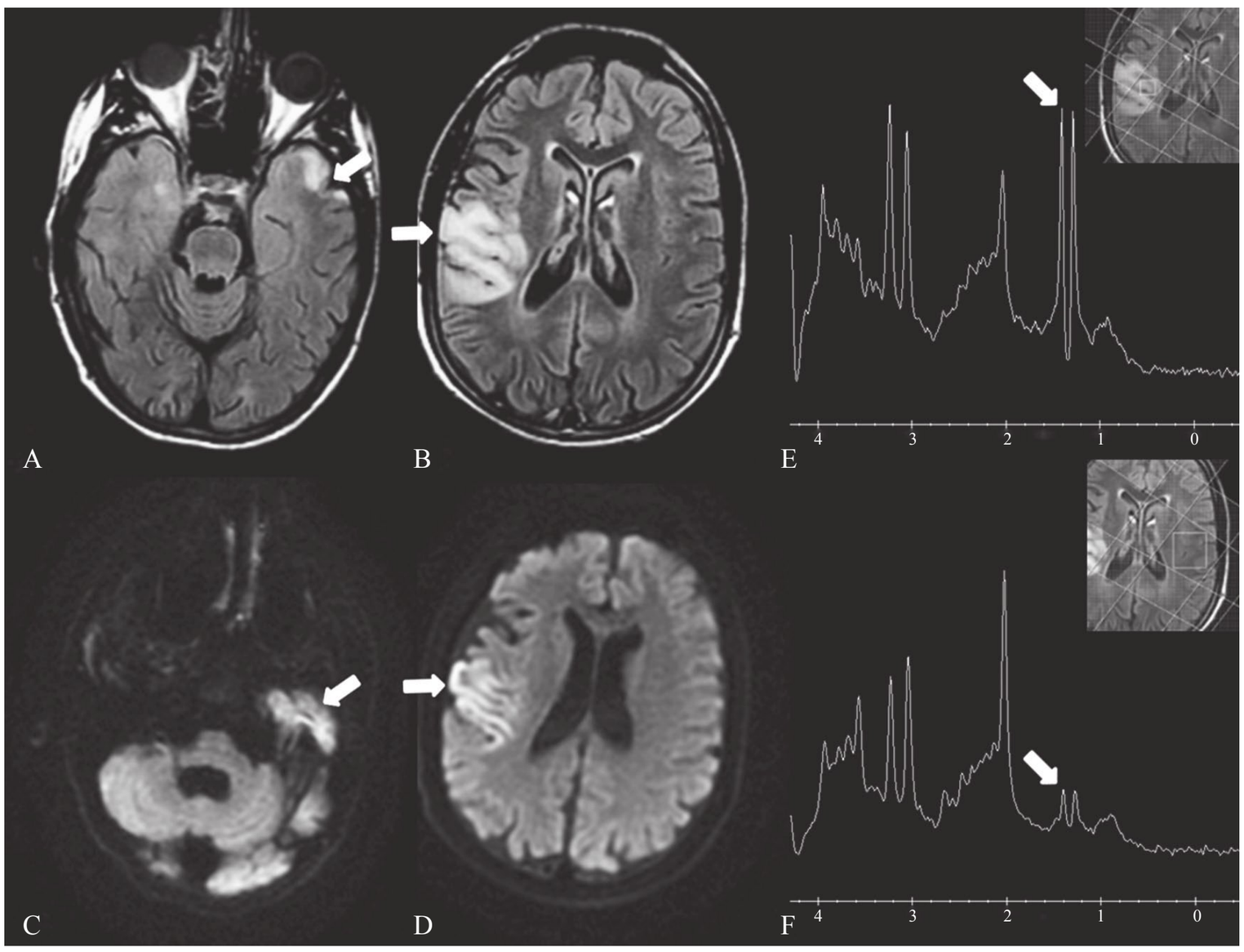
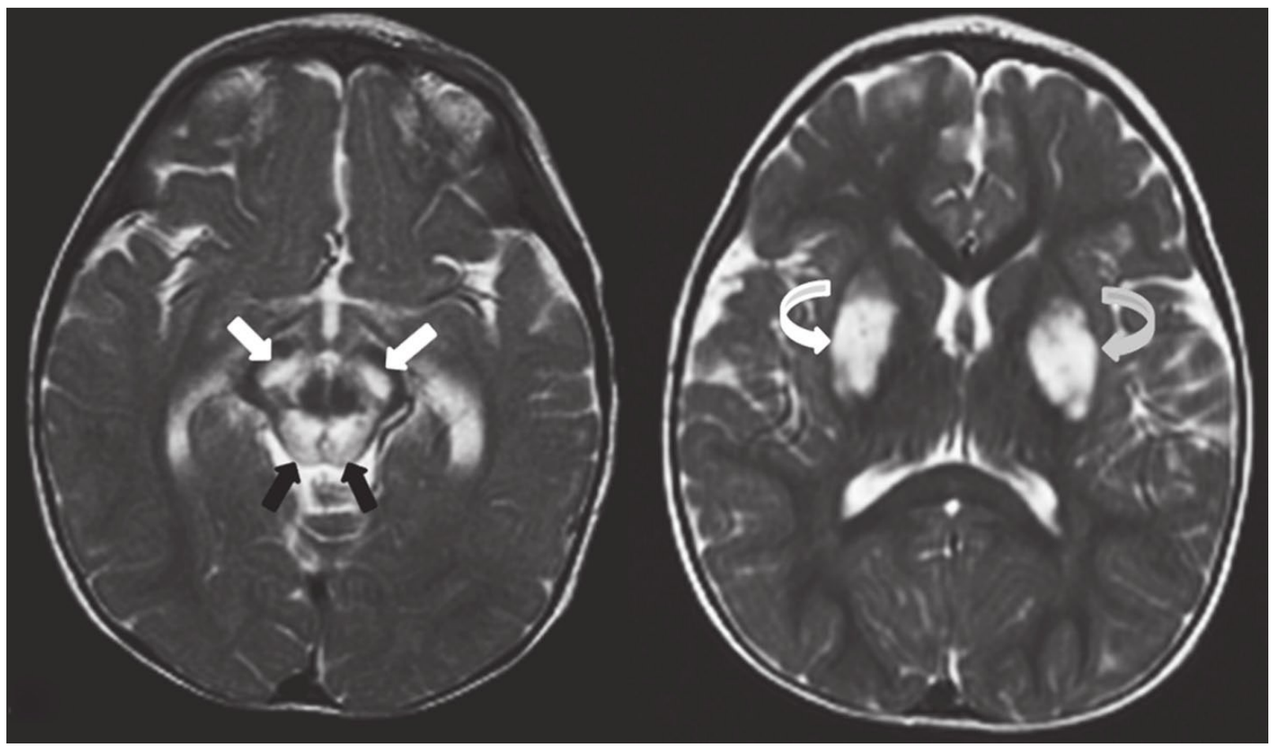


FIGURE 5-53

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (Chap. 56). Axial T2 FLAIR MRI (A, B) shows areas of increased T2 signal involving the cortex and subcortical white matter in the posterior right frontal lobe and anterior left temporal lobe, consistent with edema (arrows). Axial diffusion-weighted images (C, D) show reduced diffusion from cytotoxic edema, consistent with infarcts (arrows). MR spectroscopy of the right frontal lesion (E) demonstrates markedly increased lactate (arrow), an expected finding in infarction regardless of etiology. However, MR spectroscopy of the normal-appearing contralateral brain parenchyma (F) shows mildly elevated lactate (arrow), which is suggestive of a mitochondrial disorder.

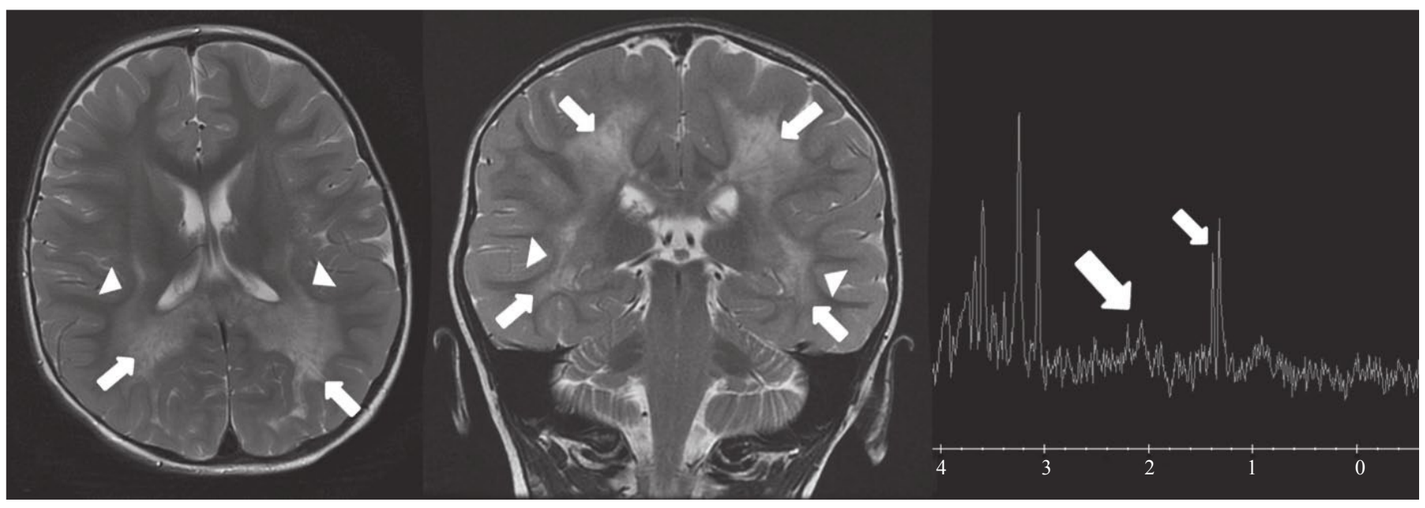
www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 5-54

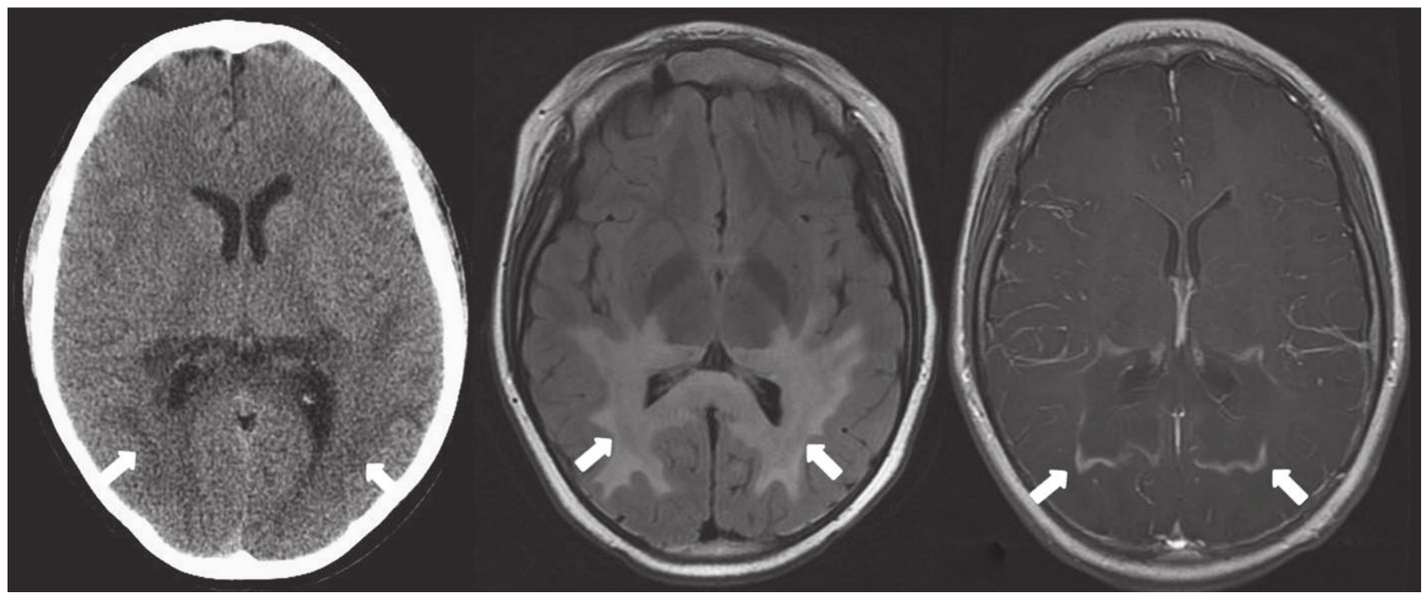
Leigh's disease (subacute necrotizing encephalomyelopathy. Axial T2-weighted MRI (A, B) demonstrates increased T2 signal involving the substantia nigra (white arrows) and dorsal midbrain (black arrows), as well as the putamin bilaterally (curved arrows). This is a common pattern for the mitochondrial disorder Leigh's disease secondary to cytochrome oxidase (CO IV) deficiency.



A B C

FIGURE 5-55

Krabbe's disease. Axial and coronal T2-weighted MRIs (A, B) show increased T2 signal involving predominantly the posterior white matter bilaterally (arrows) with sparing of the subcortical U-fibers (arrowheads). MR spectroscopy of the left parietal white matter (C) shows markedly decreased N-acetylaspartate (large arrow) and increased lactate/lipids (small arrow), consistent with severe neuronal injury.



A B C

FIGURE 5-56

X-linked adrenoleukodystrophy (Chap. 53). Axial unenhanced CT (A) demonstrates areas of attenuation involving the posterior white matter bilaterally (arrows). Axial T2 FLAIR MRI (B) displays increased T2 signal consistent with edema (arrows). Axial T1-weighted image postgadolinium (C) shows peripheral enhancement of the parietal lesions bilaterally (arrows). These findings are typical of adrenoleukodystrophy.

www.ketabpezeshki.com (021) 66485457 - 66485438

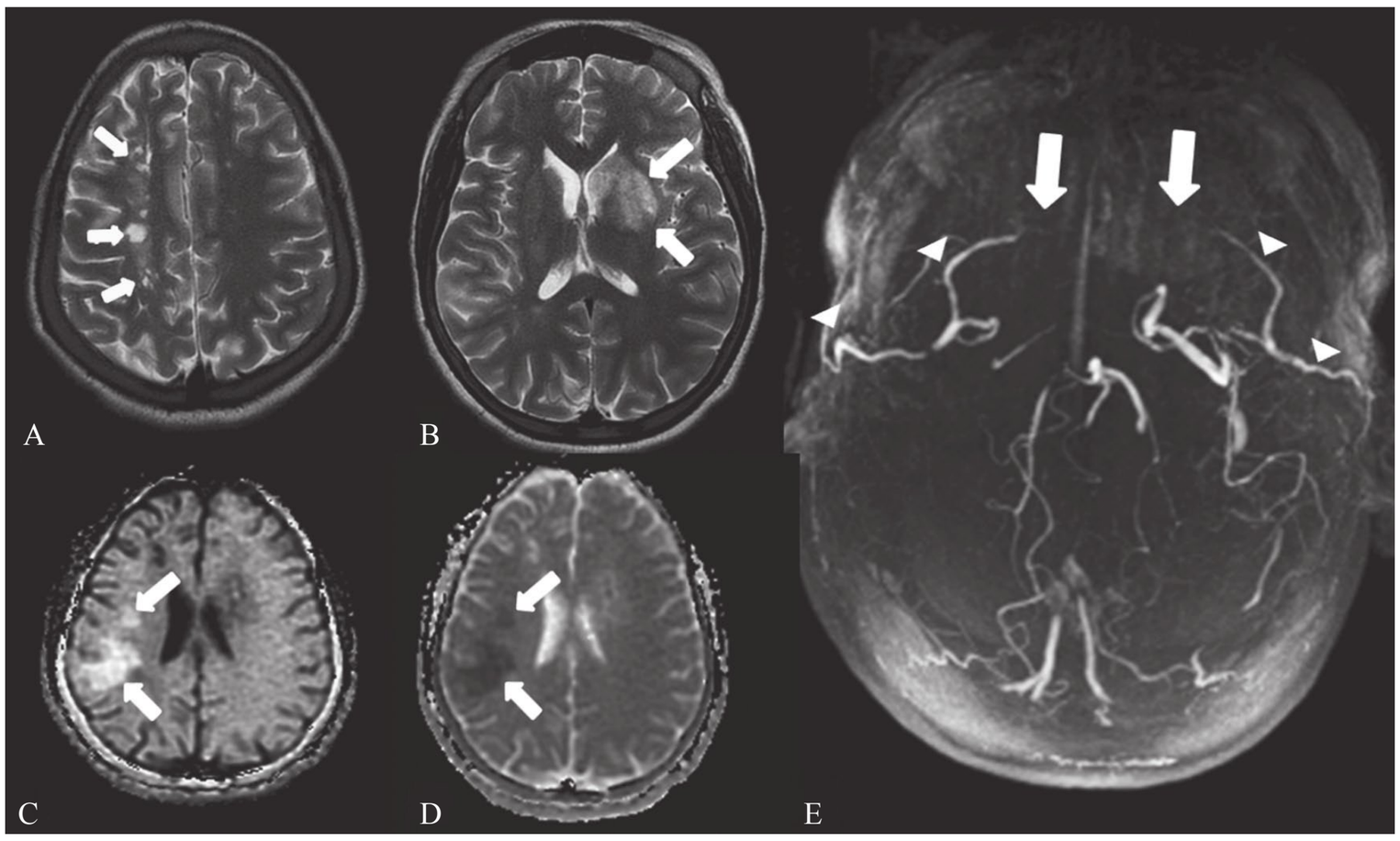


FIGURE 5-57

Sickle cell disease and moyamoya disease (Chap. 32). Axial T2-weighted MRI (A, B) shows multiple small areas of encephalomalacia from prior infarcts in the watershed zones between the anterior and middle cerebral artery territories (small arrows). There is also an area of edema involving the left basal ganglia from an evolving subacute infarct (arrow). An axial diffusion-weighted image (C) with corresponding ADC map (D) shows an area of restricted diffusion in the right frontoparietal region, consistent with an acute infarct (arrows). Time-of-flight MR angiography (E) shows absence of flow in the distal internal carotid arteries and proximal middle cerebral arteries (arrows) due to moyamoya disease. Also note that this patient is status post–bilateral encephalo-duro-arterio-synangiosis (EDAS) (arrowheads), a surgical procedure to create indirect anastomosis between branches of the external carotid artery with distal branches of the middle cerebral artery.

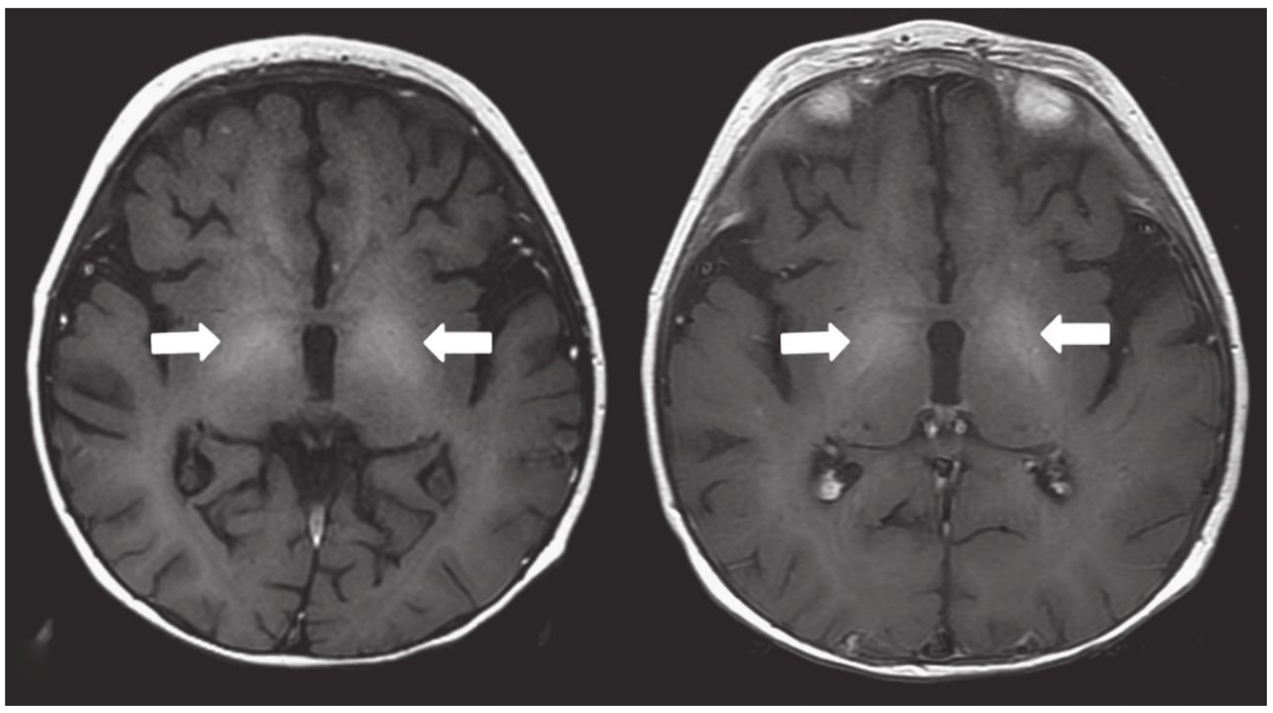
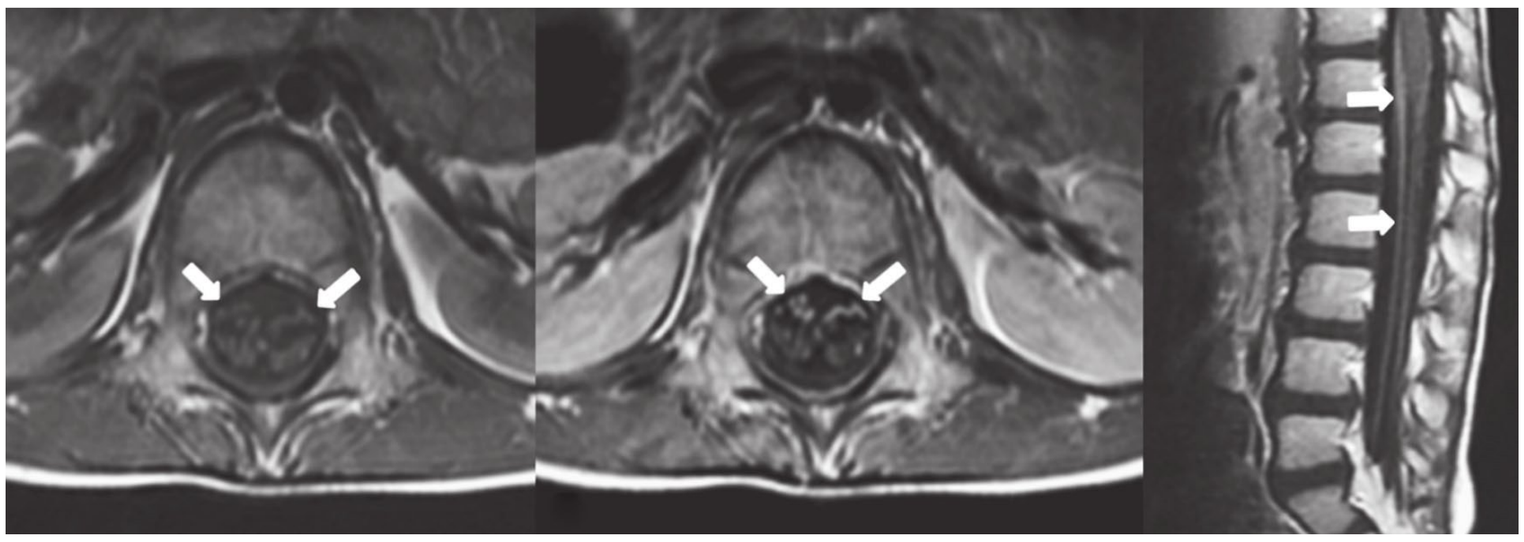


FIGURE 5-58

Hepatic encephalopathy (Chap. 33). Axial T1-weighted MRI (A, B) shows increased intrinsic T1 signal involving the basal ganglia bilaterally, particularly the globus pallidus (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438



A B C

FIGURE 5-59

Guillain-Barré syndrome (Chap. 54). Axial precontrast T1-weighted MRI (A) and axial and sagittal T1-weighted postgadolinium (B, C) images show thickening and increased enhancement of the anterior roots of the cauda equina (arrows).

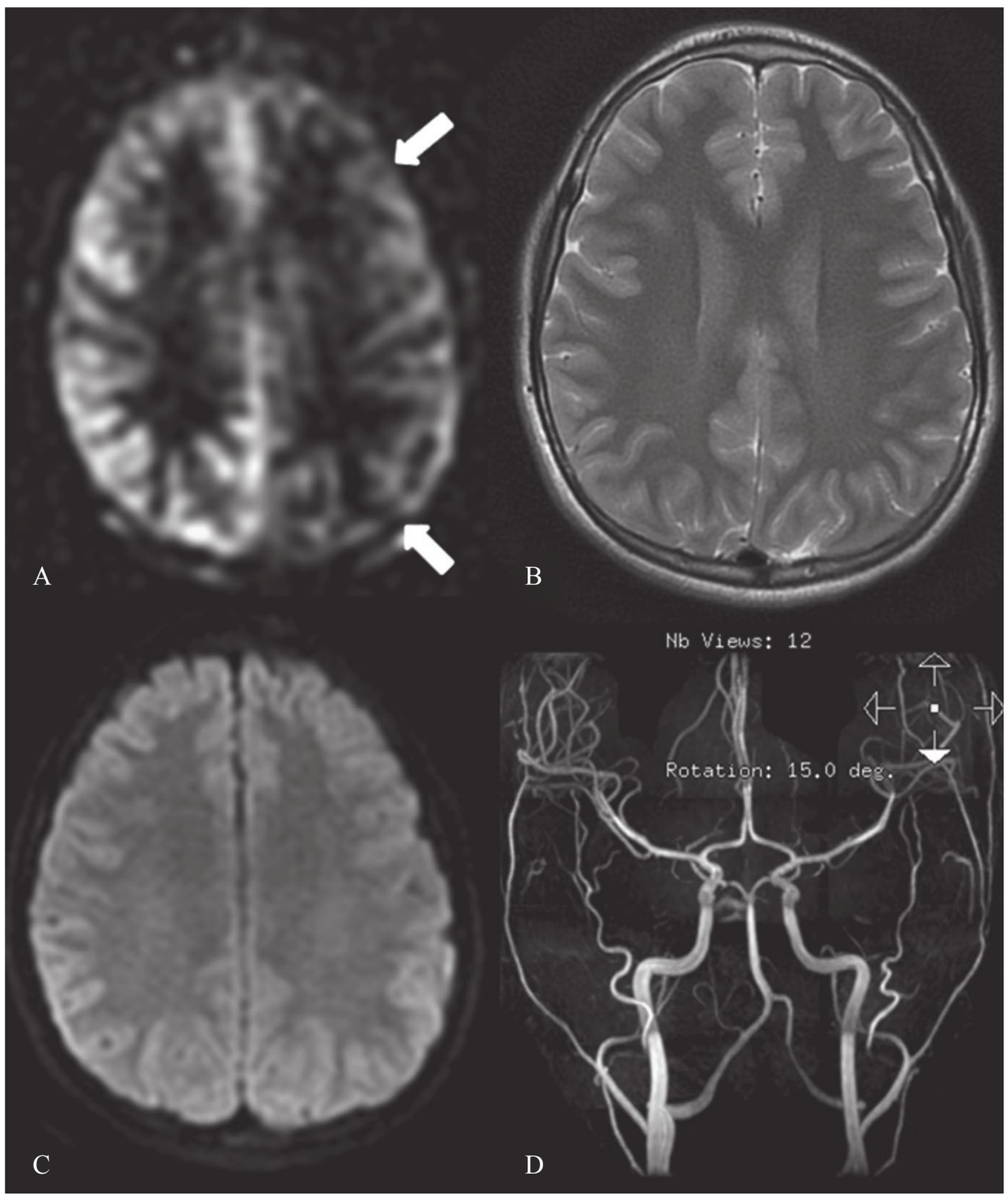


FIGURE 5-60

Hemiplegic migraine (Chap. 34). Axial noncontrast perfusion MRI using an arterial spin labeling technique (A) demonstrates decreased cerebral blood flow to the left hemisphere (arrows) in a patient with right hemiparesis associated with migraine symptoms. No abnormality was seen on T2-weighted images, diffusion-weighted images, or time-of-flight MR angiography (B–D) to suggest stroke.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 6

ELECTRODIAGNOSTIC STUDIES OF NERVOUS SYSTEM DISORDERS: EEG, EVOKED POTENTIALS, AND EMG

Michael J. Aminoff

ELECTROENCEPHALOGRAPHY

The electrical activity of the brain (the electroencephalogram [EEG]) is easily recorded from electrodes placed on the scalp. The potential difference between pairs of electrodes on the scalp (bipolar derivation) or between individual scalp electrodes and a relatively inactive common reference point (referential derivation) is amplified and displayed on a computer monitor, oscilloscope, or paper. Digital systems allow the EEG to be reconstructed and displayed with any desired format and to be manipulated for more detailed analysis and also permit computerized techniques to be used to detect certain abnormalities. The characteristics of the normal EEG depend on the patient's age and level of arousal. The rhythmic activity normally recorded represents the postsynaptic potentials of vertically oriented pyramidal cells of the cerebral cortex and is characterized by its frequency. In normal awake adults lying quietly with the eyes closed, an 8- to 13-Hz alpha rhythm is seen posteriorly in the EEG, intermixed with a variable amount of generalized faster (beta) activity (>13 Hz); the alpha rhythm is attenuated when the eyes are opened **(Fig. 6-1)**. During drowsiness, the alpha rhythm is also attenuated; with light sleep, slower activity in the theta (4–7 Hz) and delta (<4 Hz) ranges becomes more conspicuous.

Activating procedures are generally undertaken while the EEG is recorded in an attempt to provoke abnormalities. Such procedures commonly include hyperventilation (for 3 or 4 min), photic stimulation, sleep, and sleep deprivation on the night prior to the recording.

Electroencephalography is relatively inexpensive and may aid clinical management in several different contexts.

THE EEG AND EPILEPSY

The EEG is most useful in evaluating patients with suspected epilepsy. The presence of electrographic seizure activity—i.e., of abnormal, repetitive, rhythmic activity having an abrupt onset and termination and a characteristic evolution—clearly establishes the diagnosis. The absence of such electrocerebral accompaniment to an episodic behavioral disturbance does not exclude a seizure disorder, however, because there may be no changes in the scalp-recorded EEG during certain focal seizures. With generalized tonic-clonic seizures, the EEG is always abnormal during the episode. It is often not possible to obtain an EEG during clinical events that may represent seizures, especially when such events occur unpredictably or infrequently. Continuous monitoring for prolonged periods in video-EEG telemetry units has made it easier to capture the electrocerebral accompaniments of such clinical episodes. Monitoring by these means is sometimes helpful in confirming that seizures are occurring, characterizing the nature of clinically equivocal episodes, and determining the frequency of epileptic events.

The EEG findings in the interictal period may show certain abnormalities that are strongly supportive of a diagnosis of epilepsy. Such epileptiform activity consists of bursts of abnormal discharges containing spikes or sharp waves. The presence of epileptiform activity is not specific for epilepsy, but it has a much greater prevalence in epileptic patients than in normal individuals. However, even in individuals with epilepsy, the initial routine interictal EEG may be normal up to 60% of the time. Thus, the EEG cannot establish the diagnosis of epilepsy in many cases.

www.ketabpezeshki.com (021) 66485457 - 66485438

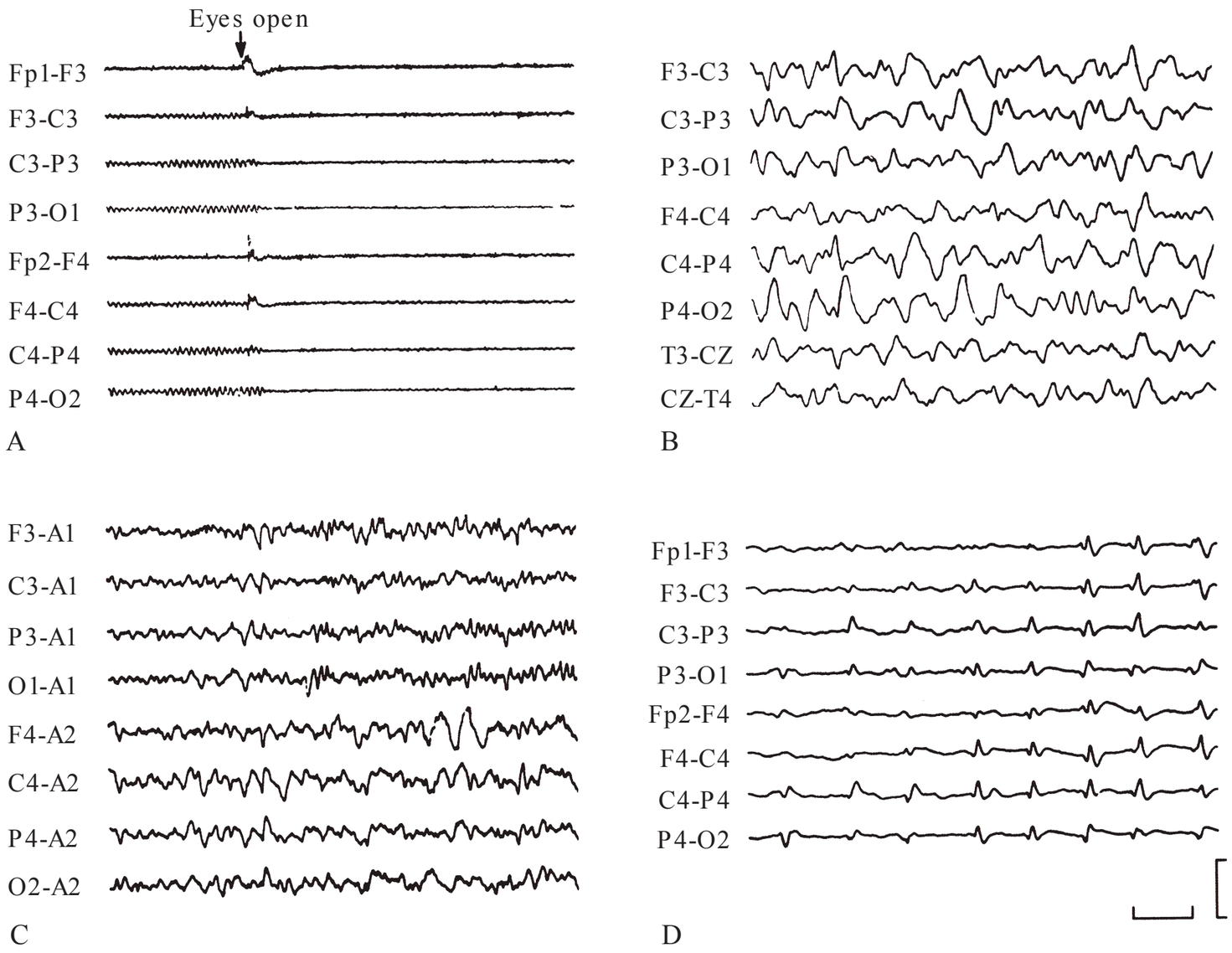


FIGURE 6-1

A. Normal electroencephalogram (EEG) showing a posteriorly situated 9-Hz alpha rhythm that attenuates with eye opening. B. Abnormal EEG showing irregular diffuse slow activity in an obtunded patient with encephalitis. C. Irregular slow activity in the right central region, on a diffusely slowed background, in a patient with a right parietal glioma. D. Periodic complexes occurring once every second in a patient with Creutzfeldt-Jakob disease. Horizontal calibration: 1 s; vertical calibration: 200 μV in A, 300 μV in other panels. In this and the following figure, electrode placements are indicated at the left of each panel and accord with the international 10:20 system. A, earlobe; C, central; F, frontal; Fp, frontal polar; P, parietal; T, temporal; O, occipital. Right-sided placements are indicated by even numbers, left-sided placements by odd numbers, and midline placements by Z. (From MJ Aminoff [ed]: Aminoff's Electrodiagnosis in Clinical Neurology, 6th ed. Oxford, Elsevier Saunders, 2012.)

The EEG findings have been used in classifying seizure disorders and selecting appropriate anticonvulsant medication for individual patients **(Fig. 6-2)**. The episodic generalized spike-wave activity that occurs during and between seizures in patients with typical absence epilepsy contrasts with focal interictal epileptiform discharges or ictal patterns found in patients with focal seizures. These latter seizures may have no correlates in the scalp-recorded EEG or may be associated with abnormal rhythmic activity of variable frequency, a localized or generalized distribution, and a stereotyped pattern that varies with the patient. Focal or lateralized epileptogenic lesions are important to recognize, especially if surgical treatment is contemplated. Intensive long-term monitoring of clinical behavior and the EEG is required for operative candidates, however, and this generally also involves recording from intracranial (subdural, extradural, or intracerebral) electrodes.

The EEG findings may indicate the prognosis of seizure disorders: In general, a normal EEG implies a better prognosis than otherwise, whereas an abnormal background or profuse epileptiform activity suggests a poor outlook. The EEG findings are not helpful in determining which patients with head injuries, stroke, or brain tumors will go on to develop seizures, because in such circumstances epileptiform activity is commonly encountered regardless of whether seizures occur. The EEG findings are of limited utility in determining whether anticonvulsant medication can be discontinued after several seizure-free years. Further seizures may occur after withdrawal of anticonvulsant medication despite a normal EEG or, conversely, may not occur despite a continuing EEG abnormality. The decision to discontinue anticonvulsant medication is made on clinical grounds, and the EEG is helpful only for providing guidance when there is clinical ambiguity or the patient requires reassurance about a particular course of action.

The EEG has no role in the management of tonic-clonic status epilepticus except when there is clinical uncertainty about whether seizures are continuing in a comatose patient. In patients treated by drug-induced coma for refractory status epilepticus, the EEG findings indicate the level of anesthesia and whether seizures

www.ketabpezeshki.com (021) 66485457 - 66485438

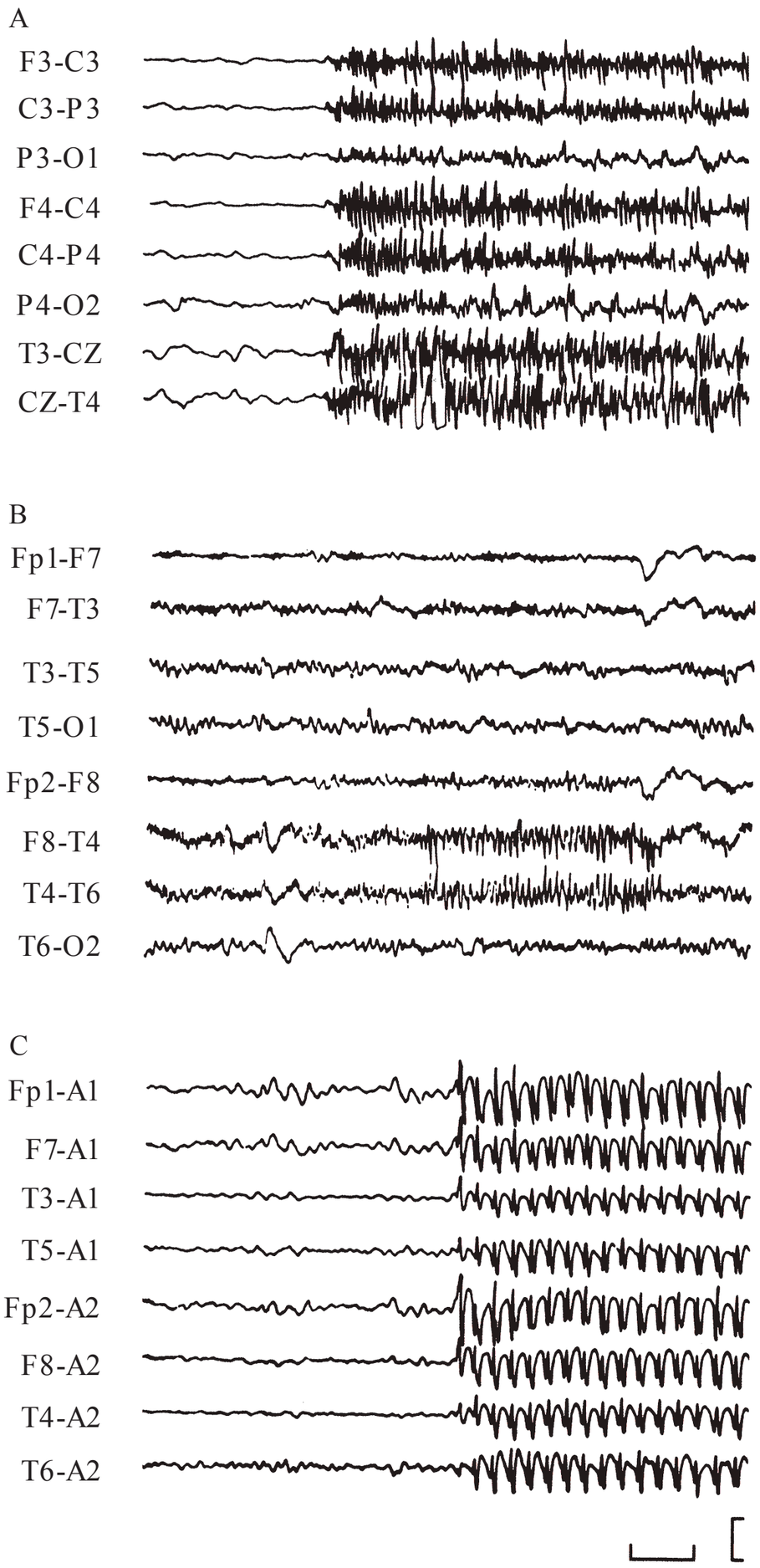


FIGURE 6-2

Electrographic seizures. A. Onset of a tonic seizure showing generalized repetitive sharp activity with synchronous onset over both hemispheres. B. Burst of repetitive spikes occurring with sudden onset in the right temporal region during a clinical spell characterized by transient impairment of external awareness. C. Generalized 3-Hz spike-wave activity occurring synchronously over both hemispheres during an absence (petit mal) attack. Horizontal calibration: 1 s; vertical calibration: 400 μV in A, 200 μV in B, and 750 μV in C. (From MJ Aminoff [ed]: Aminoff's Electrodiagnosis in Clinical Neurology, 6th ed. Oxford, Elsevier Saunders, 2012.)

are occurring. During status epilepticus, the EEG shows repeated electrographic seizures or continuous spike-wave discharges. In nonconvulsive status epilepticus, a disorder that may not be recognized unless an EEG is performed, the EEG may also show continuous spike-wave activity ("spike-wave stupor") or, less commonly, repetitive electrographic seizures (focal status epilepticus).

THE EEG AND COMA

The EEG tends to become slower as consciousness is depressed, regardless of the underlying cause (Fig. 6-1). Other findings may suggest diagnostic possibilities, as when electrographic seizures are found or a focal abnormality indicates a structural lesion. The EEG generally slows in metabolic encephalopathies, and triphasic waves may be present. The findings do not permit differentiation of the underlying metabolic disturbance but help to exclude other encephalopathic processes by indicating the diffuse extent of cerebral dysfunction. An EEG responsive to external stimulation is helpful prognostically because electrocerebral responsiveness implies a lighter level of coma than a nonreactive EEG, and thus a better prognosis. Serial records provide a better guide to prognosis than a single record and supplement the clinical examination in following the course of events. As the depth of coma increases, the EEG becomes nonreactive and may show a burst-suppression pattern, with bursts of mixed-frequency activity separated by intervals of relative cerebral inactivity. In other instances there is a reduction in amplitude of the EEG until eventually activity cannot be detected. Such electrocerebral silence does not necessarily reflect irreversible brain damage, because it may occur reversibly in hypothermic patients or with drug overdose. The prognosis of electrocerebral silence, when recorded using an adequate technique, therefore depends on the clinical context in which it is found. In patients with severe cerebral anoxia, for example, electrocerebral silence in a technically satisfactory record implies that useful cognitive recovery will not occur.

In patients with clinically suspected brain death, an EEG recorded using appropriate technical standards may be confirmatory by showing electrocerebral silence, but disorders that may produce a similar but reversible EEG appearance must be excluded. The presence of residual EEG activity in suspected brain death fails to confirm the diagnosis but does not exclude it. The EEG is usually normal in patients with locked-in syndrome **(Chap. 32)**, and helps in distinguishing this disorder from the comatose state with which it is sometimes confused clinically.

THE EEG IN OTHER NEUROLOGIC DISORDERS

In developed countries, computed tomography (CT) scanning and magnetic resonance imaging (MRI) are used as a noninvasive means of screening for focal structural abnormalities of the brain, such as tumors, infarcts, or hematomas (Fig. 6-1). The EEG is still used for this purpose in many parts of the world, however, although infratentorial or slowly expanding lesions may not be recognized. Focal slow-wave disturbances,

www.ketabpezeshki.com (021) 66485457 - 66485438

a localized loss of electrocerebral activity, or more generalized electrocerebral disturbances are common findings but do not indicate the nature of the underlying pathology.

In patients with an acute encephalopathy, focal or lateralized periodic slow-wave complexes, sometimes with a sharpened outline, suggest a diagnosis of herpes simplex encephalitis, and periodic lateralizing epileptiform discharges (PLEDs) are commonly found with acute hemispheric pathology such as a hematoma, abscess, or rapidly expanding tumor. T e EEG findings in dementia are usually nonspecific and do not distinguish reliably between different underlying causes except in rare instances when the presence of complexes occurring with a regular repetition rate ("periodic complexes") supports a diagnosis of Creutzfeldt-Jakob disease (Fig. 6-1) or subacute sclerosing panencephalitis. In most patients with dementia, the EEG is normal or diffusely slowed, and the findings alone cannot indicate whether a patient is demented or distinguish between dementia and pseudodementia.

CONTINUOUS EEG MONITORING

T e brief EEG obtained routinely in the laboratory often fails to reveal abnormalities that are transient and infrequent. Continuous monitoring over 12 or 24 hours or longer may detect abnormalities or capture clinical events that otherwise would be missed. T e EEG is often recorded continuously in critically ill patients to detect early changes in neurologic status. Continuous EEG recording in this context has been used to detect acute events such as from nonconvulsive seizures or developing cerebral ischemia, to monitor cerebral function in patients with metabolic disorders such as liver failure, and to manage the level of anesthesia in pharmacologically induced coma.

MAGNETOENCEPHALOGRAPHY AND MAGNETIC SOURCE IMAGING

Recording the magnetic field of the electrical activity of the brain (magnetoencephalography [MEG]) provides a means of examining cerebral activity that is less subject to distortion by other biologic tissues than the EEG. MEG is used in only a few specialized centers because of the complexity and expense of the necessary equipment. It permits the source of activity to be localized and coregistered with the MRI in a technique that is known as magnetic source imaging. In patients with focal epilepsy, MEG is useful in localizing epileptogenic foci for surgery and for guiding the placement of intracranial electrodes for electrophysiologic monitoring. MEG has also been used for mapping brain tumors, identifying the central fissure preoperatively, and localizing functionally eloquent cortical areas such as those concerned with language.

EVOKED POTENTIALS

SENSORY EVOKED POTENTIALS

T e noninvasive recording of spinal or cerebral potentials elicited by stimulation of specific afferent pathways allows the functional integrity of these pathways to be monitored but does not indicate the pathologic basis of lesions involving them. Such evoked potentials (EPs) are small compared to the background EEG activity, and the responses to a number of stimuli are therefore recorded and averaged with a computer to permit their recognition and definition. T e background EEG activity, which has no fixed temporal relationship to the stimulus, is averaged out by this procedure.

Visual evoked potentials (VEPs) are elicited by monocular stimulation with a reversing checkerboard pattern and are recorded from the occipital region in the midline and on either side of the scalp. T e component of major clinical importance is the so-called P100 response, a positive peak having a latency of approximately 100 ms. Its presence, latency, and symmetry over the two sides of the scalp are noted. Amplitude changes are less helpful for the recognition of pathology. VEPs are most useful in detecting dysfunction of the visual pathways anterior to the optic chiasm. In acute severe optic neuritis, the P100 is frequently lost or grossly attenuated; as clinical recovery occurs, it is restored but with an increased latency that generally remains abnormal indefinitely. T e VEP findings are therefore helpful in indicating previous or subclinical optic neuritis. T ey may also be abnormal with ocular abnormalities and with other causes of optic nerve disease, such as ischemia or compression by a tumor. Flash-elicited VEPs may be normal in patients with cortical blindness.

Routine VEPs record a mass response over a relatively large cortical area and thus may be insensitive to localized waveform abnormalities. A newer technique, multifocal VEP, measures responses from 120 individual sectors within each affected eye and is more sensitive than routine VEP.

Brainstem auditory evoked potentials (BAEPs) are elicited by monaural stimulation with repetitive clicks and are recorded between the vertex of the scalp and the mastoid process or earlobe. A series of potentials, designated by roman numerals, occurs in the first 10 ms after the stimulus and represents in part the sequential activation of different structures in the pathway between the auditory nerve (wave I) and the inferior colliculus (wave V) in the midbrain. T e presence,

www.ketabpezeshki.com (021) 66485457 - 66485438

latency, and interpeak latency of the first five positive potentials recorded at the vertex are evaluated. T e findings are helpful in screening for acoustic neuromas, detecting brainstem pathology, and evaluating comatose patients. T e BAEPs are often normal in coma due to metabolic/toxic disorders or bihemispheric disease but are typically abnormal in the presence of brainstem pathology.

Somatosensory evoked potentials (SSEPs) are recorded over the scalp and spine in response to electrical stimulation of a peripheral (mixed or cutaneous) nerve. T e configuration, polarity, and latency of the responses depend on the nerve that is stimulated and on the recording arrangements. SSEPs are used to evaluate proximal (otherwise inaccessible) portions of the peripheral nervous system and the integrity of the central somatosensory pathways, especially in patients who are comatose or suspected to be brain dead.

Clinical utility of EPs

EP studies may detect and localize lesions in afferent pathways in the central nervous system (CNS). T ey have been used particularly to investigate patients with suspected multiple sclerosis (MS), the diagnosis of which requires the recognition of multifocal white-matter lesions. In patients with clinical evidence of a single lesion, the electrophysiologic recognition of abnormalities in other sites helps to support the diagnosis but does not establish it unequivocally. Multimodality EP abnormalities are not specific for MS; they may occur in AIDS, Lyme disease, systemic lupus erythematosus, neurosyphilis, spinocerebellar degenerations, familial spastic paraplegia, and deficiency of vitamin E or B_{12}, among other disorders. T e diagnostic utility of the EP findings therefore depends on the circumstances in which they are found. Abnormalities may aid in the localization of lesions to broad areas of the CNS, but attempts at precise localization may be misleading because the generators of many components are unknown.

T e EP findings are sometimes of prognostic relevance. Bilateral loss of cortically generated SSEP components implies that cognition may not be regained in posttraumatic or postanoxic coma, and EP studies may also be useful in evaluating patients with suspected brain death. In patients who are comatose for uncertain reasons, preserved BAEPs suggest either a metabolic-toxic etiology or bihemispheric disease. In patients with spinal cord injuries, SSEPs have been used to indicate the completeness of the lesion. T e presence or early return of a cortically generated response to stimulation of a nerve below the injured segment of the cord indicates an incomplete lesion and thus a better prognosis for functional recovery than otherwise. In surgery, intraoperative EP monitoring of neural structures placed at risk by the procedure may permit the early recognition of dysfunction and thereby permit a neurologic complication to be averted or minimized.

Visual and auditory acuity may be determined using EP techniques in patients whose age or mental state precludes traditional ophthalmologic or audiologic examinations.

COGNITIVE EVOKED POTENTIALS

Certain EP components depend on the mental attention of the subject and the setting in which the stimulus occurs, rather than simply on the physical characteristics of the stimulus. Such "event-related" potentials (ERPs) or "endogenous" potentials are related in some manner to the cognitive aspects of distinguishing an infrequently occurring target stimulus from other stimuli occurring more frequently. For clinical purposes, attention has been directed particularly at the so-called P3 component of the ERP, which is also designated the P300 component because of its positive polarity and latency of approximately 300–400 ms after onset of an auditory target stimulus. T e P3 component is prolonged in latency in many patients with dementia, whereas it is generally normal in patients with depression or other disorders simulating dementia. ERPs are, therefore, sometimes helpful in making this distinction when there is clinical uncertainty, although a response of normal latency does not exclude dementia.

MOTOR EVOKED POTENTIALS

T e electrical potentials recorded from muscle or the spinal cord following stimulation of the motor cortex or central motor pathways are referred to as motor evoked potentials. For clinical purposes, such responses are recorded most often as the compound muscle action potentials elicited by transcutaneous magnetic stimulation of the motor cortex. A strong but brief magnetic field is produced by passing a current through a coil, and this induces stimulating currents in the subjacent neural tissue. T e procedure is painless and apparently safe. Abnormalities have been described in several neurologic disorders with clinical or subclinical involvement of central motor pathways, including MS and motor neuron disease. In addition to a possible role in diagnosis or evaluating the extent of pathologic involvement, the technique provides information of prognostic relevance (e.g., in suggesting the likelihood of recovery of motor function after stroke) and provides a means of monitoring intraoperatively the functional integrity of central motor tracts. Nevertheless, it is not used widely for clinical purposes.

www.ketabpezeshki.com (021) 66485457 - 66485438

ELECTROPHYSIOLOGIC STUDIES OF MUSCLE AND NERVE

The motor unit is the basic element subserving motor function. It is defined as an anterior horn cell, its axon and neuromuscular junctions, and all the muscle fibers innervated by the axon. The number of motor units in a muscle ranges from approximately 10 in the extraocular muscles to several thousand in the large muscles of the legs. There is considerable variation in the average number of muscle fibers within the motor units of an individual muscle, i.e., in the innervation ratio of different muscles. Thus the innervation ratio is <25 in the human external rectus or platysma muscle and between 1600 and 1700 in the medial head of the gastrocnemius muscle. The muscle fibers of individual motor units are divided into two general types by distinctive contractile properties, histochemical stains, and characteristic responses to fatigue. Within each motor unit, all of the muscle fibers are of the same type.

ELECTROMYOGRAPHY

The pattern of electrical activity in muscle, i.e., the electromyogram (EMG), may be recorded both at rest and during activity from a needle electrode inserted into the muscle. The nature and pattern of abnormalities relate to disorders at different levels of the motor unit.

Relaxed muscle normally is electrically silent except in the end-plate region, but abnormal spontaneous activity **(Fig. 6-3)** occurs in various neuromuscular disorders, especially those associated with denervation or inflammatory changes in affected muscle. Fibrillation potentials and positive sharp waves (which reflect muscle fiber irritability) and complex repetitive discharges are most often—but not always—found in denervated muscle and may also occur after muscle injury and in certain myopathic disorders, especially inflammatory disorders such as polymyositis. After an acute neuropathic lesion, they occur earlier in proximal than distal muscles and sometimes do not develop distally in the extremities for 4–6 weeks; once present, they may persist indefinitely unless reinnervation occurs or the muscle degenerates so completely that no viable tissue remains. Fasciculation potentials (which reflect the spontaneous activity of individual motor units) are characteristic of slowly progressive neuropathic disorders, especially those with degeneration of anterior horn cells (such as amyotrophic lateral sclerosis). Myotonic discharges—high-frequency discharges of potentials derived from single muscle fibers that wax and wane in amplitude and frequency—are the signature of myotonic disorders such as myotonic dystrophy or myotonia congenita but occur occasionally in polymyositis or other, rarer, disorders.

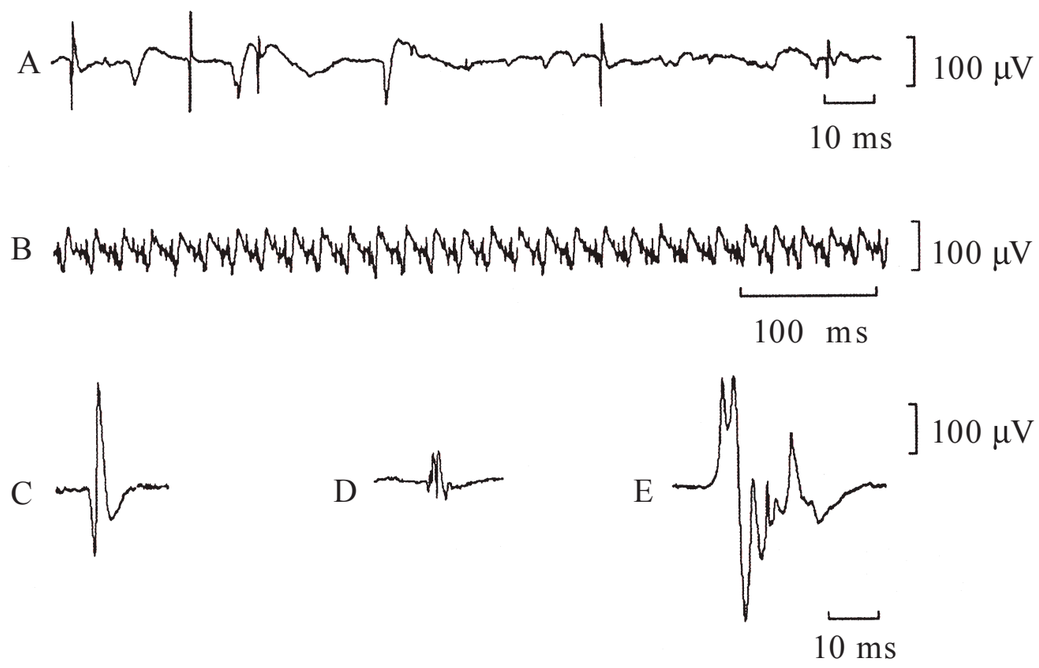


FIGURE 6-3
Activity recorded during electromyography (EMG). A. Spontaneous fibrillation potentials and positive sharp waves. B. Complex repetitive discharges recorded in partially denervated muscle at rest. C. Normal triphasic motor unit action potential. D. Small, short-duration, polyphasic motor unit action potential such as is commonly encountered in myopathic disorders. E. Long-duration polyphasic motor unit action potential such as may be seen in chronic neuropathic disorders.

Slight voluntary contraction of a muscle leads to activation of a small number of motor units. The potentials generated by muscle fibers of these units that are within the pickup range of the needle electrode will be recorded (Fig. 6-3). The parameters of normal motor unit action potentials depend on the muscle under study and age of the patient, but their duration is normally between 5 and 15 ms, amplitude is between 200 μV and 2 mV, and most are bi- or triphasic. The number of units activated depends on the degree of voluntary activity. An increase in muscle contraction is associated with an increase in the number of motor units that are activated (recruited) and in the frequency of discharge. With a full contraction, so many motor units are normally activated that individual motor unit action potentials can no longer be distinguished, and a complete interference pattern is said to have been produced.

The incidence of small, short-duration, polyphasic motor unit action potentials (i.e., having more than four phases) is usually increased in myopathic muscle, and an excessive number of units is activated for a specified degree of voluntary activity. By contrast, the loss of motor units that occurs in neuropathic disorders leads to a reduction in number of units activated during a maximal contraction and an increase in their firing rate, i.e., there is an incomplete or reduced interference pattern. The configuration and dimensions of the potentials may also be abnormal, depending on the duration of the neuropathic process. The surviving motor units are initially normal in configuration but, as reinnervation occurs, they increase in amplitude and duration and become polyphasic (Fig. 6-3).

www.ketabpezeshki.com (021) 66485457 - 66485438

Action potentials from the same motor unit sometimes fire with a consistent temporal relationship to each other, so that double, triple, or multiple discharges are recorded, especially in tetany, hemifacial spasm, or myokymia.

Electrical silence characterizes the involuntary, sustained muscle contraction that occurs in phosphorylase deficiency, which is designated a contracture.

EMG enables disorders of the motor units to be detected and characterized as either neurogenic or myopathic. In neurogenic disorders, the pattern of affected muscles may localize the lesion to the anterior horn cells or to a specific site as the axons traverse a nerve root, limb plexus, and peripheral nerve to their terminal arborizations. T e findings do not enable a specific etiologic diagnosis to be made, however, except in conjunction with the clinical findings and results of other laboratory studies.

T e findings may provide a guide to the severity of an acute disorder of a peripheral or cranial nerve (by indicating whether denervation has occurred and the completeness of the lesion) and whether the pathologic process is active or progressive in chronic or degenerative disorders such as amyotrophic lateral sclerosis. Such information is important for prognostic purposes.

Various quantitative EMG approaches have been developed. T e most common is to determine the mean duration and amplitude of 20 motor unit action potentials using a standardized technique. T e technique of macro-EMG provides information about the number and size of muscle fibers in a larger volume of the motor unit territory and has also been used to estimate the number of motor units in a muscle. Scanning EMG is a computer-based technique that has been used to study the topography of motor unit action potentials and, in particular, the spatial and temporal distribution of activity in individual units. T e technique of single-fiber EMG is discussed separately below.

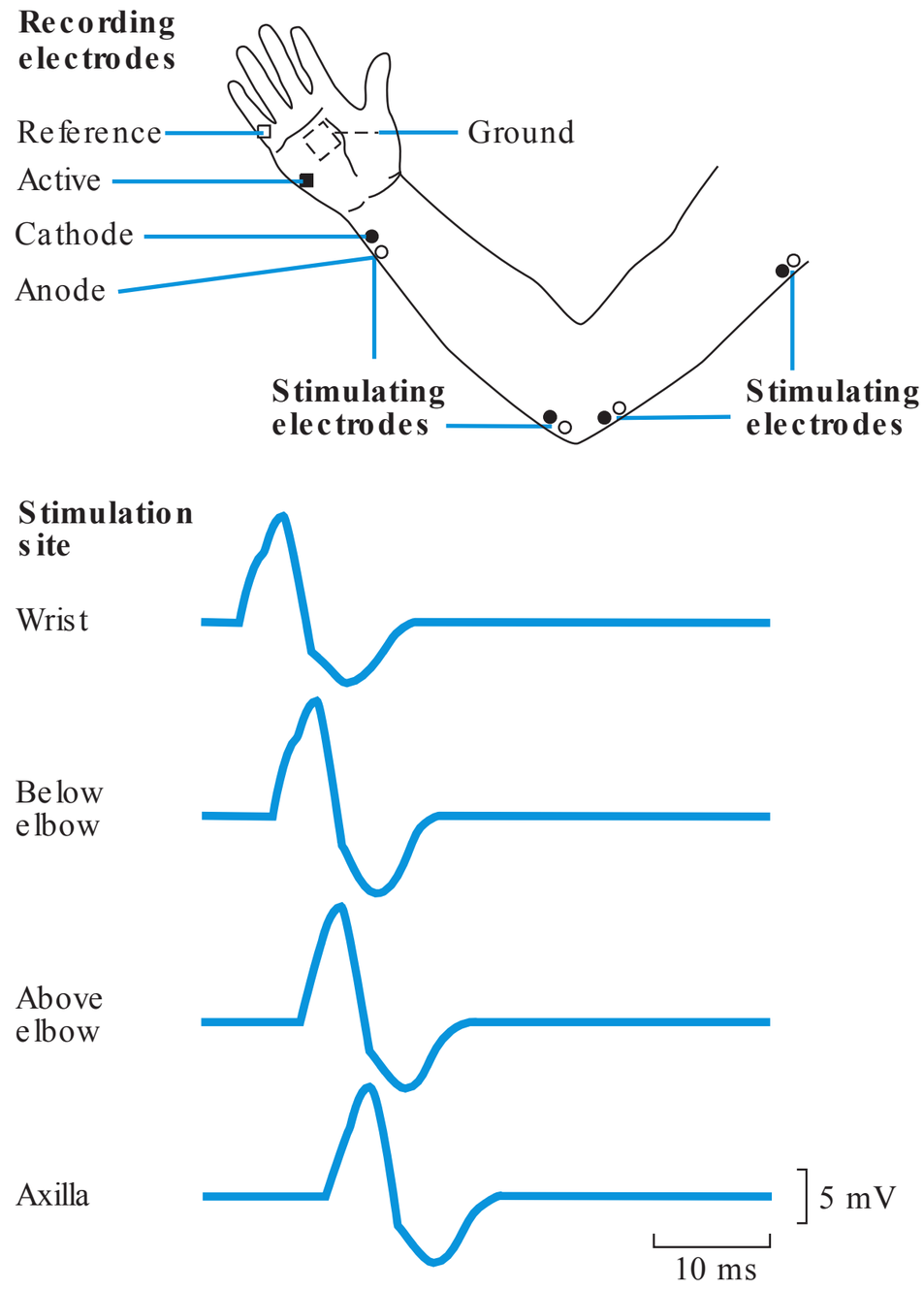


FIGURE 6-4

Arrangement for motor conduction studies of the ulnar nerve. Responses are recorded with a surface electrode from the abductor digiti minimi muscle to supramaximal stimulation of the nerve at different sites, and are shown in the lower panel. (From MJ Aminof : Electromyography in Clinical Practice: Electrodiagnostic Aspects of Neuromuscular Disease, 3rd ed. New York, Churchill Livingstone, 1998.)

NERVE CONDUCTION STUDIES

Recording of the electrical response of a muscle to stimulation of its motor nerve at two or more points along its course **(Fig. 6-4)** permits conduction velocity to be determined in the fastest conducting motor fibers between the points of stimulation. T e latency and amplitude of the electrical response of muscle (i.e., of the compound muscle action potential) to stimulation of its motor nerve at a distal site are also compared with values defined in normal subjects. Sensory nerve conduction studies are performed by determining the conduction velocity and amplitude of action potentials in sensory fibers when these fibers are stimulated at one point and the responses are recorded at another point along the course of the nerve. In adults, conduction velocity in the arms is normally between 50 and 70 m/s, and in the legs is between 40 and 60 m/s.

Nerve conduction studies complement the EMG examination, enabling the presence and extent of peripheral nerve pathology to be determined. T ey are particularly helpful in determining whether sensory symptoms are arising from pathology proximal or distal to the dorsal root ganglia (in the former instance, peripheral sensory conduction studies is normal) and whether neuromuscular dysfunction relates to peripheral nerve disease. In patients with a mononeuropathy, they are invaluable as a means of localizing a focal nerve lesion, determining the extent and severity of the underlying pathology, providing a guide to prognosis, and detecting subclinical involvement of other nerves. T ey enable a polyneuropathy to be distinguished from a mononeuropathy multiplex, which has important etiologic implications. Nerve conduction studies provide a means of following the progression and therapeutic response of peripheral nerve disorders and are used

www.ketabpezeshki.com (021) 66485457 - 66485438

widely for this purpose in clinical trials. They may suggest the underlying pathologic basis in individual cases. Conduction velocity is often markedly slowed, terminal motor latencies are prolonged, and compound motor and sensory nerve action potentials may be dispersed in the demyelinative neuropathies (such as in Guillain-Barré syndrome, chronic inflammatory polyneuropathy, metachromatic leukodystrophy, or certain hereditary neuropathies); conduction block is frequent in acquired varieties of these neuropathies. By contrast, conduction velocity is normal or slowed only mildly, sensory nerve action potentials are small or absent, and there is EMG evidence of denervation in axonal neuropathies such as occur in association with metabolic or toxic disorders.

The utility and complementary role of EMG and nerve conduction studies are best illustrated by reference to a common clinical problem. Numbness and paresthesias of the little finger and associated wasting of the intrinsic muscles of the hand may result from a spinal cord lesion, C8/T1 radiculopathy, brachial plexopathy (lower trunk or medial cord), or a lesion of the ulnar nerve. If sensory nerve action potentials can be recorded normally at the wrist following stimulation of the digital fibers in the affected finger, the pathology is probably proximal to the dorsal root ganglia (i.e., there is a radiculopathy or more central lesion); absence of the sensory potentials, by contrast, suggests distal pathology. EMG examination will indicate whether the pattern of affected muscles conforms to radicular or ulnar nerve territory or is more extensive (thereby favoring a plexopathy). Ulnar motor conduction studies will generally also distinguish between a radiculopathy (normal findings) and ulnar neuropathy (abnormal findings) and will often identify the site of an ulnar nerve lesion. The nerve is stimulated at several points along its course to determine whether the compound action potential recorded from a distal muscle that it supplies shows a marked alteration in size or area or a disproportionate change in latency, with stimulation at a particular site. The electrophysiologic findings thus permit a definitive diagnosis to be made and specific treatment instituted in circumstances where there is clinical ambiguity.

F-WAVE STUDIES

Stimulation of a motor nerve causes impulses to travel antidromically (i.e., toward the spinal cord) as well as orthodromically (to the nerve terminals). Such antidromic impulses cause a few of the anterior horn cells to discharge, producing a small motor response that occurs considerably later than the direct response elicited by nerve stimulation. The F wave so elicited is sometimes abnormal (absent or delayed) with proximal pathology of the peripheral nervous system, such as a radiculopathy, and may therefore be helpful in detecting abnormalities when conventional nerve conduction studies are normal. In general, however, the clinical utility of F-wave studies has been disappointing, except perhaps in Guillain-Barré syndrome, where they are often absent or delayed.

H-REFLEX STUDIES

The H reflex is easily recorded only from the soleus muscle (S1) in normal adults. It is elicited by low-intensity stimulation of the tibial nerve and represents a monosynaptic reflex in which spindle (Ia) afferent fibers constitute the afferent arc and alpha motor axons the efferent pathway. The H reflexes are often absent bilaterally in elderly patients or with polyneuropathies and may be lost unilaterally in S1 radiculopathies.

MUSCLE RESPONSE TO REPETITIVE NERVE STIMULATION

The size of the electrical response of a muscle to supramaximal electrical stimulation of its motor nerve relates to the number of muscle fibers that are activated. Neuromuscular transmission can be tested by several different protocols, but the most helpful is to record with surface electrodes the electrical response of a muscle to supramaximal stimulation of its motor nerve by repetitive (2–3 Hz) shocks delivered before and at selected intervals after a maximal voluntary contraction.

There is normally little or no change in size of the muscle response to repetitive stimulation of a motor nerve at 2–3 Hz with stimuli delivered at intervals after voluntary contraction of the muscle for about 20–30 s, even though preceding activity in the junctional region influences the release of acetylcholine and thus the size of the end-plate potentials elicited by a test stimulus. This is because more acetylcholine is normally released than is required to bring the motor end-plate potentials to the threshold for generating muscle fiber action potentials. In disorders of neuromuscular transmission this safety factor is reduced. Thus in myasthenia gravis, repetitive stimulation, particularly at a rate of between 2 and 5 Hz, may lead to a depression of neuromuscular transmission, with a decrement in size of the response recorded from affected muscles. Similarly, immediately after a period of maximal voluntary activity, single or repetitive stimuli of the motor nerve may elicit larger muscle responses than before, indicating that more muscle fibers are responding. This postactivation facilitation of neuromuscular transmission is followed by a longer-lasting period of depression, maximal between 2 and 4 min after the conditioning period and lasting for as long as 10 min or so, during which responses are reduced in size.

www.ketabpezeshki.com (021) 66485457 - 66485438

Decrementing responses to repetitive stimulation at 2–5 Hz are common in myasthenia gravis but may also occur in the congenital myasthenic syndromes **(Chap. 55)**. In Lambert-Eaton myasthenic syndrome, in which there is defective release of acetylcholine at the neuromuscular junction, the compound muscle action potential elicited by a single stimulus is generally very small. With repetitive stimulation at rates of up to 10 Hz, the first few responses may decline in size, but subsequent responses increase. If faster rates of stimulation are used (20–50 Hz), the increment may be dramatic so that the amplitude of compound muscle action potentials eventually reaches a size that is several times larger than the initial response. In patients with botulism, the response to repetitive stimulation is similar to that in Lambert-Eaton myasthenic syndrome, although the findings are somewhat more variable and not all muscles are affected.

SINGLE-FIBER ELECTROMYOGRAPHY

T is technique is particularly helpful in detecting disorders of neuromuscular transmission. A special needle electrode is placed within a muscle and positioned to record action potentials from two muscle fibers belonging to the same motor unit. T e time interval between the two potentials will vary in consecutive discharges; this is called the neuromuscular jitter. T e jitter can be quantified as the mean difference between consecutive interpotential intervals and is normally between 10 and 50 μs. T is value is increased when neuromuscular transmission is disturbed for any reason, and in some instances impulses in individual muscle fibers may fail to occur because of impulse blocking at the neuromuscular junction. Single-fiber EMG is more sensitive than repetitive nerve stimulation or determination of acetylcholine receptor antibody levels in diagnosing myasthenia gravis.

Single-fiber EMG can also be used to determine the mean fiber density of motor units (i.e., mean number of muscle fibers per motor unit within the recording area) and to estimate the number of motor units in a muscle, but this is of less immediate clinical relevance.

BLINK REFLEXES

Electrical or mechanical stimulation of the supraorbital nerve on one side leads to two separate ref ex responses of the orbicularis oculi—an ipsilateral R1 response having a latency of approximately 10 ms and a bilateral R2 response with a latency in the order of 30 ms. T e trigeminal and facial nerves constitute the afferent and efferent arcs of the ref ex, respectively. Abnormalities of either nerve or intrinsic lesions of the medulla or pons may lead to uni- or bilateral loss of the response, and the findings may therefore be helpful in identifying or localizing such pathology.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 7

TECHNIQUE OF LUMBAR PUNCTURE

Elizabeth Robbins ■ Stephen L. Hauser

In experienced hands, lumbar puncture (LP) is usually a safe procedure. Major complications are extremely uncommon but can include cerebral herniation, injury to the spinal cord or nerve roots, hemorrhage (spinal hematoma), or infection. Minor complications occur with greater frequency and can include backache, post-LP headache, and radicular pain or numbness.

IMAGING AND LABORATORY STUDIES PRIOR TO LP

Patients with an altered level of consciousness, a focal neurologic deficit, new-onset seizure, papilledema, or an immunocompromised state are at increased risk for potentially fatal cerebellar or tentorial herniation following LP. Neuroimaging should be obtained in these patients prior to LP to exclude a focal mass lesion or diffuse swelling. Imaging studies should include the spine in patients with symptoms suggesting spinal cord compression, such as back pain, leg weakness, urinary retention, or incontinence. In patients with suspected meningitis who require neuroimaging prior to diagnostic LP, administration of antibiotics, preferably following blood culture, should precede the neuroimaging study.

LP should not be performed through infected skin, as organisms can be introduced into the subarachnoid space (SAS).

Patients with coagulation defects including thrombocytopenia are at increased risk of post-LP spinal subdural or epidural hematomas, either of which can produce permanent nerve injury and/or paralysis. If a bleeding disorder is suspected, the platelet count, international normalized ratio (INR), and partial thromboplastin time should be checked prior to LP. T ere are no data available to assess the safety of LP in patients with low platelet counts; a count of <20,000/μL is considered to be a contraindication to LP. Bleeding complications rarely occur in patients with platelet counts ≥50,000/μL and an INR ≤1.5. Some institutions recommend that the platelet count be >40,000 prior to LP.

GUIDELINES FOR PATIENTS RECEIVING ANTICOAGULANT OR ANTIPLATELT MEDICATIONS

T ere is an increased risk of bleeding complications if an LP is performed in a patient receiving antiplatelet or anticoagulant medications. T e risk is further increased when multiple anticoagulant medications are used or when the level of anticoagulation is high. T e most common site of bleeding is the epidural space. Symptoms of bleeding following an LP can include a sensory or motor deficit and/or bowel/bladder dysfunction; back pain occurs less commonly. For serious deficits such as paraparesis, immediate surgical intervention, ideally within 8 h of onset of weakness, is important to minimize permanent disability; surgical intervention after 24 h is associated with a poor outcome.

Only limited data are available to guide decisions about performing LPs in patients receiving anticoagulant drugs. Information about managing antiplatelet and anticoagulation drugs during invasive surgical procedures is often available from the prescribing information provided by the drug manufacturer. Evidence-based guidelines for management of regional anesthetic procedures including spinal and epidural blocks in patients receiving anticoagulation have been developed by the American Society of Regional Anesthesia and Pain (ASRA); these guidelines can help guide decisions by physicians considering LP in patients receiving anticoagulation. Management of these patients can be complex and needs to consider both the risk of LP-related hemorrhage as well as the risk of reversing therapeutic anticoagulation prior to LP. Guidelines for some commonly used anticoagulants are summarized below.

www.ketabpezeshki.com (021) 66485457 - 66485438

Unfractionated heparin, therapeutic dosing

The ASRA 2010 Practice Advisory recommends discontinuing unfractionated heparin (UFH) 2–4 h prior to removal of spinal or epidural catheters to minimize risk of hematoma. Similar guidelines are reasonable for patients undergoing LP: discontinue UFH 2–4 h prior to LP; document normal partial thromboplastin time (PTT) prior to the procedure; and document a normal platelet count in patients who have received heparin for 4 days or longer because of the risk of heparin-induced thrombocytopenia (HIT). The half-life of heparin is 60–90 min.

Unfractionated heparin, prophylactic dosing

There are only a few case reports of spinal hematoma resulting from spinal or epidural anesthetic procedures in patients receiving low-dose subcutaneous UFH; ASRA guidelines state that there is no contraindication to the use of these techniques for anesthesia in patients receiving prophylactic UFH at a dose of 5000 U subcutaneously twice daily. Similarly, LP in patients receiving 5000 U of UFH subcutaneously twice daily is unlikely to cause spinal hematoma. Precautions to minimize risk include the following: document a normal PTT prior to the LP; document a normal platelet count in patients who have received heparin for 4 days or longer; and perform the LP 1–2 h prior to the next heparin dose, when the heparin effect should be minimal.

Low-molecular-weight heparin, therapeutic dose (e.g., enoxaparin 1 mg/kg subcutaneously q12h)

Patients receiving low-molecular-weight heparin (LMWH) are at increased risk of post-LP spinal or epidural hematoma. LMWH dose should be held for at least 24 h before the procedure.

Low-molecular-weight heparin, prophylactic dose (e.g., enoxaparin 0.5 mg/kg subcutaneously q12h)

Patients receiving prophylactic-dose LMWH have altered coagulation. ASRA guidelines recommend waiting at least 10–12 h after a prophylactic dose of LMWH before inserting a spinal or epidural catheter to minimize the risk of spinal or epidural hematoma. Similar guidelines are reasonable for patients undergoing LP.

Warfarin

Spinal puncture is contraindicated during warfarin therapy.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)

ASRA guidelines conclude that use of these drugs does not appear to be associated with an added significant risk of spinal bleeding in patients having spinal or epidural anesthesia. Similarly, LP in patients receiving one of these drugs is unlikely to cause bleeding. Reversal of drug effect on platelet function requires stopping the drug for approximately 10 days for aspirin and for 48 h for NSAIDs.

Ticlopidine/clopidogrel

The actual risk of spinal hematoma with these drugs is unknown. Based on drug prescribing information and surgical reviews, ASRA guidelines suggest discontinuing ticlopidine 14 days prior to a spinal or epidural procedure and discontinuing clopidogrel 7 days prior to the procedure. Similar guidelines are reasonable for performing LP.

Abciximab, eptifibatide, and other platelet glycoprotein IIb/IIIa inhibitors

The actual risk of spinal hematoma with these drugs is unknown. Platelet aggregation remains abnormal for 24–48 h following discontinuation of abciximab and 4–8 h following discontinuation of eptifibatide. ASRA guidelines recommend avoiding spinal or epidural procedures until platelet function is normal. Similar guidelines are reasonable for performing LP.

Direct thrombin inhibitors (e.g., argatroban, bivalirudin)

ASRA guidelines recommend against performing spinal or epidural anesthesia in patients receiving thrombin inhibitors.

Oral factor Xa inhibitor (e.g., rivaroxaban)

Rivaroxaban prescribing information includes a black box warning that epidural or spinal hematomas have occurred in patients treated with rivaroxaban who are receiving spinal or epidural anesthesia or undergoing LP. LP should be avoided in patients receiving this drug.

ANALGESIA

Anxiety and pain can be minimized prior to beginning the procedure. Anxiety can be allayed by the use of lorazepam, 1–2 mg given PO 30 min prior to the procedure or IV 5 min prior to the procedure. Topical anesthesia can be achieved by the application of a lidocaine-based cream. Lidocaine 4% is effective when

www.ketabpezeshki.com (021) 66485457 - 66485438

applied 30 min prior to the procedure; lidocaine/prilocaine requires 60–120 min. The cream should be applied in a thick layer so that it completely covers the skin; an occlusive dressing is used to keep the cream in place.

POSITIONING

Proper positioning of the patient is essential. The procedure should be performed on a firm surface; if the procedure is to be performed at the bedside, the patient should be positioned at the edge of the bed and not in the middle. The patient is asked to lie on his or her side, facing away from the examiner, and to "roll up into a ball." The neck is gently ante-flexed and the thighs pulled up toward the abdomen; the shoulders and pelvis should be vertically aligned without forward or backward tilt **(Fig. 7-1)**. The spinal cord terminates at approximately the L1 vertebral level in 94% of individuals. In the remaining 6%, the conus extends to the L2–L3 interspace. LP is therefore performed at or below the L3–L4 interspace. A useful anatomic guide is a line drawn between the posterior superior iliac crests, which corresponds closely to the level of the L3–L4 interspace. The interspace is chosen following gentle palpation to identify the spinous processes at each lumbar level.

An alternative to the lateral recumbent position is the seated position. The patient sits at the side of the bed, with feet supported on a chair. The patient is instructed to curl forward, trying to touch the nose to the umbilicus. It is important that the patient not simply lean forward onto a bedside tabletop, as this is not an optimal position for opening up the spinous processes. LP is sometimes more easily performed in obese patients if they are sitting. A disadvantage of the seated position is that measurement of opening pressure is not accurate. In situations in which LP is difficult using palpable spinal landmarks, bedside ultrasound to guide needle placement may be used. In some particularly difficult situations, a computed tomography (CT)-guided needle placement may be necessary.

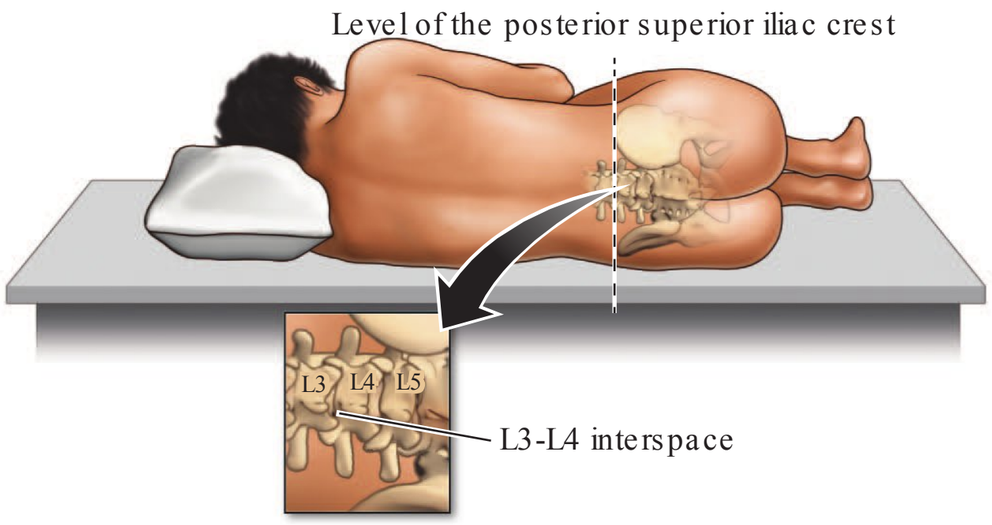


FIGURE 7-1
Proper positioning of a patient in the lateral decubitus position. Note that the shoulders and hips are in a vertical plane; the torso is perpendicular to the bed. (From RP Simon et al [eds]: Clinical Neurology, 7th ed. New York, McGraw-Hill, 2009.)

TECHNIQUE

Once the desired site for needle insertion has been identified, the examiner should put on sterile gloves. A mask is worn if the clinician will be injecting material into the spinal or epidural space to prevent droplet spread of oral flora during the procedure. After cleansing the skin with povidone-iodine or similar disinfectant, the area is draped with a sterile cloth; the needle insertion site is blotted dry using a sterile gauze pad. Proper local disinfection reduces the risk of introducing skin bacteria into the SAS or other sites. Local anesthetic, typically 1% lidocaine, 3–5 mL total, is injected into the subcutaneous tissue; in nonemergency situations, a topical anesthetic cream can be applied (see above). When time permits, pain associated with the injection of lidocaine can be minimized by slow, serial injections, each one progressively deeper than the last, over a period of ~5 min. Approximately 0.5–1 mL of lidocaine is injected at a time; the needle is not usually withdrawn between injections. A pause of ~15 s between injections helps to minimize the pain of the subsequent injection. The goal is to inject each mini-bolus of anesthetic into an area of skin that has become numb from the preceding injection. Approximately 5–10 mini-boluses are injected, using a total of ~5 mL of lidocaine.

If possible, the LP should be delayed for 10–15 min following the completion of the injection of anesthetic; this significantly decreases and can even eliminate pain from the procedure. Even a delay of 5 min will help to reduce pain.

The LP needle (typically 20- to 22-gauge) is inserted in the midline, midway between two spinous processes, and slowly advanced. The bevel of the needle should be maintained in a horizontal position, parallel to the direction of the dural fibers and with the flat portion of the bevel pointed upward; this minimizes injury to the fibers as the dura is penetrated. When LP is performed in patients who are sitting, the bevel should be maintained in the vertical position. In most adults, the needle is advanced 4–5 cm (1–2 in.) before the SAS is reached; the examiner usually recognizes entry as a sudden release of resistance, a "pop." If no fluid appears despite apparently correct needle placement, then the needle may be rotated 90°–180°. If there is still no fluid, the stylet is reinserted and the needle is advanced slightly. Some examiners halt needle advancement periodically to remove the stylet and check for

www.ketabpezeshki.com (021) 66485457 - 66485438

flow of cerebrospinal fluid (CSF). If the needle cannot be advanced because it hits bone, if the patient experiences sharp radiating pain down one leg, or if no fluid appears ("dry tap"), the needle is partially withdrawn and reinserted at a different angle. If on the second attempt the needle still hits bone (indicating lack of success in introducing it between the spinous processes), then the needle should be completely withdrawn and the patient should be repositioned. The second attempt is sometimes more successful if the patient straightens the spine completely prior to repositioning. The needle can then be reinserted at the same level or at an adjacent one.

Once the SAS is reached, a manometer is attached to the needle and the opening pressure measured. The examiner should look for normal oscillations in CSF pressure associated with pulse and respirations. The upper limit of normal opening pressure with the patient supine is 180 mmH_2O in adults but may be as high as 200–250 mmH_2O in obese adults.

CSF is allowed to drip into collection tubes; it should not be withdrawn with a syringe. Depending on the clinical indication, fluid is obtained for studies including: (1) cell count with differential; (2) protein and glucose concentrations; (3) culture (bacterial, fungal, mycobacterial, viral); (4) smears (e.g., Gram's and acid-fast stained smears); (5) antigen tests (e.g., latex agglutination); (6) polymerase chain reaction (PCR) amplification of DNA or RNA of microorganisms (e.g., herpes simplex virus, enteroviruses); (7) antibody levels against microorganisms; (8) immunoelectrophoresis for determination of γ-globulin level and oligoclonal banding; and (9) cytology. Although 15 mL of CSF is sufficient to obtain all of the listed studies, the yield of fungal and mycobacterial cultures and cytology increases when larger volumes are sampled. In general 20–30 mL may be safely removed from adults.

A bloody tap due to penetration of a meningeal vessel (a "traumatic tap") may result in confusion with subarachnoid hemorrhage (SAH). In these situations a specimen of CSF should be centrifuged immediately after it is obtained; clear supernatant following CSF centrifugation supports the diagnosis of a bloody tap, whereas xanthochromic supernatant suggests SAH. In general, bloody CSF due to the penetration of a meningeal vessel clears gradually in successive tubes, whereas blood due to SAH does not. In addition to SAH, xanthochromic CSF may also be present in patients with liver disease and when the CSF protein concentration is markedly elevated (>1.5–2 g/L [150–200 mg/dL]).

Prior to removing the LP needle, the stylet is reinserted to avoid the possibility of entrapment of a nerve root in the dura as the needle is being withdrawn; entrapment could result in a dural CSF leak, causing headache. Some practitioners question the safety of this maneuver, with its potential risk of causing a needlestick injury to the examiner. Injury is unlikely, however, given the flexibility of the small-diameter stylet, which tends to bend, rather than penetrate, on contact. Following LP, the patient is customarily positioned in a comfortable, recumbent position for 30–60 min before rising, although this may be unnecessary because it does not appear to affect the development of headache (see below).

POST-LP HEADACHE

The principal complication of LP is headache, occurring in 10–30% of patients. Younger age and female gender are associated with an increased risk of post-LP headache. Headache usually begins within 48 h but may be delayed for up to 12 days. Head pain is dramatically positional; it begins when the patient sits or stands upright; there is relief upon reclining or with abdominal compression. The longer the patient is upright, the longer the latency before head pain subsides. The pain is usually a dull ache but may be throbbing; its location is occipitofrontal. Nausea and stiff neck often accompany headache, and occasionally, patients report blurred vision, photophobia, tinnitus, and vertigo. In more than three-quarters of patients, symptoms completely resolve within a week, but in a minority they can persist for weeks or even months.

Post-LP headache is caused by a drop in CSF pressure related to persistent leakage of CSF at the site where the needle entered the SAS. Loss of CSF volume decreases the brain's supportive cushion, so that when a patient is upright there is probably dilation and tension placed on the brain's anchoring structures, the pain-sensitive dural sinuses, resulting in pain. Although intracranial hypotension is the usual explanation for severe LP headache, the syndrome can occur in patients with normal CSF pressure.

Because post-LP headache usually resolves without specific treatment, care is largely supportive with oral analgesics (acetaminophen, NSAIDs, opioids **[Chap. 8]**) and antiemetics. Patients may obtain relief by lying in a comfortable (especially a recumbent or head-down Trendelenburg) position. For some patients, beverages with caffeine can provide temporary pain relief.

For patients with persistent pain, treatment with IV caffeine (500 mg in 500 mL saline administered over 2 h) may be effective; atrial fibrillation is a rare side effect. Alternatively, an epidural blood patch accomplished by injection of 15 mL of autologous whole blood is usually effective; the injection is directed at the epidural space at the level of the initial LP. This procedure is most often performed by a pain specialist or anesthesiologist. The blood patch has an immediate effect, making it unlikely

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 7-1

REDUCING THE INCIDENCE OF POST-LP HEADACHE

Ef ective Strategies
Use of small-diameter needle (22-gauge or smaller)
Use of atraumatic needle (Sprotte and others)
Replacement of stylet prior to removal of needle
Insertion of needle with bevel oriented in a cephalad to caudad direction (when using standard needle)
Inef ective Strategies
Bed rest (up to 4 h) following LP
Supplemental fluids
Minimizing the volume of spinal fluid removed
Immediate mobilization following LP

Abbreviation: LP, lumbar puncture.

that sealing off a dural hole with blood clot is its sole mechanism of action. T e acute benefit may be due to compression of the CSF space by the clot, increasing CSF pressure. Some clinicians reserve epidural blood patch for patients who do not respond to caffeine, while others prefer to use blood patch as initial management for unremitting post-LP symptoms.

Strategies to decrease the incidence of post-LP headache are listed in **Table 7-1**. Use of a smaller caliber needle is associated with a lower risk: in one study, the risk of headache following use of a 24- to 27-gauge standard (Quincke) needle was 5–12%, compared to 20–40% when a 20- or 22-gauge needle was used. T e smallest gauge needles usually require the use of an introducer needle and are associated with a slower CSF flow rate. Use of an "atraumatic" (Sprotte, "pencil point," or "noncutting") needle also reduces the incidence of moderate to severe headache compared with standard LP (Quincke, or "traumatic") needles **(Fig. 7-2)**. However, because atraumatic needles are more dif cult to use, more attempts may be required to perform the LP, particularly in overweight patients. It may also be necessary to use an introducer with the atraumatic needle, which does not have the customary cutting, beveled tip. T ere is a low risk of needle damage, e.g., breakage, with the Sprotte atraumatic needle. Another strategy to decrease the incidence of headache is to replace the stylet before removing the LP needle.

Patients are often advised to remain in a recumbent position for up to an hour following LP. However, studies comparing mobilization immediately following LP with bed rest for periods up to 4 h show no significant differences in the incidence of headache, suggesting that the customary practice of remaining in a recumbent position post-LP may be unnecessary.

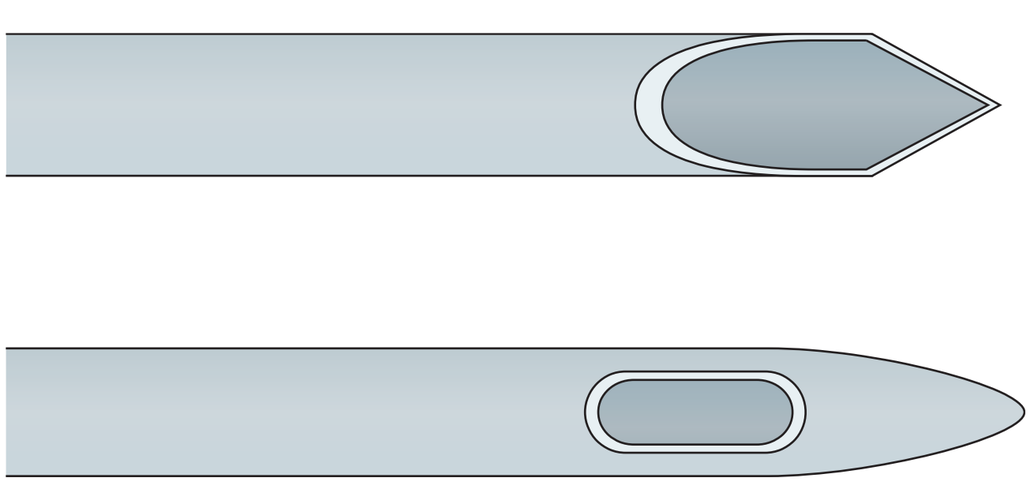


FIGURE 7-2
Comparison of the standard ("cutting" or Quincke) lumbar puncture (LP) needle with the "atraumatic" (Sprotte). The "atraumatic" needle has its opening on the top surface of the needle, a design intended to reduce the chance of cutting dural f bers that, by protruding through the dura, could be responsible for subsequent cerebrospinal fluid leak and post-LP headache. (From SR Thomas et al: BMJ 321:986, 2000.)

TABLE 7-2

CEREBROSPINAL FLUID (CSF)[a]

CONSTITUENT	SI UNITS	CONVENTIONAL UNITS
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
CSF pressure		50–180 mmH_2O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per mm^3	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Because CSF concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fluctuate rapidly (such as plasma glucose) may not achieve stable values until after a sig-nif cant lag phase.
[b]IgG index = CSF IgG (mg/dL) × Serum albumin (g/dL)/Serum IgG (g/dL) × CSF albumin (mg/dL).

www.ketabpezeshki.com (021) 66485457 - 66485438

NORMAL VALUES

(See Table 7-2.) In uninfected CSF, the normal white blood cell count is fewer than five mononuclear cells (lymphocytes and monocytes) per μL. Polymorphonuclear leukocytes (PMNs) are not found in normal unconcentrated CSF; however, rare PMNs can be found in centrifuged or concentrated CSF specimens such as those used for cytologic examination. Red blood cells (RBCs) are not normally present in CSF; if RBCs are present from a traumatic tap, their number decreases as additional CSF is collected. CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal.

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION II

CLINICAL MANIFESTATIONS OF NEUROLOGIC DISEASE

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 8

PAIN: PATHOPHYSIOLOGY AND MANAGEMENT

James P. Rathmell ■ Howard L. Fields

The province of medicine is to preserve and restore health and to relieve suffering. Understanding pain is essential to both of these goals. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to protect the body and maintain homeostasis. It does this by detecting, localizing, and identifying potential or actual tissue-damaging processes. Because different diseases produce characteristic patterns of tissue damage, the quality, time course, and location of a patient's pain lend important diagnostic clues. It is the physician's responsibility to provide rapid and effective pain relief.

THE PAIN SENSORY SYSTEM

Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling. These properties illustrate the duality of pain: it is both sensation and emotion. When it is acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present.

PERIPHERAL MECHANISMS

The primary afferent nociceptor

A peripheral nerve consists of the axons of three different types of neurons: primary sensory afferents, motor neurons, and sympathetic postganglionic neurons (Fig. 8-1). The cell bodies of primary sensory afferents are located in the dorsal root ganglia within the vertebral foramina. The primary afferent axon has two branches: one projects centrally into the spinal cord and the other projects peripherally to innervate tissues. Primary afferents are classified by their diameter, degree of myelination, and conduction velocity. The largest diameter afferent fibers, A-beta (Aβ), respond maximally to light touch and/or moving stimuli; they are present primarily in nerves that innervate the skin. In normal individuals, the activity of these fibers does not produce pain. There are two other classes of primary afferent nerve fibers: the small diameter myelinated A-delta (Aδ) and the unmyelinated (C) axons (Fig. 8-1). These fibers are present in nerves to the skin and to deep somatic and visceral structures. Some tissues, such as the cornea, are innervated only by Aδ and C fiber afferents. Most Aδ and C fiber afferents respond maximally only to intense (painful) stimuli and produce the subjective experience of pain when they are electrically stimulated; this defines them as primary *afferent* nociceptors (pain receptors). The ability to detect painful stimuli is completely abolished when conduction in Aδ and C fiber axons is blocked.

Individual primary afferent nociceptors can respond to several different types of noxious stimuli. For example, most nociceptors respond to heat; intense cold; intense mechanical distortion, such as a pinch; changes in pH, particularly an acidic environment; and application of chemical irritants including adenosine triphosphate (ATP), serotonin, bradykinin, and histamine.

Sensitization

When intense, repeated, or prolonged stimuli are applied to damaged or inflamed tissues, the threshold for activating primary afferent nociceptors is lowered,

www.ketabpezeshki.com (021) 66485457 - 66485438

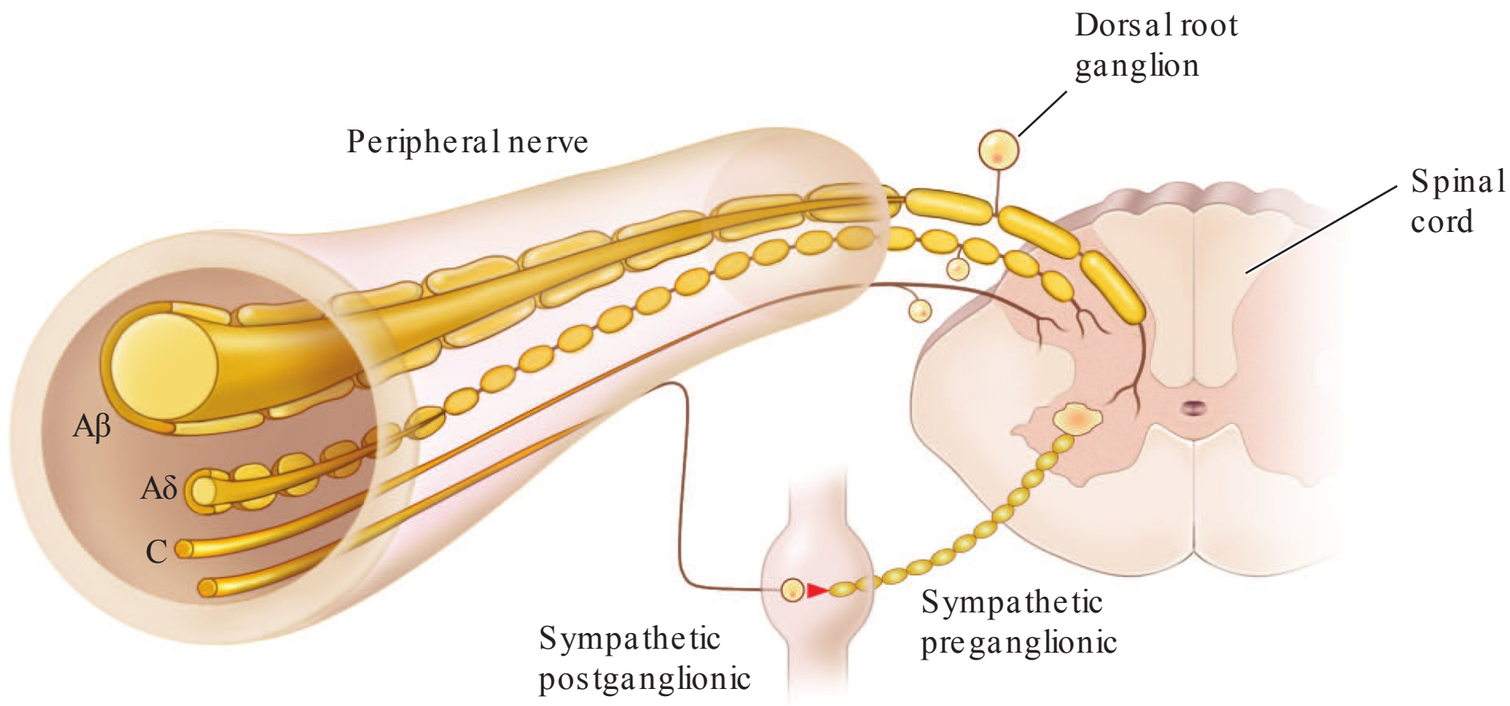


FIGURE 8-1

Components of a typical cutaneous nerve. There are two distinct functional categories of axons: primary afferents with cell bodies in the dorsal root ganglion, and sympathetic postganglionic fibers with cell bodies in the sympathetic ganglion. Primary afferents include those with large-diameter myelinated (Aβ), small-diameter myelinated (Aδ), and unmyelinated (C) axons. All sympathetic postganglionic fibers are unmyelinated.

and the frequency of firing is higher for all stimulus intensities. Inflammatory mediators such as bradykinin, nerve-growth factor, some prostaglandins, and leukotrienes contribute to this process, which is called sensitization. Sensitization occurs at the level of the peripheral nerve terminal (peripheral sensitization) as well as at the level of the dorsal horn of the spinal cord (central sensitization). Peripheral sensitization occurs in damaged or inflamed tissues, when inflammatory mediators activate intracellular signal transduction in nociceptors, prompting an increase in the production, transport, and membrane insertion of chemically gated and voltage-gated ion channels. These changes increase the excitability of nociceptor terminals and lower their threshold for activation by mechanical, thermal, and chemical stimuli. Central sensitization occurs when activity, generated by nociceptors during inflammation, enhances the excitability of nerve cells in the dorsal horn of the spinal cord. Following injury and resultant sensitization, normally innocuous stimuli can produce pain (termed allodynia). Sensitization is a clinically important process that contributes to tenderness, soreness, and hyperalgesia (increased pain intensity in response to the same noxious stimulus; e.g., moderate pressure causes severe pain). A striking example of sensitization is sunburned skin, in which severe pain can be produced by a gentle slap on the back or a warm shower.

Sensitization is of particular importance for pain and tenderness in deep tissues. Viscera are normally relatively insensitive to noxious mechanical and thermal stimuli, although hollow viscera do generate significant discomfort when distended. In contrast, when affected by a disease process with an inflammatory component, deep structures such as joints or hollow viscera characteristically become exquisitely sensitive to mechanical stimulation.

A large proportion of Aδ and C fiber afferents innervating viscera are completely insensitive in normal noninjured, noninflamed tissue. That is, they cannot be activated by known mechanical or thermal stimuli and are not spontaneously active. However, in the presence of inflammatory mediators, these afferents become sensitive to mechanical stimuli. Such afferents have been termed silent nociceptors, and their characteristic properties may explain how, under pathologic conditions, the relatively insensitive deep structures can become the source of severe and debilitating pain and tenderness. Low pH, prostaglandins, leukotrienes, and other inflammatory mediators such as bradykinin play a significant role in sensitization.

Nociceptor-induced inflammation

Primary afferent nociceptors also have a neuroeffector function. Most nociceptors contain polypeptide mediators that are released from their peripheral terminals when they are activated **(Fig. 8-2)**. An example is substance P, an 11-amino-acid peptide. Substance P is released from primary afferent nociceptors and has multiple biologic activities. It is a potent vasodilator, degranulates mast cells, is a chemoattractant for leukocytes, and increases the production and release of inflammatory mediators. Interestingly, depletion of substance P from joints reduces the severity of experimental arthritis. Primary afferent nociceptors are not simply passive messengers of threats to tissue injury but also play an active role in tissue protection through these neuroeffector functions.

www.ketabpezeshki.com (021) 66485457 - 66485438

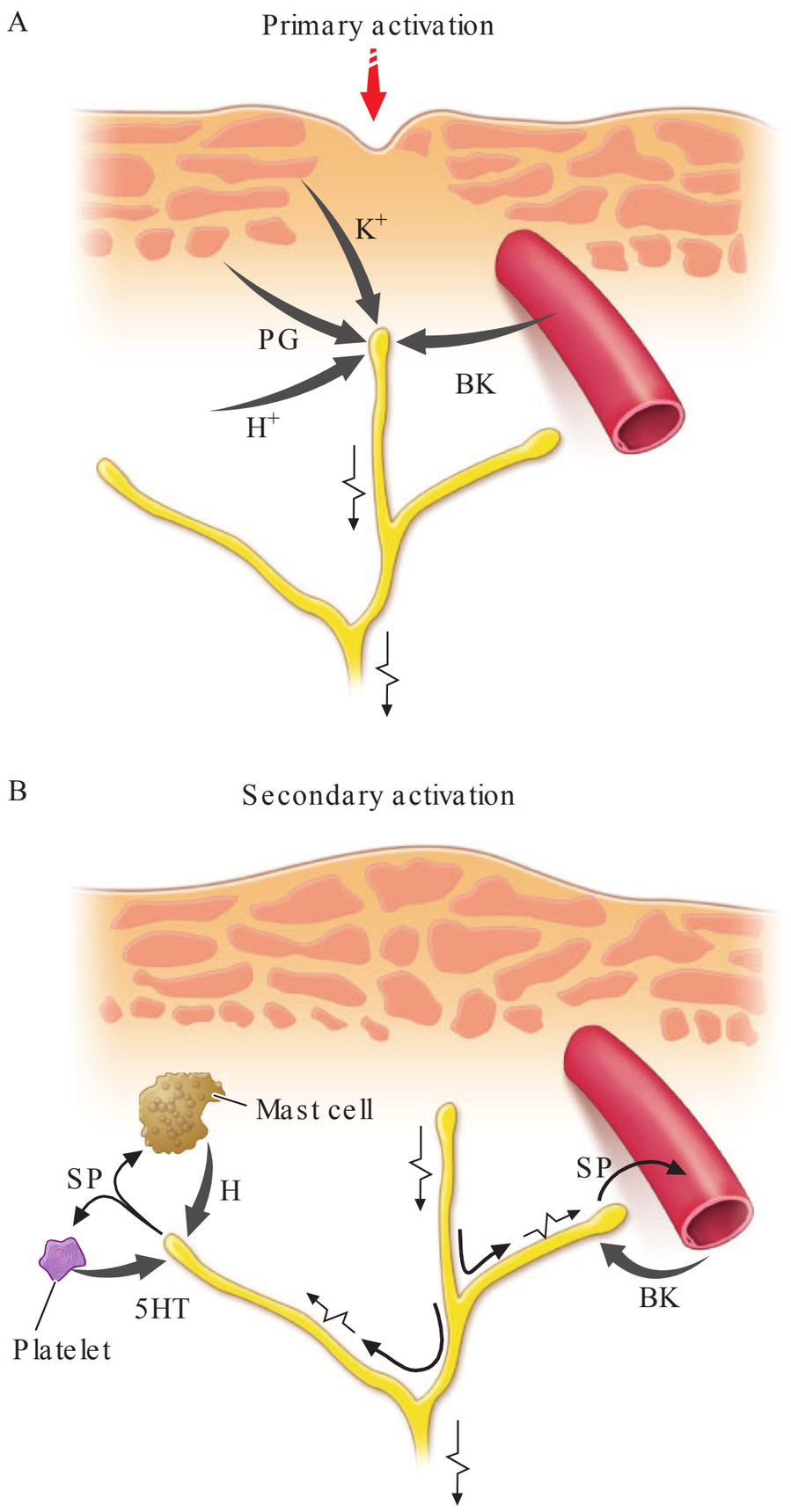


FIGURE 8-2
Events leading to activation, sensitization, and spread of sensitization of primary afferent nociceptor terminals. A. Direct activation by intense pressure and consequent cell damage. Cell damage induces lower pH (H^+) and leads to release of potassium (K^+) and to synthesis of prostaglandins (PG) and bradykinin (BK). Prostaglandins increase the sensitivity of the terminal to bradykinin and other pain-producing substances. B. Secondary activation. Impulses generated in the stimulated terminal propagate not only to the spinal cord but also into other terminal branches where they induce the release of peptides, including substance P (SP). Substance P causes vasodilation and neurogenic edema with further accumulation of bradykinin (BK). Substance P also causes the release of histamine (H) from mast cells and serotonin (5HT) from platelets.

CENTRAL MECHANISMS

The spinal cord and referred pain

The axons of primary afferent nociceptors enter the spinal cord via the dorsal root. They terminate in the dorsal horn of the spinal gray matter **(Fig. 8-3)**. The terminals of primary afferent axons contact spinal neurons that transmit the pain signal to brain sites involved in pain perception. When primary afferents are activated by noxious stimuli, they release neurotransmitters from their terminals that excite the spinal cord neurons. The major neurotransmitter released is glutamate, which rapidly excites dorsal horn neurons. Primary afferent nociceptor terminals also release peptides, including substance P and calcitonin gene-related peptide, which produce a slower and longer-lasting excitation of the dorsal horn neurons. The axon of each primary afferent contacts many spinal neurons, and each spinal neuron receives convergent inputs from many primary afferents.

The convergence of sensory inputs to a single spinal pain-transmission neuron is of great importance because it underlies the phenomenon of referred pain. All spinal neurons that receive input from the viscera and deep musculoskeletal structures also receive input from the skin. The convergence patterns are determined by the spinal segment of the dorsal root ganglion that supplies the afferent innervation of a structure. For example, the afferents that supply the central diaphragm are derived from the third and fourth cervical dorsal root ganglia. Primary afferents with cell bodies in these same ganglia supply the skin of the shoulder and lower neck. Thus, sensory inputs from both the shoulder skin and the central diaphragm converge on pain-transmission neurons in the third and fourth cervical spinal segments. Because *of* this convergence and the *fact* that the spinal neurons are most *often* activated by inputs *from* the skin, activity evoked in spinal neurons by input *from* deep structures is mislocalized by the patient to a place that roughly corresponds with the region *of* skin innervated by the same spinal segment. Thus, inflammation near the central diaphragm is often reported as shoulder discomfort. This spatial displacement of pain sensation from the site of the injury that produces it is known as *referred* pain.

Ascending pathways for pain

A majority of spinal neurons contacted by primary afferent nociceptors send their axons to the contralateral thalamus. These axons form the contralateral spinothalamic tract, which lies in the anterolateral white matter of the spinal cord, the lateral edge of the medulla, and the lateral pons and midbrain. The spinothalamic pathway is crucial for pain sensation in humans. Interruption of this pathway produces permanent deficits in pain and temperature discrimination.

Spinothalamic tract axons ascend to several regions of the thalamus. There is tremendous divergence of the pain signal from these thalamic sites to several distinct areas of the cerebral cortex that subserve different aspects of the pain experience **(Fig. 8-4)**. One of the

www.ketabpezeshki.com (021) 66485457 - 66485438

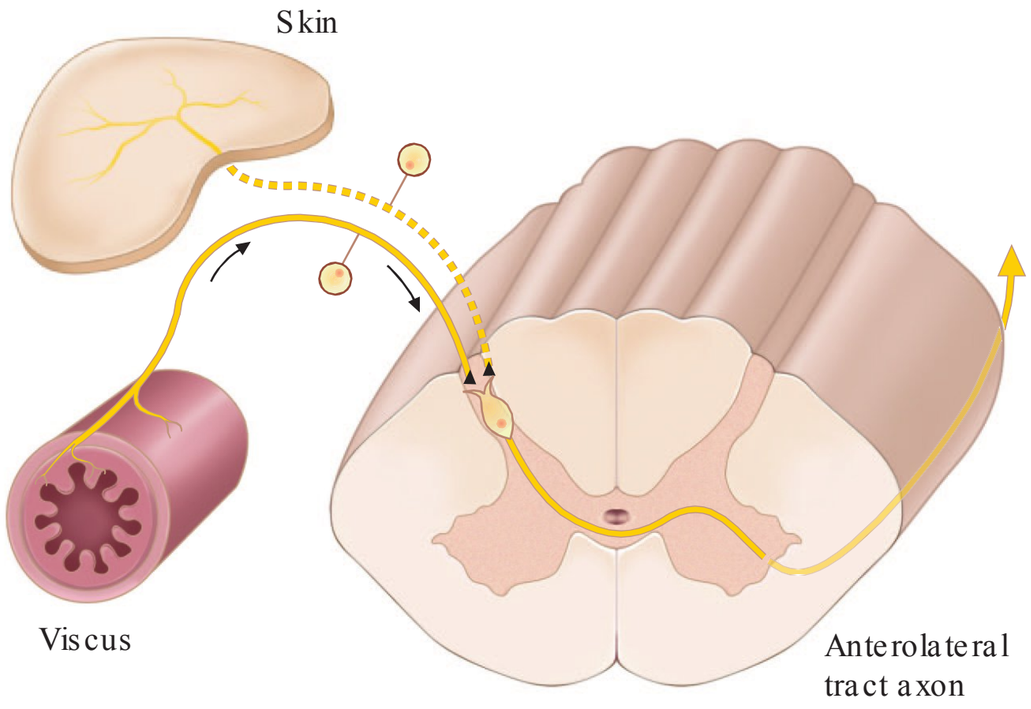


FIGURE 8-3
The convergence-projection hypothesis of referred pain. According to this hypothesis, visceral afferent nociceptors converge on the same pain-projection neurons as the afferents from the somatic structures in which the pain is perceived. The brain has no way of knowing the actual source of input and mistakenly "projects" the sensation to the somatic structure.

thalamic projections is to the somatosensory cortex. This projection mediates the purely sensory aspects of pain, i.e., its location, intensity, and quality. Other thalamic neurons project to cortical regions that are linked to emotional responses, such as the cingulate gyrus and other areas of the frontal lobes, including the insular cortex. These pathways to the frontal cortex subserve the affective or unpleasant emotional dimension of pain. This affective dimension of pain produces suffering and exerts potent control of behavior. Because of this dimension, fear is a constant companion of pain. As a consequence, injury or surgical lesions to areas of the frontal cortex activated by painful stimuli can diminish the emotional impact of pain while largely preserving the individual's ability to recognize noxious stimuli as painful.

PAIN MODULATION

The pain produced by injuries of similar magnitude is remarkably variable in different situations and in different individuals. For example, athletes have been known to sustain serious fractures with only minor pain, and Beecher's classic World War II survey revealed that many soldiers in battle were unbothered by injuries that would have produced agonizing pain in civilian patients. Furthermore, even the suggestion that a treatment will relieve pain can have a significant analgesic effect (the placebo *effect*). On the other hand, many patients find even minor injuries (such as venipuncture) frightening and unbearable, and the expectation of pain can induce pain even without a noxious stimulus. The suggestion that pain will worsen following

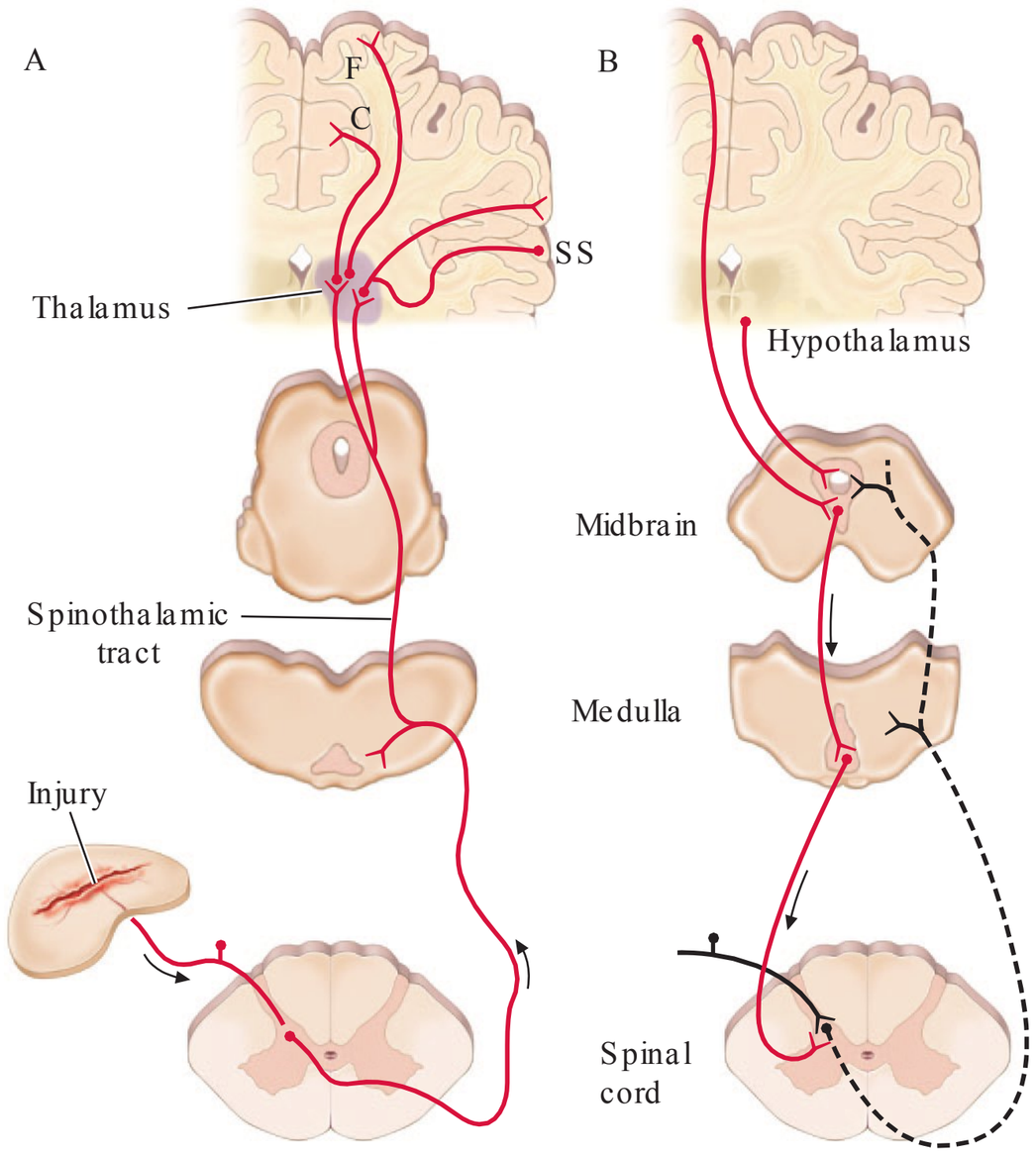


FIGURE 8-4
Pain transmission and modulatory pathways. A. Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). B. Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

administration of an inert substance can increase its perceived intensity (the nocebo *effect*).

The powerful effect of expectation and other psychological variables on the perceived intensity of pain is explained by brain circuits that modulate the activity of the pain-transmission pathways. One of these circuits has links to the hypothalamus, midbrain, and medulla, and it selectively controls spinal pain-transmission neurons through a descending pathway (Fig. 8-4).

Human brain–imaging studies have implicated this pain-modulating circuit in the pain-relieving effect of attention, suggestion, and opioid analgesic medications **(Fig. 8-5)**. Furthermore, each of the component structures of the pathway contains opioid receptors and is sensitive to the direct application of opioid drugs. In animals, lesions of this descending modulatory system reduce the analgesic effect of systemically administered opioids such as morphine. Along with the opioid receptor, the component nuclei of this pain-modulating

www.ketabpezeshki.com (021) 66485457 - 66485438

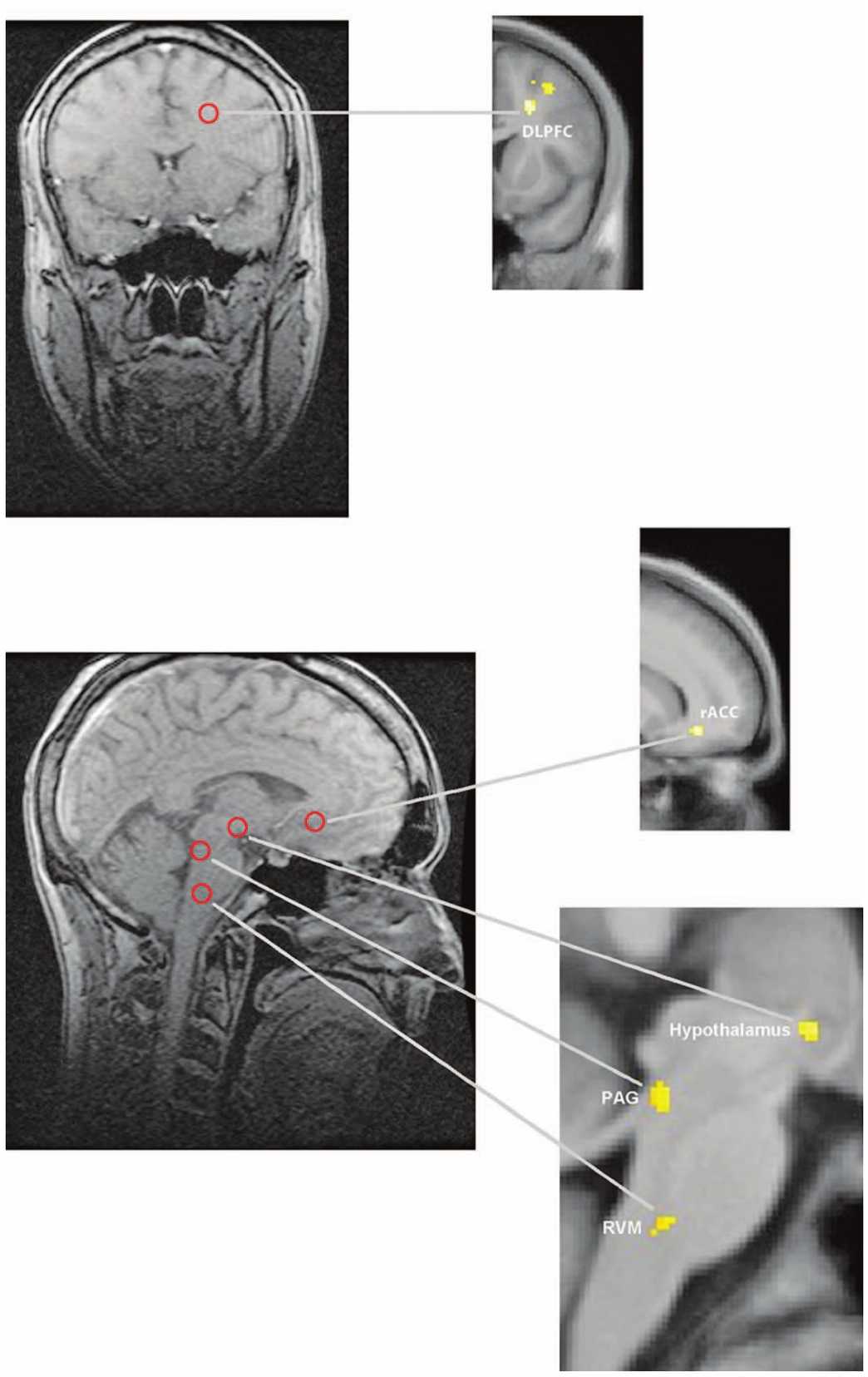


FIGURE 8-5
Functional magnetic resonance imaging **(f**MRI**)** demonstrates placebo-enhanced brain activity in anatomic regions correlating with the opioidergic descending pain control system. Top panel: Frontal fMRI image shows placebo-enhanced brain activity in the dorsal lateral prefrontal cortex (DLPFC). Bottom panel: Sagittal fMRI images show placebo-enhanced responses in the rostral anterior cingulate cortex (rACC), the rostral ventral medullae (RVM), the periaqueductal gray (PAG) area, and the hypothalamus. The placebo-enhanced activity in all areas was reduced by naloxone, demonstrating the link between the descending opioidergic system and the placebo analgesic response. (Adapted with permission from F Eippert et al: Neuron 63:533, 2009.)

circuit contain endogenous opioid peptides such as the enkephalins and β-endorphin.

T e most reliable way to activate this endogenous opioid-mediated modulating system is by suggestion of pain relief or by intense emotion directed away from the pain-causing injury (e.g., during severe threat or an athletic competition). In fact, pain-relieving endogenous opioids are released following surgical procedures and in patients given a placebo for pain relief.

Pain-modulating circuits can enhance as well as suppress pain. Both pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons. Because pain-transmission neurons can be activated by modulatory neurons, it is theoretically possible to generate a pain signal with no peripheral noxious stimulus. In fact, human functional imaging studies have demonstrated increased activity in this circuit during migraine headaches. A central circuit that facilitates pain could account for the finding that pain can be induced by suggestion or enhanced by expectation and provides a framework for understanding how psychological factors can contribute to chronic pain.

NEUROPATHIC PAIN

Lesions of the peripheral or central nociceptive pathways typically result in a loss or impairment of pain sensation. Paradoxically, damage to or dysfunction of these pathways can also produce pain. For example, damage to peripheral nerves, as occurs in diabetic neuropathy, or to primary afferents, as in herpes zoster infection, can result in pain that is referred to the body region innervated by the damaged nerves. Pain may also be produced by damage to the central nervous system (CNS), for example, in some patients following trauma or vascular injury to the spinal cord, brainstem, or thalamic areas that contain central nociceptive pathways. Such neuropathic pains are often severe and are typically resistant to standard treatments for pain.

Neuropathic pain typically has an unusual burning, tingling, or electric shock–like quality and may be triggered by very light touch. T ese features are rare in other types of pain. On examination, a sensory deficit is characteristically present in the area of the patient's pain. Hyperpathia, a greatly exaggerated pain sensation to innocuous or mild nociceptive stimuli, is also characteristic of neuropathic pain; patients often complain that the very lightest moving stimulus evokes exquisite pain (allodynia). In this regard, it is of clinical interest that a topical preparation of 5% lidocaine in patch form is effective for patients with postherpetic neuralgia who have prominent allodynia.

A variety of mechanisms contribute to neuropathic pain. As with sensitized primary afferent nociceptors, damaged primary afferents, including nociceptors, become highly sensitive to mechanical stimulation and may generate impulses in the absence of stimulation. Increased sensitivity and spontaneous activity are due, in part, to an increased concentration of sodium channels in the damaged nerve fiber. Damaged primary afferents may also develop sensitivity to norepinephrine. Interestingly, spinal cord pain-transmission neurons cut

www.ketabpezeshki.com (021) 66485457 - 66485438

off from their normal input may also become spontaneously active. Thus, both CNS and peripheral nervous system hyperactivity contribute to neuropathic pain.

Sympathetically maintained pain

Patients with peripheral nerve injury occasionally develop spontaneous pain in the region innervated by the nerve. This pain is often described as having a burning quality. The pain typically begins after a delay of hours to days or even weeks and is accompanied by swelling of the extremity, periarticular bone loss, and arthritic changes in the distal joints. The pain may be relieved by a local anesthetic block of the sympathetic innervation to the affected extremity. Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow. This constellation of spontaneous pain and signs of sympathetic dysfunction following injury has been termed complex regional pain syndrome (CRPS). When this occurs after an identifiable nerve injury, it is termed CRPS type II (also known as posttraumatic neuralgia or, if severe, causalgia). When a similar clinical picture appears without obvious nerve injury, it is termed CRPS type I (also known as reflex sympathetic dystrophy). CRPS can be produced by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke **(Chap. 32)**. CRPS type I typically resolves with symptomatic treatment; however, when it persists, detailed examination often reveals evidence of peripheral nerve injury. Although the pathophysiology of CRPS is poorly understood, the pain and the signs of inflammation, when acute, can be rapidly relieved by blocking the sympathetic nervous system. This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present. Signs of sympathetic hyperactivity should be sought in patients with posttraumatic pain and inflammation and no other obvious explanation.

TREATMENT Acute Pain

The ideal treatment for any pain is to remove the cause; thus, while treatment can be initiated immediately, efforts to establish the underlying etiology should always proceed as treatment begins. Sometimes, treating the underlying condition does not immediately relieve pain. Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, or sickle cell crisis). Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.

ASPIRIN, ACETAMINOPHEN, AND NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)

These drugs are considered together because they are used for similar problems and may have a similar mechanism of action **(Table 8-1)**. All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

Because they are effective for these common types of pain and are available without prescription, COX inhibitors are by far the most commonly used analgesics. They are absorbed well from the gastrointestinal tract and, with occasional use, have only minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa leading to bleeding or perforation. Because aspirin irreversibly acetylates platelet cyclooxygenase and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Older age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to the well-known gastrointestinal toxicity of NSAIDs, nephrotoxicity is a significant problem for patients using these drugs on a chronic basis. Patients at risk for renal insufficiency, particularly those with significant contraction of their intravascular volume as occurs with chronic diuretic use or acute hypovolemia, should be monitored closely. NSAIDs can also increase blood pressure in some individuals. Long-term treatment with NSAIDs requires regular blood pressure monitoring and treatment if necessary. Although toxic to the liver when taken in high doses, acetaminophen rarely produces gastric irritation and does not interfere with platelet function.

The introduction of parenteral forms of NSAIDs, ketorolac and diclofenac, extends the usefulness of this class of compounds in the management of acute severe pain. Both agents are sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe headache and musculoskeletal pain.

There are two major classes of COX: COX-1 is constitutively expressed, and COX-2 is induced in the inflammatory state. COX-2–selective drugs have similar analgesic potency and produce less gastric irritation than the nonselective COX inhibitors. The use of COX-2–selective drugs does not appear to lower the risk of nephrotoxicity compared to nonselective NSAIDs. On the other hand, COX-2–selective drugs offer a significant benefit in the management of acute postoperative pain because they do not affect blood coagulation. Nonselective COX inhibitors are usually contraindicated postoperatively because they impair platelet-mediated blood clotting and are thus associated with increased bleeding at the operative site. COX-2 inhibitors, including celecoxib (Celebrex), are associated with increased cardiovascular risk. It appears that this is a class effect of NSAIDs, excluding aspirin. These drugs are contraindicated in patients in the immediate period after coronary artery bypass surgery and should be used with caution in elderly patients and those with a history of or significant risk factors for cardiovascular disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 8-1

DRUGS FOR RELIEF OF PAIN

GENERIC NAME	DOSE, MG	INTERVAL	COMMENTS
Nonnarcotic analgesics: usual doses and intervals			
Acetylsalicylic acid	650 PO	q4h	Enteric-coated preparations available
Acetamino-phen	650 PO	q4h	Side effects uncommon
Ibuprofen	400 PO	q4–6h	Available without prescription
Naproxen	250–500 PO	q12h	Delayed effects may be due to long half-life
Fenoprofen	200 PO	q4–6h	Contraindicated in renal disease
Indomethacin	25–50 PO	q8h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q4–6h	Available for parenteral use
Celecoxib	100–200 PO	q12–24h	Useful for arthritis
Valdecoxib	10–20 PO	q12–24h	Removed from U.S. market in 2005

GENERIC NAME	PARENTERAL DOSE, mg	PO DOSE, mg	COMMENTS
Narcotic analgesics: usual doses and intervals			
Codeine	30–60 q4h	30–60 q4h	Nausea common
Oxycodone	—	5–10 q4–6h	Usually available with acetaminophen or aspirin
Morphine	5 q4h	30 q4h	
Morphine sustained release	—	15–60 bid to tid	Oral slow-release preparation
Hydromor-phone	1–2 q4h	2–4 q4h	Shorter acting than morphine sulfate
Levorphanol	2 q6–8h	4 q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	5–10 q6–8h	5–20 q6–8h	Delayed sedation due to long half-life; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days
Meperidine	50–100 q3–4h	300 q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	—	1–2 q4h	Intranasal spray
Fentanyl	25–100 µg/h		72-h transdermal patch
Buprenor-phine	5–20 µg/h	—	7-day transdermal patch
Buprenor-phine	0.3 q6–8h		Parenteral administration
Tramadol		50–100 q4–6h	Mixed opioid/adrenergic action

		UPTAKE BLOCKADE						
GENERIC NAME	5-HT	NE	SEDATIVE POTENCY	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC ARRHYTHMIA	AVE. DOSE, MG/D	RANGE, MG/D
Antidepressants[a]								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 8-1

DRUGS FOR RELIEF OF PAIN (CONTINUED)

GENERIC NAME	DOSE, MG		INTERVAL	COMMENTS				
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60

GENERIC NAME	PO DOSE, MG	INTERVAL	GENERIC NAME	PO DOSE, MG	INTERVAL
Anticonvulsants and antiarrhythmics[a]					
Phenytoin	300	daily/qhs	Clonazepam	1	q6h
Carbamazepine	200–300	q6h	Gabapentin[b]	600–1200	q8h
Oxcarbazepine	300	bid	Pregabalin	150–600	bid

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.
[b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.
Abbreviations: 5-HT, serotonin; NE, norepinephrine.

OPIOID ANALGESICS Opioids are the most potent pain-relieving drugs currently available. Of all analgesics, they have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief. Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone. Many physicians, nurses, and patients have a certain trepidation about using opioids that is based on an exaggerated fear of addiction. In fact, there is a vanishingly small chance of patients becoming addicted to narcotics as a result of their appropriate medical use. The physician should not hesitate to use opioid analgesics in patients with acute severe pain. Table 8-1 lists the most commonly used opioid analgesics.

Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (μ-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. At higher doses of meperidine, typically greater than 1 g/d, accumulation of normeperidine can produce hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.

The most rapid pain relief is obtained by intravenous administration of opioids; relief with oral administration is significantly slower. Because of the potential for respiratory depression, patients with any form of respiratory compromise must be kept under close observation following opioid administration; an oxygen-saturation monitor may be useful, but only in a setting where the monitor is under constant surveillance. Opioid-induced respiratory depression is typically accompanied by sedation and a reduction in respiratory rate. A fall in oxygen saturation represents a critical level of respiratory depression and the need for immediate intervention to prevent life-threatening hypoxemia. Ventilatory assistance should be maintained until the opioid-induced respiratory depression has resolved. The opioid antagonist naloxone should be readily available whenever opioids are used at high doses or in patients with compromised pulmonary function. Opioid effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects. Synergistic respiratory depression is common when opioids are administered with other CNS depressants, most commonly the benzodiazepines. Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires determining whether the drug has adequately relieved the pain and frequent reassessment to determine the optimal interval for dosing. The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Because many patients are reluctant to complain, this practice leads to needless suffering. In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

An innovative approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA uses a microprocessor-controlled infusion

www.ketabpezeshki.com (021) 66485457 - 66485438

device that can deliver a baseline continuous dose of an opioid drug as well as preprogrammed additional doses whenever the patient pushes a button. T e patient can then titrate the dose to the optimal level. T is approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for short-term home care of patients with intractable pain, such as that caused by metastatic cancer.

It is important to understand that the PCA device delivers small, repeated doses to maintain pain relief; in patients with severe pain, the pain must first be brought under control with a loading dose before transitioning to the PCA device. T e bolus dose of the drug (typically 1 mg of morphine, 0.2 mg of hydromorphone, or 10 μg of fentanyl) can then be delivered repeatedly as needed. To prevent overdosing, PCA devices are programmed with a lockout period after each demand dose is delivered (5–10 min) and a limit on the total dose delivered per hour. Although some have advocated the use of a simultaneous continuous or basal infusion of the PCA drug, this increases the risk of respiratory depression and has not been shown to increase the overall ef cacy of the technique.

T e availability of new routes of administration has extended the usefulness of opioid analgesics. Most important is the availability of spinal administration. Opioids can be infused through a spinal catheter placed either intrathecally or epidurally. By applying opioids directly to the spinal or epidural space adjacent to the spinal cord, regional analgesia can be obtained using relatively low total doses. Indeed, the dose required to produce effective localized analgesia when using morphine intrathecally (0.1–0.3 mg) is a fraction of that required to produce similar analgesia when administered intravenously (5–10 mg). In this way, side effects such as sedation, nausea, and respiratory depression can be minimized. T is approach has been used extensively during labor and delivery and for postoperative pain relief following surgical procedures. Continuous intrathecal delivery via implanted spinal drug-delivery systems is now commonly used, particularly for the treatment of cancer-related pain that would require sedating doses for adequate pain control if given systemically. Opioids can also be given intranasally (butorphanol), rectally, and transdermally (fentanyl and buprenorphine), or through the oral mucosa (fentanyl), thus avoiding the discomfort of frequent injections in patients who cannot be given oral medication. T e fentanyl and buprenorphine transdermal patches have the advantage of providing fairly steady plasma levels, which maximizes patient comfort.

Recent additions to the armamentarium for treating opioid-induced side effects are the peripherally acting opioid antagonists alvimopan (Entereg) and methylnaltrexone (Rellistor). Alvimopan is available as an orally administered agent that is restricted to the intestinal lumen by limited absorption; methylnaltrexone is available in a subcutaneously administered form that has virtually no penetration into the CNS. Both agents act by binding to peripheral μ-receptors, thereby inhibiting or reversing the effects of opioids at these peripheral sites. T e action of both agents is restricted to receptor sites outside of the CNS; thus, these drugs can reverse the adverse effects of opioid analgesics that are mediated through their peripheral receptors without reversing their analgesic effects. Alvimopan has proven effective in lowering the duration of persistent ileus following abdominal surgery in patients receiving opioid analgesics for postoperative pain control. Methylnaltrexone has proven effective for relief of opioid-induced constipation in patients taking opioid analgesics on a chronic basis.

Opioid and COX Inhibitor Combinations When used in combination, opioids and COX inhibitors have additive effects. Because a lower dose of each can be used to achieve the same degree of pain relief and their side effects are nonadditive, such combinations are used to lower the severity of dose-related side effects. However, fixed-ratio combinations of an opioid with acetaminophen carry an important risk. Dose escalation as a result of increased severity of pain or decreased opioid effect as a result of tolerance may lead to ingestion of levels of acetaminophen that are toxic to the liver. Although acetaminophen-related hepatotoxicity is uncommon, it remains a significant cause for liver failure. T us, many practitioners have moved away from the use of opioid-acetaminophen combination analgesics to avoid the risk of excessive acetaminophen exposure as the dose of the analgesic is escalated.

CHRONIC PAIN

Managing patients with chronic pain is intellectually and emotionally challenging. T e patient's problem is often dif cult or impossible to diagnose with certainty; such patients are demanding of the physician's time and often appear emotionally distraught. T e traditional medical approach of seeking an obscure organic pathology is usually unhelpful. On the other hand, psychological evaluation and behaviorally based treatment paradigms are frequently helpful, particularly in the setting of a multidisciplinary pain-management center. Unfortunately, this approach, while effective, remains largely underused in current medical practice.

T ere are several factors that can cause, perpetuate, or exacerbate chronic pain. First, of course, the patient may simply have a disease that is characteristically painful for which there is presently no cure. Arthritis, cancer, chronic daily headaches, fibromyalgia, and diabetic neuropathy are examples of this. Second, there may be secondary perpetuating factors that are initiated by disease and persist after that disease has resolved. Examples include damaged sensory nerves, sympathetic efferent activity, and painful reflex muscle contraction

www.ketabpezeshki.com (021) 66485457 - 66485438

(spasm). Finally, a variety of psychological conditions can exacerbate or even cause pain.

T ere are certain areas to which special attention should be paid in a patient's medical history. Because depression is the most common emotional disturbance in patients with chronic pain, patients should be questioned about their mood, appetite, sleep patterns, and daily activity. A simple standardized questionnaire, such as the Beck Depression Inventory, can be a useful screening device. It is important to remember that major depression is a common, treatable, and potentially fatal illness.

Other clues that a significant emotional disturbance is contributing to a patient's chronic pain complaint include pain that occurs in multiple, unrelated sites; a pattern of recurrent, but separate, pain problems beginning in childhood or adolescence; pain beginning at a time of emotional trauma, such as the loss of a parent or spouse; a history of physical or sexual abuse; and past or present substance abuse.

On examination, special attention should be paid to whether the patient guards the painful area and whether certain movements or postures are avoided because of pain. Discovering a mechanical component to the pain can be useful both diagnostically and therapeutically. Painful areas should be examined for deep tenderness, noting whether this is localized to muscle, ligamentous structures, or joints. Chronic myofascial pain is very common, and, in these patients, deep palpation may reveal highly localized trigger points that are firm bands or knots in muscle. Relief of the pain following injection of local anesthetic into these trigger points supports the diagnosis. A neuropathic component to the pain is indicated by evidence of nerve damage, such as sensory impairment, exquisitely sensitive skin (allodynia), weakness, and muscle atrophy, or loss of deep tendon reflexes. Evidence suggesting sympathetic nervous system involvement includes the presence of diffuse swelling, changes in skin color and temperature, and hypersensitive skin and joint tenderness compared with the normal side. Relief of the pain with a sympathetic block supports the diagnosis, but once the condition becomes chronic, the response to sympathetic blockade is of variable magnitude and duration; the role for repeated sympathetic blocks in the overall management of CRPS is not established.

A guiding principle in evaluating patients with chronic pain is to assess both emotional and organic factors before initiating therapy. Addressing these issues together, rather than waiting to address emotional issues after organic causes of pain have been ruled out, improves compliance in part because it assures patients that a psychological evaluation does not mean that the physician is questioning the validity of their complaint. Even when an organic cause for a patient's pain can be found, it is still wise to look for other factors. For example, a cancer patient with painful bony metastases may have additional pain due to nerve damage and may also be depressed. Optimal therapy requires that each of these factors be looked for and treated.

TREATMENT Chronic Pain

Once the evaluation process has been completed and the likely causative and exacerbating factors identified, an explicit treatment plan should be developed. An important part of this process is to identify specific and realistic functional goals for therapy, such as getting a good night's sleep, being able to go shopping, or returning to work. A multidisciplinary approach that uses medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve the patient's quality of life. T ere are also some newer, relatively invasive procedures that can be helpful for some patients with intractable pain. T ese include image-guided interventions such as epidural injection of glucocorticoids for acute radicular pain and radiofrequency treatment of the facet joints for chronic facet-related back and neck pain. For patients with severe and persistent pain that is unresponsive to more conservative treatment, placement of electrodes within the spinal canal overlying the dorsal columns of the spinal cord (spinal cord stimulation) or implantation of intrathecal drug-delivery systems has shown significant benefit. T e criteria for predicting which patients will respond to these procedures continue to evolve. T ey are generally reserved for patients who have not responded to conventional pharmacologic approaches. Referral to a multidisciplinary pain clinic for a full evaluation should precede any invasive procedure. Such referrals are clearly not necessary for all chronic pain patients. For some, pharmacologic management alone can provide adequate relief.

ANTIDEPRESSANT MEDICATIONS T e tricyclic antidepressants (TCAs), particularly nortriptyline and desipramine (Table 8-1), are useful for the management of chronic pain. Although developed for the treatment of depression, the TCAs have a spectrum of dose-related biologic activities that include analgesia in a variety of chronic clinical conditions. Although the mechanism is unknown, the analgesic effect of TCAs has a more rapid onset and occurs at a lower dose than is typically required for the treatment of depression. Furthermore, patients with chronic pain who are not depressed obtain pain relief with antidepressants. T ere is evidence that TCAs potentiate opioid analgesia, so they may be useful adjuncts for the treatment of severe persistent pain such as occurs with malignant tumors. **Table 8-2** lists some of the painful conditions that respond to TCAs. TCAs are of particular value in the management of neuropathic pain such as occurs in diabetic neuropathy and postherpetic neuralgia, for which there are few other therapeutic options.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 8-2

PAINFUL CONDITIONS THAT RESPOND TO TRICYCLIC ANTIDEPRESSANTS
Postherpetic neuralgia[a]
Diabetic neuropathy[a]
Tension headache[a]
Migraine headache[a]
Rheumatoid arthritis[a,b]
Chronic low back pain[b]
Cancer
Central poststroke pain

[a]Controlled trials demonstrate analgesia.
[b]Controlled studies indicate benef t but not analgesia.

T e TCAs that have been shown to relieve pain have significant side effects (Table 8-1; **Chap. 61)**. Some of these side effects, such as orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation, and urinary retention, are particularly problematic in elderly patients, and several are additive to the side effects of opioid analgesics. T e selective serotonin reuptake inhibitors such as fluoxetine (Prozac) have fewer and less serious side effects than TCAs, but they are much less effective for relieving pain. It is of interest that venlafaxine (Effexor) and duloxetine (Cymbalta), which are nontricyclic antidepressants that block both serotonin and norepinephrine reuptake, appear to retain most of the pain-relieving effect of TCAs with a side effect profile more like that of the selective serotonin reuptake inhibitors. T ese drugs may be particularly useful in patients who cannot tolerate the side effects of TCAs.

ANTICONVULSANTS AND ANTIARRHYTHMICS T ese drugs are useful primarily for patients with neuropathic pain. Phenytoin (Dilantin) and carbamazepine (Tegretol) were first shown to relieve the pain of trigeminal neuralgia. T is pain has a characteristic brief, shooting, electric shock–like quality. In fact, anticonvulsants seem to be particularly helpful for pains that have such a lancinating quality. Newer anticonvulsants, gabapentin (Neurontin) and pregabalin (Lyrica), are effective for a broad range of neuropathic pains. Furthermore, because of their favorable side effect profile, these newer anticonvulsants are often used as first-line agents.

CHRONIC OPIOID MEDICATION T e long-term use of opioids is accepted for patients with pain due to malignant disease. Although opioid use for chronic pain of nonmalignant origin is controversial, it is clear that, for many patients, opioids are the only option that produces meaningful pain relief. T is is understandable because opioids are the most potent and have the broadest range of ef cacy of any analgesic medications. Although addiction is rare in patients who first use opioids for pain relief, some degree of tolerance and physical dependence is likely with long-term use. Furthermore, animal studies suggest that long-term opioid therapy may worsen pain in some individuals. T erefore, before embarking on opioid therapy, other options should be explored, and the limitations and risks of opioids should be explained to the patient. It is also important to point out that some opioid analgesic medications have mixed agonist-antagonist properties (e.g., butorphanol and buprenorphine). From a practical standpoint, this means that they may worsen pain by inducing an abstinence syndrome in patients who are physically dependent on other opioid analgesics.

With long-term outpatient use of orally administered opioids, it is desirable to use long-acting compounds such as levorphanol, methadone, sustained-release morphine, or transdermal fentanyl (Table 8-1). T e pharmacokinetic profiles of these drug preparations enable the maintenance of sustained analgesic blood levels, potentially minimizing side effects such as sedation that are associated with high peak plasma levels, and reducing the likelihood of rebound pain associated with a rapid fall in plasma opioid concentration. Although long-acting opioid preparations may provide superior pain relief in patients with a continuous pattern of ongoing pain, others suffer from intermittent severe episodic pain and experience superior pain control and fewer side effects with the periodic use of short-acting opioid analgesics. Constipation is a virtually universal side effect of opioid use and should be treated expectantly. As noted above in the discussion of acute pain treatment, a recent advance for patients is the development of peripherally acting opioid antagonists that can reverse the constipation associated with opioid use without interfering with analgesia.

Soon after the introduction of a controlled-release oxycodone formulation (OxyContin) in the late 1990s, a dramatic rise in emergency department visits and deaths associated with oxycodone ingestion appeared, focusing public attention on misuse of prescription pain medications. T e magnitude of prescription opioid abuse has grown over the last decade, leading the Centers for Disease Control and Prevention to classify prescription opioid analgesic abuse as an epidemic. T is appears to be due in large part to individuals using a prescription drug nonmedically, most often an opioid analgesic. Drug-induced deaths have rapidly risen and are now the second leading cause of death in Americans, just behind motor vehicle fatalities. In 2011, the Of ce of National Drug Control Policy established a multifaceted approach to address prescription drug abuse, including Prescription Drug Monitoring Programs that allow practitioners to determine if patients are receiving prescriptions from multiple providers and use of law enforcement to eliminate improper prescribing practices. T is increased scrutiny leaves many practitioners hesitant to prescribe opioid analgesics, other than for brief periods to control pain associated with illness or injury. For now, the choice to begin chronic opioid therapy for a given patient is left to the individual practitioner. Pragmatic guidelines for properly selecting and monitoring patients receiving chronic opioid therapy are shown in **Table 8-3**.

TREATMENT OF NEUROPATHIC PAIN It is important to individualize treatment for patients with neuropathic pain. Several general principles should guide therapy: the first is to move quickly to provide relief, and the second is to minimize drug

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 8-3

GUIDELINES FOR SELECTING AND MONITORING PATIENTS RECEIVING CHRONIC OPIOID THERAPY (COT) FOR THE TREATMENT OF CHRONIC, NONCANCER PAIN

Patient Selection

- Conduct a history, physical examination, and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction.
- Consider a trial of COT if pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh potential harms.
- A benefit-to-harm evaluation, including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during COT.

Informed Consent and Use of Management Plans

- Informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT.
- Consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education.

Initiation and Titration

- Initial treatment with opioids should be considered as a therapeutic trial to determine whether COT is appropriate.
- Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms.

Monitoring

- Reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies.
- In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care.
- In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care.

Source: Adapted with permission from R Chou et al: J Pain 10:113, 2009.

side effects. For example, in patients with postherpetic neuralgia and significant cutaneous hypersensitivity, topical lidocaine (Lidoderm patches) can provide immediate relief without side effects. Anticonvulsants (gabapentin or pregabalin; see above) or antidepressants (nortriptyline, desipramine, duloxetine, or venlafaxine) can be used as first-line drugs for patients with neuropathic pain. Systemically administered antiarrhythmic drugs such as lidocaine and mexiletine are less likely to be effective; although intravenous infusion of lidocaine can provide analgesia for patients with different types of neuropathic pain, the relief is usually transient, typically lasting just hours after the cessation of the infusion. The oral lidocaine congener mexiletine is poorly tolerated, producing frequent gastrointestinal adverse effects. There is no consensus on which class of drug should be used as a first-line treatment for any chronically painful condition. However, because relatively high doses of anticonvulsants are required for pain relief, sedation is very common. Sedation is also a problem with TCAs but is much less of a problem with serotonin/norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine and duloxetine). Thus, in the elderly or in patients whose daily activities require high-level mental activity, these drugs should be considered the first line. In contrast, opioid medications should be used as a second- or third-line drug class. Although highly effective for many painful conditions, opioids are sedating, and their effect tends to lessen over time, leading to dose escalation and, occasionally, a worsening of pain due to physical dependence. Drugs of different classes can be used in combination to optimize pain control. Repeated injections of botulinum toxin is an emerging approach to focal neuropathic pain based on recent studies.

It is worth emphasizing that many patients, especially those with chronic pain, seek medical attention primarily because they are suffering and because only physicians can provide the medications required for pain relief. A primary responsibility of all physicians is to minimize the physical and emotional discomfort of their patients. Familiarity with pain mechanisms and analgesic medications is an important step toward accomplishing this aim.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 9

HEADACHE

Peter J. Goadsby ■ Neil H. Raskin

Headache is among the most common reasons patients seek medical attention, on a global basis being responsible for more disability than any other neurologic problem. Diagnosis and management are based on a careful clinical approach augmented by an understanding of the anatomy, physiology, and pharmacology of the nervous system pathways mediating the various headache syndromes. T is chapter will focus on the general approach to a patient with headache; migraine and other primary headache disorders are discussed in **Chap. 34**.

GENERAL PRINCIPLES

A classification system developed by the International Headache Society (www.ihs-headache.org/) characterizes headache as primary or secondary **(Table 9-1)**. Primary headaches are those in which headache and its associated features are the disorder in itself, whereas secondary headaches are those caused by exogenous disorders (Headache Classification Committee of the International Headache Society, 2013). Primary headache often results in considerable disability and a decrease in the patient's quality of life. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but rarely worrisome. Life-threatening headache is relatively uncommon, but vigilance is required in order to recognize and appropriately treat such patients.

TABLE 9-1

COMMON CAUSES OF HEADACHE

PRIMARY HEADACHE		SECONDARY HEADACHE	
TYPE	%	TYPE	%
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: After J Olesen et al: The Headaches. Philadelphia, Lippincott Williams & Wilkins, 2005.

ANATOMY AND PHYSIOLOGY OF HEADACHE

Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors **(Chap. 8)**. In such situations, pain perception is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain-producing pathways of the peripheral or central nervous system (CNS) are damaged or activated inappropriately. Headache may originate from either or both mechanisms. Relatively few cranial structures are pain-producing; these include the scalp, middle meningeal artery, dural sinuses, falx cerebri, and proximal segments of the large pial arteries. T e ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are not pain-producing.

T e key structures involved in primary headache appear to be the following:

- T e large intracranial vessels and dura mater and the peripheral terminals of the trigeminal nerve that innervate these structures
- T e caudal portion of the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex)
- Rostral pain-processing regions, such as the ventroposteromedial thalamus and the cortex
- T e pain-modulatory systems in the brain that modulate input from trigeminal nociceptors at all levels of the pain-processing pathways and influence vegetative functions, such as hypothalamus and brainstem structures

www.ketabpezeshki.com (021) 66485457 - 66485438

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the trigeminovascular system. Cranial autonomic symptoms, such as lacrimation, conjunctival injection, nasal congestion, rhinorrhea, periorbital swelling, aural fullness, and ptosis, are prominent in the trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania, and may also be seen in migraine, even in children. These autonomic symptoms reflect activation of cranial parasympathetic pathways, and functional imaging studies indicate that vascular changes in migraine and cluster headache, when present, are similarly driven by these cranial autonomic systems. Moreover, they can often be mistaken for symptoms or signs of cranial sinus inflammation, which is thus overdiagnosed and inappropriately managed. Migraine and other primary headache types are not "vascular headaches"; these disorders do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects. Migraine is a brain disorder and is best understood and managed as such.

CLINICAL EVALUATION OF ACUTE, NEW-ONSET HEADACHE

The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache. Patients with recent onset of pain require prompt evaluation and appropriate treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumor, and purulent sinusitis. When worrisome symptoms and signs are present **(Table 9-2)**, rapid diagnosis and management are critical.

A careful neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a computed tomography (CT) or magnetic resonance imaging (MRI) study. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. In some circumstances, a lumbar puncture (LP) is also required, unless a benign etiology can be otherwise established. A general evaluation of acute headache might include cranial arteries by palpation; cervical spine by the effect of passive movement of the head and by imaging; the investigation of cardiovascular and renal status by blood pressure monitoring and urine examination; and eyes by funduscopy, intraocular pressure measurement, and refraction.

The psychological state of the patient should also be evaluated because a relationship exists between head pain and depression. This is intended to identify comorbidity rather than provide an explanation for the headache, because troublesome headache is seldom simply caused by mood change. Although it is notable that medicines with antidepressant actions are also effective in the prophylactic treatment of both tension-type headache and migraine, each symptom must be treated optimally.

Underlying recurrent headache disorders may be activated by pain that follows otologic or endodontic surgical procedures. Thus, pain about the head as the result of diseased tissue or trauma may reawaken an otherwise quiescent migraine syndrome. Treatment of the headache is largely ineffective until the cause of the primary problem is addressed.

Serious underlying conditions that are associated with headache are described below. Brain tumor is a rare cause of headache and even less commonly a cause of severe pain. The vast majority of patients presenting with severe headache have a benign cause.

TABLE 9-2

HEADACHE SYMPTOMS THAT SUGGEST A SERIOUS UNDERLYING DISORDER
Sudden-onset headache
First severe headache
"Worst" headache ever
Vomiting that precedes headache
Subacute worsening over days or weeks
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Fever or unexplained systemic signs
Abnormal neurologic examination
Pain associated with local tenderness, e.g., region of temporal artery

SECONDARY HEADACHE

The management of secondary headache focuses on diagnosis and treatment of the underlying condition.

MENINGITIS

Acute, severe headache with stiff neck and fever suggests meningitis. LP is mandatory. Often there is striking accentuation of pain with eye movement. Meningitis can be easily mistaken for migraine in that the cardinal symptoms of pounding headache,

www.ketabpezeshki.com (021) 66485457 - 66485438

photophobia, nausea, and vomiting are frequently present, perhaps reflecting the underlying biology of some of the patients.

Meningitis is discussed in Chaps. 46 and 47.

INTRACRANIAL HEMORRHAGE

Acute, severe headache with stiff neck but without fever suggests subarachnoid hemorrhage. A ruptured aneurysm, arteriovenous malformation, or intraparenchymal hemorrhage may also present with headache alone. Rarely, if the hemorrhage is small or below the foramen magnum, the head CT scan can be normal. T erefore, LP may be required to definitively diagnose subarachnoid hemorrhage.

Intracranial hemorrhage is discussed in Chap. 33.

BRAIN TUMOR

Approximately 30% of patients with brain tumors consider headache to be their chief complaint. T e head pain is usually nondescript—an intermittent deep, dull aching of moderate intensity, which may worsen with exertion or change in position and may be associated with nausea and vomiting. T is pattern of symptoms results from migraine far more often than from brain tumor. T e headache of brain tumor disturbs sleep in about 10% of patients. Vomiting that precedes the appearance of headache by weeks is highly characteristic of posterior fossa brain tumors. A history of amenorrhea or galactorrhea should lead one to question whether a prolactin-secreting pituitary adenoma (or the polycystic ovary syndrome) is the source of headache. Headache arising de novo in a patient with known malignancy suggests either cerebral metastases or carcinomatous meningitis, or both. Head pain appearing abruptly after bending, lifting, or coughing can be due to a posterior fossa mass, a Chiari malformation, or low cerebrospinal fluid (CSF) volume.

Brain tumors are discussed in Chap. 49.

TEMPORAL ARTERITIS

(See also Chap. 25) Temporal (giant cell) arteritis is an inflammatory disorder of arteries that frequently involves the extracranial carotid circulation. It is a common disorder of the elderly; its annual incidence is 77 per 100,000 individuals age 50 and older. T e average age of onset is 70 years, and women account for 65% of cases. About half of patients with untreated temporal arteritis develop blindness due to involvement of the ophthalmic artery and its branches; indeed, the ischemic optic neuropathy induced by giant cell arteritis is the major cause of rapidly developing bilateral blindness in patients >60 years. Because treatment with glucocorticoids is effective in preventing this complication, prompt recognition of the disorder is important.

Typical presenting symptoms include headache, polymyalgia rheumatica, jaw claudication, fever, and weight loss. Headache is the dominant symptom and often appears in association with malaise and muscle aches. Head pain may be unilateral or bilateral and is located temporally in 50% of patients but may involve any and all aspects of the cranium. Pain usually appears gradually over a few hours before peak intensity is reached; occasionally, it is explosive in onset. T e quality of pain is only seldom throbbing; it is almost invariably described as dull and boring, with superimposed episodic stabbing pains similar to the sharp pains that appear in migraine. Most patients can recognize that the origin of their head pain is superficial, external to the skull, rather than originating deep within the cranium (the pain site for migraineurs). Scalp tenderness is present, often to a marked degree; brushing the hair or resting the head on a pillow may be impossible because of pain. Headache is usually worse at night and often aggravated by exposure to cold. Additional findings may include reddened, tender nodules or red streaking of the skin overlying the temporal arteries, and tenderness of the temporal or, less commonly, the occipital arteries.

T e erythrocyte sedimentation rate (ESR) is often, although not always, elevated; a normal ESR does not exclude giant cell arteritis. A temporal artery biopsy followed by immediate treatment with prednisone 80 mg daily for the first 4–6 weeks should be initiated when clinical suspicion is high. T e prevalence of migraine among the elderly is substantial, considerably higher than that of giant cell arteritis. Migraineurs often report amelioration of their headaches with prednisone; thus, caution must be used when interpreting the therapeutic response.

GLAUCOMA

Glaucoma may present with a prostrating headache associated with nausea and vomiting. T e headache often starts with severe eye pain. On physical examination, the eye is often red with a fixed, moderately dilated pupil.

Glaucoma is discussed in Chap. 25.

PRIMARY HEADACHE DISORDERS

Primary headaches are disorders in which headache and associated features occur in the absence of any exogenous cause. T e most common are migraine, tension-type headache, and the trigeminal autonomic cephalalgias, notably cluster headache. T ese entities are discussed in detail in **Chap. 34**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 9-3

CLASSIFICATION OF CHRONIC DAILY HEADACHE

PRIMARY		
>4 H DAILY	<4 H DAILY	SECONDARY
Chronic migraine[a]	Chronic cluster headache[b]	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache[a]	Chronic paroxysmal hemicrania	Inf ammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua[a]	SUNCT/SUNA	Chronic CNS infection
New daily persistent headache[a]	Hypnic headache	Medication-overuse headache[a]

[a]May be complicated by medication overuse.
[b]Some patients may have headache >4 h/d.
Abbreviations: CNS, central nervous system; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

CHRONIC DAILY HEADACHE

T e broad diagnosis of chronic daily headache (CDH) can be applied when a patient experiences headache on 15 days or more per month. CDH is not a single entity; it encompasses a number of different headache syndromes, both primary and secondary **(Table 9-3)**. In aggregate, this group presents considerable disability and is thus specially dealt with here. Population-based estimates suggest that about 4% of adults have daily or near-daily headache.

APPROACH TO THE PATIENT: Chronic Daily Headache

T e first step in the management of patients with CDH is to diagnose any secondary headache and treat that problem (Table 9-3). T is can sometimes be a challenge where the underlying cause triggers a worsening of a primary headache. For patients with primary headaches, diagnosis of the headache type will guide therapy. Preventive treatments such as tricyclics, either amitriptyline or nortriptyline at doses up to 1 mg/kg, are very useful in patients with CDH arising from migraine or tension-type headache or where the secondary cause has activated the underlying primary headache. Tricyclics are started in low doses (10–25 mg) daily and may be given 12 h before the expected time of awakening in order to avoid excess morning sleepiness. Anticonvulsants, such as topiramate, valproate, flunarizine (not available in the United States), and candesartan are also useful in migraine.

MANAGEMENT OF MEDICALLY INTRACTABLE DISABLING PRIMARY CHRONIC DAILY HEADACHE T e management of medically intractable headache is dif cult. Currently there are a number of promising neuromodulatory approaches, such as occipital nerve stimulation, which appears to modulate thalamic processing in migraine, and has also shown promise in chronic cluster headache, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua **(Chap. 34)**. Single-pulse transcranial magnetic stimulation is in use in Europe and is approved for migraine with aura in the United States. Other modalities are discussed in **Chap. 34**.

MEDICATION-OVERUSE HEADACHE Overuse of analgesic medication for headache can aggravate headache frequency, markedly impair the effect of preventive medicines, and induce a state of refractory daily or near-daily headache called medication-overuse headache. A proportion of patients who stop taking analgesics will experience substantial improvement in the severity and frequency of their headache. However, even after cessation of analgesic use, many patients continue to have headache, although they may feel clinically improved in some way, especially if they have been using opioids or barbiturates regularly. T e residual symptoms probably represent the underlying primary headache disorder, and most commonly, this issue occurs in patients prone to migraine.

Management of medication overuse: outpatients For patients who overuse medications, it is essential that analgesic use be reduced and eliminated. One approach is to reduce the medication dose by 10% every 1–2 weeks. Immediate cessation of analgesic use is possible for some patients, provided there is no contraindication. Both approaches are facilitated by the use of a medication diary maintained during the month or two before cessation; this helps to identify the scope of the problem. A small dose of a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen, 500 mg bid, if tolerated, will help relieve residual pain as analgesic use is reduced. NSAID overuse is not usually a problem for patients with daily headache when a NSAID with a longer half-life is taken once or twice daily; however, overuse problems may develop with more frequent dosing schedules or shorter acting NSAIDS. Once the patient has substantially reduced analgesic use, a preventive medication should be introduced. It must be emphasized that preventives generally do not work in the presence *of* analgesic overuse. The most common cause of unresponsiveness to treatment is the use of a preventive when analgesics continue to be used regularly. For some patients, discontinuing analgesics is very difficult; often the best approach is to directly inform the patient that some degree of pain is inevitable during this initial period.

www.ketabpezeshki.com (021) 66485457 - 66485438

Management of medication overuse: inpatients Some patients will require hospitalization for detoxification. Such patients have typically failed efforts at outpatient withdrawal or have a significant medical condition, such as diabetes mellitus, which would complicate withdrawal as an outpatient. Following admission to the hospital, acute medications are withdrawn completely on the first day, in the absence of a contraindication. Antiemetics and fluids are administered as required; clonidine is used for opioid withdrawal symptoms. For acute intolerable pain during the waking hours, aspirin, 1 g IV (not approved in United States), is useful. IM chlorpromazine can be helpful at night; patients must be adequately hydrated. Three to 5 days into the admission, as the effect of the withdrawn substance wears off, a course of IV dihydroergotamine (DHE) can be used. DHE, administered every 8 h for 5 consecutive days, can induce a significant remission that allows a preventive treatment to be established. 5-HT_3 antagonists, such as ondansetron or granisetron, or the neurokinin receptor antagonist, aprepitant, may be required with DHE to prevent significant nausea, and domperidone (not approved in the United States) orally or by suppository can be very helpful. Avoiding sedating or otherwise side effect prone antiemetics is helpful.

NEW DAILY PERSISTENT HEADACHE

New daily persistent headache (NDPH) is a clinically distinct syndrome; its causes are listed in **Table 9-4**.

Clinical presentation The patient with NDPH presents with headache on most if not all days, and the patient can clearly, and often vividly, recall the moment of onset. The headache usually begins abruptly, but onset may be more gradual; evolution over 3 days has been proposed as the upper limit for this syndrome. Patients typically recall the exact day and circumstances of the onset of headache; the new, persistent head pain does not remit. The first priority is to distinguish between a primary and a secondary cause of this syndrome. Subarachnoid hemorrhage is the most serious of the secondary causes and must be excluded either by history or appropriate investigation **(Chap. 33)**.

TABLE 9-4

DIFFERENTIAL DIAGNOSIS OF NEW DAILY PERSISTENT HEADACHE

PRIMARY	SECONDARY
Migrainous-type	Subarachnoid hemorrhage
Featureless (tension-type)	Low cerebrospinal fluid (CSF) volume headache
	Raised CSF pressure headache
	Posttraumatic headache[a]
	Chronic meningitis

[a]Includes postinfectious forms.

Secondary NDPH • Low CSF volume headache In these syndromes, head pain is positional: it begins when the patient sits or stands upright and resolves upon reclining. The pain, which is occipitofrontal, is usually a dull ache but may be throbbing. Patients with chronic low CSF volume headache typically present with a history of headache from one day to the next that is generally not present on waking but worsens during the day. Recumbency usually improves the headache within minutes, and it can take only minutes to an hour for the pain to return when the patient resumes an upright position.

The most common cause of headache due to persistent low CSF volume is CSF leak following LP. Post-LP headache usually begins within 48 h but may be delayed for up to 12 days. Its incidence is between 10 and 30%. Beverages with caffeine may provide temporary relief. Besides LP, index events may include epidural injection or a vigorous Valsalva maneuver, such as from lifting, straining, coughing, clearing the eustachian tubes in an airplane, or multiple orgasms. Spontaneous CSF leaks are well recognized, and the diagnosis should be considered whenever the headache history is typical, even when there is no obvious index event. As time passes from the index event, the postural nature may become less apparent; cases in which the index event occurred several years before the eventual diagnosis have been recognized. Symptoms appear to result from low volume rather than low pressure: although low CSF pressures, typically 0–50 mmH_2O, are usually identified, a pressure as high as 140 mmH_2O has been noted with a documented leak.

Postural orthostatic tachycardia syndrome (POTS; **Chap. 41)** can present with orthostatic headache similar to low CSF volume headache and is a diagnosis that needs consideration in this setting.

When imaging is indicated to identify the source of a presumed leak, an MRI with gadolinium is the initial study of choice **(Fig. 9-1)**. A striking pattern of diffuse meningeal enhancement is so typical that in the appropriate clinical context the diagnosis is established. Chiari malformations may sometimes be noted on MRI; in such cases, surgery to decompress the posterior fossa usually worsens the headache. Spinal MRI with T2 weighting may reveal a leak, and spinal MRI may demonstrate spinal meningeal cysts whose role in these syndromes is yet to be elucidated. The source of CSF leakage may be identified by spinal MRI with appropriate sequences, by CT, or increasingly by MR myelography. Less used now, ^{111}In-DTPA CSF studies in the absence of a directly identified site of leakage, may demonstrate early emptying of ^{111}In-DTPA tracer into the bladder or slow progress of tracer across the brain suggesting a CSF leak.

Initial treatment for low CSF volume headache is bed rest. For patients with persistent pain, IV caffeine (500 mg in 500 mL of saline administered over 2 h) can

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 9-1
Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low cerebrospinal fluid (CSF) volume headache.

be very effective. An electrocardiogram (ECG) to screen for arrhythmia should be performed before administration. It is reasonable to administer at least two infusions of caffeine before embarking on additional tests to identify the source of the CSF leak. Because IV caffeine is safe and can be curative, it spares many patients the need for further investigations. If unsuccessful, an abdominal binder may be helpful. If a leak can be identified, an autologous blood patch is usually curative. A blood patch is also effective for post-LP headache; in this setting, the location is empirically determined to be the site of the LP. In patients with intractable pain, oral theophylline is a useful alternative; however, its effect is less rapid than caffeine.

Raised CSF pressure headache Raised CSF pressure is well recognized as a cause of headache. Brain imaging can often reveal the cause, such as a space-occupying lesion. NDPH due to raised CSF pressure can be the presenting symptom for patients with idiopathic intracranial hypertension (pseudotumor cerebri) without visual problems, particularly when the fundi are normal. Persistently raised intracranial pressure can trigger chronic migraine. These patients typically present with a history of generalized headache that is present on waking and improves as the day goes on. It is generally worse with recumbency. Visual obscurations are frequent. The diagnosis is relatively straightforward when papilledema is present, but the possibility must be considered even in patients without funduscopic changes. Formal visual field testing should be performed even in the absence of overt ophthalmic involvement. Headache on rising in the morning or nocturnal headache is also characteristic of obstructive sleep apnea or poorly controlled hypertension.

Evaluation of patients suspected to have raised CSF pressure requires brain imaging. It is most efficient to obtain an MRI, including an MR venogram, as the initial study. If there are no contraindications, the CSF pressure should be measured by LP; this should be done when the patient is symptomatic so that both the pressure and the response to removal of 20–30 mL of CSF can be determined. An elevated opening pressure and improvement in headache following removal of CSF are diagnostic.

Initial treatment is with acetazolamide (250–500 mg bid); the headache may improve within weeks. If ineffective, topiramate is the next treatment of choice; it has many actions that may be useful in this setting, including carbonic anhydrase inhibition, weight loss, and neuronal membrane stabilization, likely mediated via effects on phosphorylation pathways. Severely disabled patients who do not respond to medical treatment require intracranial pressure monitoring and may require shunting.

Posttraumatic headache A traumatic event can trigger a headache process that lasts for many months or years after the event. The term trauma is used in a very broad sense: headache can develop following an injury to the head, but it can also develop after an infectious episode, typically viral meningitis, a flulike illness, or a parasitic infection. Complaints of dizziness, vertigo, and impaired memory can accompany the headache. Symptoms may remit after several weeks or persist for months and even years after the injury. Typically the neurologic examination is normal and CT or MRI studies are unrevealing. Chronic subdural hematoma may on occasion mimic this disorder. Posttraumatic headache may also be seen after carotid dissection and subarachnoid hemorrhage and after intracranial surgery. The underlying theme appears to be that a traumatic event involving the pain-producing meninges can trigger a headache process that lasts for many years.

Other causes In one series, one-third of patients with NDPH reported headache beginning after a transient flulike illness characterized by fever, neck stiffness, photophobia, and marked malaise. Evaluation typically reveals no apparent cause for the headache. There is no convincing evidence that persistent Epstein-Barr virus infection plays a role in NDPH. A complicating factor is that many patients undergo LP during the acute illness; iatrogenic low CSF volume headache must be considered in these cases.

Treatment Treatment is largely empirical. Tricyclic antidepressants, notably amitriptyline, and anticonvulsants, such as topiramate, valproate, and gabapentin, have been used with reported benefit. The monoamine oxidase inhibitor phenelzine may also be useful in carefully selected patients. The headache usually resolves within 3–5 years, but it can be quite disabling.

www.ketabpezeshki.com (021) 66485457 - 66485438

PRIMARY CARE AND HEADACHE MANAGEMENT

Most patients with headache will be seen first in a primary care setting. T e task of the primary care physician is to identify the very few worrisome secondary headaches from the very great majority of primary and less troublesome secondary headaches (Table 9-2).

Absent any warning signs, a reasonable approach is to treat when a diagnosis is established. As a general rule, the investigation should focus on identifying worrisome causes of headache or on gaining confidence if no primary headache diagnosis can be made.

After treatment has been initiated, follow-up care is essential to identify whether progress has been made against the headache complaint. Not all headaches will respond to treatment, but, in general, worrisome headaches will progress and will be easier to identify.

When a primary care physician feels the diagnosis is a primary headache disorder, it is worth noting that more than 90% of patients who present to primary care with a complaint of headache will have migraine **(Chap. 34)**.

In general, patients who do not have a clear diagnosis, have a primary headache disorder other than migraine or tension-type headache, or are unresponsive to two or more standard therapies for the considered headache type should be considered for referral to a specialist. In a practical sense, the threshold for referral is also determined by the experience of the primary care physician in headache medicine and the availability of secondary care options.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 10

BACK AND NECK PAIN

John W. Engstrom ■ Richard A. Deyo

The importance of back and neck pain in our society is underscored by the following: (1) the cost of back pain in the United States exceeds $100 billion annually; approximately one-third of these costs are direct health care expenses, and two-thirds are indirect costs resulting from loss of wages and productivity; (2) back symptoms are the most common cause of disability in those <45 years; (3) low back pain is the second most common reason for visiting a physician in the United States; and (4) 70% of persons will have back pain at some point in their lives.

ANATOMY OF THE SPINE

The anterior spine consists of cylindrical vertebral bodies separated by intervertebral disks and held together by the anterior and posterior longitudinal ligaments. The intervertebral disks are composed of a central gelatinous nucleus pulposus surrounded by a tough cartilaginous ring, the annulus fibrosis. Disks are responsible for 25% of spinal column length and allow the bony vertebrae to move easily upon each other **(Figs. 10-1 and 10-2)**. Desiccation of the nucleus pulposus and degeneration of the annulus fibrosus increase with age and result in loss of disk height. The disks are largest in the cervical and lumbar regions where movements of the spine are greatest. The anterior spine absorbs the shock of bodily movements such as walking and running and, with the posterior spine, protects the spinal cord and nerve roots in the spinal canal.

The posterior spine consists of the vertebral arches and processes. Each arch consists of paired cylindrical pedicles anteriorly and paired lamina posteriorly. The vertebral arch also gives rise to two transverse processes laterally, one spinous process posteriorly, plus two superior and two inferior articular facets. The apposition of a superior and inferior facet constitutes a facet joint. The posterior spine provides an anchor for the attachment of muscles and ligaments. The contraction of muscles attached to the spinous and transverse processes and lamina works like a system of pulleys and levers that results in flexion, extension, and lateral bending movements of the spine.

Nerve root injury (radiculopathy) is a common cause of neck, arm, low back, buttock, and leg pain **(see Figs. 15-2 and 15-3)**. The nerve roots exit at a level above their respective vertebral bodies in the cervical region (e.g., the C7 nerve root exits at the C6-C7 level) and below their respective vertebral bodies in the thoracic and lumbar regions (e.g., the T1 nerve root exits at the T1-T2 level). The cervical nerve roots follow a short intraspinal course before exiting. By contrast, because the spinal cord ends at the vertebral L1 or L2 level, the lumbar nerve roots follow a long intraspinal course and can be injured anywhere from the upper lumbar spine to their exit at the intervertebral foramen. For example, disk herniation at the L4-L5 level can produce not only L5 root compression, but also compression of the traversing S1 nerve root **(Fig. 10-3)**. The lumbar nerve roots are mobile in the spinal canal, but eventually pass through the narrow lateral recess of the spinal canal and intervertebral foramen (Figs. 10-2 and 10-3). Neuroimaging of the spine must include both sagittal and axial views to assess possible compression in either the lateral recess or intervertebral foramen.

Pain-sensitive structures of the spine include the periosteum of the vertebrae, dura, facet joints, annulus fibrosus of the intervertebral disk, epidural veins and arteries, and the longitudinal ligaments. Disease of these diverse structures may explain many cases of back pain without nerve root compression. Under normal circumstances, the nucleus pulposus of the intervertebral disk is not pain sensitive.

www.ketabpezeshki.com (021) 66485457 - 66485438

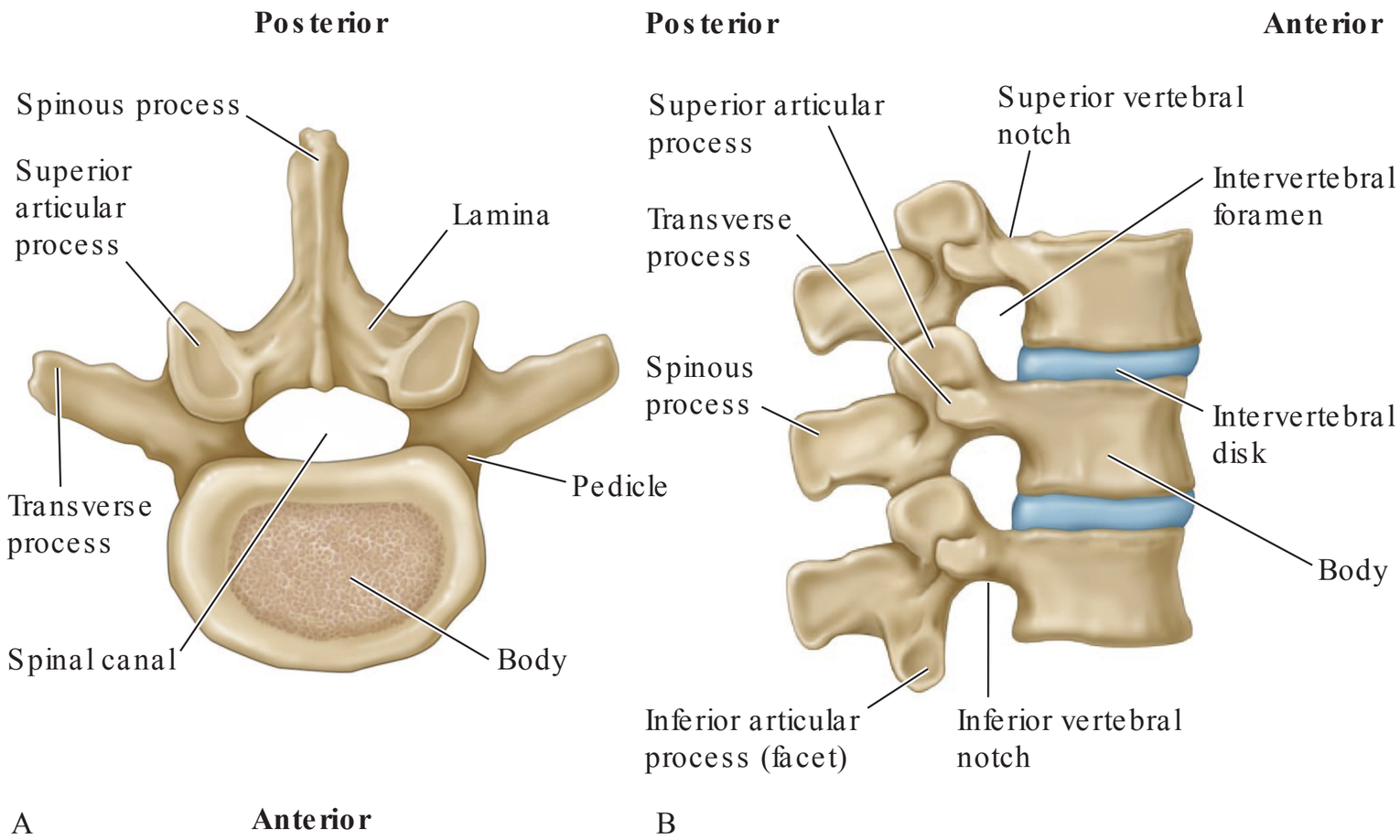


FIGURE 10-1
Vertebral anatomy. (From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.)

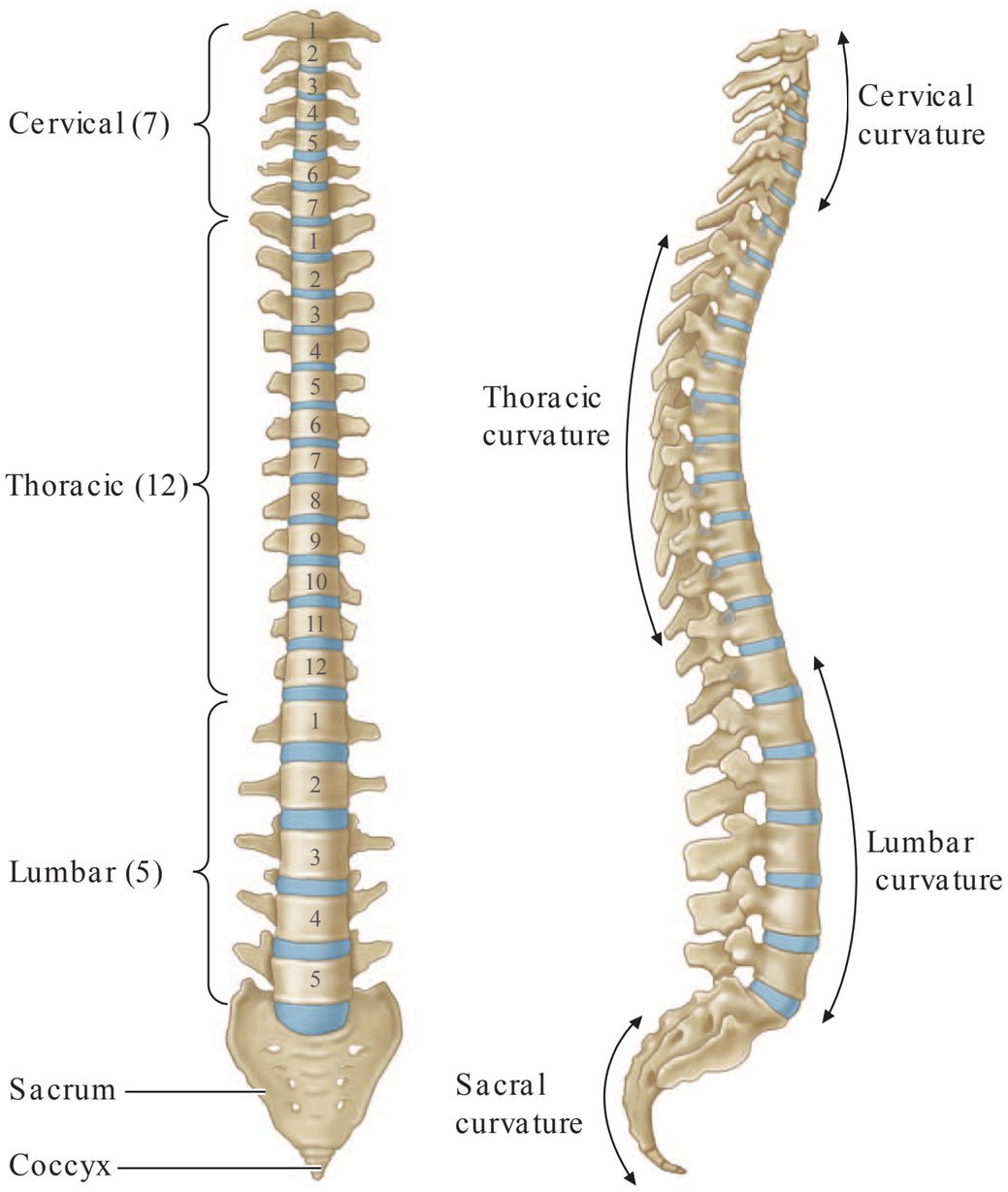


FIGURE 10-2
Spinal column. (From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.)

APPROACH TO THE PATIENT: Back Pain

TYPES OF BACK PAIN Delineating the type of pain reported by the patient is the essential first step. Attention is also focused on identification of risk factors for a serious underlying etiology. The most frequent causes of back pain are radiculopathy, fracture, tumor, infection, or referred pain from visceral structures **(Table 10-1)**.

Local pain is caused by injury to pain-sensitive structures that compress or irritate sensory nerve endings. The site of the pain is near the affected part of the back.

Pain referred to the back may arise from abdominal or pelvic viscera. The pain is usually described as primarily abdominal or pelvic, accompanied by back pain and usually unaffected by posture. The patient may occasionally complain of back pain only.

Pain of spine origin may be located in the back or referred to the buttocks or legs. Diseases affecting the upper lumbar spine tend to refer pain to the lumbar region, groin, or anterior thighs. Diseases affecting the lower lumbar spine tend to produce pain referred to the buttocks, posterior thighs, calves, or feet. Referred pain can explain pain syndromes that cross multiple dermatomes without evidence of nerve root compression.

Radicular pain is typically sharp and radiates from the low back to a leg within the territory of a nerve root (see "Lumbar Disk Disease," below). Coughing, sneezing, or voluntary contraction of abdominal muscles (lifting heavy objects or straining at stool) may elicit the radiating pain. The pain may increase in postures that stretch the nerves and nerve roots. Sitting with the leg outstretched places

www.ketabpezeshki.com (021) 66485457 - 66485438

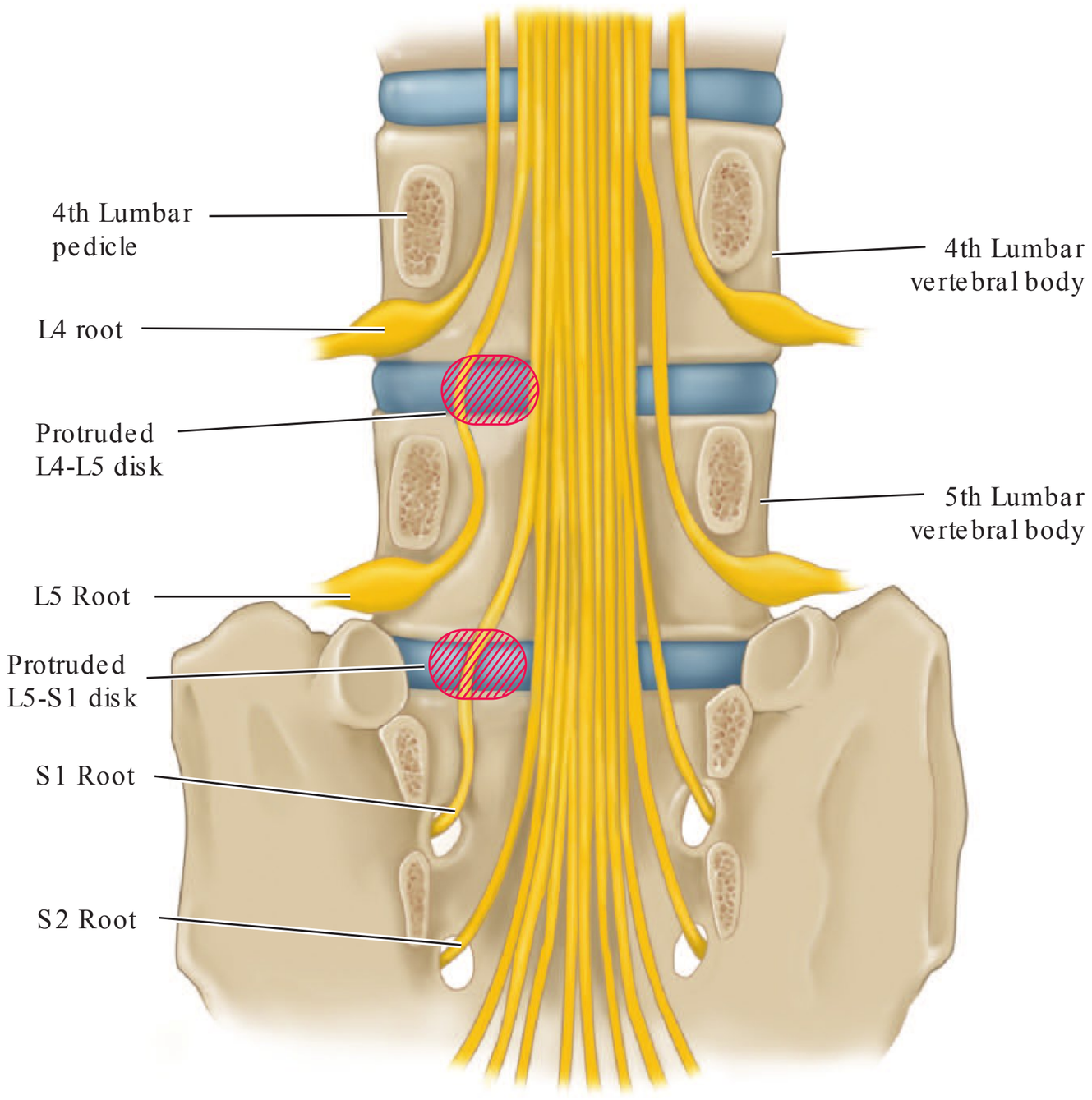


FIGURE 10-3
Compression of L5 and S1 roots by herniated disks. (From AH Ropper, MA Samuels: Adams and Victor's Principles of Neurology, 9th ed. New York, McGraw-Hill, 2009; with permission.)

TABLE 10-1

ACUTE LOW BACK PAIN: RISK FACTORS FOR AN IMPORTANT STRUCTURAL CAUSE
History
Pain worse at rest or at night
Prior history of cancer
History of chronic infection (especially lung, urinary tract, skin)
History of trauma
Incontinence
Age >70 years
Intravenous drug use
Glucocorticoid use
History of a rapidly progressive neurologic deficit
Examination
Unexplained fever
Unexplained weight loss
Percussion tenderness over the spine
Abdominal, rectal, or pelvic mass
Internal/external rotation of the leg at the hip; heel percussion sign
Straight leg or reverse straight leg—raising signs
Progressive focal neurologic deficit

traction on the sciatic nerve and L5 and S1 roots because the nerve passes posterior to the hip. The femoral nerve (L2, L3, and L4 roots) passes anterior to the hip and is not stretched by sitting. The description of the pain alone often fails to distinguish between referred pain and radiculopathy, although a burning or electric quality favors radiculopathy.

Pain associated with muscle spasm, although of obscure origin, is commonly associated with many spine disorders. The spasms are accompanied by abnormal posture, tense paraspinal muscles, and dull or achy pain in the paraspinal region.

Knowledge of the circumstances associated with the onset of back pain is important when weighing possible serious underlying causes for the pain. Some patients involved in accidents or work-related injuries may exaggerate their pain for the purpose of compensation or for psychological reasons.

EXAMINATION OF THE BACK. A physical examination that includes the abdomen and rectum is advisable. Back pain referred from visceral organs may be reproduced during palpation of the abdomen (pancreatitis, abdominal aortic aneurysm [AAA]) or percussion over the costovertebral angles (pyelonephritis).

The normal spine has a cervical and lumbar lordosis and a thoracic kyphosis. Exaggeration of these normal

www.ketabpezeshki.com (021) 66485457 - 66485438

alignments may result in hyperkyphosis of the thoracic spine or hyperlordosis of the lumbar spine. Inspection may reveal a lateral curvature of the spine (scoliosis). An asymmetry in the prominence of the paraspinal muscles suggests muscle spasm. Spine pain reproduced by palpation over the spinous process reflects injury of the affected vertebrae or adjacent pain-sensitive structures.

Forward bending is often limited by paraspinal muscle spasm; the latter may flatten the usual lumbar lordosis. Flexion at the hips is normal in patients with lumbar spine disease, but flexion of the lumbar spine is limited and sometimes painful. Lateral bending to the side opposite the injured spinal element may stretch the damaged tissues, worsen pain, and limit motion. Hyperextension of the spine (with the patient prone or standing) is limited when nerve root compression, facet joint pathology, or other bony spine disease is present.

Pain from hip disease may mimic the pain of lumbar spine disease. Hip pain can be reproduced by internal and external rotation at the hip with the knee and hip in flexion or by compressing the heel with the examiner's palm while the leg is extended (heel percussion sign).

The straight leg–raising (SLR) maneuver is a simple bedside test for nerve root disease. With the patient supine, passive flexion of the extended leg at the hip stretches the L5 and S1 nerve roots and the sciatic nerve. Passive dorsiflexion of the foot during the maneuver adds to the stretch. In healthy individuals, flexion to at least 80° is normally possible without causing pain, although a tight, stretching sensation in the hamstring muscles is common. The SLR test is positive if the maneuver reproduces the patient's usual back or limb pain. Eliciting the SLR sign in both the supine and sitting positions can help determine if the finding is reproducible. The patient may describe pain in the low back, buttocks, posterior thigh, or lower leg, but the key feature is reproduction of the patient's usual pain. The crossed SLR sign is present when flexion of one leg reproduces the usual pain in the opposite leg or buttocks. In disk herniation, the crossed SLR sign is less sensitive but more specific than the SLR sign. The reverse SLR sign is elicited by standing the patient next to the examination table and passively extending each leg with the knee fully extended. This maneuver, which stretches the L2-L4 nerve roots, lumbosacral plexus, and femoral nerve, is considered positive if the patient's usual back or limb pain is reproduced. For all of these tests, the nerve or nerve root lesion is always on the side of the pain.

The neurologic examination includes a search for focal weakness or muscle atrophy, focal reflex changes, diminished sensation in the legs, or signs of spinal cord injury. The examiner should be alert to the possibility of breakaway weakness, defined as fluctuations in the maximum power generated during muscle testing. Breakaway weakness may be due to pain or a combination of pain and an underlying true weakness. Breakaway weakness without pain is almost always due to a lack of effort. In uncertain cases, electromyography (EMG) can determine if true weakness due to nerve tissue injury is present. Findings with specific lumbosacral nerve root lesions are shown in **Table 10-2** and are discussed below.

TABLE 10-2

LUMBOSACRAL RADICULOPATHY: NEUROLOGIC FEATURES

LUMBOSACRAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
L2[a]	—	Upper anterior thigh	Psoas (hip flexors)	Anterior thigh
L3[a]	—	Lower anterior thigh Anterior knee	Psoas (hip flexors) Quadriceps (knee extensors) Thigh adductors	Anterior thigh, knee
L4[a]	Quadriceps (knee)	Medial calf	Quadriceps (knee extensors)[b] Thigh adductors	Knee, medial calf Anterolateral thigh
L5[c]	—	Dorsal surface—foot Lateral calf	Peronei (foot evertors)[b] Tibialis anterior (foot dorsiflexors) Gluteus medius (hip abductors) Toe dorsiflexors	Lateral calf, dorsal foot, posterolateral thigh, buttocks
S1[c]	Gastrocnemius/soleus (ankle)	Plantar surface—foot Lateral aspect—foot	Gastrocnemius/soleus (foot plantar flexors)[b] Abductor hallucis (toe flexors)[b] Gluteus maximus (hip extensors)	Bottom foot, posterior calf, posterior thigh, buttocks

[a]Reverse straight leg–raising sign present—see "Examination of the Back." [b]These muscles receive the majority of innervation from this root.
[c]Straight leg–raising sign present—see "Examination of the Back."

www.ketabpezeshki.com (021) 66485457 - 66485438

LABORATORY, IMAGING, AND EMG STUDIES Laboratory studies are rarely needed for the initial evaluation of nonspecific acute (<3 months in duration) low back pain (ALBP). Risk factors for a serious underlying cause and for infection, tumor, or fracture, in particular, should be sought by history and exam. If risk factors are present (Table 10-1), then laboratory studies (complete blood count [CBC], erythrocyte sedimentation rate [ESR], urinalysis) are indicated. If risk factors are absent, then management is conservative (see "Treatment," below)

Computed tomography (CT) scanning is superior to routine x-rays for the detection of fractures involving posterior spine structures, craniocervical and cervicothoracic junctions, C1 and C2 vertebrae, bone fragments within the spinal canal, or misalignment. CT scans are increasingly used as a primary screening modality for moderate to severe acute trauma. Magnetic resonance imaging (MRI) or CT myelography is the radiologic test of choice for evaluation of most serious diseases involving the spine. MRI is superior for the definition of soft tissue structures, whereas CT myelography provides optimal imaging of the lateral recess of the spinal canal and is better tolerated by claustrophobic patients.

Annual population surveys in the United States suggest that patients with back pain have reported progressively worse functional limitations in recent years, rather than progressive improvements, despite rapid increases in spine imaging, opioid prescribing, injections, and spine surgery. T is suggests that more selective use of diagnostic and treatment modalities may be appropriate.

Spine imaging often reveals abnormalities of dubious clinical relevance that may alarm clinicians and patients alike and prompt further testing and unnecessary therapy. Both randomized trials and observational studies have suggested such a "cascade effect" of imaging may create a gateway to other unnecessary care. Based in part on such evidence, the American College of Physicians has made parsimonious spine imaging a high priority in its "Choosing Wisely" campaign, aimed at reducing unnecessary care. Successful efforts to reduce unnecessary imaging have typically been multifaceted. Some include physician education by clinical leaders and computerized decision support, to identify any recent relevant imaging tests and require approved indications for ordering an imaging test. Other strategies have included audit and feedback regarding individual rates of ordering and indications, and more rapid access to physical therapy or consultation for patients without imaging indications.

When imaging tests are reported, it may be useful to indicate that certain degenerative findings are common in normal, pain-free individuals. In an observational study, this strategy was associated with lower rates of repeat imaging, opioid therapy, and physical therapy referral.

Electrodiagnostic studies can be used to assess the functional integrity of the peripheral nervous system **(Chap. 6)**. Sensory nerve conduction studies are normal when focal sensory loss confirmed by examination is due to nerve root damage because the nerve roots are proximal to the nerve cell bodies in the dorsal root ganglia. Injury to nerve tissue distal to the dorsal root ganglion (e.g., plexus or peripheral nerve) results in reduced sensory nerve signals. Needle EMG complements nerve conduction studies by detecting denervation or reinnervation changes in a myotomal (segmental) distribution. Multiple muscles supplied by different nerve roots and nerves are sampled; the pattern of muscle involvement indicates the nerve root(s) responsible for the injury. Needle EMG provides objective information about motor nerve fiber injury when clinical evaluation of weakness is limited by pain or poor effort. EMG and nerve conduction studies will be normal when sensory nerve root injury or irritation is the pain source.

CAUSES OF BACK PAIN

(Table 10-3)

LUMBAR DISK DISEASE

T is is a common cause of acute, chronic, or recurrent low back and leg pain **(Figs. 10-3 and 10-4)**. Disk disease is most likely to occur at the L4-L5 or L5-S1 levels, but upper lumbar levels are involved occasionally. T e cause is often unknown, but the risk is increased in overweight individuals. Disk herniation is unusual prior to age 20 years and is rare in the fibrotic disks of the elderly. Complex genetic factors may play a role in predisposing some patients to disk disease. T e pain may be located in the low back only or referred to a leg, buttock, or hip. A sneeze, cough, or trivial movement may cause the nucleus pulposus to prolapse, pushing the frayed and weakened annulus posteriorly. With severe disk disease, the nucleus may protrude through the annulus (herniation) or become extruded to lie as a free fragment in the spinal canal.

T e mechanism by which intervertebral disk injury causes back pain is controversial. T e inner annulus fibrosus and nucleus pulposus are normally devoid of innervation. Inflammation and production of proinflammatory cytokines within a ruptured nucleus pulposus may trigger or perpetuate back pain. Ingrowth of nociceptive (pain) nerve fibers into inner portions of a diseased disk may be responsible for some chronic "diskogenic" pain. Nerve root injury (radiculopathy) from disk herniation is usually due to inflammation, but lateral herniation may produce compression in the lateral recess or at the intervertebral foramen.

A ruptured disk may be asymptomatic or cause back pain, abnormal posture, limitation of spine motion

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 10-3

CAUSES OF BACK OR NECK PAIN
Lumbar Disk Disease
Degenerative Spine Disease
Lumbar spinal stenosis without or with neurogenic claudication
Intervertebral foraminal or lateral recess narrowing
Disk-osteophyte complex
Facet or uncovertebral joint hypertrophy
Lateral disk protrusion
Spondylosis (osteoarthritis) and spondylolisthesis
Spine Infection
Vertebral osteomyelitis
Spinal epidural abscess
Septic disk (diskitis)
Meningitis
Lumbar arachnoiditis
Neoplasms—Metastatic, Hematologic, Primary Bone Tumors
Fractures
Trauma/falls, motor vehicle accidents
Atraumatic fractures: osteoporosis, neoplastic infiltration, osteomyelitis
Minor Trauma
Strain or sprain
Whiplash injury
Metabolic Spine Disease
Osteoporosis—hyperparathyroidism, immobility
Osteosclerosis (e.g., Paget's disease)
Congenital/Developmental
Spondylolysis
Kyphoscoliosis
Spina bifida occulta
Tethered spinal cord
Autoimmune Inf ammatory Arthritis
Other Causes of Back Pain
Referred pain from visceral disease (e.g., abdominal aortic aneurysm)
Postural
Psychiatric, malingering, chronic pain syndromes

(particularly flexion), a focal neurologic deficit, or radicular pain. A dermatomal pattern of sensory loss or a reduced or absent deep tendon reflex is more suggestive of a specific root lesion than is the pattern of pain. Motor findings (focal weakness, muscle atrophy, or fasciculations) occur less frequently than focal sensory or reflex changes. Symptoms and signs are usually unilateral, but bilateral involvement does occur with large central disk herniations that compress multiple roots or cause inflammation of nerve roots within the spinal canal. Clinical manifestations of specific nerve root lesions are summarized in Table 10-2.

T e differential diagnosis covers a variety of serious and treatable conditions, including epidural abscess, hematoma, fracture, or tumor. Fever, constant pain uninfluenced by position, sphincter abnormalities, or signs of spinal cord disease suggest an etiology other than lumbar disk disease. Absence of ankle reflexes can be a normal finding in persons older than age 60 years or a sign of bilateral S1 radiculopathy. An absent deep tendon reflex or focal sensory loss may indicate injury to a nerve root, but other sites of injury along the nerve must also be considered. For example, an absent knee reflex may be due to a femoral neuropathy or an L4 nerve root injury. A loss of sensation over the foot and lateral lower calf may result from a peroneal or lateral sciatic neuropathy or an L5 nerve root injury. Focal muscle atrophy may reflect injury to the anterior horn cells of the spinal cord, a nerve root, peripheral nerve, or disuse.

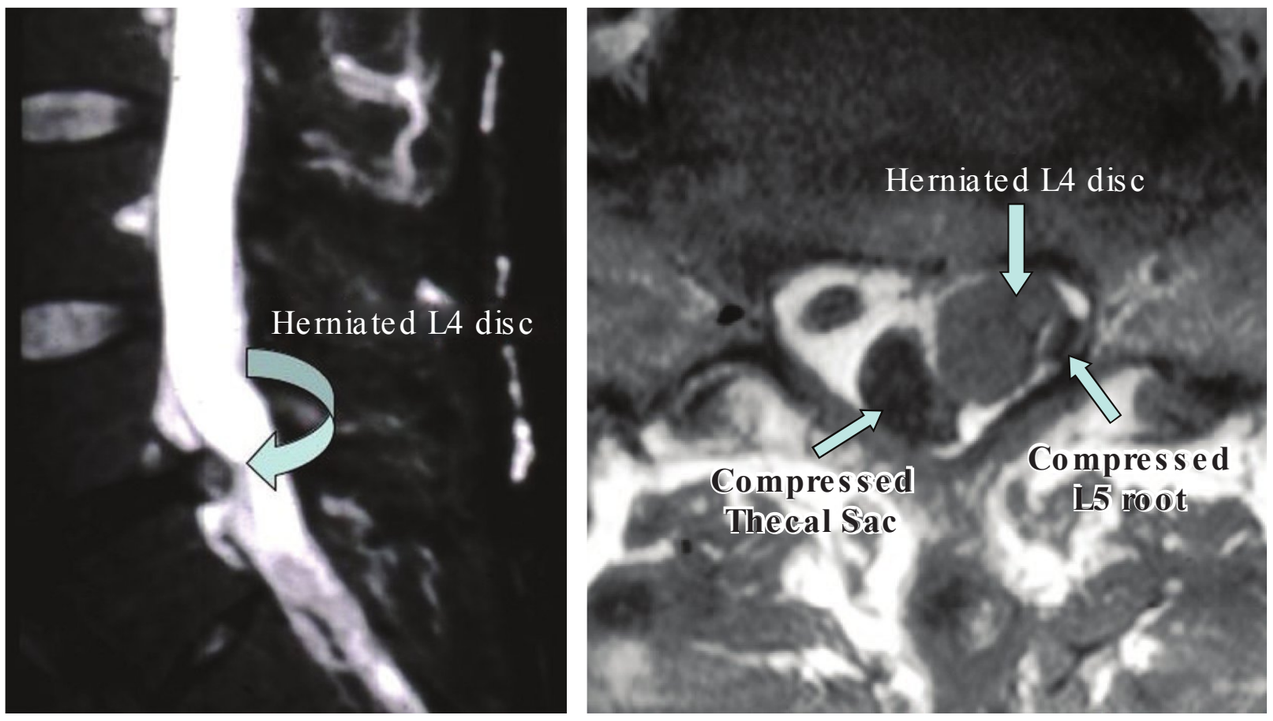
A lumbar spine MRI scan or CT myelogram is necessary to establish the location and type of pathology. Spine MRIs yield exquisite views of intraspinal and adjacent soft tissue anatomy. Bony lesions of the lateral recess or intervertebral foramen are optimally visualized by CT myelography. T e correlation of neuroradiologic findings to symptoms, particularly pain, is not simple. Contrast-enhancing tears in the annulus fibrosus or disk protrusions are widely accepted as common sources of back pain; however, studies have found that many asymptomatic adults have similar findings. Asymptomatic disk protrusions are also common and may enhance with contrast. Furthermore, in patients with known disk herniation treated either medically or surgically, persistence of the herniation 10 years later had no relationship to the clinical outcome. In summary, MRI findings of disk protrusion, tears in the annulus fibrosus, or hypertrophic facet joints are common incidental findings that, by themselves, should not dictate management decisions for patients with back pain.

T e diagnosis of nerve root injury is most secure when the history, examination, results of imaging studies, and the EMG are concordant. T e correlation between CT and EMG for localization of nerve root injury is between 65 and 73%. Up to one-third of asymptomatic adults have a lumbar disk protrusion detected by CT or MRI scans.

Management of lumbar disk disease is discussed below.

Cauda equina syndrome (CES) signifies an injury of multiple lumbosacral nerve roots within the spinal canal distal to the termination of the spinal cord at L1-L2. Low back pain, weakness and areflexia in the legs, saddle anesthesia, or loss of bladder function may occur. T e problem must be distinguished from disorders of the lower spinal cord (conus medullaris syndrome), acute transverse myelitis **(Chap. 43)**, and Guillain-Barré syndrome **(Chap. 54)**. Combined involvement of the conus medullaris and cauda equina can occur. CES is commonly due to a ruptured lumbosacral intervertebral

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 10-4

Left L5 radiculopathy. A. Sagittal T2-weighted image on the left reveals disk herniation at the L4-L5 level. B. Axial T1-weighted image shows paracentral disk herniation with displacement of the thecal sac medially and the left L5 nerve root posteriorly in the left lateral recess.

disk, lumbosacral spine fracture, hematoma within the spinal canal (e.g., following lumbar puncture in patients with coagulopathy), compressive tumor, or other mass lesion. Treatment options include surgical decompression, sometimes urgently in an attempt to restore or preserve motor or sphincter function, or radiotherapy for metastatic tumors **(Chap. 49)**.

DEGENERATIVE CONDITIONS

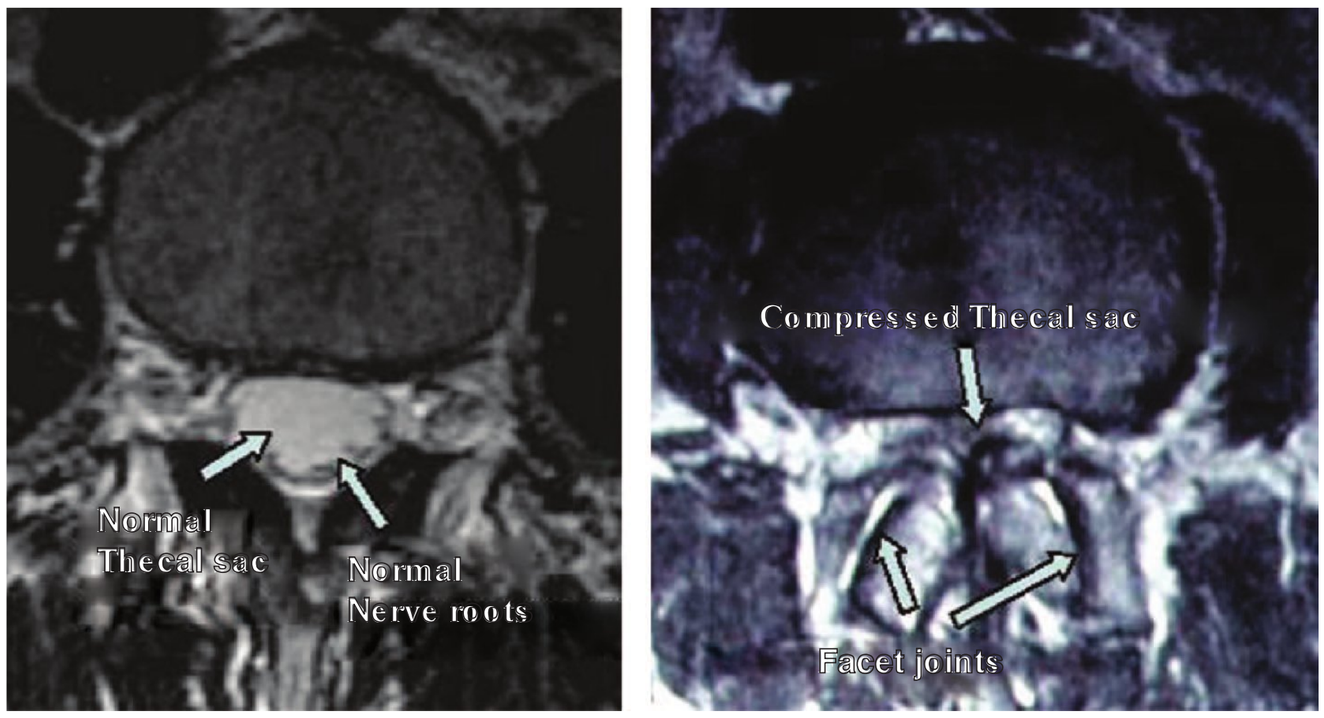
Lumbar spinal stenosis (LSS) describes a narrowed lumbar spinal canal and is frequently asymptomatic. Typical is neurogenic claudication, consisting of back and buttock or leg pain induced by walking or standing and relieved by sitting. Symptoms in the legs are usually bilateral. Unlike vascular claudication, symptoms are often provoked by standing without walking. Unlike lumbar disk disease, symptoms are usually relieved by sitting. Patients with neurogenic claudication can often walk much farther when leaning over a shopping cart and can pedal a stationary bike with ease while sitting. T ese flexed positions increase the anteroposterior spinal canal diameter and reduce intraspinal venous hypertension, resulting in pain relief. Focal weakness, sensory loss, or reflex changes may occur when spinal stenosis is associated with neural foraminal narrowing and radiculopathy. Severe neurologic deficits, including paralysis and urinary incontinence, occur only rarely.

LSS by itself is frequently asymptomatic, and the correlation between the severity of symptoms and degree of stenosis of the spinal canal is variable. LSS can be acquired (75%), congenital, or both. Congenital forms (achondroplasia, idiopathic) are characterized by short, thick pedicles that produce both spinal canal and lateral recess stenosis. Acquired factors that contribute to spinal stenosis include degenerative diseases (spondylosis, spondylolisthesis, scoliosis), trauma, spine surgery, metabolic or endocrine disorders (epidural lipomatosis, osteoporosis, acromegaly, renal osteodystrophy, hypoparathyroidism), and Paget's disease. MRI provides the best definition of the abnormal anatomy **(Fig. 10-5)**.

Conservative treatment of symptomatic LSS includes nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, exercise programs, and symptomatic treatment of acute pain episodes. T ere is insuf cient evidence to support the routine use of epidural glucocorticoid injections. Surgical therapy is considered when medical therapy does not relieve symptoms sufficiently to allow for resumption of activities of daily living or when focal neurologic signs are present. Most patients with neurogenic claudication who are treated medically do not improve over time. Surgical management can produce significant relief of back and leg pain within 6 weeks, and pain relief persists for at least 2 years. However, up to one-quarter develop recurrent stenosis at the same spinal level or an adjacent level 7–10 years after the initial surgery; recurrent symptoms usually respond to a second surgical decompression.

Neural foraminal narrowing with radiculopathy is a common consequence of osteoarthritic processes that cause lumbar spinal stenosis **(Figs. 10-1** and **10-6)**, including osteophytes, lateral disk protrusion, calcified disk-osteophytes, facet joint hypertrophy, uncovertebral joint hypertrophy (cervical spine), congenitally shortened pedicles, or, frequently, a combination of these processes. Neoplasms (primary or metastatic), fractures, infections (epidural abscess), or hematomas are other considerations. T ese conditions can produce unilateral nerve root symptoms or signs due to compression at the intervertebral foramen or in the lateral recess;

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 10-5
Axial T2-weighted images of the lumbar spine. A. The image shows a normal thecal sac within the lumbar spinal canal. The thecal sac is bright. The lumbar roots are dark punctuate dots in the posterior thecal sac with the patient supine. B. The thecal sac is not well visualized due to severe lumbar spinal canal stenosis, partially the result of hypertrophic facet joints.

symptoms are indistinguishable from disk-related radiculopathy, but treatment may differ depending on the specific etiology. T e history and neurologic examination alone cannot distinguish between these possibilities. A spine neuroimaging (CT or MRI) procedure is required to identify the anatomic cause. Neurologic findings from the examination and EMG can help direct the attention of the radiologist to specific nerve roots, especially on axial images. For facet joint hypertrophy, surgical foraminotomy produces long-term relief of leg and back pain in 80–90% of patients. T e usefulness of therapeutic facet joint blocks for pain is controversial. Medical causes of lumbar or cervical radiculopathy unrelated to anatomic spine disease include infections (e.g., herpes zoster, Lyme disease), carcinomatous meningitis, and root avulsion or traction (severe trauma).

SPONDYLOSIS AND SPONDYLOLISTHESIS

Spondylosis, or osteoarthritic spine disease, typically occurs in later life and primarily involves the cervical and lumbosacral spine. Patients often complain of back pain that increases with movement, is associated with stiffness, and is better when inactive. T e relationship between clinical symptoms and radiologic findings is usually not straightforward. Pain may be prominent when x-ray, CT, or MRI findings are minimal, and prominent degenerative spine disease can be seen in asymptomatic patients. Osteophytes or combined disk-osteophytes may cause or contribute to central spinal canal stenosis, lateral recess stenosis, or neural foraminal narrowing.

Spondylolisthesis is the anterior slippage of the vertebral body, pedicles, and superior articular facets, leaving the posterior elements behind. Spondylolisthesis can be associated with spondylolysis, congenital anomalies, degenerative spine disease, or other causes of mechanical weakness of the pars (e.g., infection, osteoporosis, tumor, trauma, prior surgery). T e slippage may be asymptomatic or may cause low back pain and hamstring tightness, nerve root injury (the L5 root most frequently), symptomatic spinal stenosis, or CES in severe cases. Tenderness may be elicited near the segment that has "slipped" forward (most often L4 on L5 or occasionally L5 on S1). Focal anterolisthesis or retrolisthesis can occur at any cervical or lumbar level and be the source of neck or low back pain. Plain x-rays with the neck or low back in flexion and extension will reveal the movement at the abnormal spinal segment. Surgery is considered for pain symptoms that do not respond to conservative measures (e.g., rest, physical therapy) and in cases with progressive neurologic deficit, postural deformity, slippage >50%, or scoliosis.

NEOPLASMS

Back pain is the most common neurologic symptom in patients with systemic cancer and is the presenting symptom in 20%. T e cause is usually vertebral body metastasis but can also result from spread of cancer through the intervertebral foramen (especially with lymphoma), from carcinomatous meningitis, or from metastasis to the spinal cord. Cancer-related back pain tends to be constant, dull, unrelieved by rest, and worse at night. By contrast, mechanical low back pain usually improves with rest. MRI, CT, and CT myelography are the studies of choice when spinal metastasis is suspected. Once a metastasis is found, imaging of the entire spine reveals additional tumor deposits in one-third of patients. MRI is preferred for soft

www.ketabpezeshki.com (021) 66485457 - 66485438

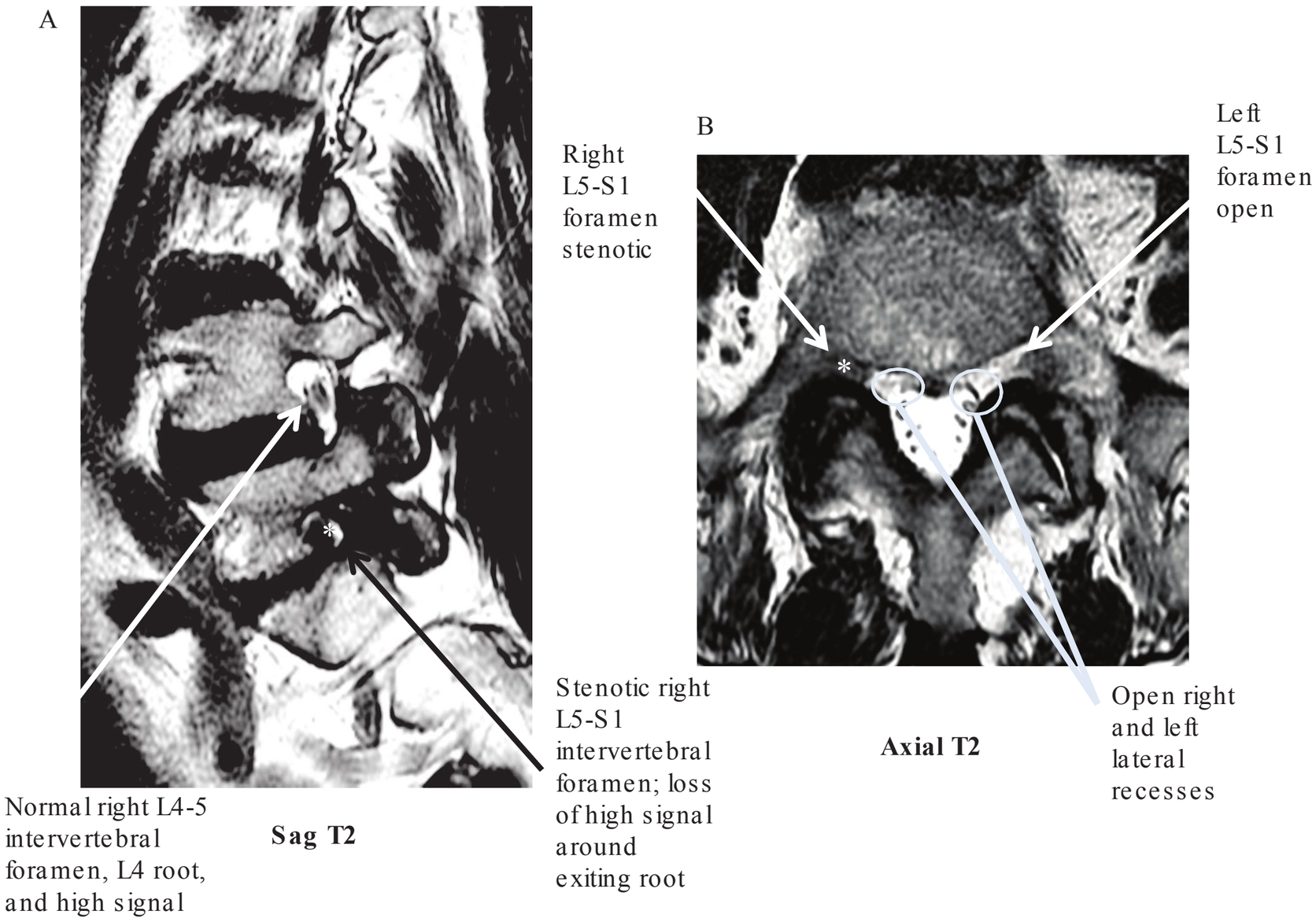


FIGURE 10-6
Right L5 radiculopathy. A. Sagittal T2-weighted image. There is normal high signal around the exiting right L4 nerve root in the right neural foramen at L4-L5; ef acement of the high signal in the right L5-S1 foramen is present one level caudal on the right at L5-S1. B. Axial T2-weighted image. The lateral recesses are normal bilaterally; the intervertebral foramen is normal on the left, but severely stenotic on the right. *Severe right L5-S1 foraminal stenosis.

tissue definition, but the most rapidly available imaging modality is best because the patient's condition may worsen quickly without intervention. Fewer than 5% of patients who are nonambulatory at the time of diagnosis ever regain the ability to walk; thus, early diagnosis is crucial. **T e management of spinal metastasis is discussed in detail in Chap. 49**.

INFECTIONS/INFLAMMATION

Vertebral osteomyelitis is often caused by staphylococci, but other bacteria or tuberculosis (Pott's disease) may be responsible. T e primary source of infection is usually the urinary tract, skin, or lungs. Intravenous drug use is a well-recognized risk factor. Whenever pyogenic osteomyelitis is found, the possibility of bacterial endocarditis should be considered. Back pain unrelieved by rest, spine tenderness over the involved spine segment, and an elevated ESR are the most common findings in vertebral osteomyelitis. Fever or an elevated white blood cell count is found in a minority of patients. MRI and CT are sensitive and specific for early detection of osteomyelitis; CT may be more readily available in emergency settings and better tolerated by some patients with severe back pain. T e intervertebral disk can also be affected by infection (diskitis) and, very rarely, by tumor.

Spinal epidural abscess **(Chap. 43)** presents with back pain (aggravated by movement or palpation), fever, radiculopathy, or signs of spinal cord compression. T e subacute development of two or more of these findings should increase the index of suspicion for spinal epidural abscess. T e abscess may track over multiple spinal levels and is best delineated by spine MRI.

Lumbar adhesive arachnoiditis with radiculopathy is due to fibrosis following inflammation within the subarachnoid space. T e fibrosis results in nerve root adhesions and presents as back and leg pain associated with focal motor, sensory, or reflex changes. Causes of arachnoiditis include multiple lumbar operations, chronic spinal infections (especially tuberculosis in the developing world), spinal cord injury, intrathecal hemorrhage, myelography (rare), intrathecal injections (glucocorticoids, anesthetics, or other agents), and foreign bodies. T e MRI shows clumped nerve roots or loculations of cerebrospinal fluid within the thecal sac. Clumped nerve roots may also occur with demyelinating polyneuropathy or neoplastic infiltration. Treatment is usually unsatisfactory. Microsurgical lysis of adhesions, dorsal rhizotomy, dorsal root ganglionectomy, and epidural glucocorticoids have been tried, but outcomes have been poor. Dorsal column stimulation for pain relief has produced varying results.

www.ketabpezeshki.com (021) 66485457 - 66485438

TRAUMA

A patient complaining of back pain and an inability to move the legs may have a spine fracture or dislocation; with fractures above L1 the spinal cord is at risk for compression. Care must be taken to avoid further damage to the spinal cord or nerve roots by immobilizing the back or neck pending the results of radiologic studies. Vertebral fractures frequently occur in the absence of trauma in association with osteoporosis, glucocorticoid use, osteomyelitis, or neoplastic infiltration.

Sprains and strains

The terms low back sprain, strain, and mechanically induced muscle spasm refer to minor, self-limited injuries associated with lifting a heavy object, a fall, or a sudden deceleration such as in an automobile accident. These terms are used loosely and do not clearly describe a specific anatomic lesion. The pain is usually confined to the lower back, and there is no radiation to the buttocks or legs. Patients with paraspinal muscle spasm often assume unusual postures.

Traumatic vertebral fractures

Most traumatic fractures of the lumbar vertebral bodies result from injuries producing anterior wedging or compression. With severe trauma, the patient may sustain a fracture-dislocation or a "burst" fracture involving the vertebral body and posterior elements. Traumatic vertebral fractures are caused by falls from a height, sudden deceleration in an automobile accident, or direct injury. Neurologic impairment is common, and early surgical treatment is indicated. In victims of blunt trauma, CT scans of the chest, abdomen, or pelvis can be reformatted to detect associated vertebral fractures.

METABOLIC CAUSES

Osteoporosis and osteosclerosis

Immobilization, osteomalacia, the postmenopausal state, renal disease, multiple myeloma, hyperparathyroidism, hyperthyroidism, metastatic carcinoma, or glucocorticoid use may accelerate osteoporosis and weaken the vertebral body, leading to compression fractures and pain. Up to two-thirds of compression fractures seen on radiologic imaging are asymptomatic. The most common nontraumatic vertebral body fractures are due to postmenopausal or senile osteoporosis **(Chap. 425)**. The risk of an additional vertebral fracture at 1 year following a first vertebral fracture is 20%. The presence of fever, weight loss, fracture at a level above T4, or the conditions described above should increase suspicion for a cause other than senile osteoporosis. The sole manifestation of a compression fracture may be localized back or radicular pain exacerbated by movement and often reproduced by palpation over the spinous process of the affected vertebra.

Relief of acute pain can often be achieved with acetaminophen or a combination of opioids and acetaminophen. The role of NSAIDs is controversial. Both pain and disability are improved with bracing. Antiresorptive drugs, especially bisphosphonates (e.g., alendronate), have been shown to reduce the risk of osteoporotic fractures and are the preferred treatment to prevent additional fractures. Less than one-third of patients with prior compression fractures are adequately treated for osteoporosis despite the increased risk for future fractures; even fewer at-risk patients without a history of fracture are adequately treated. Given the negative results of sham-controlled studies of percutaneous vertebroplasty (PVP) and of kyphoplasty for osteoporotic compression fractures associated with debilitating pain, these procedures are not routinely recommended.

Osteosclerosis, an abnormally increased bone density often due to Paget's disease, is readily identifiable on routine x-ray studies and can sometimes be a source of back pain. It may be associated with an isolated increase in alkaline phosphatase in an otherwise healthy older person. Spinal cord or nerve root compression can result from bony encroachment. The diagnosis of Paget's disease as the cause of a patient's back pain is a diagnosis of exclusion.

AUTOIMMUNE INFLAMMATORY ARTHRITIS

Autoimmune inflammatory disease of the spine can present with the insidious onset of low back, buttock, or neck pain. Examples include rheumatoid arthritis, ankylosing spondylitis, reactive arthritis, psoriatic arthritis, or inflammatory bowel disease.

CONGENITAL ANOMALIES OF THE LUMBAR SPINE

Spondylolysis is a bony defect in the vertebral pars interarticularis (a segment near the junction of the pedicle with the lamina); the cause is usually a stress microfracture in a congenitally abnormal segment. It occurs in up to 6% of adolescents. The defect (usually bilateral) is best visualized on plain x-rays, CT scan, or bone scan and is frequently asymptomatic. Symptoms may occur in the setting of a single injury, repeated minor injuries, or during a growth spurt. Spondylolysis is the most common cause of persistent low back pain in adolescents and is often associated with sports-related activities.

www.ketabpezeshki.com (021) 66485457 - 66485438

Scoliosis refers to an abnormal curvature in the coronal (lateral) plane of the spine. With kyphoscoliosis, there is, in addition, a forward curvature of the spine. The abnormal curvature may be congenital due to abnormal spine development, acquired in adulthood due to degenerative spine disease, or occasionally progressive due to neuromuscular disease. The deformity can progress until ambulation or pulmonary function is compromised.

Spina bifida occulta is a failure of closure of one or several vertebral arches posteriorly; the meninges and spinal cord are normal. A dimple or small lipoma may overlie the defect. Most cases are asymptomatic and discovered incidentally during an evaluation for back pain.

Tethered cord syndrome usually presents as a progressive cauda equina disorder (see below), although myelopathy may also be the initial manifestation. The patient is often a young adult who complains of perineal or perianal pain, sometimes following minor trauma. MRI studies reveal a low-lying conus (below L1 and L2) and a short and thickened filum terminale.

REFERRED PAIN FROM VISCERAL DISEASE

Diseases of the thorax, abdomen, or pelvis may refer pain to the posterior portion of the spinal segment that innervates the diseased organ. Occasionally, back pain may be the first and only manifestation. Upper abdominal diseases generally refer pain to the lower thoracic or upper lumbar region (eighth thoracic to the first and second lumbar vertebrae), lower abdominal diseases to the midlumbar region (second to fourth lumbar vertebrae), and pelvic diseases to the sacral region. Local signs (pain with spine palpation, paraspinal muscle spasm) are absent, and little or no pain accompanies routine movements of the spine.

Low thoracic or lumbar pain with abdominal disease

Tumors of the posterior wall of the stomach or duodenum typically produce epigastric pain, but midline back or paraspinal pain may occur if retroperitoneal extension is present. Fatty foods occasionally induce back pain associated with biliary disease. Diseases of the pancreas can produce right or left paraspinal back pain. Pathology in retroperitoneal structures (hemorrhage, tumors, pyelonephritis) can produce paraspinal pain that radiates to the lower abdomen, groin, or anterior thighs. A mass in the iliopsoas region can produce unilateral lumbar pain with radiation toward the groin, labia, or testicle. The sudden appearance of lumbar pain in a patient receiving anticoagulants suggests retroperitoneal hemorrhage.

Isolated low back pain occurs in some patients with a contained rupture of an abdominal aortic aneurysm (AAA). The classic clinical triad of abdominal pain, shock, and back pain occurs in <20% of patients. The typical patient at risk is an elderly male smoker with back pain. The diagnosis may be missed because the symptoms and signs can be nonspecific. Misdiagnoses include nonspecific back pain, diverticulitis, renal colic, sepsis, and myocardial infarction. A careful abdominal examination revealing a pulsatile mass (present in 50–75% of patients) is an important physical finding. Patients with suspected AAA should be evaluated with abdominal ultrasound, CT, or MRI.

Sacral pain with gynecologic and urologic disease

Pelvic organs rarely cause low back pain, except for gynecologic disorders involving the uterosacral ligaments. The pain is referred to the sacral region. Endometriosis or uterine cancers may invade the uterosacral ligaments. Pain associated with endometriosis is typically premenstrual and often continues until it merges with menstrual pain. Uterine malposition may cause uterosacral ligament traction (retroversion, descensus, and prolapse) or produce sacral pain after prolonged standing.

Menstrual pain may be felt in the sacral region sometimes with poorly localized, cramping pain radiating down the legs. Pain due to neoplastic infiltration of nerves is typically continuous, progressive in severity, and unrelieved by rest at night. Less commonly, radiation therapy of pelvic tumors may produce sacral pain from late radiation necrosis of tissue. Low back pain that radiates into one or both thighs is common in the last weeks of pregnancy.

Urologic sources of lumbosacral back pain include chronic prostatitis, prostate cancer with spinal metastasis, and diseases of the kidney or ureter. Lesions of the bladder and testes do not often produce back pain. Infectious, inflammatory, or neoplastic renal diseases may produce ipsilateral lumbosacral pain, as can renal artery or vein thrombosis. Paraspinal lumbar pain may be a symptom of ureteral obstruction due to nephrolithiasis.

OTHER CAUSES OF BACK PAIN

Postural back pain

There is a group of patients with nonspecific chronic low back pain (CLBP) in whom no specific anatomic lesion can be found despite exhaustive investigation. These individuals complain of vague, diffuse back pain

www.ketabpezeshki.com (021) 66485457 - 66485438

with prolonged sitting or standing that is relieved by rest. Exercises to strengthen the paraspinal and abdominal muscles are sometimes helpful.

Psychiatric disease

CLBP may be encountered in patients who seek financial compensation; in malingerers; or in those with concurrent substance abuse. Many patients with CLBP have a history of psychiatric illness (depression, anxiety states) or childhood trauma (physical or sexual abuse) that antedates the onset of back pain. Preoperative psychological assessment has been used to exclude patients with marked psychological impairments that predict a poor surgical outcome from spine surgery.

IDIOPATHIC

The cause of low back pain occasionally remains unclear. Some patients have had multiple operations for disk disease but have persistent pain and disability. The original indications for surgery may have been questionable, with back pain only, no definite neurologic signs, or a minor disk bulge noted on CT or MRI. Scoring systems based on neurologic signs, psychological factors, physiologic studies, and imaging studies have been devised to minimize the likelihood of unsuccessful surgery.

TREATMENT Back Pain

HEALTH CARE FOR POPULATIONS OF BACK PAIN PATIENTS: A CLINICAL CARE SYSTEMS VIEW There are increasing pressures to contain health care costs, especially when expensive care is not based on sound evidence. Physicians, patients, the insurance industry, and government providers of health care will need to work together to ensure cost-effective care for patients with back pain.

Surveys in the United States indicate that patients with back pain have reported progressively worse functional limitations in recent years, despite rapid increases in spine imaging, opioid prescribing, injections, and spine surgery. This suggests that more selective use of diagnostic and treatment modalities may be appropriate.

Spine imaging often reveals abnormalities of dubious clinical relevance that may alarm clinicians and patients and prompt further testing and unnecessary therapy. Both randomized trials and observational studies have suggested a "cascade effect" of imaging, which may create a gateway to other unnecessary care. Based in part on such evidence, the American College of Physicians has made parsimonious spine imaging a high priority in its "Choosing Wisely" campaign, aimed at reducing unnecessary care. Successful efforts to reduce unnecessary imaging have included physician education by clinical leaders, computerized decision support to identify recent imaging tests and eliminate duplication, and requiring an approved indication to order an imaging test. Other strategies have included audit and feedback regarding individual practitioners' rates of ordering and indications and facilitating rapid access to physical therapy for patients who do not need imaging. When imaging tests are reported, it may also be useful to routinely note that some degenerative findings are common in normal, pain-free individuals. In an observational study, this strategy was associated with lower rates of repeat imaging, opioid therapy, and referral for physical therapy.

Mounting evidence of morbidities from long-term opioid therapy (including overdose, dependency, addiction, falls, fractures, accident risk, and sexual dysfunction) has prompted efforts to reduce use for chronic pain, including back pain **(Chap. 18)**. Safety may be improved with automated reminders for high doses, early refills, or overlapping opioid and benzodiazepine prescriptions. Greater access to alternative treatments for chronic pain, such as tailored exercise programs and cognitive-behavioral therapy, may also reduce opioid prescribing.

The high cost, wide geographic variations, and rapidly increasing rates of spinal fusion surgery have prompted scrutiny over appropriate indications. Some insurance carriers have begun to limit coverage for the most controversial indications, such as low back pain without radiculopathy. Finally, educating patients and the public about the risks of imaging and excessive therapy may be necessary. A successful media campaign in Australia provides a successful model for this approach.

ALBP WITHOUT RADICULOPATHY ALBP is defined as pain of <3 months in duration. Full recovery can be expected in more than 85% of adults with ALBP without leg pain. Most have purely "mechanical" symptoms (i.e., pain that is aggravated by motion and relieved by rest).

The initial assessment excludes serious causes of spine pathology that require urgent intervention including infection, cancer, or trauma. Risk factors for a serious cause of ALBP are shown in **Table 10-1**. Laboratory and imaging studies are unnecessary if risk factors are absent. CT, MRI, or plain spine films are rarely indicated in the first month of symptoms unless a spine fracture, tumor, or infection is suspected.

The prognosis is generally excellent. Many patients do not seek medical care and improve on their own. Even among those seen in primary care, two-thirds report being substantially improved after 7 weeks. This spontaneous improvement can mislead clinicians and researchers about the efficacy of treatment interventions unless subjected to rigorous prospective trials. Many treatments commonly used in the past but now known to be ineffective, including bed rest, lumbar traction, and coccygectomy, have been largely abandoned.

www.ketabpezeshki.com (021) 66485457 - 66485438

Clinicians should reassure patients that improvement is very likely and instruct them in self-care. Education is an important part of treatment. Satisfaction and the likelihood of follow-up increase when patients are educated about prognosis, treatment methods, activity modifications, and strategies to prevent future exacerbations. Patients who report that they did not receive an adequate explanation for their symptoms are likely to request further diagnostic tests. In general, bed rest should be avoided for relief of severe symptoms or kept to a day or two at most. Several randomized trials suggest that bed rest does not hasten the pace of recovery. In general, the best activity recommendation is for early resumption of normal physical activity, avoiding only strenuous manual labor. Possible advantages of early ambulation for ALBP include maintenance of cardiovascular conditioning, improved disk and cartilage nutrition, improved bone and muscle strength, and increased endorphin levels. Specific back exercises or early vigorous exercise have not shown benefits for acute back pain, but may be useful for chronic pain. Use of heating pads or blankets is sometimes helpful.

Evidence-based guidelines recommend over-the-counter medicines such as acetaminophen and NSAIDs as first-line options for treatment of ALBP. In otherwise healthy patients, a trial of acetaminophen can be followed by NSAIDs for time-limited periods. In theory, the anti-inflammatory effects of NSAIDs might provide an advantage over acetaminophen to suppress inflammatory changes that accompany many causes of ALBP, but in practice, there is no clinical evidence to support the superiority of NSAIDs. T e risk of renal and gastrointestinal toxicity with NSAIDs is increased in patients with preexisting medical comorbidities (e.g., renal insufficiency, cirrhosis, prior gastrointestinal hemorrhage, use of anticoagulants or steroids, heart failure). Skeletal muscle relaxants, such as cyclobenzaprine or methocarbamol, may be useful, but sedation is a common side effect. Limiting the use of muscle relaxants to nighttime only may be an option for patients with back pain that interferes with sleep.

T ere is no good evidence to support the use of opioid analgesics or tramadol as first-line therapy for ALBP. T eir use is best reserved for patients who cannot tolerate acetaminophen or NSAIDs or for those with severe refractory pain. As with muscle relaxants, these drugs are often sedating, so it may be useful to prescribe them at nighttime only. Side effects of short-term opioid use include nausea, constipation, and pruritus; risks of long-term opioid use include hypersensitivity to pain, hypogonadism, and dependency. Falls, fractures, driving accidents, and fecal impaction are other risks. Clinical ef cacy of opioids beyond 16 weeks of use is unproven.

T ere is no evidence to support use of oral or injected glucocorticoids for ALBP without radiculopathy. Similarly, therapies for neuropathic pain, such as gabapentin or tricyclic antidepressants, are not indicated for ALBP.

Nonpharmacologic treatments for ALBP include spinal manipulation, exercise, physical therapy, massage, acupuncture, transcutaneous electrical nerve stimulation, and ultrasound. Spinal manipulation appears to be roughly equivalent to conventional medical treatments and may be a useful alternative for patients who wish to avoid or who cannot tolerate drug therapy. T ere is little evidence to support the use of physical therapy, massage, acupuncture, laser therapy, therapeutic ultrasound, corsets, or lumbar traction. Although important for chronic pain, back exercises for ALBP are generally not supported by clinical evidence. T ere is no convincing evidence regarding the value of ice or heat applications for ABLP; however, many patients report temporary symptomatic relief from ice or frozen gel packs, and heat may produce a short-term reduction in pain after the first week. Patients often report improved satisfaction with the care that they receive when they actively participate in the selection of symptomatic approaches that are tried.

CLBP WITHOUT RADICULOPATHY CLBP is defined as pain lasting >12 weeks; it accounts for 50% of total back pain costs. Risk factors include obesity, female gender, older age, prior history of back pain, restricted spinal mobility, pain radiating into a leg, high levels of psychological distress, poor self-rated health, minimal physical activity, smoking, job dissatisfaction, and widespread pain. In general, the same treatments that are recommended for ALBP can be useful for patients with CLBP. In this setting, however, the long-term benefit of opioid therapy or muscle relaxants is less clear.

Evidence supports the use of exercise therapy, and this can be one of the mainstays of treatment for CLBP. Effective regimens have generally included a combination of gradually increasing aerobic exercise, strengthening exercises, and stretching exercises. Motivating patients is sometimes challenging, and in this setting, a program of supervised exercise can improve compliance. In general, activity tolerance is the primary goal, while pain relief is secondary. Supervised intensive physical exercise or “work hardening” regimens have been effective in returning some patients to work, improving walking distance, and reducing pain. In addition, some forms of yoga have been evaluated in randomized trials and may be helpful for patients who are interested. A long-term benefit of spinal manipulation or massage for CLBP is unproven.

Medications for CLBP may include acetaminophen, NSAIDs, and tricyclic antidepressants. Trials of tricyclics suggest benefit even for patients without evidence of depression. Trials do not support the ef cacy of selective serotonin reuptake inhibitors (SSRIs) for CLBP. However, depression is common among patients with chronic pain and should be appropriately treated.

Cognitive-behavioral therapy is based on evidence that psychological and social factors, as well as somatic pathology, are important in the genesis of chronic pain and disability. Cognitive-behavioral therapy includes efforts to identify and modify patients’ thinking about their pain and disability. A systematic review concluded that such treatments are more effective than a waiting list control group for short-term pain relief; however, long-term results remain unclear. Behavioral treatments may have effects similar in magnitude to exercise therapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

Back pain is the most frequent reason for seeking complementary and alternative treatments. T e most common of these for back pain are spinal manipulation, acupuncture, and massage. T e role of most complementary and alternative medicine approaches remains unclear. Biofeedback has not been studied rigorously. T ere is no convincing evidence that either spinal manipulation or transcutaneous electrical nerve stimulation (TENS) is effective in treating CLBP. Rigorous recent trials of acupuncture suggest that true acupuncture is not superior to sham acupuncture, but that both may offer an advantage over routine care. Whether this is due entirely to placebo effects provided even by sham acupuncture is uncertain. Some trials of massage therapy have been encouraging, but this has been less well studied than spinal manipulation or acupuncture.

Various injections, including epidural glucocorticoid injections, facet joint injections, and trigger point injections, have been used for treating CLBP. However, in the absence of radiculopathy, there is no evidence that these approaches are effective.

Injection studies are sometimes used diagnostically to help determine the anatomic source of back pain. T e use of discography to provide evidence that a specific disk is the pain generator is not recommended. Pain relief following a glucocorticoid injection into a facet is commonly used as evidence that the facet joint is the pain source; however, the possibility that the response was a placebo effect or due to systemic absorption of the glucocorticoids is dif cult to exclude.

Another category of intervention for chronic back pain is electrothermal and radiofrequency therapy. Intradiskal therapy has been proposed using both types of energy to thermocoagulate and destroy nerves in the intervertebral disk, using specially designed catheters or electrodes. Current evidence does not support the use of these intradiskal therapies.

Radiofrequency denervation is sometimes used to destroy nerves that are thought to mediate pain, and this technique has been used for facet joint pain (with the target nerve being the medial branch of the primary dorsal ramus), for back pain thought to arise from the intervertebral disk (ramus communicans), and radicular back pain (dorsal root ganglia). A few small trials have produced conflicting results for facet joint and diskogenic pain. A trial in patients with chronic radicular pain found no difference between radiofrequency denervation of the dorsal root ganglia and sham treatment. T ese interventional therapies have not been studied in sufficient detail to draw conclusions of their value for CLBP.

Surgical intervention for CLBP without radiculopathy has been evaluated in a small number of randomized trials, all conducted in Europe. Each of these studies included patients with back pain and a degenerative disk, but no sciatica. T ree of the four trials concluded that lumbar fusion surgery was no more effective than highly structured, rigorous rehabilitation combined with cognitive-behavioral therapy. T e fourth trial found an advantage of fusion surgery over haphazard "usual care," which appeared to be less effective than the structured rehabilitation in other trials. Given conflicting evidence, indications for surgery for CLBP without radiculopathy have remained controversial. Both U.S. and British guidelines suggest considering referral for an opinion on spinal fusion for people who have completed an optimal nonsurgical treatment program (including combined physical and psychological treatment) and who have persistent severe back pain for which they would consider surgery.

Lumbar disk replacement with prosthetic disks is U.S. Food and Drug Administration approved for uncomplicated patients needing single-level surgery at the L3-S1 levels. T e disks are generally designed as metal plates with a polyethylene cushion sandwiched in between. T e trials that led to approval of these devices compared them to spine fusion and concluded that the artificial disks were "not inferior." Serious complications are somewhat more likely with the artificial disk. T is treatment remains controversial for CLBP.

Intensive multidisciplinary rehabilitation programs may involve daily or frequent physical therapy, exercise, cognitive-behavioral therapy, a workplace evaluation, and other interventions. For patients who have not responded to other approaches, such programs appear to offer some benefit. Systematic reviews suggest that the evidence is limited and benefits are incremental.

Some observers have raised concern that CLBP may often be overtreated. For CLBP without radiculopathy, new British guidelines explicitly recommend against use of SSRIs, any type of injection, TENS, lumbar supports, traction, radiofrequency facet joint denervation, intradiskal electrothermal therapy, or intradiskal radiofrequency thermocoagulation. T ese treatments are also not recommended in guidelines from the American College of Physicians and the American Pain Society. On the other hand, exercise therapy and treatment of depression appear to be useful and underused.

LOW BACK PAIN WITH RADICULOPATHY A common cause of back pain with radiculopathy is a herniated disk with nerve root impingement, resulting in back pain with radiation down the leg. T e term sciatica is used when the leg pain radiates posteriorly in a sciatic or L5/S1 distribution. T e prognosis for acute low back and leg pain with radiculopathy due to disk herniation is generally favorable, with most patients showing substantial improvement over months. Serial imaging studies suggest spontaneous regression of the herniated portion of the disk in two-thirds of patients over 6 months. Nonetheless, there are several important treatment options to provide symptomatic relief while this natural healing process unfolds.

Resumption of normal activity is recommended. Randomized trial evidence suggests that bed rest is ineffective for treating sciatica as well as back pain alone. Acetaminophen and NSAIDs are useful for pain relief, although severe pain may require short courses of opioid analgesics.

Epidural glucocorticoid injections have a role in providing temporary symptom relief for sciatica due to a herniated disk. However, there does not appear to be a benefit in terms of reducing subsequent surgical interventions. Diagnostic

www.ketabpezeshki.com (021) 66485457 - 66485438

nerve root blocks have been advocated to determine if pain originates from a specific nerve root. However, improvement may result even when the nerve root is not responsible for the pain; this may occur as a placebo effect, from a pain-generating lesion located distally along the peripheral nerve, or from effects of systemic absorption. T e utility of diagnostic nerve root blocks remains a subject of debate.

Surgical intervention is indicated for patients who have progressive motor weakness due to nerve root injury demonstrated on clinical examination or EMG. Urgent surgery is recommended for patients who have evidence of CES or spinal cord compression, generally suggested by bowel or bladder dysfunction, diminished sensation in a saddle distribution, a sensory level on the trunk, and bilateral leg weakness or spasticity.

Surgery is also an important option for patients who have disabling radicular pain despite optimal conservative treatment. Sciatica is perhaps the most common reason for recommending spine surgery. Because patients with a herniated disk and sciatica generally experience rapid improvement over a matter of weeks, most experts do not recommend considering surgery unless the patient has failed to respond to 6–8 weeks of maximum nonsurgical management. For patients who have not improved, randomized trials indicate that, compared to nonsurgical treatment, surgery results in more rapid pain relief. However, after the first year or two of follow-up, patients with sciatica appear to have much the same level of pain relief and functional improvement with or without surgery. T us, both treatment approaches are reasonable, and patient preferences and needs (e.g., rapid return to employment) strongly influence decision making. Some patients will want the fastest possible relief and find surgical risks acceptable. Others will be more risk-averse and more tolerant of symptoms and will choose watchful waiting if they understand that improvement is likely in the end.

T e usual surgical procedure is a partial hemilaminectomy with excision of the prolapsed disk (diskectomy). Fusion of the involved lumbar segments should be considered only if significant spinal instability is present (i.e., degenerative spondylolisthesis). T e costs associated with lumbar interbody fusion have increased dramatically in recent years. T ere are no large prospective, randomized trials comparing fusion to other types of surgical intervention. In one study, patients with persistent low back pain despite an initial diskectomy fared no better with spine fusion than with a conservative regimen of cognitive intervention and exercise. Artificial disks have been in use in Europe for the past decade; their utility remains controversial in the United States.

PAIN IN THE NECK AND SHOULDER

Neck pain, which usually arises from diseases of the cervical spine and soft tissues of the neck, is common. Neck pain arising from the cervical spine is typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion. Many of the prior comments made regarding causes of low back pain also apply to disorders of the cervical spine. T e text below will emphasize differences. Pain arising from the brachial plexus, shoulder, or peripheral nerves can be confused with cervical spine disease **(Table 10-4)**, but the history and examination usually identify a more distal origin for the pain. Cervical spine trauma, disk disease, or spondylosis with intervertebral foraminal narrowing may be asymptomatic or painful and can produce a myelopathy, radiculopathy, or both. T e same risk factors for serious causes of low back pain also apply to neck pain with the additional feature that neurologic signs of myelopathy (incontinence, sensory level, spastic legs) may also occur. Lhermitte's sign, an electrical shock down the spine with neck flexion, suggests involvement of the cervical spinal cord.

TRAUMA TO THE CERVICAL SPINE

Trauma to the cervical spine (fractures, subluxation) places the spinal cord at risk for compression. Motor vehicle accidents, violent crimes, or falls account for 87% of cervical spinal cord injuries **(Chap. 43)**. Immediate immobilization of the neck is essential to minimize further spinal cord injury from movement of unstable cervical spine segments. T e decision to obtain imaging should be based on the nature of the injury. T e NEXUS low-risk criteria established that normally alert patients without palpation tenderness in the midline; intoxication; neurologic deficits; or painful distracting injuries were very unlikely to have sustained a clinically significant traumatic injury to the cervical spine. T e Canadian C-spine rule recommends that imaging should be obtained following neck region trauma if the patient is >65 years old or has limb paresthesias or if there was a dangerous mechanism for the injury (e.g., bicycle collision with tree or parked car, fall from height >3 feet or five stairs, diving accident). T ese guidelines are helpful but must be tailored to individual circumstances; for example, patients with advanced osteoporosis, glucocorticoid use, or cancer may warrant imaging after even mild trauma. A CT scan is the diagnostic procedure of choice for detection of acute fractures following severe trauma; plain x-rays can be used for lesser degrees of trauma. When traumatic injury to the vertebral arteries or cervical spinal cord is suspected, visualization by MRI with magnetic resonance angiography is preferred.

Whiplash injury is due to rapid flexion and extension of the neck, usually in automobile accidents. T e exact mechanism of the injury is unclear. T is diagnosis should not be applied to patients with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness. Up to 50% of persons reporting whiplash injury acutely have persistent neck pain

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 10-4

CERVICAL RADICULOPATHY: NEUROLOGIC FEATURES

CERVICAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
C5	Biceps	Lateral deltoid	Rhomboids[a] (elbow extends backward with hand on hip) Infraspinatus[a] (arm rotates externally with elbow flexed at the side) Deltoid[a] (arm raised laterally 30–45° from the side)	Lateral arm, medial scapula
C6	Biceps	Thumb/index finger; Dorsal hand/lateral forearm	Biceps[a] (arm flexed at the elbow in supination) Pronator teres (forearm pronated)	Lateral forearm, thumb/index fingers
C7	Triceps	Middle fingers Dorsal forearm	Triceps[a] (forearm extension, flexed at elbow) Wrist/finger extensors[a]	Posterior arm, dorsal forearm, dorsal hand
C8	Finger flexors	Palmar surface of little finger Medial hand and forearm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Fourth and fifth fingers, medial hand and forearm
T1	Finger flexors	Axilla and medial arm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Medial arm, axilla

[a]These muscles receive the majority of innervation from this root.

1 year later. Once personal compensation for pain and suffering was removed from the Australian health care system, the prognosis for recovery at 1 year from whiplash injury improved also. Imaging of the cervical spine is not cost-effective acutely but is useful to detect disk herniations when symptoms persist for >6 weeks following the injury. Severe initial symptoms have been associated with a poor long-term outcome.

CERVICAL DISK DISEASE

Herniation of a lower cervical disk is a common cause of pain or tingling in the neck, shoulder, arm, or hand. Neck pain, stiffness, and a range of motion limited by pain are the usual manifestations. Herniated cervical disks are responsible for ~25% of cervical radiculopathies. Extension and lateral rotation of the neck narrow the ipsilateral intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young adults, acute nerve root compression from a ruptured cervical disk is often due to trauma. Cervical disk herniations are usually posterolateral near the lateral recess. Typical patterns of reflex, sensory, and motor changes that accompany cervical nerve root lesions are summarized in Table 10-4. Although the classic patterns are clinically helpful, there are numerous exceptions because (1) there is overlap in sensory function between adjacent nerve roots, (2) symptoms and signs may be evident in only part of the injured nerve root territory, and (3) the location of pain is the most variable of the clinical features.

CERVICAL SPONDYLOSIS

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms, or may be the source of headaches in the posterior occipital region (supplied by the C2-C4 nerve roots). Osteophytes, disk protrusions, or hypertrophic facet or uncovertebral joints may alone or in combination compress one or several nerve roots at the intervertebral foramina; these causes together account for 75% of cervical radiculopathies. T e roots most commonly affected are C7 and C6. Narrowing of the spinal canal by osteophytes, ossification of the posterior longitudinal ligament (OPLL), or a large central disk may compress the cervical spinal cord and produce signs of radiculopathy and myelopathy in combination (myeloradiculopathy). When little or no neck pain accompanies cervical cord involvement, other diagnoses to

www.ketabpezeshki.com (021) 66485457 - 66485438

be considered include amyotrophic lateral sclerosis **(Chap. 39)**, multiple sclerosis **(Chap. 45)**, spinal cord tumors, or syringomyelia **(Chap. 43)**. T e possibility of cervical spondylosis should be considered even when the patient presents with symptoms or signs in the legs only. MRI is the study of choice to define anatomic abnormalities of soft tissues in the cervical region including the spinal cord, but plain CT is adequate to assess bony spurs, foraminal narrowing, lateral recess stenosis, or OPLL. EMG and nerve conduction studies can localize and assess the severity of nerve root injury.

OTHER CAUSES OF NECK PAIN

Rheumatoid arthritis (RA) of the cervical facet joints produces neck pain, stiffness, and limitation of motion. Synovitis of the atlantoaxial joint (C1-C2; **Fig. 10-2**) may damage the transverse ligament of the atlas, producing forward displacement of the atlas on the axis (atlantoaxial subluxation). Radiologic evidence of atlantoaxial subluxation occurs in up to 30% of patients with RA. T e degree of subluxation correlates with the severity of erosive disease. When subluxation is present, careful assessment is important to identify early signs of myelopathy. Occasional patients develop high spinal cord compression leading to quadriparesis, respiratory insuf ciency, and death. Surgery should be considered when myelopathy or spinal instability is present. MRI is the imaging modality of choice. Ankylosing spondylitis can cause neck pain and less commonly atlantoaxial subluxation; surgery may be required to prevent spinal cord compression.

Acute herpes zoster can presents as acute posterior occipital or neck pain prior to the outbreak of vesicles. Neoplasms metastatic to the cervical spine, infections (osteomyelitis and epidural abscess), and metabolic bone diseases may be the cause of neck pain, as discussed above among causes of low back pain. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

THORACIC OUTLET SYNDROMES

T e thoracic outlet contains the first rib, the subclavian artery and vein, the brachial plexus, the clavicle, and the lung apex. Injury to these structures may result in postural or movement-induced pain around the shoulder and supraclavicular region, classified as follows.

True neurogenic thoracic outlet syndrome (TOS) is an uncommon disorder resulting from compression of the lower trunk of the brachial plexus or ventral rami of the C8 or T1 nerve roots, caused most often by an anomalous band of tissue connecting an elongate transverse process at C7 with the first rib. Pain is mild or may be absent. Signs include weakness and wasting of intrinsic muscles of the hand and diminished sensation on the palmar aspect of the fifth digit. An anteroposterior cervical spine x-ray will show an elongate C7 transverse process (an anatomic marker for the anomalous cartilaginous band), and EMG and nerve conduction studies confirm the diagnosis. Treatment consists of surgical resection of the anomalous band. T e weakness and wasting of intrinsic hand muscles typically does not improve, but surgery halts the insidious progression of weakness.

Arterial TOS results from compression of the subclavian artery by a cervical rib, resulting in poststenotic dilatation of the artery and in some cases secondary thrombus formation. Blood pressure is reduced in the affected limb, and signs of emboli may be present in the hand. Neurologic signs are absent. Ultrasound can confirm the diagnosis noninvasively. Treatment is with thrombolysis or anticoagulation (with or without embolectomy) and surgical excision of the cervical rib compressing the subclavian artery.

Venous TOS is due to subclavian vein thrombosis resulting in swelling of the arm and pain. T e vein may be compressed by a cervical rib or anomalous scalene muscle. Venography is the diagnostic test of choice.

Disputed TOS accounts for 95% of patients diagnosed with TOS; chronic arm and shoulder pain are prominent and of unclear cause. T e lack of sensitive and specific findings on physical examination or specific markers for this condition results in diagnostic uncertainty. T e role of surgery in disputed TOS is controversial. Multidisciplinary pain management is a conservative approach, although treatment is often unsuccessful.

BRACHIAL PLEXUS AND NERVES

Pain from injury to the brachial plexus or peripheral nerves of the arm can occasionally mimic referred pain of cervical spine origin including cervical radiculopathy. Neoplastic infiltration of the lower trunk of the brachial plexus may produce shoulder or supraclavicular pain radiating down the arm, numbness of the fourth and fifth fingers or medial forearm, and weakness of intrinsic hand muscles innervated by the ulnar and median nerves. Delayed radiation injury may produce similar findings, although pain is less often present and almost always less severe. A Pancoast tumor of the lung **(Chap. 107)** is another cause and should be considered, especially when a concurrent Horner's syndrome is present. Suprascapular neuropathy may produce severe shoulder pain, weakness, and wasting of the supraspinatus and infraspinatus muscles. Acute brachial neuritis is often confused with radiculopathy; the acute onset of severe shoulder or scapular pain is followed typically over days by weakness of the proximal arm and shoulder girdle muscles innervated by the upper brachial plexus. T e onset may be preceded by an infection, vaccination, or

www.ketabpezeshki.com (021) 66485457 - 66485438

minor surgical procedure. The long thoracic nerve may be affected resulting in a winged scapula. Brachial neuritis may also present as an isolated paralysis of the diaphragm with or without involvement of other nerves of the upper limb. Recovery may take up to 3 years.

Occasional cases of carpal tunnel syndrome produce pain and paresthesias extending into the forearm, arm, and shoulder resembling a C5 or C6 root lesion. Lesions of the radial or ulnar nerve can mimic a radiculopathy at C7 or C8, respectively. EMG and nerve conduction studies can accurately localize lesions to the nerve roots, brachial plexus, or peripheral nerves.

For further discussion of peripheral nerve disorders, see Chap. 53.

SHOULDER

Pain arising from the shoulder can on occasion mimic pain from the spine. If symptoms and signs of radiculopathy are absent, then the differential diagnosis includes mechanical shoulder pain (tendonitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, or rotator cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast tumor). Mechanical pain is often worse at night, associated with local shoulder tenderness and aggravated by passive abduction, internal rotation, or extension of the arm. Pain from shoulder disease may radiate into the arm or hand, but focal neurologic signs (sensory, motor, or reflex changes) are absent.

TREATMENT Neck Pain without Radiculopathy

The evidence regarding treatment for neck pain is less complete than that for low back pain, but the approach is remarkably similar in many respects. As with low back pain, spontaneous improvement is the norm for acute neck pain. The usual goals of therapy are to promote a rapid return to normal function and provide symptom relief while healing proceeds.

The evidence in support of nonsurgical treatments for whiplash-associated disorders is generally of limited quality and neither supports nor refutes the common treatments used for symptom relief. Gentle mobilization of the cervical spine combined with exercise programs may be beneficial. Evidence is insufficient to recommend for or against the routine use of acupuncture, cervical traction, TENS, ultrasound, diathermy, or massage. Some patients obtain modest relief using a soft neck collar; there is little risk or cost.

For patients with neck pain unassociated with trauma, supervised exercise with or without mobilization appears to be effective. Exercises often include shoulder rolls and neck stretches. The evidence for the use of muscle relaxants, analgesics, and NSAIDs in acute and chronic neck pain is of lower quality and less consistent than for low back pain.

Low-level laser therapy directed at areas of tenderness, local acupuncture points, or a grid of predetermined points is a controversial approach to the treatment of neck pain. A 2009 meta-analysis suggested that this treatment may provide greater pain relief than sham therapy for both acute and chronic neck pain, but comparison to other conservative and less expensive treatment measures is needed.

Although some surgical studies have proposed a role for anterior diskectomy and fusion in patients with neck pain, these studies generally have not been rigorously conducted. A systematic review suggested that there was no valid clinical evidence to support either cervical fusion or cervical disk arthroplasty in patients with neck pain without radiculopathy. Similarly, there is no evidence to support radiofrequency neurotomy or cervical facet injections for neck pain without radiculopathy.

TREATMENT Neck Pain with Radiculopathy

The natural history of neck pain with acute radiculopathy due to disk disease is favorable, and many patients will improve without specific therapy. Although there are no randomized trials of NSAIDs for neck pain, a course of NSAIDs, acetaminophen, or both, with or without muscle relaxants, is reasonable as initial therapy. Other nonsurgical treatments are commonly used, including opioid analgesics, oral glucocorticoids, cervical traction, and immobilization with a hard or soft cervical collar. However, there are no randomized trials that establish the effectiveness of these treatments. Soft cervical collars can be modestly helpful by limiting spontaneous and reflex neck movements that exacerbate pain.

As for lumbar radiculopathy, epidural glucocorticoids appear to provide short-term symptom relief in cervical radiculopathy, but rigorous studies addressing this question have not been conducted. If cervical radiculopathy is due to bony compression from cervical spondylosis with foraminal narrowing, periodic follow-up to assess for progression is indicated and consideration of surgical decompression is reasonable.

Surgical treatment can produce rapid pain relief, although it is unclear whether long-term outcomes are improved over nonsurgical therapy. Indications for cervical disk surgery include a progressive radicular motor deficit, functionally limiting pain that fails to respond to conservative management, or spinal cord compression.

Surgical treatments include anterior cervical diskectomy alone, laminectomy with diskectomy, or diskectomy with fusion. The risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to a fusion is ~3% per year and 26% per decade. Although this risk is sometimes portrayed as a late complication of surgery, it may also reflect the natural history of degenerative cervical disk disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 11

SYNCOPE

Roy Freeman

Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. T e onset is rapid, duration brief, and recovery spontaneous and complete. Other causes of transient loss of consciousness need to be distinguished from syncope; these include seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia. A syncopal prodrome (presyncope) is common, although loss of consciousness may occur without any warning symptoms. Typical presyncopal symptoms include dizziness, lightheadedness or faintness, weakness, fatigue, and visual and auditory disturbances. T e causes of syncope can be divided into three general categories: (1) neurally mediated syncope (also called ref ex or vasovagal syncope), (2) orthostatic hypotension, and (3) cardiac syncope.

Neurally mediated syncope comprises a heterogeneous group of functional disorders that are characterized by a transient change in the reflexes responsible for maintaining cardiovascular homeostasis. Episodic vasodilation (or loss of vasoconstrictor tone) and bradycardia occur in varying combinations, resulting in temporary failure of blood pressure control. In contrast, in patients with orthostatic hypotension due to autonomic failure, these cardiovascular homeostatic reflexes are chronically impaired. Cardiac syncope may be due to arrhythmias or structural cardiac diseases that cause a decrease in cardiac output. T e clinical features, underlying pathophysiologic mechanisms, therapeutic interventions, and prognoses differ markedly among these three causes.

EPIDEMIOLOGY AND NATURAL HISTORY

Syncope is a common presenting problem, accounting for approximately 3% of all emergency room visits and 1% of all hospital admissions. T e annual cost for syncope-related hospitalization in the United States is ~$2.4 billion. Syncope has a lifetime cumulative incidence of up to 35% in the general population. T e peak incidence in the young occurs between ages 10 and 30 years, with a median peak around 15 years. Neurally mediated syncope is the etiology in the vast majority of these cases. In elderly adults, there is a sharp rise in the incidence of syncope after 70 years.

In population-based studies, neurally mediated syncope is the most common cause of syncope. T e incidence is slightly higher in females than males. In young subjects, there is often a family history in first-degree relatives. Cardiovascular disease due to structural disease or arrhythmias is the next most common cause in most series, particularly in emergency room settings and in older patients. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. In the elderly, orthostatic hypotension is substantially more common in institutionalized (54–68%) than community-dwelling (6%) individuals, an observation most likely explained by the greater prevalence of predisposing neurologic disorders, physiologic impairment, and vasoactive medication use among institutionalized patients.

T e prognosis after a single syncopal event for all age groups is generally benign. In particular, syncope of noncardiac and unexplained origin in younger individuals has an excellent prognosis; life expectancy is unaffected. By contrast, syncope due to a cardiac cause, either structural heart disease or primary arrhythmic disease, is associated with an increased risk of sudden cardiac death and mortality from other causes. Similarly, mortality rate is increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid conditions **(Table 11-1)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 11-1

HIGH-RISK FEATURES INDICATING HOSPITALIZATION OR INTENSIVE EVALUATION OF SYNCOPE
Chest pain suggesting coronary ischemia
Features of congestive heart failure
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular arrhythmias
Prolonged QT interval (>500 ms)
Repetitive sinoatrial block or sinus pauses
Persistent sinus bradycardia
Bi- or trifascicular block or intraventricular conduction delay with QRS duration≥120 ms
Atrial fibrillation
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG
Palpitations at time of syncope
Syncope at rest or during exercise

PATHOPHYSIOLOGY

The upright posture imposes a unique physiologic stress upon humans; most, although not all, syncopal episodes occur from a standing position. Standing results in pooling of 500–1000 mL of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and reduced ventricular filling that result in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased sympathetic outflow and decreased vagal nerve activity **(Fig. 11-1)**. The reflex increases peripheral resistance, venous return to the heart, and cardiac output and thus limits the fall in blood pressure. If this response fails, as is the case chronically in orthostatic hypotension and transiently in neurally mediated syncope, cerebral hypoperfusion occurs.

Syncope is a consequence of global cerebral hypoperfusion and thus represents a failure of cerebral blood flow autoregulatory mechanisms. Myogenic factors, local metabolites, and to a lesser extent autonomic neurovascular control are responsible for the autoregulation of cerebral blood flow **(Chap. 33)**. The latency of the autoregulatory response is 5–10 s. Typically cerebral blood flow ranges from 50 to 60 mL/min per 100 g brain tissue and remains relatively constant over perfusion pressures ranging from 50 to 150 mmHg. Cessation of blood flow for 6–8 s will result in loss of consciousness, while impairment of consciousness ensues when blood flow decreases to 25 mL/min per 100 g brain tissue.

From the clinical standpoint, a fall in systemic systolic blood pressure to ~50 mmHg or lower will result in syncope. A decrease in cardiac output and/or systemic vascular resistance—the determinants of blood pressure—thus underlies the pathophysiology of syncope. Common causes of impaired cardiac output include decreased effective circulating blood volume; increased thoracic pressure; massive pulmonary embolus; cardiac brady- and tachyarrhythmias; valvular heart disease; and myocardial dysfunction. Systemic vascular resistance may be decreased by central and peripheral autonomic nervous system diseases, sympatholytic medications, and transiently during neurally mediated syncope. Increased cerebral vascular resistance, most frequently due to hypocarbia induced by hyperventilation, may also contribute to the pathophysiology of syncope.

Two patterns of electroencephalographic (EEG) changes occur in syncopal subjects. The first is a "slow-flat-slow" pattern **(Fig. 11-2)** in which normal background activity is replaced with high-amplitude slow delta waves. This is followed by sudden flattening of the EEG—a cessation or attenuation of cortical activity—followed by the return of slow waves, and then normal activity. A second pattern, the "slow pattern," is characterized by increasing and decreasing slow wave activity only. The EEG flattening that occurs in the slow-flat-slow pattern is a marker of more severe cerebral hypoperfusion. Despite the presence of myoclonic movements and other motor activity during some syncopal events, EEG seizure discharges are not detected.

CLASSIFICATION

NEURALLY MEDIATED SYNCOPE

Neurally mediated (reflex; vasovagal) syncope is the final pathway of a complex central and peripheral nervous system reflex arc. There is a sudden, transient change in autonomic efferent activity with increased parasympathetic outflow, plus sympathoinhibition (the vasodepressor response), resulting in bradycardia, vasodilation, and/or reduced vasoconstrictor tone. The resulting fall in systemic blood pressure can then reduce cerebral blood flow to below the compensatory limits of autoregulation **(Fig. 11-3)**. In order to elicit neutrally mediated syncope, a functioning autonomic nervous system is necessary, in contrast to syncope resulting from autonomic failure (discussed below).

www.ketabpezeshki.com (021) 66485457 - 66485438

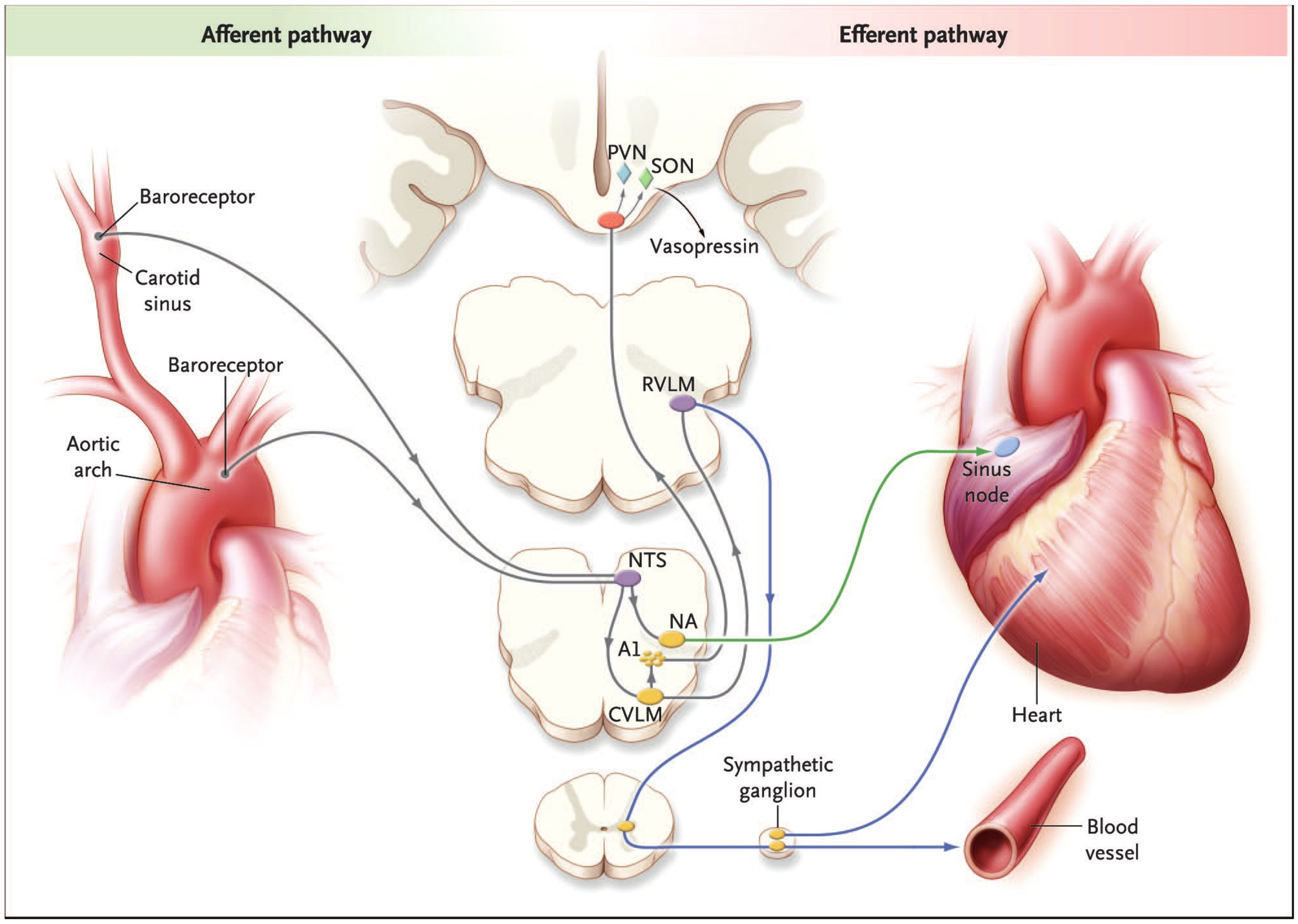


FIGURE 11-1

The baroreflex. A decrease in arterial pressure unloads the baroreceptors—the terminals of afferent fibers of the glossopharyngeal and vagus nerves—that are situated in the carotid sinus and aortic arch. This leads to a reduction in the afferent impulses that are relayed from these mechanoreceptors through the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. The reduced baroreceptor afferent activity produces a decrease in vagal nerve input to the sinus node that is mediated via connections of the NTS to the nucleus ambiguus (NA). There is an increase in sympathetic efferent activity that is mediated by the NTS projections to the caudal ventrolateral medulla (CVLM) (an excitatory pathway) and from there to the rostral ventrolateral medulla (RVLM) (an inhibitory pathway). The activation of RVLM presympathetic neurons in response to hypotension is thus predominantly due to disinhibition. In response to a sustained fall in blood pressure, vasopressin release is mediated by projections from the A1 noradrenergic cell group in the ventrolateral medulla. This projection activates vasopressin-synthesizing neurons in the magnocellular portion of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. Blue denotes sympathetic neurons, and green denotes parasympathetic neurons. (From R Freeman: N Engl J Med 358:615, 2008.)

Multiple triggers of the afferent limb of the reflex arc can result in neutrally mediated syncope. In some situations, these can be clearly defined, e.g., the carotid sinus, the gastrointestinal tract, or the bladder. Often, however, the trigger is less easily recognized and the cause is multifactorial. Under these circumstances, it is likely that different afferent pathways converge on the central autonomic network within the medulla that integrates the neural impulses and mediates the vasodepressor-bradycardic response.

Classification of Neurally Mediated Syncope

Neurally mediated syncope may be subdivided based on the afferent pathway and provocative trigger. Vasovagal syncope (the common faint) is provoked by intense emotion, pain, and/or orthostatic stress, whereas the situational reflex syncopes have specific localized stimuli that provoke the reflex vasodilation and bradycardia that leads to syncope. The underlying mechanisms have been identified and pathophysiology delineated for most of these situational reflex syncopes. The afferent trigger may originate in the pulmonary system, gastrointestinal system, urogenital system, heart, and carotid artery **(Table 11-2)**. Hyperventilation leading to hypocarbia and cerebral vasoconstriction, and raised intrathoracic pressure that impairs venous return to the heart, play a central role in many of the situational reflex syncopes. The afferent pathway of the reflex arc differs among these disorders, but the

www.ketabpezeshki.com (021) 66485457 - 66485438

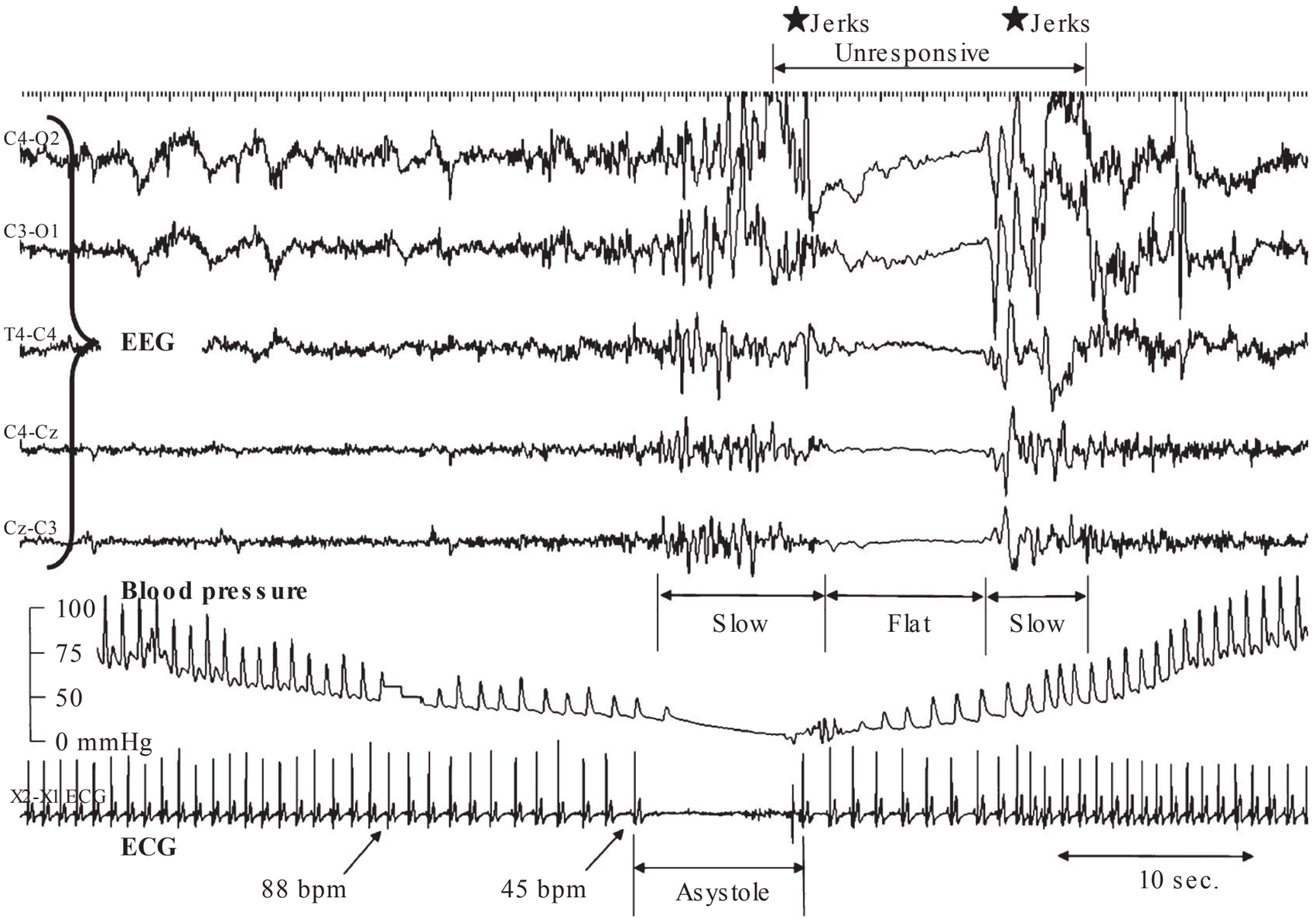


FIGURE 11-2

The electroencephalogram (EEG) in vasovagal syncope. A 1-min segment of a tilt-table test with typical vasovagal syncope demonstrating the "slow-fat-slow" EEG pattern. Finger beat-to-beat blood pressure, electrocardiogram (ECG), and selected EEG channels are shown. EEG slowing starts when systolic blood pressure drops to ~50 mmHg; heart rate is then approximately 45 beats/min (bpm). Asystole occurred, lasting about 8 s. The EEG flattens for a similar period, but with a delay. A transient loss of consciousness, lasting 14 s, was observed. There were muscle jerks just before and just after the flat period of the EEG. (Figure reproduced with permission from W Wieling et al: Brain 132:2630, 2009.)

efferent response via the vagus and sympathetic pathways is similar.

Alternately, neurally mediated syncope may be subdivided based on the predominant efferent pathway. Vasodepressor syncope describes syncope predominantly due to efferent, sympathetic, vasoconstrictor failure; cardioinhibitory syncope describes syncope predominantly associated with bradycardia or asystole

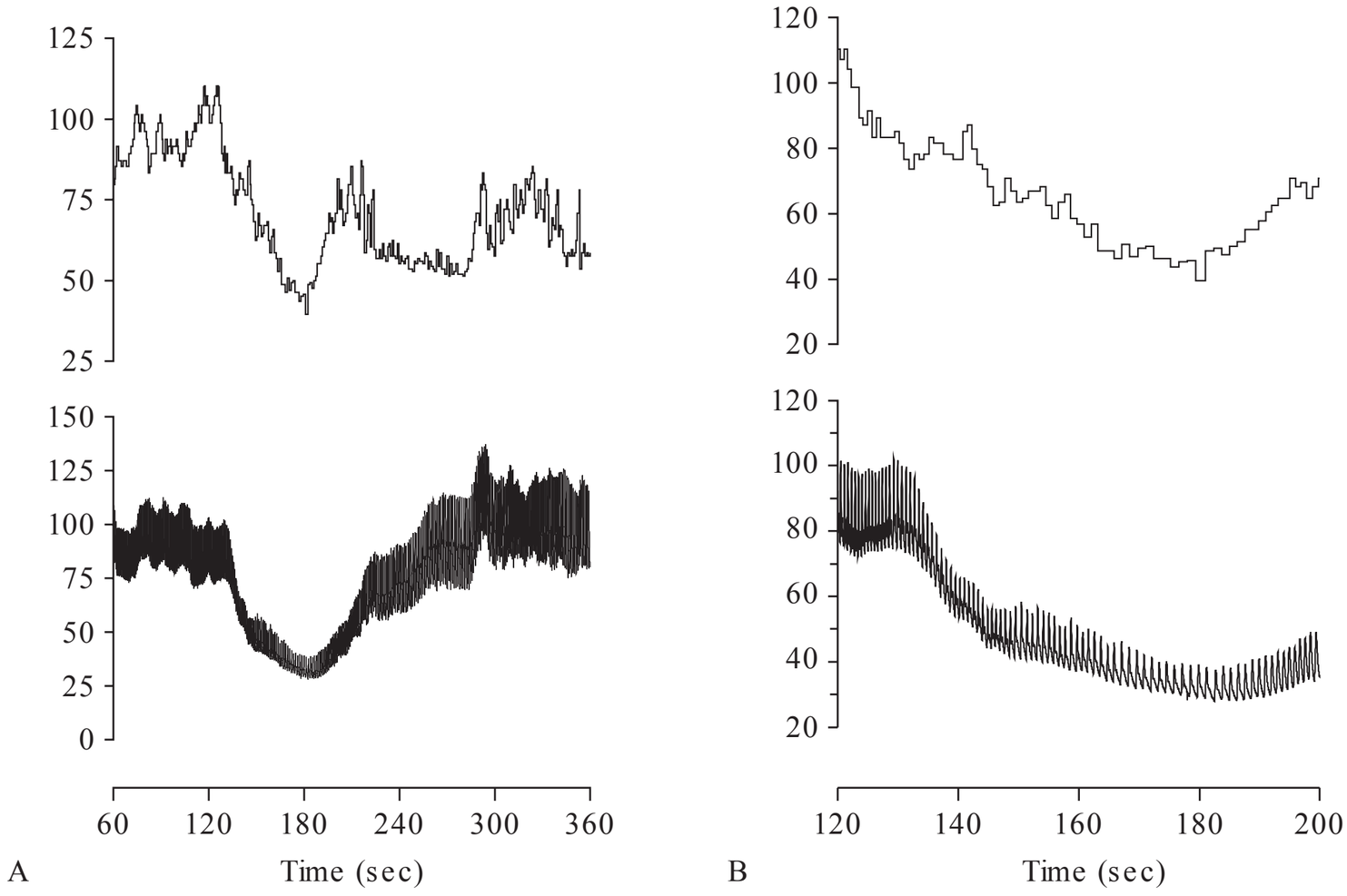


FIGURE 11-3

A. The paroxysmal hypotensive-bradycardic response that is characteristic of neurally mediated syncope. Noninvasive beat-to-beat blood pressure and heart rate are shown over 5 min (from 60 to 360 s) of an upright tilt on a tilt table. B. The same tracing expanded to show 80 s of the episode (from 80 to 200 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 11-2

CAUSES OF SYNCOPE

A. Neurally Mediated Syncope

- Vasovagal syncope
  - Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress
- Situational reflex syncope
  - Pulmonary
    - Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"[a] and "fainting lark,"[b] sneeze syncope, airway instrumentation
  - Urogenital
    - Postmicturition syncope, urogenital tract instrumentation, prostatic massage
  - Gastrointestinal
    - Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope
  - Cardiac
    - Bezold-Jarisch reflex, cardiac outflow obstruction
  - Carotid sinus
    - Carotid sinus sensitivity, carotid sinus massage
  - Ocular
    - Ocular pressure, ocular examination, ocular surgery

B. Orthostatic Hypotension

- Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies"
  - Lewy body diseases
    - Parkinson's disease
    - Lewy body dementia
    - Pure autonomic failure
  - Multiple system atrophy (the Shy-Drager syndrome)
- Secondary autonomic failure due to autonomic peripheral neuropathies
  - Diabetes
  - Hereditary amyloidosis (familial amyloid polyneuropathy)
  - Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated)
  - Hereditary sensory and autonomic neuropathies (HSAN) (especially type III—familial dysautonomia)
  - Idiopathic immune-mediated autonomic neuropathy
  - Autoimmune autonomic ganglionopathy
  - Sjögren's syndrome
  - Paraneoplastic autonomic neuropathy
  - HIV neuropathy
- Postprandial hypotension
- Iatrogenic (drug-induced)
- Volume depletion

C. Cardiac Syncope

- Arrhythmias
  - Sinus node dysfunction
  - Atrioventricular dysfunction
  - Supraventricular tachycardias
  - Ventricular tachycardias
  - Inherited channelopathies
- Cardiac structural disease
  - Valvular disease
  - Myocardial ischemia
  - Obstructive and other cardiomyopathies
  - Atrial myxoma
  - Pericardial effusions and tamponade

[a]Hyperventilation for ~1 minute, followed by sudden chest compression.
[b]Hyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.

www.ketabpezeshki.com (021) 66485457 - 66485438

due to increased vagal outflow; and mixed syncope describes syncope in which there are both vagal and sympathetic reflex changes.

Features of neurally mediated syncope

In addition to symptoms of orthostatic intolerance such as dizziness, lightheadedness, and fatigue, premonitory features of autonomic activation may be present in patients with neurally mediated syncope. These include diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. During the syncopal event, proximal and distal myoclonus (typically arrhythmic and multifocal) may occur, raising the possibility of epilepsy. The eyes typically remain open and usually deviate upward. Pupils are usually dilated. Roving eye movements may occur. Grunting, moaning, snorting, and stertorous breathing may be present. Urinary incontinence may occur. Fecal incontinence is very rare. Postictal confusion is also rare, although visual and auditory hallucinations and near death and out-of-body experiences are sometimes reported.

Although some predisposing factors and provocative stimuli are well established (for example, motionless upright posture, warm ambient temperature, intravascular volume depletion, alcohol ingestion, hypoxemia, anemia, pain, the sight of blood, venipuncture, and intense emotion), the underlying basis for the widely different thresholds for syncope among individuals exposed to the same provocative stimulus is not known. A genetic basis for neurally mediated syncope may exist; several studies have reported an increased incidence of syncope in first-degree relatives of fainters, but no gene or genetic marker has been identified, and environmental, social, and cultural factors have not been excluded by these studies.

TREATMENT Neurally Mediated Syncope

Reassurance, avoidance of provocative stimuli, and plasma volume expansion with fluid and salt are the cornerstones of the management of neurally mediated syncope. Isometric counterpressure maneuvers of the limbs (leg crossing or handgrip and arm tensing) may raise blood pressure by increasing central blood volume and cardiac output. By maintaining pressure in the autoregulatory zone, these maneuvers avoid or delay the onset of syncope. Randomized controlled trials support this intervention.

Fludrocortisone, vasoconstricting agents, and beta-adrenoreceptor antagonists are widely used by experts to treat refractory patients, although there is no consistent evidence from randomized controlled trials for any pharmacotherapy to treat neurally mediated syncope. Because vasodilation is the dominant pathophysiologic syncopal mechanism in most patients, use of a cardiac pacemaker is rarely beneficial. Possible exceptions are older patients (>40 years) in whom syncope is associated with asystole or severe bradycardia and patients with prominent cardioinhibition due to carotid sinus syndrome. In these patients, dual-chamber pacing may be helpful.

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension, defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing or head-up tilt on a tilt table, is a manifestation of sympathetic vasoconstrictor (autonomic) failure **(Fig. 11-4)**. In many (but not all) cases, there is no compensatory increase in heart rate despite hypotension; with partial autonomic failure, heart rate may

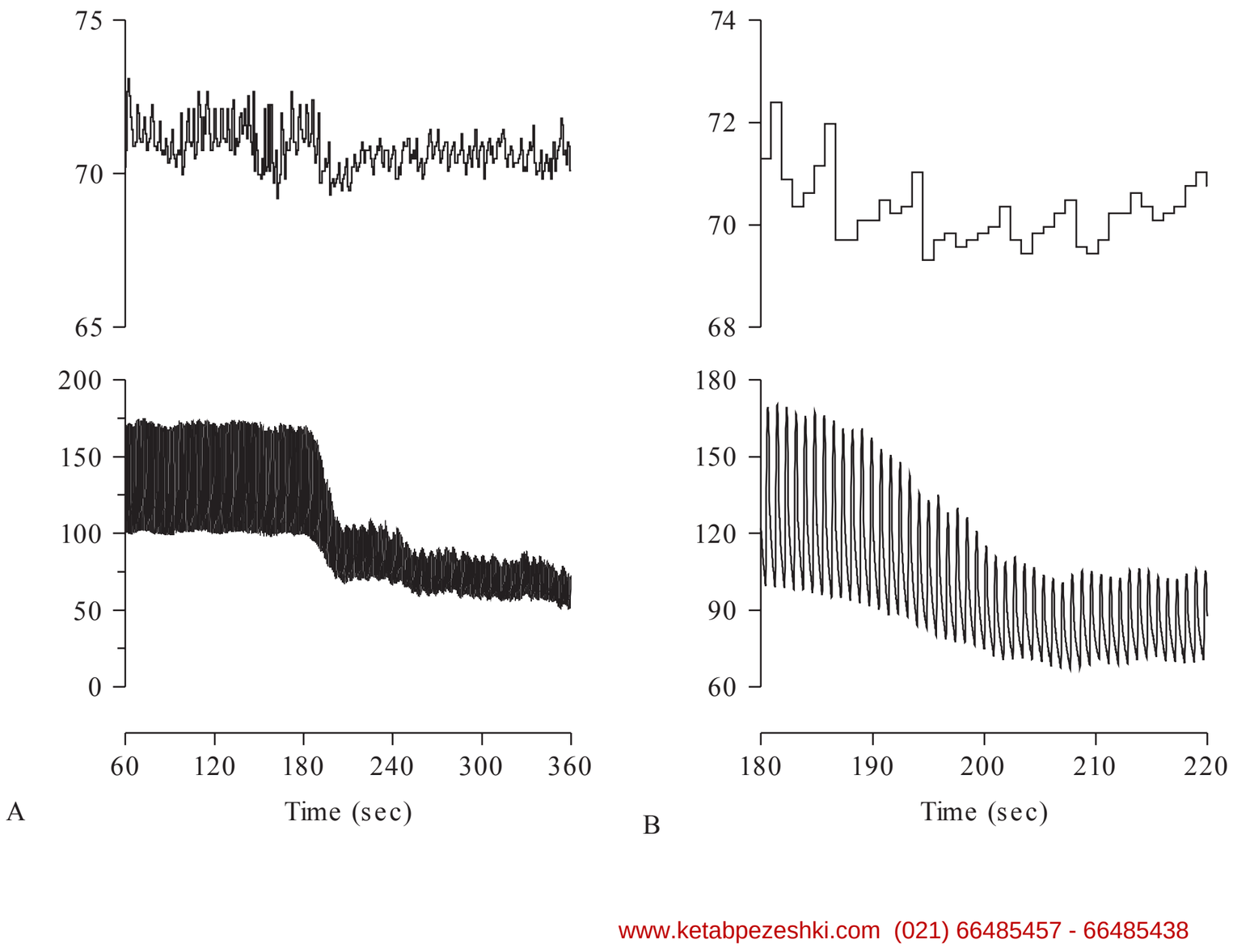


FIGURE 11-4
A. The gradual fall in blood pressure without a compensatory heart rate increase that is characteristic of orthostatic hypotension due to autonomic failure. Blood pressure and heart rate are shown over 5 min (from 60 to 360 s) of an upright tilt on a tilt table. B. The same tracing expanded to show 40 s of the episode (from 180 to 220 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

www.ketabpezeshki.com (021) 66485457 - 66485438

increase to some degree but is insuf cient to maintain cardiac output. A variant of orthostatic hypotension is "delayed" orthostatic hypotension, which occurs beyond 3 min of standing; this may reflect a mild or early form of sympathetic adrenergic dysfunction. In some cases, orthostatic hypotension occurs within 15 s of standing (so-called "initial" orthostatic hypotension), a finding that may reflect a transient mismatch between cardiac output and peripheral vascular resistance and does not represent autonomic failure.

Characteristic symptoms of orthostatic hypotension include light-headedness, dizziness, and presyncope (near-faintness) occurring in response to sudden postural change. However, symptoms may be absent or nonspecific, such as generalized weakness, fatigue, cognitive slowing, leg buckling, or headache. Visual blurring may occur, likely due to retinal or occipital lobe ischemia. Neck pain, typically in the suboccipital, posterior cervical, and shoulder region (the "coat-hanger headache"), most likely due to neck muscle ischemia, may be the only symptom. Patients may report orthostatic dyspnea (thought to reflect ventilation-perfusion mismatch due to inadequate perfusion of ventilated lung apices) or angina (attributed to impaired myocardial perfusion even with normal coronary arteries). Symptoms may be exacerbated by exertion, prolonged standing, increased ambient temperature, or meals. Syncope is usually preceded by warning symptoms, but may occur suddenly, suggesting the possibility of a seizure or cardiac cause.

Supine hypertension is common in patients with orthostatic hypotension due to autonomic failure, affecting over 50% of patients in some series. Orthostatic hypotension may present after initiation of therapy for hypertension, and supine hypertension may follow treatment of orthostatic hypotension. However, in other cases, the association of the two conditions is unrelated to therapy; it may in part be explained by baroreflex dysfunction in the presence of residual sympathetic outflow, particularly in patients with central autonomic degeneration.

Causes of neurogenic orthostatic hypotension

Causes of neurogenic orthostatic hypotension include central and peripheral autonomic nervous system dysfunction **(Chap. 41)**. Autonomic dysfunction of other organ systems (including the bladder, bowels, sexual organs, and sudomotor system) of varying severity frequently accompanies orthostatic hypotension in these disorders (Table 11-2).

T e primary autonomic degenerative disorders are multiple system atrophy (the Shy-Drager syndrome; **Chap. 41**), Parkinson's disease **(Chap. 36)**, dementia with Lewy bodies **(Chap. 35)**, and pure autonomic failure **(Chap. 41)**. T ese are often grouped together as "synucleinopathies" due to the presence of alpha-synuclein, a small protein that precipitates predominantly in the cytoplasm of neurons in the Lewy body disorders (Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure) and in the glia in multiple system atrophy.

Peripheral autonomic dysfunction may also accompany small-fiber peripheral neuropathies such as those seen in diabetes, amyloid, immune-mediated neuropathies, hereditary sensory and autonomic neuropathies (HSAN; particularly HSAN type III, familial dysautonomia), and inflammatory neuropathies **(Chaps. 53 and 54)**. Less frequently, orthostatic hypotension is associated with the peripheral neuropathies that accompany vitamin B_{12} deficiency, neurotoxic exposure, HIV and other infections, and porphyria.

Patients with autonomic failure and the elderly are susceptible to falls in blood pressure associated with meals. T e magnitude of the blood pressure fall is exacerbated by large meals, meals high in carbohydrate, and alcohol intake. T e mechanism of postprandial syncope is not fully elucidated.

Orthostatic hypotension is often iatrogenic. Drugs from several classes may lower peripheral resistance (e.g., alpha-adrenoreceptor antagonists used to treat hypertension and prostatic hypertrophy; antihypertensive agents of several classes; nitrates and other vasodilators; tricyclic agents and phenothiazines). Iatrogenic volume depletion due to diuresis and volume depletion due to medical causes (hemorrhage, vomiting, diarrhea, or decreased fluid intake) may also result in decreased effective circulatory volume, orthostatic hypotension, and syncope.

TREATMENT Orthostatic Hypotension

T e first step is to remove reversible causes—usually vasoactive medications **(Table 41-6)**. Next, nonpharmacologic interventions should be introduced. T ese interventions include patient education regarding staged moves from supine to upright; warnings about the hypotensive effects of large meals; instructions about the isometric counterpressure maneuvers that increase intravascular pressure (see above); and raising the head of the bed to reduce supine hypertension. Intravascular volume should be expanded by increasing dietary fluid and salt. If these nonpharmacologic measures fail, pharmacologic intervention with fludrocortisone acetate and vasoconstricting agents such as midodrine, l-dihydroxyphenylserine, and pseudoephedrine should be introduced. Some patients with intractable symptoms require additional therapy with supplementary agents that include pyridostigmine, yohimbine, desmopressin acetate (DDAVP), and erythropoietin **(Chap. 41)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

کتاب پزشکی

66485457 - 66485438

www.ketabpezeshki.com

CARDIAC SYNCOPE

Cardiac (or cardiovascular) syncope is caused by arrhythmias and structural heart disease. T ese may occur in combination because structural disease renders the heart more vulnerable to abnormal electrical activity.

Arrhythmias

Bradyarrhythmias that cause syncope include those due to severe sinus node dysfunction (e.g., sinus arrest or sinoatrial block) and atrioventricular (AV) block (e.g., Mobitz type II, high-grade, and complete AV block). T e bradyarrhythmias due to sinus node dysfunction are often associated with an atrial tachyarrhythmia, a disorder known as the tachycardia-bradycardia syndrome. A prolonged pause following the termination of a tachycardic episode is a frequent cause of syncope in patients with the tachycardia-bradycardia syndrome. Medications of several classes may also cause bradyarrhythmias of suf cient severity to cause syncope. Syncope due to bradycardia or asystole is referred to as a Stokes-Adams attack.

Ventricular tachyarrhythmias frequently cause syncope. T e likelihood of syncope with ventricular tachycardia is in part dependent on the ventricular rate; rates below 200 beats/min are less likely to cause syncope. T e compromised hemodynamic function during ventricular tachycardia is caused by ineffective ventricular contraction, reduced diastolic filling due to abbreviated filling periods, loss of AV synchrony, and concurrent myocardial ischemia.

Several disorders associated with cardiac electrophysiologic instability and arrhythmogenesis are due to mutations in ion channel subunit genes. T ese include the long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. T e long QT syndrome is a genetically heterogeneous disorder associated with prolonged cardiac repolarization and a predisposition to ventricular arrhythmias. Syncope and sudden death in patients with long QT syndrome result from a unique polymorphic ventricular tachycardia called torsades des pointes that degenerates into ventricular fibrillation. T e long QT syndrome has been linked to genes encoding K^+ channel α-subunits, K^+ channel β-subunits, voltage-gated Na^+ channel, and a scaffolding protein, ankyrin B (ANK2). Brugada syndrome is characterized by idiopathic ventricular fibrillation in association with right ventricular electrocardiogram (ECG) abnormalities without structural heart disease. T is disorder is also genetically heterogeneous, although it is most frequently linked to mutations in the Na^+ channel α-subunit, SCN5A. Catecholaminergic polymorphic tachycardia is an inherited, genetically heterogeneous disorder associated with exercise- or stress-induced ventricular arrhythmias, syncope, or sudden death. Acquired QT interval prolongation, most commonly due to drugs, may also result in ventricular arrhythmias and syncope.

Structural disease

Structural heart disease (e.g., valvular disease, myocardial ischemia, hypertrophic and other cardiomyopathies, cardiac masses such as atrial myxoma, and pericardial effusions) may lead to syncope by compromising cardiac output. Structural disease may also contribute to other pathophysiologic mechanisms of syncope. For example, cardiac structural disease may predispose to arrhythmogenesis; aggressive treatment of cardiac failure with diuretics and/or vasodilators may lead to orthostatic hypotension; and inappropriate reflex vasodilation may occur with structural disorders such as aortic stenosis and hypertrophic cardiomyopathy, possibly provoked by increased ventricular contractility.

TREATMENT Cardiac Syncope

Treatment of cardiac disease depends on the underlying disorder. T erapies for arrhythmias include cardiac pacing for sinus node disease and AV block, and ablation, antiarrhythmic drugs, and cardioverter-defibrillators for atrial and ventricular tachyarrhythmias. T ese disorders are best managed by physicians with specialized skills in this area.

APPROACH TO THE PATIENT: Syncope

DIFFERENTIAL DIAGNOSIS Syncope is easily diagnosed when the characteristic features are present; however, several disorders with transient real or apparent loss of consciousness may create diagnostic confusion.

Generalized and partial seizures may be confused with syncope; however, there are a number of differentiating features. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also may occur in up to 90% of syncopal episodes. Myoclonic jerks associated with syncope may be multifocal or generalized. T ey are typically arrhythmic and of short duration (<30 s). Mild flexor and extensor posturing also may occur. Partial or partial-complex seizures with secondary generalization are usually preceded by an aura, commonly an unpleasant smell; fear; anxiety; abdominal discomfort; or other visceral sensations. T ese phenomena should be differentiated from the premonitory features of syncope.

www.ketabpezeshki.com (021) 66485457 - 66485438

Autonomic manifestations of seizures (autonomic epilepsy) may provide a more dif cult diagnostic challenge. Autonomic seizures have cardiovascular, gastrointestinal, pulmonary, urogenital, pupillary, and cutaneous manifestations that are similar to the premonitory features of syncope. Furthermore, the cardiovascular manifestations of autonomic epilepsy include clinically significant tachycardias and bradycardias that may be of suf cient magnitude to cause loss of consciousness. T e presence of accompanying nonautonomic auras may help differentiate these episodes from syncope.

Loss of consciousness associated with a seizure usually lasts longer than 5 min and is associated with prolonged postictal drowsiness and disorientation, whereas reorientation occurs almost immediately after a syncopal event. Muscle aches may occur after both syncope and seizures, although they tend to last longer and be more severe following a seizure. Seizures, unlike syncope, are rarely provoked by emotions or pain. Incontinence of urine may occur with both seizures and syncope; however, fecal incontinence occurs very rarely with syncope.

Hypoglycemia may cause transient loss of consciousness, typically in individuals with type 1 or type 2 diabetes treated with insulin. T e clinical features associated with impending or actual hypoglycemia include tremor, palpitations, anxiety, diaphoresis, hunger, and paresthesias. T ese symptoms are due to autonomic activation to counter the falling blood glucose. Hunger, in particular, is not a typical premonitory feature of syncope. Hypoglycemia also impairs neuronal function, leading to fatigue, weakness, dizziness, and cognitive and behavioral symptoms. Diagnostic dif culties may occur in individuals in strict glycemic control; repeated hypoglycemia impairs the counterregulatory response and leads to a loss of the characteristic warning symptoms that are the hallmark of hypoglycemia.

Patients with cataplexy experience an abrupt partial or complete loss of muscular tone triggered by strong emotions, typically anger or laughter. Unlike syncope, consciousness is maintained throughout the attacks, which typically last between 30 s and 2 min. T ere are no premonitory symptoms. Cataplexy occurs in 60–75% of patients with narcolepsy.

T e clinical interview and interrogation of eyewitnesses usually allow differentiation of syncope from falls due to vestibular dysfunction, cerebellar disease, extrapyramidal system dysfunction, and other gait disorders. If the fall is accompanied by head trauma, a postconcussive syndrome, amnesia for the precipitating events, and/or the presence of loss of consciousness may contribute to diagnostic dif culty.

Apparent loss of consciousness can be a manifestation of psychiatric disorders such as generalized anxiety, panic disorders, major depression, and somatization disorder. T ese possibilities should be considered in individuals who faint frequently without prodromal symptoms. Such patients are rarely injured despite numerous falls. T ere are no clinically significant hemodynamic changes concurrent with these episodes. In contrast, transient loss of consciousness due to vasovagal syncope precipitated by fear, stress, anxiety, and emotional distress is accompanied by hypotension, bradycardia, or both.

INITIAL EVALUATION T e goals of the initial evaluation are to determine whether the transient loss of consciousness was due to syncope; to identify the cause; and to assess risk for future episodes and serious harm (Table 11-1). T e initial evaluation should include a detailed history, thorough questioning of eyewitnesses, and a complete physical and neurologic examination. Blood pressure and heart rate should be measured in the supine position and after 3 min of standing to determine whether orthostatic hypotension is present. An ECG should be performed if there is suspicion of syncope due to an arrhythmia or underlying cardiac disease. Relevant electrocardiographic abnormalities include bradyarrhythmias or tachyarrhythmias, AV block, ischemia, old myocardial infarction, long QT syndrome, and bundle branch block. T is initial assessment will lead to the identification of a cause of syncope in approximately 50% of patients and also allows stratification of patients at risk for cardiac mortality.

Laboratory tests Baseline laboratory blood tests are rarely helpful in identifying the cause of syncope. Blood tests should be performed when specific disorders, e.g., myocardial infarction, anemia, and secondary autonomic failure, are suspected (Table 11-2).

Autonomic nervous system testing Autonomic testing, including tilt-table testing, can be performed in specialized centers (Chap. 41). Autonomic testing is helpful to uncover objective evidence of autonomic failure and also to demonstrate a predisposition to neurally mediated syncope. Autonomic testing includes assessments of parasympathetic autonomic nervous system function (e.g., heart rate variability to deep respiration and a Valsalva maneuver), sympathetic cholinergic function (e.g., thermoregulatory sweat response and quantitative sudomotor axon reflex test), and sympathetic adrenergic function (e.g., blood pressure response to a Valsalva maneuver and a tilt-table test with beat-to-beat blood pressure measurement). T e hemodynamic abnormalities demonstrated on tilt-table test (Figs. 11-3 and 11-4) may be useful in distinguishing orthostatic hypotension due to autonomic failure from the hypotensive bradycardic response of neurally mediated syncope. Similarly, the tilt-table test may help identify patients with syncope due to immediate or delayed orthostatic hypotension.

Carotid sinus massage should be considered in patients with symptoms suggestive of carotid sinus syncope and in patients over age 50 years with recurrent syncope of

www.ketabpezeshki.com (021) 66485457 - 66485438

unknown etiology. T is test should only be carried out under continuous ECG and blood pressure monitoring and should be avoided in patients with carotid bruits, plaques, or stenosis.

Cardiac evaluation ECG monitoring is indicated for patients with a high pretest probability of arrhythmia causing syncope. Patients should be monitored in hospital if the likelihood of a life-threatening arrhythmia is high, e.g., patients with severe structural or coronary artery disease, nonsustained ventricular tachycardia, trifascicular heart block, prolonged QT interval, Brugada syndrome ECG pattern, or family history of sudden cardiac death (Table 11-1). Outpatient Holter monitoring is recommended for patients who experience frequent syncopal episodes (one or more per week), whereas loop recorders, which continually record and erase cardiac rhythm, are indicated for patients with suspected arrhythmias with low risk of sudden cardiac death. Loop recorders may be external (recommended for evaluation of episodes that occur at a frequency of greater than one per month) or implantable (if syncope occurs less frequently).

Echocardiography should be performed in patients with a history of cardiac disease or if abnormalities are found on physical examination or the ECG. Echocardiographic diagnoses that may be responsible for syncope include aortic stenosis, hypertrophic cardiomyopathy, cardiac tumors, aortic dissection, and pericardial tamponade. Echocardiography also has a role in risk stratification based on the left ventricular ejection fraction.

Treadmill exercise testing with ECG and blood pressure monitoring should be performed in patients who have experienced syncope during or shortly after exercise. Treadmill testing may help identify exercise-induced arrhythmias (e.g., tachycardia-related AV block) and exercise-induced exaggerated vasodilation.

Electrophysiologic studies are indicated in patients with structural heart disease and ECG abnormalities in whom noninvasive investigations have failed to yield a diagnosis. Electrophysiologic studies have low sensitivity and specificity and should only be performed when a high pretest probability exists. Currently, this test is rarely performed to evaluate patients with syncope.

Psychiatric evaluation Screening for psychiatric disorders may be appropriate in patients with recurrent unexplained syncope episodes. Tilt-table testing, with demonstration of symptoms in the absence of hemodynamic change, may be useful in reproducing syncope in patients with suspected psychogenic syncope.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 12

DIZZINESS AND VERTIGO

Mark F. Walker ■ Robert B. Darof

Dizziness is an imprecise symptom used to describe a variety of sensations that include vertigo, light-headedness, faintness, and imbalance. When used to describe a sense of spinning or other motion, dizziness is designated as vertigo. Vertigo may be physiologic, occurring during or after a sustained head rotation, or it may be pathologic, due to vestibular dysfunction. T e term light-headedness is commonly applied to presyncopal sensations due to brain hypoperfusion but also may refer to disequilibrium and imbalance. A challenge to diagnosis is that patients often have difficulty distinguishing among these various symptoms, and the words they choose do not reliably indicate the underlying etiology.

T ere are a number of potential causes of dizziness. Vascular disorders cause presyncopal dizziness as a result of cardiac dysrhythmia, orthostatic hypotension, medication effects, or other causes. Such presyncopal sensations vary in duration; they may increase in severity until loss of consciousness occurs, or they may resolve before loss of consciousness if the cerebral ischemia is corrected. Faintness and syncope, which are discussed in detail in **Chap. 11**, should always be considered when one is evaluating patients with brief episodes of dizziness or dizziness that occurs with upright posture.

Vestibular causes of dizziness (vertigo or imbalance) may be due to peripheral lesions that affect the labyrinths or vestibular nerves or to involvement of the central vestibular pathways. T ey may be paroxysmal or due to a fixed unilateral or bilateral vestibular deficit. Acute unilateral lesions cause vertigo due to a sudden imbalance in vestibular inputs from the two labyrinths. Bilateral lesions cause imbalance and instability of vision (oscillopsia) when the head moves. Other causes of dizziness include nonvestibular imbalance and gait disorders (e.g., loss of proprioception from sensory neuropathy, parkinsonism) and anxiety.

When evaluating patients with dizziness, questions to consider include the following: (1) Is it dangerous (e.g., arrhythmia, transient ischemic attack/stroke)? (2) Is it vestibular? (3) If vestibular, is it peripheral or central? A careful history and examination often provide sufficient information to answer these questions and determine whether additional studies or referral to a specialist is necessary.

APPROACH TO THE PATIENT: Dizziness

HISTORY When a patient presents with dizziness, the first step is to delineate more precisely the nature of the symptom. In the case of vestibular disorders, the physical symptoms depend on whether the lesion is unilateral or bilateral, and whether it is acute or chronic and progressive. Vertigo, an illusion of self or environmental motion, implies asymmetry of vestibular inputs from the two labyrinths or in their central pathways that is usually acute. Symmetric bilateral vestibular hypofunction causes imbalance but no vertigo. Because of the ambiguity in patients' descriptions of their symptoms, diagnosis based simply on symptom characteristics is typically unreliable. T e history should focus closely on other features, including whether this is the first attack, the duration of this and any prior episodes, provoking factors, and accompanying symptoms.

Dizziness can be divided into episodes that last for seconds, minutes, hours, or days. Common causes of brief dizziness (seconds) include benign paroxysmal positional vertigo (BPPV) and orthostatic hypotension, both of which typically are provoked by changes in head and body position. Attacks of vestibular migraine and Ménière's disease often last hours. When episodes are of intermediate duration (minutes), transient ischemic attacks of the posterior circulation should be considered, although migraine and a number of other causes are also possible.

Symptoms that accompany vertigo may be helpful in distinguishing peripheral vestibular lesions from central

www.ketabpezeshki.com (021) 66485457 - 66485438

causes. Unilateral hearing loss and other aural symptoms (ear pain, pressure, fullness) typically point to a peripheral cause. Because the auditory pathways quickly become bilateral upon entering the brainstem, central lesions are unlikely to cause unilateral hearing loss, unless the lesion lies near the root entry zone of the auditory nerve. Symptoms such as double vision, numbness, and limb ataxia suggest a brainstem or cerebellar lesion.

EXAMINATION Because dizziness and imbalance can be a manifestation of a variety of neurologic disorders, the neurologic examination is important in the evaluation of these patients. Particular focus should be given to assessment of eye movements, vestibular function, and hearing. The range of eye movements and whether they are equal in each eye should be observed. Peripheral eye movement disorders (e.g., cranial neuropathies, eye muscle weakness) are usually disconjugate (different in the two eyes). One should check pursuit (the ability to follow a smoothly moving target) and saccades (the ability to look back and forth accurately between two targets). Poor pursuit or inaccurate (dysmetric) saccades usually indicates central pathology, often involving the cerebellum. Finally, one should look for spontaneous nystagmus, an involuntary back-and-forth movement of the eyes. Nystagmus is most often of the jerk type, in which a slow drift (slow phase) in one direction alternates with a rapid saccadic movement (quick phase or fast phase) in the opposite direction that resets the position of the eyes in the orbits. Except in the case of acute vestibulopathy (e.g., vestibular neuritis), if primary position nystagmus is easily seen in the light, it is probably due to a central cause. Two forms of nystagmus that are characteristic of lesions of the cerebellar pathways are vertical nystagmus with downward fast phases (downbeat nystagmus) and horizontal nystagmus that changes direction with gaze (gaze-evoked nystagmus). By contrast, peripheral lesions typically cause unidirectional horizontal nystagmus. Use of Frenzel eyeglasses (self-illuminated goggles with convex lenses that blur the patient's vision but allow the examiner to see the eyes greatly magnified) can aid in the detection of peripheral vestibular nystagmus, because they reduce the patient's ability to use visual fixation to suppress nystagmus. **Table 12-1** outlines key findings that help distinguish peripheral from central causes of vertigo.

The most useful bedside test of peripheral vestibular function is the head impulse test, in which the vestibuloocular reflex (VOR) is assessed with small-amplitude (~20 degrees) rapid head rotations. While the patient fixates on a target, the head is rotated to the left or right. If the VOR is deficient, the rotation is followed by a catch-up saccade in the opposite direction (e.g., a leftward saccade after a rightward rotation). The head impulse test can identify both unilateral (catch-up saccades after rotations toward the weak side) and bilateral vestibular hypofunction (catch-up saccades after rotations in both directions).

TABLE 12-1

FEATURES OF PERIPHERAL AND CENTRAL VERTIGO

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in BPPV, but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a patient with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

All patients with episodic dizziness, especially if provoked by positional change, should be tested with the Dix-Hallpike maneuver. The patient begins in a sitting position with the head turned 45 degrees; holding the back of the head, the examiner then lowers the patient into a supine position with the head extended backward by about 20 degrees while watching the eyes. Posterior canal BPPV can be diagnosed confidently if transient upbeating-torsional nystagmus is seen. If no nystagmus is observed after 15–20 s, the patient is raised to the sitting position, and the procedure is repeated with the head turned to the other side. Again, Frenzel goggles may improve the sensitivity of the test.

Dynamic visual acuity is a functional test that can be useful in assessing vestibular function. Visual acuity is measured with the head still and when the head is rotated back and forth by the examiner (about 1–2 Hz). A drop in visual acuity during head motion of more than one line on a near card or Snellen chart is abnormal and indicates vestibular dysfunction.

ANCILLARY TESTING The choice of ancillary tests should be guided by the history and examination findings. Audiometry should be performed whenever a vestibular disorder is suspected. Unilateral sensorineural hearing loss supports a peripheral disorder (e.g., vestibular schwannoma). Predominantly low-frequency hearing loss is characteristic of Ménière's disease. Electronystagmography or videonystagmography includes recordings of spontaneous nystagmus (if present) and measurement of positional nystagmus. Caloric testing assesses the responses of the two horizontal semicircular canals. The test battery often includes recording of saccades and pursuit to assess central ocular motor function. Neuroimaging is important if a central vestibular disorder is suspected. In addition, patients with unexplained unilateral hearing loss or vestibular hypofunction should undergo magnetic resonance imaging (MRI) of the internal auditory canals, including administration of gadolinium, to rule out a schwannoma.

www.ketabpezeshki.com (021) 66485457 - 66485438

DIFFERENTIAL DIAGNOSIS AND TREATMENT

Treatment of vestibular symptoms should be driven by the underlying diagnosis. Simply treating dizziness with vestibular suppressant medications is often not helpful and may make the symptoms worse and prolong recovery. T e diagnostic and specific treatment approaches for the most commonly encountered vestibular disorders are discussed below.

ACUTE PROLONGED VERTIGO (VESTIBULAR NEURITIS)

An acute unilateral vestibular lesion causes constant vertigo, nausea, vomiting, oscillopsia (motion of the visual scene), and imbalance. T ese symptoms are due to a sudden asymmetry of inputs from the two labyrinths or in their central connections, simulating a continuous rotation of the head. Unlike BPPV, continuous vertigo persists even when the head remains still.

When a patient presents with an acute vestibular syndrome, the most important question is whether the lesion is central (e.g., a cerebellar or brainstem infarct or hemorrhage), which may be life-threatening, or peripheral, affecting the vestibular nerve or labyrinth (vestibular neuritis). Attention should be given to any symptoms or signs that point to central dysfunction (diplopia, weakness or numbness, dysarthria). T e pattern of spontaneous nystagmus, if present, may be helpful (Table 12-1). If the head impulse test is normal, an acute peripheral vestibular lesion is unlikely. A central lesion cannot always be excluded with certainty based on symptoms and examination alone; thus, older patients with vascular risk factors who present with an acute vestibular syndrome should be evaluated for the possibility of stroke even when there are no specific findings that indicate a central lesion.

Most patients with vestibular neuritis recover spontaneously, but glucocorticoids can improve outcome if administered within 3 days of symptom onset. Antiviral medications are of no proven benefit and are not typically given unless there is evidence to suggest herpes zoster oticus (Ramsay Hunt syndrome). Vestibular suppressant medications may reduce acute symptoms but should be avoided after the first several days because they may impede central compensation and recovery. Patients should be encouraged to resume a normal level of activity as soon as possible, and directed vestibular rehabilitation therapy may accelerate improvement.

BENIGN PAROXYSMAL POSITIONAL VERTIGO

BPPV is a common cause of recurrent vertigo. Episodes are brief (<1 min and typically 15–20 s) and are always provoked by changes in head position relative to gravity, such as lying down, rolling over in bed, rising from a supine position, and extending the head to look upward. T e attacks are caused by free-f oating otoconia (calcium carbonate crystals) that have been dislodged from the utricular macula and have moved into one of the semicircular canals, usually the posterior canal. When head position changes, gravity causes the otoconia to move within the canal, producing vertigo and nystagmus. With posterior canal BPPV, the nystagmus beats upward and torsionally (the upper poles of the eyes beat toward the affected lower ear). Less commonly, the otoconia enter the horizontal canal, resulting in a horizontal nystagmus when the patient is lying with either ear down. Superior (also called anterior) canal involvement is rare. BPPV is treated with repositioning maneuvers that use gravity to remove the otoconia from the semicircular canal. For posterior canal BPPV, the Epley maneuver **(Fig. 12-1)** is the most commonly used procedure. For more refractory cases of BPPV, patients can be taught a variant of this maneuver that they can perform alone at home. A demonstration of the Epley maneuver is available online (http://www.dizziness-and-balance.com/disorders/bppv/bppv.html).

VESTIBULAR MIGRAINE

Vestibular symptoms occur frequently in migraineurs, sometimes as a headache aura but usually independent of headache. T e duration of vertigo may be from minutes to hours, and some patients also experience more prolonged periods of disequilibrium (lasting days to weeks). Motion sensitivity and sensitivity to visual motion (e.g., movies) are common in patients with vestibular migraine. Although data from controlled studies are generally lacking, vestibular migraine typically is treated with medications that are used for prophylaxis of migraine headaches. Antiemetics may be helpful to relieve symptoms at the time of an attack.

MÉNIÈRE'S DISEASE

Attacks of Ménière's disease consist of vertigo and hearing loss, as well as pain, pressure, and/or fullness in the affected ear. T e low-frequency hearing loss and aural symptoms are key features that distinguish Ménière's disease from other peripheral vestibulopathies and from vestibular migraine. Audiometry at the time of an attack shows a characteristic asymmetric low-frequency hearing loss; hearing commonly improves between attacks, although permanent hearing loss may eventually occur. Ménière's disease is thought to be due to excess f uid (endolymph) in the inner ear; hence the term endolymphatic hydrops. Patients suspected of having Ménière's disease should be referred to an otolaryngologist for further evaluation. Diuretics and sodium restriction are the initial treatments. If attacks persist, injections

www.ketabpezeshki.com (021) 66485457 - 66485438

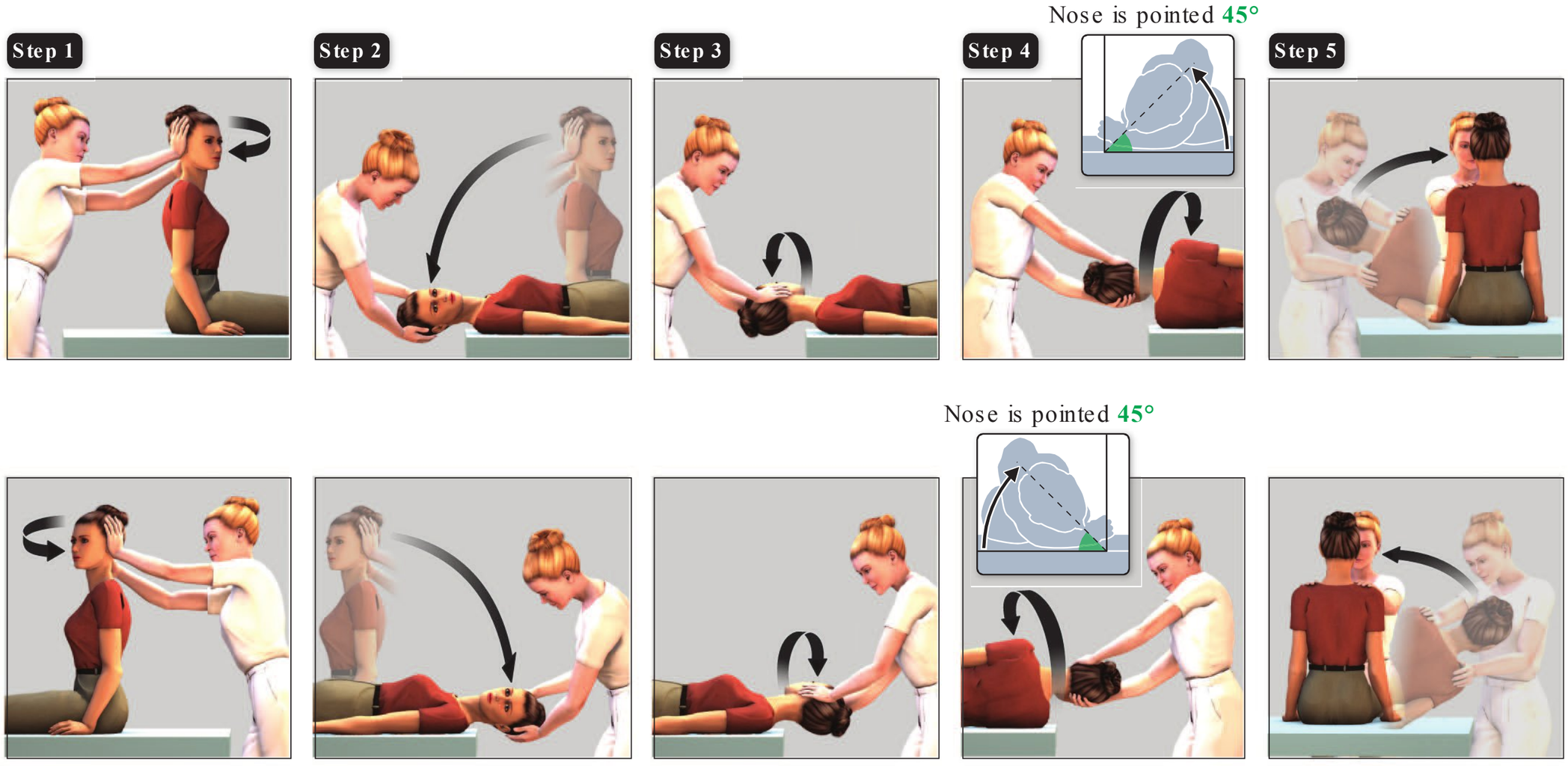


FIGURE 12-1
Modified Epley maneuver for treatment of benign paroxysmal positional vertigo of the right (top panels) and left (bottom panels) posterior semicircular canals. Step 1. With the patient seated, turn the head 45 degrees toward the affected ear. Step 2. Keeping the head turned, lower the patient to the head-hanging position and hold for at least 30 s and until nystagmus disappears. Step 3. Without lifting the head, turn it 90 degrees toward the other side. Hold for another 30 s. Step 4. Rotate the patient onto her side while turning the head another 90 degrees, so that the nose is pointed down 45 degrees. Hold again for 30 s. Step 5. Have the patient sit up on the side of the table. After a brief rest, the maneuver should be repeated to confirm successful treatment. (Figure adapted from http://www.dizziness-and-balance.com/disorders/bppv/movies/Epley-480x640.avi.)

of gentamicin into the middle ear are typically the next line of therapy. Full ablative procedures (vestibular nerve section, labyrinthectomy) are seldom required.

VESTIBULAR SCHWANNOMA

Vestibular schwannomas (sometimes termed acoustic neuromas) and other tumors at the cerebellopontine angle cause slowly progressive unilateral sensorineural hearing loss and vestibular hypofunction. These patients typically do not have vertigo, because the gradual vestibular deficit is compensated centrally as it develops. The diagnosis often is not made until there is sufficient hearing loss to be noticed. The examination will show a deficient response to the head impulse test when the head is rotated toward the affected side. As noted above, patients with unexplained unilateral sensorineural hearing loss or vestibular hypofunction require MRI of the internal auditory canals to look for a schwannoma.

BILATERAL VESTIBULAR HYPOFUNCTION

Patients with bilateral loss of vestibular function also typically do not have vertigo, because vestibular function is lost on both sides simultaneously, and there is no asymmetry of vestibular input. Symptoms include loss of balance, particularly in the dark, where vestibular input is most critical, and oscillopsia during head movement, such as while walking or riding in a car. Bilateral vestibular hypofunction may be (1) idiopathic and progressive, (2) part of a neurodegenerative disorder, or (3) iatrogenic, due to medication ototoxicity (most commonly gentamicin or other aminoglycoside antibiotics). Other causes include bilateral vestibular schwannomas (neurofibromatosis type 2), autoimmune disease, superficial siderosis, and meningeal-based infection or tumor. It also may occur in patients with peripheral polyneuropathy; in these patients, both vestibular loss and impaired proprioception may contribute to poor balance. Finally, unilateral processes such as vestibular neuritis and Ménière's disease may involve both ears sequentially, resulting in bilateral vestibulopathy.

Examination findings include diminished dynamic visual acuity (see above) due to loss of stable vision when the head is moving, abnormal head impulse responses in both directions, and a Romberg sign. Responses to caloric testing are reduced. Patients with bilateral vestibular hypofunction should be referred for vestibular rehabilitation therapy. Vestibular suppressant medications should not be used, as they will increase the imbalance. Evaluation by a neurologist is important

www.ketabpezeshki.com (021) 66485457 - 66485438

not only to confirm the diagnosis but also to consider any other associated neurologic abnormalities that may clarify the etiology.

CENTRAL VESTIBULAR DISORDERS

Central lesions causing vertigo typically involve vestibular pathways in the brainstem and/or cerebellum. T ey may be due to discrete lesions, such as from ischemic or hemorrhagic stroke **(Chap. 32)**, demyelination **(Chap. 45)**, or tumors **(Chap. 49)**, or they may be due to neurodegenerative conditions that include the vestibulocerebellum **(Chap. 35)**. Subacute cerebellar degeneration may be due to immune, including paraneoplastic, processes **(Chaps. 50 and 37)**. Table 12-1 outlines important features of the history and examination that help to identify central vestibular disorders. Acute central vertigo is a medical emergency, due to the possibility of life-threatening stroke or hemorrhage. All patients with suspected central vestibular disorders should undergo brain MRI, and the patient should be referred for full neurologic evaluation.

PSYCHOSOMATIC DIZZINESS/VERTIGO

Psychological factors play an important role in chronic dizziness. First, dizziness may be a somatic manifestation of a psychiatric condition such as major depression, anxiety, or panic disorder **(Chap. 60)**. Second, patients may develop anxiety and autonomic symptoms as a consequence or comorbidity of an independent vestibular disorder. One particular form of this has been termed variously phobic postural vertigo, psychophysiologic vertigo, or chronic subjective dizziness. T ese patients have a chronic feeling (months or longer) of dizziness and disequilibrium, an increased sensitivity to self-motion and visual motion (e.g., movies), and a particular intensification of symptoms when moving through complex visual environments such as supermarkets (visual vertigo). Although there may be a past history of an acute vestibular disorder (e.g., vestibular neuritis), the neurootologic examination and vestibular testing are normal or indicative of a compensated vestibular deficit, indicating that the ongoing subjective dizziness cannot be explained by a primary vestibular disorder. Anxiety disorders are particularly common in patients with chronic dizziness and contribute substantially to the morbidity. T us, treatment with antianxiety medications (selective serotonin reuptake inhibitors [SSRIs]) and cognitive-behavioral therapy may be helpful. Vestibular rehabilitation therapy is also sometimes beneficial. Vestibular suppressant medications generally should be avoided. T is condition should be suspected when the patient states, "My dizziness is so bad, I'm afraid to leave my house" (agoraphobia).

TREATMENT Vertigo

Table 12-2 provides a list of commonly used medications for suppression of vertigo. As noted, these medications should be reserved for short-term control of active vertigo, such as during the first few days of acute vestibular neuritis, or for acute attacks of Ménière's disease. T ey are less helpful for chronic dizziness and, as previously stated, may hinder central compensation. An exception is that benzodiazepines may attenuate psychosomatic dizziness and the associated anxiety, although SSRIs are generally preferable in such patients.

TABLE 12-2

TREATMENT OF VERTIGO

AGENT[a]	DOSE[b]
Antihistamines	
Meclizine	25–50 mg 3 times daily
Dimenhydrinate	50 mg 1–2 times daily
Promethazine	25 mg 2–3 times daily (also can be given rectally and IM)
Benzodiazepines	
Diazepam	2.5 mg 1–3 times daily
Clonazepam	0.25 mg 1–3 times daily
Anticholinergic	
Scopolamine transdermal[c]	Patch
Physical therapy	
Repositioning maneuvers[d]	
Vestibular rehabilitation	
Other	
Diuretics and/or low-sodium (1000 mg/d) diet[e]	
Antimigrainous drugs[f]	
Methylprednisolone[g]	100 mg daily days 1–3; 80 mg daily days 4–6; 60 mg daily days 7–9; 40 mg daily days 10–12; 20 mg daily days 13–15; 10 mg daily days 16–18, 20, 22
Selective serotonin reuptake inhibitors[h]	

[a] All listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo.
[b] Usual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase.
[c] For motion sickness only.
[d] For benign paroxysmal positional vertigo.
[e] For Ménière's disease.
[f] For vestibular migraine.
[g] For acute vestibular neuritis (started within 3 days of onset).
[h] For psychosomatic vertigo.

Vestibular rehabilitation therapy promotes central adaptation processes that compensate for vestibular loss and also may help habituate motion sensitivity and other symptoms of psychosomatic dizziness. T e general approach is to use a graded series of exercises that progressively challenge gaze stabilization and balance.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 13

FATIGUE

Jeffrey M. Gelfand ■ Vanja C. Douglas

Fatigue is one of the most common symptoms in clinical medicine. It is a prominent manifestation of a number of systemic, neurologic, and psychiatric syndromes, although a precise cause will not be identified in a substantial minority of patients. Fatigue refers to an inherently subjective human experience of physical and mental weariness, sluggishness, and exhaustion. In the context of clinical medicine, fatigue is most typically and practically defined as difficulty initiating or maintaining voluntary mental or physical activity. Nearly everyone who has ever been ill with a self-limited infection has experienced this near-universal symptomatology, and fatigue is usually brought to medical attention only when it is either of unclear cause or the severity is out of proportion with what would be expected for the associated trigger. Fatigue should be distinguished from muscle weakness, a reduction of neuromuscular power **(Chap. 14)**; most patients complaining of fatigue are not truly weak when direct muscle power is tested. By definition, fatigue is also distinct from somnolence and dyspnea on exertion, although patients may use the word fatigue to describe those two symptoms. The task facing clinicians when a patient presents with fatigue is to identify an underlying cause if one exists and to develop a therapeutic alliance, the goal of which is to spare patients expensive and fruitless diagnostic workups and steer them toward effective therapy.

EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS

Variability in the definitions of fatigue and the survey instruments used in different studies makes it difficult to arrive at precise figures about the global burden of fatigue. The point prevalence of fatigue was 6.7% and the lifetime prevalence was 25% in a large National Institute of Mental Health survey of the U.S. general population. In primary care clinics in Europe and the United States, between 10 and 25% of patients surveyed endorsed symptoms of prolonged (present for >1 month) or chronic (present for >6 months) fatigue, but fatigue was the primary reason for seeking medical attention in only a minority of patients. In a community survey of women in India, 12% reported chronic fatigue. By contrast, the prevalence of chronic fatigue syndrome, as defined by the U.S. Centers for Disease Control and Prevention, is low **(Chap. 59)**.

DIFFERENTIAL DIAGNOSIS

Psychiatric disease

Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders. Psychiatric symptoms are reported in more than three-quarters of patients with unexplained chronic fatigue. Even in patients with systemic or neurologic syndromes in which fatigue is independently recognized as a manifestation of disease, comorbid psychiatric symptoms or disease may still be an important source of interaction.

Neurologic disease

Patients complaining of fatigue often say they feel weak, but upon careful examination, objective muscle weakness is rarely discernible. If found, muscle weakness must then be localized to the central nervous system, peripheral nervous system, neuromuscular junction, or muscle and the appropriate follow-up studies obtained **(Chap. 14)**. Fatigability of muscle power is a cardinal manifestation of some neuromuscular disorders such as myasthenia gravis and can be distinguished from fatigue by finding clinically apparent diminution of the amount of force that a muscle generates upon repeated contraction **(Chap. 55)**. Fatigue is one of the most common and

www.ketabpezeshki.com (021) 66485457 - 66485438

bothersome symptoms reported in multiple sclerosis (MS) **(Chap. 45)**, affecting nearly 90% of patients; fatigue in MS can persist between MS attacks and does not necessarily correlate with magnetic resonance imaging (MRI) disease activity. Fatigue is also increasingly identified as a troublesome feature of many other neurodegenerative diseases, including Parkinson's disease, central dysautonomias, and amyotrophic lateral sclerosis. Poststroke fatigue is a well-described but poorly understood entity with a widely varying prevalence. Episodic fatigue can be a premonitory symptom of migraine. Fatigue is also a frequent result of traumatic brain injury, often occurring in association with depression and sleep disorders.

Sleep disorders

Obstructive sleep apnea is an important cause of excessive daytime sleepiness in association with fatigue and should be investigated using overnight polysomnography, particularly in those with prominent snoring, obesity, or other predictors of obstructive sleep apnea. Whether the cumulative sleep deprivation that is common in modern society contributes to clinically apparent fatigue is not known **(Chap. 24)**.

Endocrine disorders

Fatigue, sometimes in association with true muscle weakness, can be a heralding symptom of hypothyroidism, particularly in the context of hair loss, dry skin, cold intolerance, constipation, and weight gain. Fatigue in association with heat intolerance, sweating, and palpitations is typical of hyperthyroidism. Adrenal insufficiency can also manifest with unexplained fatigue as a primary or prominent symptom, often in association with anorexia, weight loss, nausea, myalgias, and arthralgias; hyponatremia and hyperkalemia may be present at time of diagnosis. Mild hypercalcemia can cause fatigue, which may be relatively vague, whereas severe hypercalcemia can lead to lethargy, stupor, and coma. Both hypoglycemia and hyperglycemia can cause lethargy, often in association with confusion; chronic diabetes, particularly type 1 diabetes, is also associated with fatigue independent of glucose levels. Fatigue may also accompany Cushing's disease, hypoaldosteronism, and hypogonadism.

Liver and kidney disease

Both chronic liver failure and chronic kidney disease can cause fatigue. Over 80% of hemodialysis patients complain of fatigue, which makes this one of the most common patient-reported symptoms in chronic kidney disease.

Obesity

Obesity is associated with fatigue and sleepiness independent of the presence of obstructive sleep apnea. Obese patients undergoing bariatric surgery experience improvement in daytime sleepiness sooner than would be expected if the improvement were solely the result of weight loss and resolution of sleep apnea. A number of other factors common in obese patients are likely contributors as well, including depression, physical inactivity, and diabetes.

Malnutrition

Although fatigue can be a presenting feature of malnutrition, nutritional status may also be an important comorbidity and contributor to fatigue in other chronic illnesses, including cancer-associated fatigue.

Infection

Both acute and chronic infections commonly lead to fatigue as part of the broader infectious syndrome. Evaluation for undiagnosed infection as the cause of unexplained fatigue, and particularly prolonged or chronic fatigue, should be guided by the history, physical examination, and infectious risk factors, with particular attention to risk for tuberculosis, HIV, chronic hepatitis B and C, and endocarditis. Infectious mononucleosis may cause prolonged fatigue that persists for weeks to months following the acute illness, but infection with the Epstein-Barr virus is only very rarely the cause of unexplained chronic fatigue.

Drugs

Many medications, drug use, drug withdrawal, and chronic alcohol use can all lead to fatigue. Medications that are more likely to be causative in this context include antidepressants, antipsychotics, anxiolytics, opiates, antispasticity agents, antiseizure agents, and beta blockers.

Cardiovascular and pulmonary

Fatigue is one of the most taxing patient-reported symptoms of congestive heart failure and chronic obstructive pulmonary disease and negatively affects quality of life.

Malignancy

Fatigue, particularly in association with unexplained unintended weight loss, can be a sign of occult malignancy, but this is only rarely identified as causative in patients with unexplained chronic fatigue in the

www.ketabpezeshki.com (021) 66485457 - 66485438

absence of other telltale signs or symptoms. Cancer-related fatigue is experienced by 40% of patients at time of diagnosis and greater than 80% of patients later in the disease course.

Hematologic

Chronic or progressive anemia may present with fatigue, sometimes in association with exertional tachycardia and breathlessness. Anemia may also contribute to fatigue in chronic illness. Low serum ferritin in the absence of anemia may also cause fatigue that is reversible with iron replacement.

Systemic inflammatory/rheumatologic disorders

Fatigue is a prominent complaint in many chronic inflammatory disorders, including systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflammatory bowel disease, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, sarcoidosis, and Sjögren's syndrome, but is not usually an isolated symptom.

Pregnancy

Fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

Disorders of unclear cause

Chronic fatigue syndrome **(Chap. 59)** and fibromyalgia incorporate chronic fatigue as part of the syndromic definition when present in association with a number of other inclusion and exclusion criteria, as discussed in detail in their respective chapters. The pathophysiology of each is unknown. Idiopathic chronic fatigue is used to describe the syndrome of unexplained chronic fatigue in the absence of enough additional clinical features to meet the diagnostic criteria for chronic fatigue syndrome.

APPROACH TO THE PATIENT: Fatigue

A detailed history focusing on the quality, pattern, timecourse, associated symptoms, and alleviating factors of fatigue is critical in defining the syndrome, determining whether fatigue is the appropriate designation, determining whether the symptoms are acute or chronic, and determining whether fatigue is primarily mental, physical, or both in order to direct further evaluation and treatment. The review of systems should attempt to distinguish fatigue from excessive daytime sleepiness, dyspnea on exertion, exercise intolerance, and muscle weakness. The presence of fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy. A careful review of prescription, over-the-counter, herbal, and recreational drug and alcohol use is mandatory. Circumstances surrounding the onset of symptoms and potential triggers should be investigated. The social history is important, with attention paid to job stress and work hours, the social support network, and domestic affairs including a screen for intimate partner violence. Sleep habits and sleep hygiene should be questioned. The impact of fatigue on daily functioning is important to understand the patient's experience and gauge recovery and the success of treatment.

The physical examination of patients with fatigue is guided by the history and differential diagnosis. A detailed mental status examination should be performed with particular attention to symptoms of depression and anxiety. A formal neurologic examination is required to determine whether objective muscle weakness is present. This is usually a straightforward exercise, although occasionally patients with fatigue have difficulty sustaining effort against resistance and sometimes report that generating full power requires substantial mental effort. On confrontational testing, they are able to generate full power for only a brief period before suddenly giving way to the examiner. This type of weakness is often referred to as breakaway weakness and may or may not be associated with pain. This is contrasted with weakness due to lesions in the motor tracts or lower motor unit, in which the patient's resistance can be overcome in a smooth and steady fashion and full power can never be generated. Occasionally, a patient may demonstrate fatigable weakness, in which power is full when first tested but becomes weak upon repeat evaluation without interval rest. Fatigable weakness, which usually indicates a problem of neuromuscular transmission, never has the sudden breakaway quality that one occasionally observes in patients with fatigue. If the presence or absence of muscle weakness cannot be determined with the physical examination, electromyography with nerve conductions studies can be a helpful ancillary test.

The general physical examination should screen for signs of cardiopulmonary disease, malignancy, lymphadenopathy, organomegaly, infection, liver failure, kidney disease, malnutrition, endocrine abnormalities, and connective tissue disease. Although the diagnostic yield of the general physical examination may be relatively low in the context of evaluation of unexplained chronic fatigue, elucidating the cause of 2% of cases in one prospective analysis, the yield of a detailed neuropsychiatric and mental status evaluation is likely to be much higher, revealing a potential explanation for fatigue in up to 75–80% of patients in some series. Furthermore, the rite of physical examination demonstrates a thorough and systematic

www.ketabpezeshki.com (021) 66485457 - 66485438

approach to the patient's complaint and helps build trust and a therapeutic alliance.

Laboratory testing is likely to identify the cause of chronic fatigue in only about 5% of cases. Beyond a few standard screening tests, laboratory evaluation should be guided by the history and physical examination; extensive testing is more likely to lead to false-positive results that require explanation and unnecessary investigation and should be avoided in lieu of frequent clinical follow-up. A reasonable approach to screening includes a complete blood count with differential (to screen for anemia, infection, and malignancy), electrolytes (including sodium, potassium, and calcium), glucose, renal function, liver function, and thyroid function. Testing for HIV and adrenal function can also be considered. Published guidelines defining chronic fatigue syndrome also recommend an erythrocyte sedimentation rate (ESR) as part of the evaluation for mimics, but unless the value is very high, such nonspecific testing in the absence of other features is unlikely to clarify the situation. Routine screening with an antinuclear antibody (ANA) test is also unlikely to be informative in isolation and is frequently positive at low titers in otherwise healthy adults. Additional unfocused studies, such as whole-body imaging scans, are usually not indicated; in addition to their inconvenience, potential risk, and cost, they often reveal unrelated incidental findings that can prolong the workup unnecessarily.

TREATMENT Fatigue

The first priority of treatment is to address the underlying disorder or disorders that account for fatigue, because this can be curative in select contexts and palliative in others. Unfortunately, in many chronic illnesses, fatigue may be refractory to traditional disease-modifying therapies, and it is important in such cases to evaluate for other potential contributors, because the cause may be multifactorial. Antidepressant treatment **(Chap. 61)** may be helpful for treatment of chronic fatigue when symptoms of depression are present and may be most effective in the context of a multimodal approach. However, antidepressants can also cause fatigue and should be discontinued if they are not clearly effective. Cognitive-behavioral therapy has also been demonstrated to be helpful in the context of chronic fatigue syndrome as well as cancer-associated fatigue. Graded exercise therapy in which physical exercise, most typically walking, is gradually increased with attention to target heart rates to avoid overexertion, was shown to modestly improve walking times and self-reported fatigue measures in patients in the United Kingdom with chronic fatigue syndrome in the large 2011 randomized controlled PACE trial. Psychostimulants such as amphetamines, modafinil, and armodafinil can help increase alertness and concentration and reduce excessive daytime sleepiness in certain clinical contexts, which may in turn help with symptoms of fatigue in a minority of patients, but they have generally proven to be unhelpful in randomized trials for treating fatigue in posttraumatic brain injury, Parkinson's disease, and MS.

Development of more effective therapy for fatigue is hampered by limited knowledge of the biologic basis of this symptom. Tentative data suggests that proinf ammatory cytokines, such as interleukin 1β and tumor necrosis factor α, might mediate fatigue in some patients; thus, cytokine antagonists represent one possible future approach.

PROGNOSIS

Acute fatigue significant enough to require medical evaluation is more likely to lead to an identifiable medical, neurologic, or psychiatric cause than unexplained chronic fatigue. Evaluation of unexplained chronic fatigue most commonly leads to diagnosis of a psychiatric condition or remains unexplained. Identification of a previously undiagnosed serious or life-threatening culprit etiology is rare on longitudinal follow-up in patients with unexplained chronic fatigue. Complete resolution of unexplained chronic fatigue is uncommon, at least over the short term, but multidisciplinary treatment approaches can lead to symptomatic improvements that can substantially improve quality of life.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 14

NEUROLOGIC CAUSES OF WEAKNESS AND PARALYSIS

Michael J. Aminoff

Normal motor function involves integrated muscle activity that is modulated by the activity of the cerebral cortex, basal ganglia, cerebellum, red nucleus, brainstem reticular formation, lateral vestibular nucleus, and spinal cord. Motor system dysfunction leads to weakness or paralysis, discussed in this chapter, or to ataxia **(Chap. 37)** or abnormal movements **(Chap. 36)**. Weakness is a reduction in the power that can be exerted by one or more muscles. It must be distinguished from increased *f*atigability (i.e., the inability to sustain the performance of an activity that should be normal for a person of the same age, sex, and size), limitation in function due to pain or articular stiffness, or impaired motor activity because severe proprioceptive sensory loss prevents adequate feedback information about the direction and power of movements. It is also distinct from bradykinesia (in which increased time is required for full power to be exerted) and apraxia, a disorder of planning and initiating a skilled or learned movement unrelated to a significant motor or sensory deficit **(Chap. 22)**.

Paralysis or the suffix "-plegia" indicates weakness so severe that a muscle cannot be contracted at all, whereas paresis refers to less severe weakness. T e prefix "hemi-" refers to one-half of the body, "para-" to both legs, and "quadri-" to all four limbs.

T e distribution of weakness helps to localize the underlying lesion. Weakness from involvement of upper motor neurons occurs particularly in the extensors and abductors of the upper limb and the flexors of the lower limb. Lower motor neuron weakness depends on whether involvement is at the level of the anterior horn cells, nerve root, limb plexus, or peripheral nerve—only muscles supplied by the affected structure are weak. Myopathic weakness is generally most marked in proximal muscles. Weakness from impaired neuromuscular transmission has no specific pattern of involvement.

Weakness of en is accompanied by other neurologic abnormalities that help indicate the site of the responsible lesion **(Table 14-1)**.

Tone is the resistance of a muscle to passive stretch. Increased tone may be of several types. Spasticity is the increase in tone associated with disease of upper motor neurons. It is velocity-dependent, has a sudden release af er reaching a maximum (the "clasp-knife" phenomenon), and predominantly affects the antigravity muscles (i.e., upper-limb flexors and lower-limb extensors). Rigidity is hypertonia that is present throughout the range of motion (a "lead pipe" or "plastic" stiffness) and affects flexors and extensors equally; it sometimes has a cogwheel quality that is enhanced by voluntary movement of the contralateral limb (reinforcement). Rigidity occurs with certain extrapyramidal disorders, such as Parkinson's disease. Paratonia (or gegenhalten) is increased tone that varies irregularly in a manner seemingly related to the degree of relaxation, is present throughout the range of motion, and affects flexors and extensors equally; it usually results from disease of the frontal lobes. Weakness with decreased tone (*fl*accidity) or normal tone occurs with disorders of motor units. A motor unit consists of a single lower motor neuron and all the muscle fibers that it innervates.

Muscle bulk generally is not affected by upper motor neuron lesions, although mild disuse atrophy eventually may occur. By contrast, atrophy is of en conspicuous when a lower motor neuron lesion is responsible for weakness and also may occur with advanced muscle disease.

Muscle stretch (tendon) re*fl*exes are usually increased with upper motor neuron lesions, but may be decreased or absent for a variable period immediately af er onset of an acute lesion. Hyperreflexia is usually—but not invariably—accompanied by loss of cutaneous re*fl*exes (such as superficial abdominals; **Chap. 1)** and, in

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 14-1

SIGNS THAT DISTINGUISH THE ORIGIN OF WEAKNESS

SIGN	UPPER MOTOR NEURON	LOWER MOTOR NEURON	MYOPATHIC	PSYCHOGENIC
Atrophy	None	Severe	Mild	None
Fasciculations	None	Common	None	None
Tone	Spastic	Decreased	Normal/decreased	Variable/paratonia
Distribution of weakness	Pyramidal/regional	Distal/segmental	Proximal	Variable/inconsistent with daily activities
Muscle stretch reflexes	Hyperactive	Hypoactive/absent	Normal/hypoactive	Normal
Babinski sign	Present	Absent	Absent	Absent

particular, by an extensor plantar (Babinski) response. The muscle stretch reflexes are depressed with lower motor neuron lesions directly involving specific reflex arcs. They generally are preserved in patients with myopathic weakness except in advanced stages, when they sometimes are attenuated. In disorders of the neuromuscular junction, reflex responses may be affected by preceding voluntary activity of affected muscles; such activity may lead to enhancement of initially depressed reflexes in Lambert-Eaton myasthenic syndrome and, conversely, to depression of initially normal reflexes in myasthenia gravis **(Chap. 55)**.

The distinction of neuropathic (lower motor neuron) from myopathic weakness is sometimes difficult clinically, although distal weakness is likely to be neuropathic, and symmetric proximal weakness myopathic. Fasciculations (visible or palpable twitch within a muscle due to the spontaneous discharge of a motor unit) and early atrophy indicate that weakness is neuropathic.

PATHOGENESIS

Upper motor neuron weakness

Lesions of the upper motor neurons or their descending axons to the spinal cord **(Fig. 14-1)** produce weakness through decreased activation of lower motor neurons. In general, distal muscle groups are affected more severely than proximal ones, and axial movements are spared unless the lesion is severe and bilateral. Spasticity is typical but may not be present acutely. Rapid repetitive movements are slowed and coarse, but normal rhythmicity is maintained. With corticobulbar involvement, weakness occurs in the lower face and tongue; extraocular, upper facial, pharyngeal, and jaw muscles are typically spared. Bilateral corticobulbar lesions produce a pseudobulbar palsy: dysarthria, dysphagia, dysphonia, and emotional lability accompany bilateral facial weakness and a brisk jaw jerk. Electromyogram (EMG) **(Chap. 6)** shows that with weakness of the upper motor neuron type, motor units have a diminished maximal discharge frequency.

Lower motor neuron weakness

This pattern results from disorders of lower motor neurons in the brainstem motor nuclei and the anterior horn of the spinal cord or from dysfunction of the axons of these neurons as they pass to skeletal muscle **(Fig. 14-2)**. Weakness is due to a decrease in the number of muscle fibers that can be activated through a loss of α motor neurons or disruption of their connections to muscle. Loss of γ motor neurons does not cause weakness but decreases tension on the muscle spindles, which decreases muscle tone and attenuates the stretch reflexes. An absent stretch reflex suggests involvement of spindle afferent fibers.

When a motor unit becomes diseased, especially in anterior horn cell diseases, it may discharge spontaneously, producing *f*asciculations. When α motor neurons or their axons degenerate, the denervated muscle fibers also may discharge spontaneously. These single muscle fiber discharges, or f brillation potentials, cannot be seen but can be recorded with EMG. Weakness leads to delayed or reduced recruitment of motor units, with fewer than normal activated at a particular discharge frequency.

Neuromuscular junction weakness

Disorders of the neuromuscular junctions produce weakness of variable degree and distribution. The number of muscle fibers that are activated varies over time, depending on the state of rest of the neuromuscular junctions. Strength is influenced by preceding activity of the affected muscle. In myasthenia gravis, for example, sustained or repeated contractions of affected muscle decline in strength despite continuing effort **(Chap. 55)**. Thus, fatigable weakness is suggestive of disorders of the neuromuscular junction, which cause functional loss of muscle fibers due to failure of their activation.

Myopathic weakness

Myopathic weakness is produced by a decrease in the number or contractile force of muscle fibers activated within motor units. With muscular dystrophies,

www.ketabpezeshki.com (021) 66485457 - 66485438

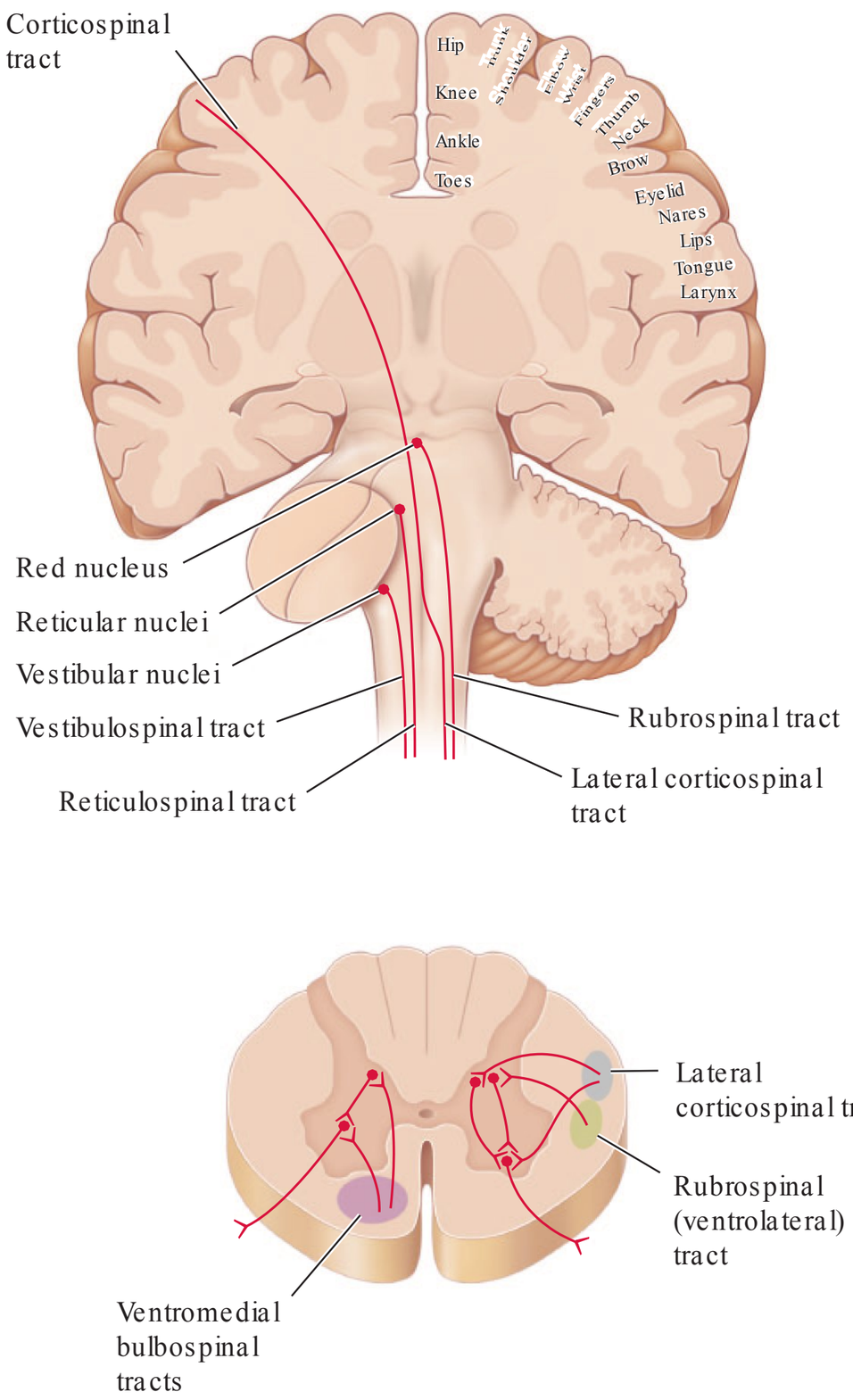


FIGURE 14-1
The corticospinal and bulbospinal upper motor neuron pathways. Upper motor neurons have their cell bodies in layer V of the primary motor cortex (the precentral gyrus, or Brodmann's area 4) and in the premotor and supplemental motor cortex (area 6). The upper motor neurons in the primary motor cortex are somatotopically organized (right side of figure).

Axons of the upper motor neurons descend through the subcortical white matter and the posterior limb of the internal capsule. Axons of the pyramidal or corticospinal system descend through the brainstem in the cerebral peduncle of the midbrain, the basis pontis, and the medullary pyramids. At the cervicomedullary junction, most corticospinal axons decussate into the contralateral corticospinal tract of the lateral spinal cord, but 10–30% remain ipsilateral in the anterior spinal cord. Corticospinal neurons synapse on premotor interneurons, but some—especially in the cervical enlargement and those connecting with motor neurons to distal limb muscles—make direct monosynaptic connections with lower motor neurons. They innervate most densely the lower motor neurons of hand muscles and are involved in the execution of learned, fine movements. Corticobulbar neurons are similar to corticospinal neurons but innervate brainstem motor nuclei.

Bulbospinal upper motor neurons influence strength and tone but are not part of the pyramidal system. The descending ventromedial bulbospinal pathways originate in the tectum of the midbrain (tectospinal pathway), the vestibular nuclei (vestibulospinal pathway), and the reticular formation (reticulospinal pathway). These pathways influence axial and proximal muscles and are involved in the maintenance of posture and integrated movements of the limbs and trunk. The descending ventrolateral bulbospinal pathways, which originate predominantly in the red nucleus (rubrospinal pathway), facilitate distal limb muscles. The bulbospinal system sometimes is referred to as the extrapyramidal upper motor neuron system. In all figures, nerve cell bodies and axon terminals are shown, respectively, as closed circles and forks.

inflammatory myopathies, or myopathies with muscle fiber necrosis, the number of muscle fibers is reduced within many motor units. On EMG, the size of each motor unit action potential is decreased, and motor units must be recruited more rapidly than normal to produce the desired power. Some myopathies produce weakness through loss of contractile force of muscle fibers or through relatively selective involvement of type II (fast) fibers. These myopathies may not affect the size of individual motor unit action potentials and are detected by a discrepancy between the electrical activity and force of a muscle.

Psychogenic weakness

Weakness may occur without a recognizable organic basis. It tends to be variable, inconsistent, and with a pattern of distribution that cannot be explained on a neuroanatomic basis. On formal testing, antagonists may contract when the patient is supposedly activating the agonist muscle. The severity of weakness is out of keeping with the patient's daily activities.

Hemiparesis

Hemiparesis results from an upper motor neuron lesion above the midcervical spinal cord; most such lesions are above the foramen magnum. The presence of other neurologic deficits helps localize the lesion. Thus, language disorders, for example, point to a cortical lesion. Homonymous visual field defects reflect either a cortical or a subcortical hemispheric lesion. A "pure motor" hemiparesis of the face, arm, and leg often is due to a small, discrete lesion in the posterior limb of the internal capsule, cerebral peduncle, or upper pons. Some brainstem lesions produce "crossed paralyses," consisting of ipsilateral cranial nerve signs and contralateral hemiparesis **(Chap. 32)**. The absence of cranial nerve signs or facial weakness suggests that a hemiparesis is due to a lesion in the high cervical spinal cord, especially if associated with the Brown-Séquard syndrome **(Chap. 43)**.

Acute or episodic hemiparesis usually results from focal structural lesions, particularly rapidly expanding lesions, or an inflammatory process. Subacute hemiparesis that evolves over days or weeks may relate to

www.ketabpezeshki.com (021) 66485457 - 66485438

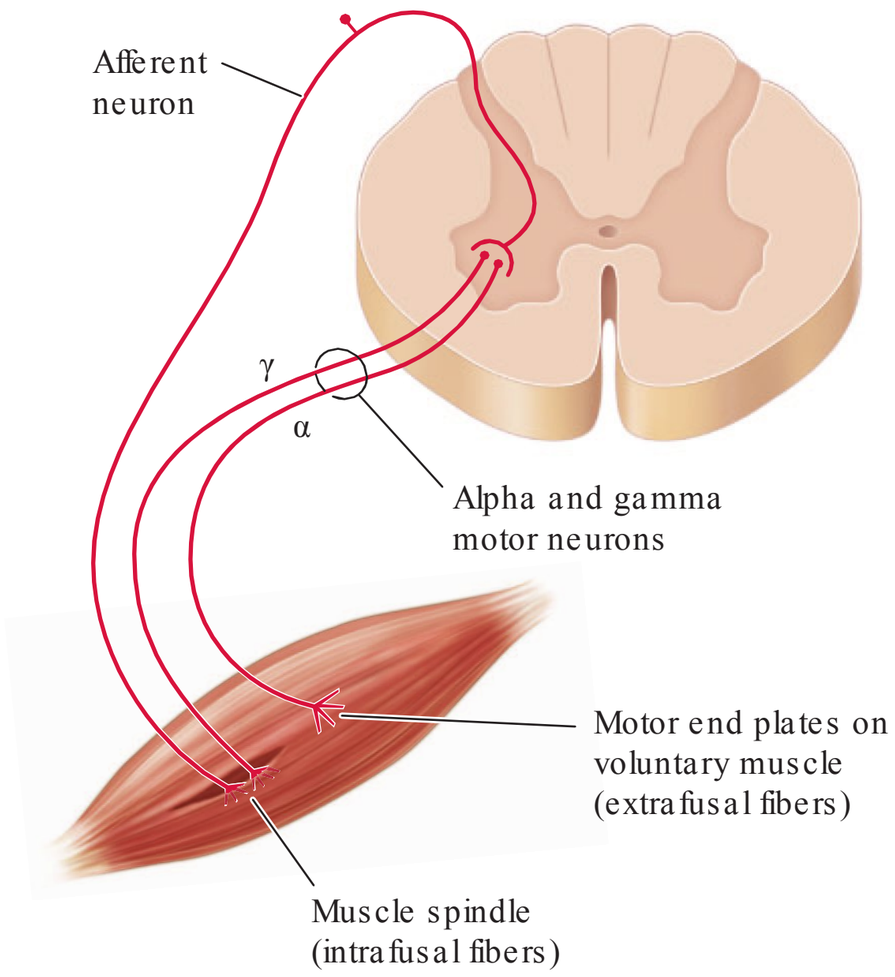


FIGURE 14-2
Lower motor neurons are divided into α and γ types. The larger α motor neurons are more numerous and innervate the extrafusal muscle fibers of the motor unit. Loss of α motor neurons or disruption of their axons produces lower motor neuron weakness. The smaller, less numerous γ motor neurons innervate the intrafusal muscle fibers of the muscle spindle and contribute to normal tone and stretch reflexes. The α motor neuron receives direct excitatory input from corticomotoneurons and primary muscle spindle afferents. The α and γ motor neurons also receive excitatory input from other descending upper motor neuron pathways, segmental sensory inputs, and interneurons. The α motor neurons receive direct inhibition from Renshaw cell interneurons, and other interneurons indirectly inhibit the α and γ motor neurons.

A muscle stretch (tendon) reflex requires the function of all the illustrated structures. A tap on a tendon stretches muscle spindles (which are tonically activated by γ motor neurons) and activates the primary spindle afferent neurons. These neurons stimulate the α motor neurons in the spinal cord, producing a brief muscle contraction, which is the familiar tendon reflex.

subdural hematoma, infectious or inflammatory disorders (e.g., cerebral abscess, fungal granuloma or meningitis, parasitic infection, multiple sclerosis, sarcoidosis), or primary and metastatic neoplasms. AIDS may present with subacute hemiparesis due to toxoplasmosis or primary central nervous system (CNS) lymphoma. Chronic hemiparesis that evolves over months usually is due to a neoplasm or vascular malformation, a chronic subdural hematoma, or a degenerative disease.

Investigation of hemiparesis **(Fig. 14-3)** of acute origin starts with a computed tomography (CT) scan of the brain and laboratory studies. If the CT is normal, or in subacute or chronic cases of hemiparesis, magnetic resonance imaging (MRI) of the brain and/or cervical spine (including the foramen magnum) is performed, depending on the clinical accompaniments.

Paraparesis

Acute paraparesis is caused most commonly by an intraspinal lesion, but its spinal origin may not be recognized initially if the legs are flaccid and areflexic. Usually, however, there is sensory loss in the legs with an upper level on the trunk, a dissociated sensory loss suggestive of a central cord syndrome **(Chap. 43)**, or hyperreflexia in the legs with normal reflexes in the arms. Imaging the spinal cord (Fig. 14-3) may reveal compressive lesions, infarction (proprioception usually is spared), arteriovenous fistulas or other vascular anomalies, or transverse myelitis **(Chap. 43)**.

Diseases of the cerebral hemispheres that produce acute paraparesis include anterior cerebral artery ischemia (shoulder shrug also is affected), superior sagittal sinus or cortical venous thrombosis, and acute hydrocephalus.

Paraparesis may result from a cauda equina syndrome, for example, after trauma to the low back, a midline disk herniation, or an intraspinal tumor; although the sphincters are often affected, hip flexion often is spared, as is sensation over the anterolateral thighs. Rarely, paraparesis is caused by a rapidly evolving anterior horn cell disease (such as poliovirus or West Nile virus infection), peripheral neuropathy (such as Guillain-Barré syndrome; **Chap. 54**), or myopathy **(Chap. 56)**.

Subacute or chronic spastic paraparesis is caused by upper motor neuron disease. When associated with lower-limb sensory loss and sphincter involvement, a chronic spinal cord disorder should be considered **(Chap. 43)**. If hemispheric signs are present, a parasagittal meningioma or chronic hydrocephalus is likely. The absence of spasticity in a long-standing paraparesis suggests a lower motor neuron or myopathic etiology.

Investigations typically begin with spinal MRI, but when upper motor neuron signs are associated with drowsiness, confusion, seizures, or other hemispheric signs, brain MRI should also be performed, sometimes as the initial investigation. Electrophysiologic studies are diagnostically helpful when clinical findings suggest an underlying neuromuscular disorder.

Quadriparesis or generalized weakness

Generalized weakness may be due to disorders of the CNS or the motor unit. Although the terms often are used interchangeably, quadriparesis is commonly used when an upper motor neuron cause is suspected, and generalized weakness is used when a disease of the motor units is likely. Weakness from CNS disorders usually is associated with changes in consciousness or cognition and accompanied by spasticity, hyperreflexia, and sensory disturbances. Most neuromuscular causes of generalized weakness are associated with normal mental function, hypotonia, and hypoactive muscle stretch reflexes. The major causes of intermittent

www.ketabpezeshki.com (021) 66485457 - 66485438

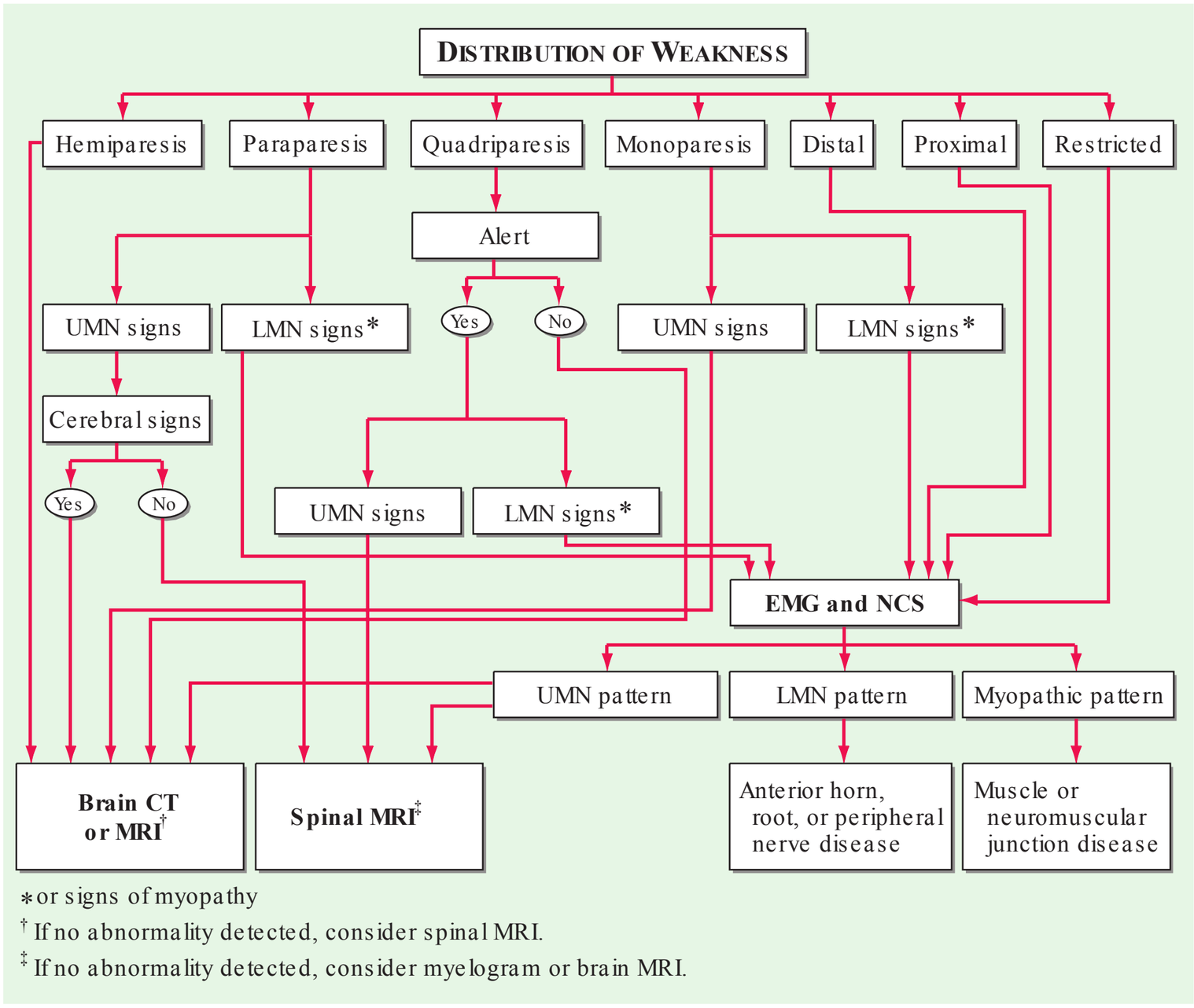


FIGURE 14-3
An algorithm for the initial workup of a patient with weakness. CT, computed tomography; EMG, electromyography; LMN, lower motor neuron; MRI, magnetic resonance imaging; NCS, nerve conduction studies; UMN, upper motor neuron.

weakness are listed in **Table 14-2**. A patient with generalized fatigability without objective weakness may have the chronic fatigue syndrome **(Chap. 59)**.

Acute quadriparesis

Quadriparesis with onset over minutes may result from disorders of upper motor neurons (such as from anoxia, hypotension, brainstem or cervical cord ischemia, trauma, and systemic metabolic abnormalities) or muscle (electrolyte disturbances, certain inborn errors of muscle energy metabolism, toxins, and periodic paralyses). Onset over hours to weeks may, in addition to these disorders, be due to lower motor neuron disorders such as Guillain-Barré syndrome **(Chap. 54)**.

In obtunded patients, evaluation begins with a CT scan of the brain. If upper motor neuron signs are present but the patient is alert, the initial test is usually an MRI of the cervical cord. If weakness is lower motor neuron, myopathic, or uncertain in origin, the clinical approach begins with blood studies to determine the level of muscle enzymes and electrolytes and with EMG and nerve conduction studies.

Subacute or chronic quadriparesis

Quadriparesis due to upper motor neuron disease may develop over weeks to years from chronic myelopathies, multiple sclerosis, brain or spinal tumors, chronic subdural hematomas, and various metabolic, toxic, and infectious disorders. It may also result from lower motor neuron disease, a chronic neuropathy (in which weakness is of en most profound distally), or myopathic weakness (typically proximal).

When quadriparesis develops acutely in obtunded patients, evaluation begins with a CT scan of the brain. If upper motor neuron signs have developed acutely but the patient is alert, the initial test is usually an MRI of the cervical cord. When onset has been gradual, disorders of the cerebral hemispheres, brainstem, and cervical spinal cord can usually be distinguished clinically, and imaging is directed first at the clinically suspected site of pathology. If weakness is lower motor neuron, myopathic, or uncertain in origin, laboratory studies to determine the levels of muscle enzymes and electrolytes, and EMG and nerve conduction studies help to localize the pathologic process.

Monoparesis

Monoparesis usually is due to lower motor neuron disease, with or without associated sensory involvement. Upper motor neuron weakness occasionally presents as a monoparesis of distal and nonantigravity muscles. Myopathic weakness rarely is limited to one limb.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 14-2

CAUSES OF EPISODIC GENERALIZED WEAKNESS

1. Electrolyte disturbances, e.g., hypokalemia, hyperkalemia, hypercalcemia, hypernatremia, hyponatremia, hypophosphatemia, hypermagnesemia
2. Muscle disorders
   a. Channelopathies (periodic paralyses)
   b. Metabolic defects of muscle (impaired carbohydrate or fatty acid utilization; abnormal mitochondrial function)
3. Neuromuscular junction disorders
   a. Myasthenia gravis
   b. Lambert-Eaton myasthenic syndrome
4. Central nervous system disorders
   a. Transient ischemic attacks of the brainstem
   b. Transient global cerebral ischemia
   c. Multiple sclerosis
5. Lack of voluntary effort
   a. Anxiety
   b. Pain or discomfort
   c. Somatization disorder

Acute monoparesis

If weakness is predominantly distal and of upper motor neuron type and is not associated with sensory impairment or pain, focal cortical ischemia is likely **(Chap. 32)**; diagnostic possibilities are similar to those for acute hemiparesis. Sensory loss and pain usually accompany acute lower motor neuron weakness; the weakness commonly localizes to a single nerve root or peripheral nerve, but occasionally reflects plexus involvement. If lower motor neuron weakness is likely, evaluation begins with EMG and nerve conduction studies.

Subacute or chronic monoparesis

Weakness and atrophy that develop over weeks or months are usually of lower motor neuron origin. When associated with sensory symptoms, a peripheral cause (nerve, root, or plexus) is likely; otherwise, anterior horn cell disease should be considered. In either case, an electrodiagnostic study is indicated. If weakness is of the upper motor neuron type, a discrete cortical (precentral gyrus) or cord lesion may be responsible, and appropriate imaging is performed.

Distal weakness

Involvement of two or more limbs distally suggests lower motor neuron or peripheral nerve disease. Acute distal lower-limb weakness results occasionally from an acute toxic polyneuropathy or cauda equina syndrome. Distal symmetric weakness usually develops over weeks, months, or years and, when associated with numbness, is due to peripheral neuropathy **(Chap. 53)**. Anterior horn cell disease may begin distally but is typically asymmetric and without accompanying numbness **(Chap. 39)**. Rarely, myopathies present with distal weakness **(Chap. 56)**. Electrodiagnostic studies help localize the disorder (Fig. 14-3).

Proximal weakness

Myopathy often produces symmetric weakness of the pelvic or shoulder girdle muscles **(Chap. 56)**. Diseases of the neuromuscular junction, such as myasthenia gravis **(Chap. 55)**, may present with symmetric proximal weakness often associated with ptosis, diplopia, or bulbar weakness and fluctuating in severity during the day. In anterior horn cell disease, proximal weakness is usually asymmetric, but it may be symmetric if familial. Numbness does not occur with any of these diseases. The evaluation usually begins with determination of the serum creatine kinase level and electrophysiologic studies.

Weakness in a restricted distribution

Weakness may not fit any of these patterns, being limited, for example, to the extraocular, hemifacial, bulbar, or respiratory muscles. If it is unilateral, restricted weakness usually is due to lower motor neuron or peripheral nerve disease, such as in a facial palsy. Weakness of part of a limb is commonly due to a peripheral nerve lesion such as an entrapment neuropathy. Relatively symmetric weakness of extraocular or bulbar muscles frequently is due to a myopathy **(Chap. 56)** or neuromuscular junction disorder **(Chap. 55)**. Bilateral facial palsy with areflexia suggests Guillain-Barré syndrome **(Chap. 54)**. Worsening of relatively symmetric weakness with fatigue is characteristic of neuromuscular junction disorders. Asymmetric bulbar weakness usually is due to motor neuron disease. Weakness limited to respiratory muscles is uncommon and usually is due to motor neuron disease, myasthenia gravis, or polymyositis/dermatomyositis **(Chap. 57)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 15

NUMBNESS, TINGLING, AND SENSORY LOSS

Michael J. Aminoff

Normal somatic sensation reflects a continuous monitoring process, little of which reaches consciousness under ordinary conditions. By contrast, disordered sensation, particularly when experienced as painful, is alarming and dominates the patient's attention. Physicians should be able to recognize abnormal sensations by how they are described, know their type and likely site of origin, and understand their implications. **Pain is considered separately in Chap. 8**.

POSITIVE AND NEGATIVE SYMPTOMS

Abnormal sensory symptoms can be divided into two categories: positive and negative. The prototypical positive symptom is tingling (pins and needles); other positive sensory phenomena include itch and altered sensations that are described as pricking, bandlike, lightning-like shooting feelings (lancinations), aching, knifelike, twisting, drawing, pulling, tightening, burning, searing, electrical, or raw feelings. Such symptoms are often painful.

Positive phenomena usually result from trains of impulses generated at sites of lowered threshold or heightened excitability along a peripheral or central sensory pathway. The nature and severity of the abnormal sensation depend on the number, rate, timing, and distribution of ectopic impulses and the type and function of nervous tissue in which they arise. Because positive phenomena represent excessive activity in sensory pathways, they are not necessarily associated with a sensory deficit (loss) on examination.

Negative phenomena represent loss of sensory function and are characterized by diminished or absent feeling that often is experienced as numbness and by abnormal findings on sensory examination. In disorders affecting peripheral sensation, at least one-half the afferent axons innervating a particular site are probably lost or functionless before a sensory deficit can be demonstrated by clinical examination. If the rate of loss is slow, however, lack of cutaneous feeling may be unnoticed by the patient and difficult to demonstrate on examination, even though few sensory fibers are functioning; if it is rapid, both positive and negative phenomena are usually conspicuous. Subclinical degrees of sensory dysfunction may be revealed by sensory nerve conduction studies or somatosensory evoked potentials **(Chap. 6)**.

Whereas sensory symptoms may be either positive or negative, sensory signs on examination are always a measure of negative phenomena.

TERMINOLOGY

Paresthesias and dysesthesias are general terms used to denote positive sensory symptoms. The term paresthesias typically refers to tingling or pins-and-needles sensations but may include a wide variety of other abnormal sensations, except pain; it sometimes implies that the abnormal sensations are perceived spontaneously. The more general term dysesthesias denotes all types of abnormal sensations, including painful ones, regardless of whether a stimulus is evident.

Another set of terms refers to sensory abnormalities found on examination. Hypesthesia or hypoesthesia refers to a reduction of cutaneous sensation to a specific type of testing such as pressure, light touch, and warm or cold stimuli; anesthesia, to a complete absence of skin sensation to the same stimuli plus pinprick; and hypalgesia or analgesia, to reduced or absent pain perception (nociception). Hyperesthesia means pain or increased sensitivity in response to touch. Similarly, allodynia describes the situation in which a nonpainful stimulus, once perceived, is experienced as painful, even excruciating. An example is elicitation of a painful sensation by application of a vibrating tuning fork. Hyperalgesia denotes severe pain in response to a mildly noxious stimulus, and hyperpathia, a broad term, encompasses all the phenomena

www.ketabpezeshki.com (021) 66485457 - 66485438

described by hyperesthesia, allodynia, and hyperalgesia. With hyperpathia, the threshold for a sensory stimulus is increased and perception is delayed, but once felt, it is unduly painful.

Disorders of deep sensation arising from muscle spindles, tendons, and joints affect proprioception (position sense). Manifestations include imbalance (particularly with eyes closed or in the dark), clumsiness of precision movements, and unsteadiness of gait, which are referred to collectively as sensory ataxia. Other findings on examination usually, but not invariably, include reduced or absent joint position and vibratory sensibility and absent deep tendon reflexes in the affected limbs. T e Romberg sign is positive, which means that the patient sways markedly or topples when asked to stand with feet close together and eyes closed. In severe states of deafferentation involving deep sensation, the patient cannot walk or stand unaided or even sit unsupported. Continuous involuntary movements (pseudoathetosis) of the outstretched hands and fingers occur, particularly with eyes closed.

ANATOMY OF SENSATION

Cutaneous receptors are classified by the type of stimulus that optimally excites them. T ey consist of naked nerve endings (nociceptors, which respond to tissue-damaging stimuli, and thermoreceptors, which respond to noninjurious thermal stimuli) and encapsulated terminals (several types of mechanoreceptor, activated by physical deformation of the skin). Each type of receptor has its own set of sensitivities to specific stimuli, size and distinctness of receptive fields, and adaptational qualities.

Afferent fibers in peripheral nerve trunks traverse the dorsal roots and enter the dorsal horn of the spinal cord **(Fig. 15-1)**. From there, the polysynaptic projections of the smaller fibers (unmyelinated and small myelinated), which subserve mainly nociception, itch, temperature sensibility, and touch, cross and ascend in the opposite anterior and lateral columns of the spinal cord, through the brainstem, to the ventral posterolateral (VPL) nucleus of the thalamus and ultimately project to the postcentral gyrus of the parietal cortex **(Chap. 8)**. T is is the spinothalamic pathway or anterolateral system. T e larger fibers, which subserve tactile and position sense and kinesthesia, project rostrally in the posterior and posterolateral columns on the same side of the spinal cord and make their first synapse in the gracile or cuneate nucleus of the lower medulla. Axons of second-order neurons decussate and ascend in the medial lemniscus located medially in the medulla and in the tegmentum of the pons and midbrain and synapse in the VPL nucleus; third-order neurons project

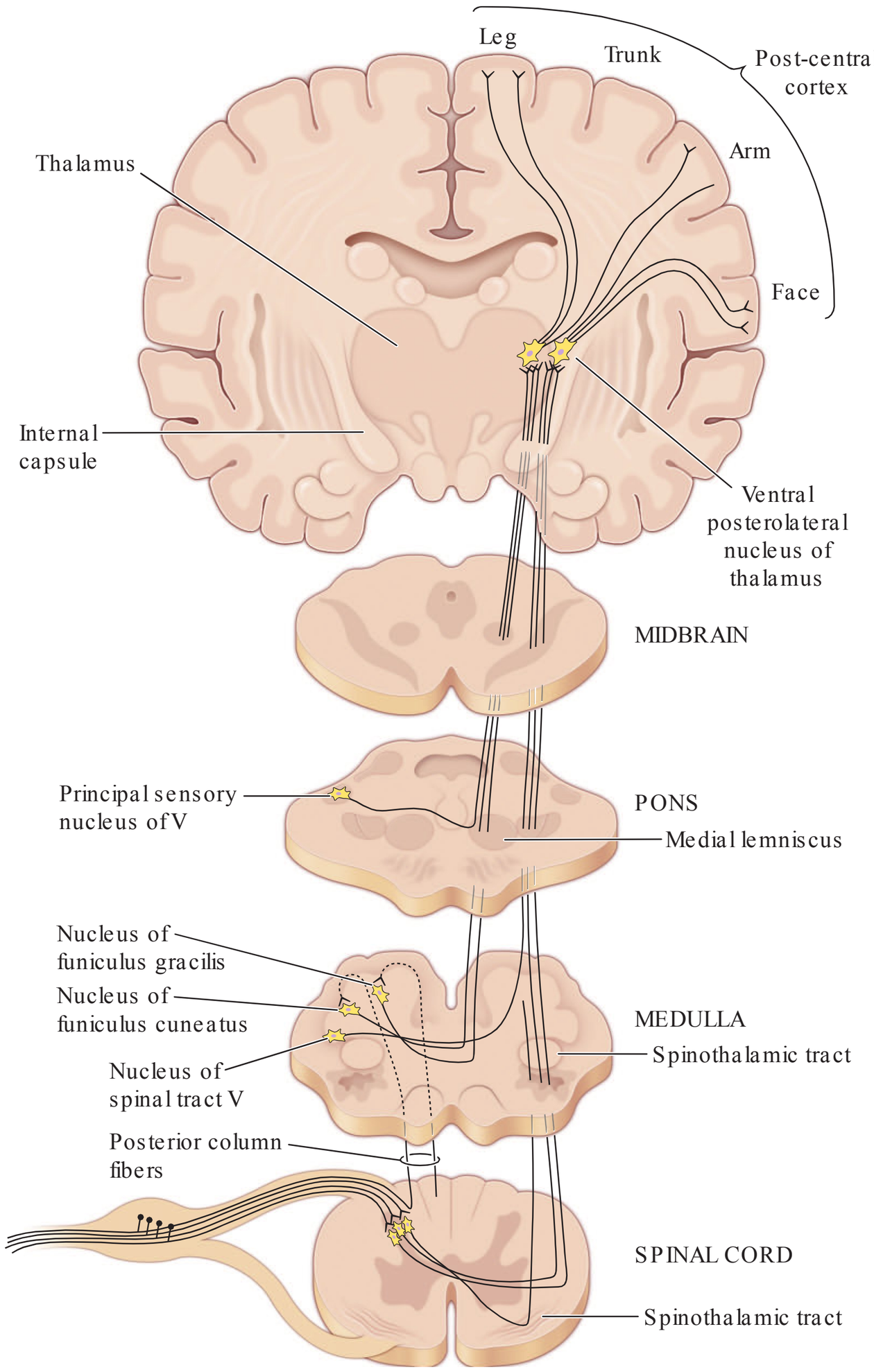


FIGURE 15-1
The main somatosensory pathways. The spinothalamic tract (pain, thermal sense) and the posterior column–lemniscal system (touch, pressure, joint position) are shown. Offshoots from the ascending anterolateral fasciculus (spinothalamic tract) to nuclei in the medulla, pons, and mesencephalon and nuclear terminations of the tract are indicated. (From AH Ropper, MA Samuels: Adams and Victor's Principles of Neurology, 9th ed. New York, McGraw-Hill, 2009.)

www.ketabpezeshki.com (021) 66485457 - 66485438

to parietal cortex as well as to other cortical areas. T is large-fiber system is referred to as the posterior column–medial lemniscal pathway (lemniscal, for short). Although the fiber types and functions that make up the spinothalamic and lemniscal systems are relatively well known, many other fibers, particularly those associated with touch, pressure, and position sense, ascend in a diffusely distributed pattern both ipsilaterally and contralaterally in the anterolateral quadrants of the spinal cord. T is explains why a complete lesion of the posterior columns of the spinal cord may be associated with little sensory deficit on examination.

Nerve conduction studies and nerve biopsy are important means of investigating the peripheral nervous system, but they do not evaluate the function or structure of cutaneous receptors and free nerve endings or of unmyelinated or thinly myelinated nerve fibers in the nerve trunks. Skin biopsy can be used to evaluate these structures in the dermis and epidermis.

CLINICAL EXAMINATION OF SENSATION

T e main components of the sensory examination are tests of primary sensation (pain, touch, vibration, joint position, and thermal sensation) **(Table 15-1)**. T e examiner must depend on patient responses, and this complicates interpretation. Further, examination may be limited in some patients. In a stuporous patient, for example, sensory examination is reduced to observing the briskness of withdrawal in response to a pinch or another noxious stimulus. Comparison of responses on the two sides of the body is essential. In an alert but uncooperative patient, it may not be possible to examine cutaneous sensation, but some idea of proprioceptive function may be gained by noting the patient's best performance of movements requiring balance and precision.

In patients with sensory complaints, testing should begin in the center of the affected region and proceed radially until sensation is perceived as normal. T e distribution of any abnormality is defined and compared to root and peripheral nerve territories **(Figs. 15-2 and 15-3)**. Some patients present with sensory symptoms that do not fit an anatomic localization and are accompanied by either no abnormalities or gross inconsistencies on examination. T e examiner should consider whether the sensory symptoms are a disguised request for help with psychologic or situational problems. Sensory examination of a patient who has no neurologic complaints can be brief and consist of pinprick, touch, and vibration testing in the hands and feet plus evaluation of stance and gait, including the Romberg maneuver **(Chap. 2)**. Evaluation of stance and gait also tests the integrity of motor and cerebellar systems.

Primary sensation

T e sense of pain usually is tested with a clean pin, which is then discarded. T e patient is asked to close the eyes and focus on the pricking or unpleasant quality of the stimulus, not just the pressure or touch sensation elicited. Areas of hypalgesia should be mapped by proceeding radially from the most hypalgesic site. Temperature sensation to both hot and cold is best tested with small containers filled with water of the desired temperature. An alternative way to test cold sensation is to touch a metal object, such as a tuning fork at room temperature, to the skin. For testing warm temperatures, the tuning fork or another metal object may be held under warm water of the desired temperature and

TABLE 15-1

TESTING PRIMARY SENSATION

SENSE	TEST DEVICE	ENDINGS ACTIVATED	FIBER SIZE MEDIATING	CENTRAL PATHWAY
Pain	Pinprick	Cutaneous nociceptors	Small	SpTh, also D
Temperature, heat	Warm metal object	Cutaneous thermoreceptors for hot	Small	SpTh
Temperature, cold	Cold metal object	Cutaneous thermoreceptors for cold	Small	SpTh
Touch	Cotton wisp, f ne brush	Cutaneous mechanoreceptors, also naked endings	Large and small	Lem, also D and SpTh
Vibration	Tuning fork, 128 Hz	Mechanoreceptors, especially pacinian corpuscles	Large	Lem, also D
Joint position	Passive movement of specif c joints	Joint capsule and tendon endings, muscle spindles	Large	Lem, also D

Abbreviations: D, diffuse ascending projections in ipsilateral and contralateral anterolateral columns; Lem, posterior column and lemniscal projection, ipsilateral; SpTh, spinothalamic projection, contralateral.

www.ketabpezeshki.com (021) 66485457 - 66485438

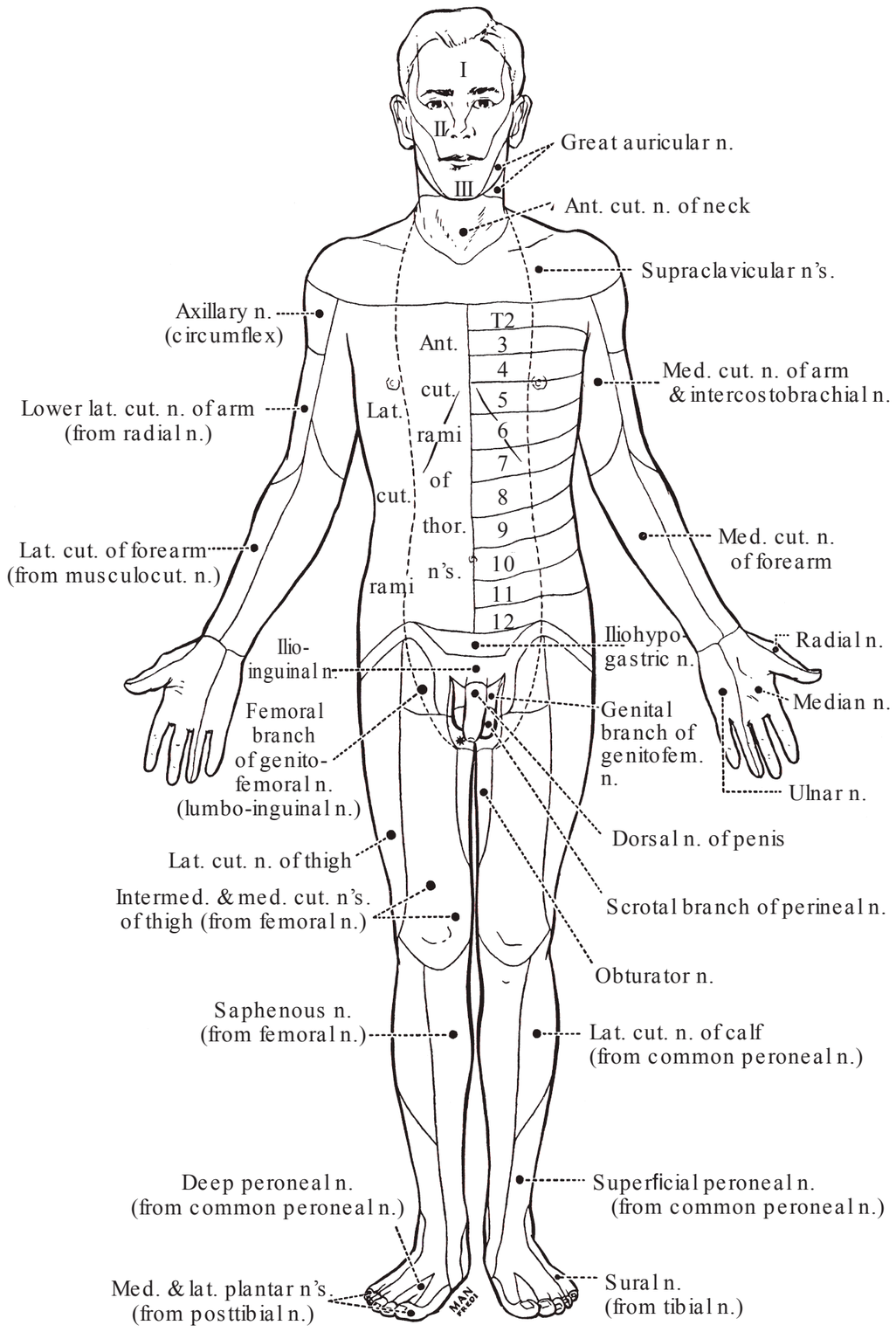


FIGURE 15-2

The cutaneous fields of peripheral nerves. (Reproduced by permission from W Haymaker, B Woodhall: Peripheral Nerve Injuries, 2nd ed. Philadelphia, Saunders, 1953.)

then used. The appreciation of both cold and warmth should be tested because different receptors respond to each. Touch usually is tested with a wisp of cotton or a fine camel hair brush, minimizing pressure on the skin. In general, it is better to avoid testing touch on hairy skin because of the profusion of the sensory endings that surround each hair follicle. The patient is tested with the eyes closed and should indicate as soon as the stimulus is perceived, indicating its location.

Joint position testing is a measure of proprioception. With the patient's eyes closed, joint position is tested in the distal interphalangeal joint of the great toe and fingers. The digit is held by its sides, distal to the joint being tested, and moved passively while more proximal joints are stabilized—the patient indicates the change in position or direction of movement. If errors are made, more proximal joints are tested. A test of proximal joint position sense, primarily at the shoulder, is performed by asking the patient to bring the two index fingers together with arms extended and eyes closed. Normal individuals can do this accurately, with errors of 1 cm or less.

The sense of vibration is tested with an oscillating tuning fork that vibrates at 128 Hz. Vibration is tested over bony points, beginning distally; in the feet, it is tested over the dorsal surface of the distal phalanx of the big toes and at the malleoli of the ankles, and in the hands, it is tested dorsally at the distal phalanx of the fingers. If abnormalities are found, more proximal sites should be examined. Vibratory thresholds at the same site in the patient and the examiner may be compared for control purposes.

Quantitative sensory testing

Effective sensory testing devices are commercially available. Quantitative sensory testing is particularly useful for serial evaluation of cutaneous sensation in clinical trials. Threshold testing for touch and vibratory and thermal sensation is the most widely used application.

www.ketabpezeshki.com (021) 66485457 - 66485438

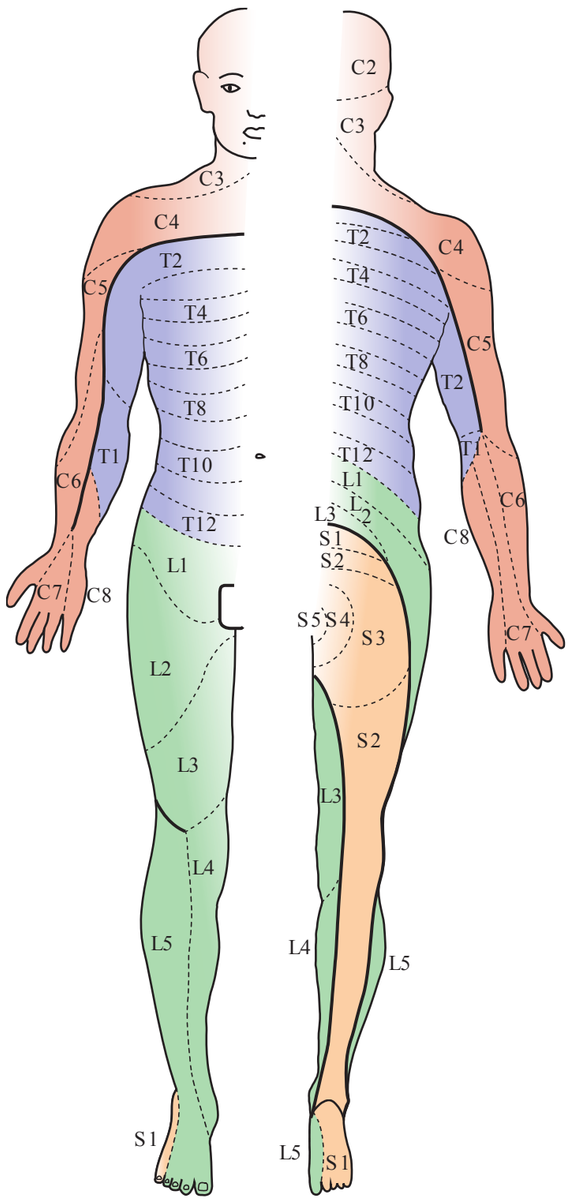


FIGURE 15-3
Distribution of the sensory spinal roots on the surface of the body (dermatomes). (From D Sinclair: Mechanisms of Cutaneous Sensation. Oxford, UK, Oxford University Press, 1981; with permission from Dr. David Sinclair.)

Cortical sensation

The most commonly used tests of cortical function are two-point discrimination, touch localization, and bilateral simultaneous stimulation and tests for graphesthesia and stereognosis. Abnormalities of these sensory tests, in the presence of normal primary sensation in an alert cooperative patient, signify a lesion of the parietal cortex or thalamocortical projections. If primary sensation is altered, these cortical discriminative functions usually will be abnormal also. Comparisons should always be made between analogous sites on the two sides of the body because the deficit with a specific parietal lesion is likely to be unilateral.

Two-point discrimination is tested with special calipers, the points of which may be set from 2 mm to several centimeters apart and then applied simultaneously to the test site. On the fingertips, a normal individual can distinguish about a 3-mm separation of points.

Touch localization is performed by light pressure for an instant with the examiner's fingertip or a wisp of cotton wool; the patient, whose eyes are closed, is required to identify the site of touch. Bilateral simultaneous stimulation at analogous sites (e.g., the dorsum of both hands) can be carried out to determine whether the perception of touch is extinguished consistently on one side (extinction or neglect). Graphesthesia refers to the capacity to recognize, with eyes closed, letters or numbers drawn by the examiner's fingertip on the palm of the hand. Once again, interside comparison is of prime importance. Inability to recognize numbers or letters is termed agraphesthesia.

Stereognosis refers to the ability to identify common objects by palpation, recognizing their shape, texture, and size. Common standard objects such as keys, paper clips, and coins are best used. Patients with normal stereognosis should be able to distinguish a dime from a penny and a nickel from a quarter without looking. Patients should feel the object with only one hand at a time. If they are unable to identify it in one hand, it should be placed in the other for comparison. Individuals who are unable to identify common objects and coins in one hand but can do so in the other are said to have astereognosis of the abnormal hand.

LOCALIZATION OF SENSORY ABNORMALITIES

Sensory symptoms and signs can result from lesions at many different levels of the nervous system from the parietal cortex to the peripheral sensory receptor. Noting their distribution and nature is the most important way to localize their source. Their extent, configuration, symmetry, quality, and severity are the key observations.

Dysesthesias without sensory findings by examination may be difficult to interpret. To illustrate, tingling dysesthesias in an acral distribution (hands and feet) can be systemic in origin, e.g., secondary to hyperventilation, or induced by a medication such as acetazolamide. Distal dysesthesias can also be an early event in an evolving polyneuropathy or may herald a myelopathy, such as from vitamin B_{12} deficiency. Sometimes distal dysesthesias have no definable basis. In contrast, dysesthesias that correspond in distribution to that of a particular peripheral nerve structure denote a lesion at that site. For instance, dysesthesias restricted to the fifth digit and the adjacent one-half of the fourth finger on one hand reliably point to disorder of the ulnar nerve, most commonly at the elbow.

Nerve and root

In focal nerve trunk lesions, sensory abnormalities are readily mapped and generally have discrete boundaries (Figs. 15-2 and 15-3). Root ("radicular") lesions frequently are accompanied by deep, aching pain along the course of the related nerve trunk. With compression of a fifth lumbar (L5) or first sacral (S1) root, as from a ruptured intervertebral disk, sciatica (radicular pain relating to the sciatic nerve trunk) is a common manifestation **(Chap. 10)**. With a lesion affecting a single

www.ketabpezeshki.com (021) 66485457 - 66485438

root, sensory deficits may be minimal or absent because adjacent root territories overlap extensively.

Isolated mononeuropathies may cause symptoms beyond the territory supplied by the affected nerve, but abnormalities on examination typically are confined to appropriate anatomic boundaries. In multiple mononeuropathies, symptoms and signs occur in discrete territories supplied by different individual nerves and—as more nerves are affected—may simulate a polyneuropathy if deficits become confluent. With polyneuropathies, sensory deficits are generally graded, distal, and symmetric in distribution **(Chap. 53)**. Dysesthesias, followed by numbness, begin in the toes and ascend symmetrically. When dysesthesias reach the knees, they usually also have appeared in the fingertips. The process is nerve length–dependent, and the deficit is often described as "stocking-glove" in type. Involvement of both hands and feet also occurs with lesions of the upper cervical cord or the brainstem, but an upper level of the sensory disturbance may then be found on the trunk and other evidence of a central lesion may be present, such as sphincter involvement or signs of an upper motor neuron lesion **(Chap. 14)**. Although most polyneuropathies are pansensory and affect all modalities of sensation, selective sensory dysfunction according to nerve fiber size may occur. Small-fiber polyneuropathies are characterized by burning, painful dysesthesias with reduced pinprick and thermal sensation but with sparing of proprioception, motor function, and deep tendon reflexes. Touch is involved variably; when it is spared, the sensory pattern is referred to as exhibiting sensory dissociation. Sensory dissociation may occur also with spinal cord lesions as well as small-fiber neuropathies. Large-fiber polyneuropathies are characterized by vibration and position sense deficits, imbalance, absent tendon reflexes, and variable motor dysfunction but preservation of most cutaneous sensation. Dysesthesias, if present at all, tend to be tingling or bandlike in quality.

Sensory neuronopathy (or ganglionopathy) is characterized by widespread but asymmetric sensory loss occurring in a non-length-dependent manner so that it may occur proximally or distally and in the arms, legs, or both. Pain and numbness progress to sensory ataxia and impairment of all sensory modalities with time. This condition is usually paraneoplastic or idiopathic in origin **(Chaps. 50 and 53)** or related to an autoimmune disease, particularly Sjögren's syndrome.

Spinal cord

(See also Chap. 43) If the spinal cord is transected, all sensation is lost below the level of transection. Bladder and bowel function also are lost, as is motor function. Lateral hemisection of the spinal cord produces the Brown-Séquard syndrome, with absent pain and temperature sensation contralaterally and loss of proprioceptive sensation and power ipsilaterally below the lesion (see Figs. 15-1 and **43-1**).

Numbness or paresthesias in both feet may arise from a spinal cord lesion; this is especially likely when the upper level of the sensory loss extends to the trunk. When all extremities are affected, the lesion is probably in the cervical region or brainstem unless a peripheral neuropathy is responsible. The presence of upper motor neuron signs **(Chap. 14)** supports a central lesion; a hyperesthetic band on the trunk may suggest the level of involvement.

A dissociated sensory loss can reflect spinothalamic tract involvement in the spinal cord, especially if the deficit is unilateral and has an upper level on the torso. Bilateral spinothalamic tract involvement occurs with lesions affecting the center of the spinal cord, such as in syringomyelia. There is a dissociated sensory loss with impairment of pinprick and temperature appreciation but relative preservation of light touch, position sense, and vibration appreciation.

Dysfunction of the posterior columns in the spinal cord or of the posterior root entry zone may lead to a bandlike sensation around the trunk or a feeling of tight pressure in one or more limbs. Flexion of the neck sometimes leads to an electric shock–like sensation that radiates down the back and into the legs (Lhermitte's sign) in patients with a cervical lesion affecting the posterior columns, such as from multiple sclerosis, cervical spondylosis, or recent irradiation to the cervical region.

Brainstem

Crossed patterns of sensory disturbance, in which one side of the face and the opposite side of the body are affected, localize to the lateral medulla. Here a small lesion may damage both the ipsilateral descending trigeminal tract and the ascending spinothalamic fibers subserving the opposite arm, leg, and hemitorso (see "Lateral medullary syndrome" in **Fig. 32-10**). A lesion in the tegmentum of the pons and midbrain, where the lemniscal and spinothalamic tracts merge, causes pansensory loss contralaterally.

Thalamus

Hemisensory disturbance with tingling numbness from head to foot is often thalamic in origin but also can arise from the anterior parietal region. If abrupt in onset, the lesion is likely to be due to a small stroke (lacunar infarction), particularly if localized to the thalamus. Occasionally, with lesions affecting the VPL nucleus or adjacent white matter, a syndrome of thalamic pain, also called Déjerine-Roussy syndrome, may ensue. There is persistent, unrelenting unilateral pain often is described in dramatic terms.

www.ketabpezeshki.com (021) 66485457 - 66485438

Cortex

With lesions of the parietal lobe involving either the cortex or the subjacent white matter, the most prominent symptoms are contralateral hemineglect, hemiinattention, and a tendency not to use the affected hand and arm. On cortical sensory testing (e.g., two-point discrimination, graphesthesia), abnormalities are often found but primary sensation is usually intact. Anterior parietal infarction may present as a pseudothalamic syndrome with contralateral loss of primary sensation from head to toe. Dysesthesias or a sense of numbness and, rarely, a painful state may also occur.

Focal sensory seizures

These seizures generally are due to lesions in the area of the postcentral or precentral gyrus. The principal symptom of focal sensory seizures is tingling, but additional, more complex sensations may occur, such as a rushing feeling, a sense of warmth, or a sense of movement without detectable motion. Symptoms typically are unilateral; commonly begin in the arm or hand, face, or foot; and often spread in a manner that reflects the cortical representation of different bodily parts, as in a Jacksonian march. Their duration is variable; seizures may be transient, lasting only for seconds, or persist for an hour or more. Focal motor features may supervene, often becoming generalized with loss of consciousness and tonic-clonic jerking.

ACKNOWLEDGMENT

Arthur Asbury authored or co-authored this chapter in earlier editions of this book.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 16

GAIT AND BALANCE DISORDERS

Lewis Sudarsky

PREVALENCE, MORBIDITY, AND MORTALITY

Gait and balance problems are common in the elderly and contribute to the risk of falls and injury. Gait disorders have been described in 15% of individuals older than 65. By age 80 one person in four will use a mechanical aid to assist with ambulation. Among those 85 and older, the prevalence of gait abnormality approaches 40%. In epidemiologic studies, gait disorders are consistently identified as a major risk factor for falls and injury.

A substantial number of older persons report insecure balance and experience falls and fear of falling. Prospective studies indicate that 30% of those older than 65 fall each year. T e proportion is even higher in frail elderly and nursing home patients. Each year, 8% of individuals older than 75 suffer a serious fall-related injury. Hip fractures result in hospitalization, can lead to nursing home admission, and are associated with an increased mortality risk in the subsequent year. For each person who is physically disabled, there are others whose functional independence is limited by anxiety and fear of falling. Nearly one in five elderly individuals voluntarily restricts his or her activity because of fear of falling. With loss of ambulation, the quality of life diminishes, and rates of morbidity and mortality increase.

ANATOMY AND PHYSIOLOGY

An upright bipedal gait depends on the successful integration of postural control and locomotion. T ese functions are widely distributed in the central nervous system. T e biomechanics of bipedal walking are complex, and the performance is easily compromised by a neurologic deficit at any level. Command and control centers in the brainstem, cerebellum, and forebrain modify the action of spinal pattern generators to promote stepping. While a form of "fictive locomotion" can be elicited from quadrupedal animals after spinal transection, this capacity is limited in primates. Step generation in primates is dependent on locomotor centers in the pontine tegmentum, midbrain, and subthalamic region. Locomotor synergies are executed through the reticular formation and descending pathways in the ventromedial spinal cord. Cerebral control provides a goal and purpose for walking and is involved in avoidance of obstacles and adaptation of locomotor programs to context and terrain.

Postural control requires the maintenance of the center of mass over the base of support through the gait cycle. Unconscious postural adjustments maintain standing balance: long latency responses are measurable in the leg muscles, beginning 110 milliseconds after a perturbation. Forward motion of the center of mass provides propulsive force for stepping, but failure to maintain the center of mass within stability limits results in falls. T e anatomic substrate for dynamic balance has not been well defined, but the vestibular nucleus and midline cerebellum contribute to balance control in animals. Patients with damage to these structures have impaired balance while standing and walking.

Standing balance depends on good-quality sensory information about the position of the body center with respect to the environment, support surface, and gravitational forces. Sensory information for postural control is primarily generated by the visual system, the vestibular system, and proprioceptive receptors in the muscle spindles and joints. A healthy redundancy of sensory afferent information is generally available, but loss of two of the three pathways is sufficient to compromise standing balance. Balance disorders in older individuals sometimes result from multiple insults in the peripheral

www.ketabpezeshki.com (021) 66485457 - 66485438

sensory systems (e.g., visual loss, vestibular deficit, peripheral neuropathy) that critically degrade the quality of afferent information needed for balance stability.

Older patients with cognitive impairment from neurodegenerative diseases appear to be particularly prone to falls and injury. T ere is a growing body of literature on the use of attentional resources to manage gait and balance. Walking is generally considered to be unconscious and automatic, but the ability to walk while attending to a cognitive task (dual-task walking) may be compromised in frail elderly individuals with a history of falls. Older patients with deficits in executive function may have particular difficulty in managing the attentional resources needed for dynamic balance when distracted.

DISORDERS OF GAIT

Disorders of gait may be attributed to frailty, fatigue, arthritis, and orthopedic deformity, but neurologic causes are disabling and important to address. T e heterogeneity of gait disorders observed in clinical practice reflects the large network of neural systems involved in the task. Walking is vulnerable to neurologic disease at every level. Gait disorders have been classified descriptively on the basis of abnormal physiology and biomechanics. One problem with this approach is that many failing gaits look fundamentally similar. T is overlap reflects common patterns of adaptation to threatened balance stability and declining performance. T e gait disorder observed clinically must be viewed as the product *of* a neurologic def cit and a *f*unctional adaptation. Unique features of the failing gait are often overwhelmed by the adaptive response. Some common patterns of abnormal gait are summarized next. Gait disorders can also be classified by etiology **(Table 16-1)**.

TABLE 16-1

ETIOLOGY OF GAIT DISORDERS

ETIOLOGY	NO. OF CASES	PERCENT
Sensory deficits	22	18.3
Myelopathy	20	16.7
Multiple infarcts	18	15.0
Parkinsonism	14	11.7
Cerebellar degeneration	8	6.7
Hydrocephalus	8	6.7
Toxic/metabolic causes	3	2.5
Psychogenic causes	4	3.3
Other	6	5.0
Unknown causes	17	14.2
Total	120	100

Source: Reproduced with permission from J Masdeu, L Sudarsky, L Wolfson: Gait Disorders of Aging. Lippincott Raven, 1997.

CAUTIOUS GAIT

T e term cautious gait is used to describe the patient who walks with an abbreviated stride and lowered center of mass, as if walking on a slippery surface. T is disorder is both common and nonspecific. It is, in essence, an adaptation to a perceived postural threat. T ere may be an associated fear of falling. T is disorder can be observed in more than one-third of older patients with gait impairment. Physical therapy often improves walking to the degree that follow-up observation may reveal a more specific underlying disorder.

STIFF-LEGGED GAIT

Spastic gait is characterized by stiffness in the legs, an imbalance of muscle tone, and a tendency to circumduct and scuff the feet. T e disorder reflects compromise of corticospinal command and overactivity of spinal reflexes. T e patient may walk on the toes. In extreme instances, the legs cross due to increased tone in the adductors. Upper motor neuron signs are present on physical examination. Shoes often reflect an uneven pattern of wear across the outside. T e disorder may be cerebral or spinal in origin.

Myelopathy from cervical spondylosis is a common cause of spastic or spastic-ataxic gait in the elderly. Demyelinating disease and trauma are the leading causes of myelopathy in younger patients. In chronic progressive myelopathy of unknown cause, a workup with laboratory and imaging tests may establish a diagnosis. A family history should suggest hereditary spastic paraplegia **(Chap. 39)**; genetic testing is now available for some of the common mutations responsible for this disorder. Tropical spastic paraparesis related to the retrovirus human T-cell lymphotropic virus 1 (HTLV-1) is endemic in parts of the Caribbean and South America. A structural lesion, such as a tumor or a spinal vascular malformation, should be excluded with appropriate testing. **Spinal cord disorders are discussed in detail in Chap. 43.**

With cerebral spasticity, asymmetry is common, the upper extremities are usually involved, and dysarthria is often an associated feature. Common causes include vascular disease (stroke), multiple sclerosis, and perinatal injury to the nervous system (cerebral palsy).

Other stiff-legged gaits include dystonia **(Chap. 36)** and stiff-person syndrome **(Chap. 50)**. Dystonia is a disorder characterized by sustained muscle contractions resulting in repetitive twisting movements and abnormal posture. It often has a genetic basis. Dystonic spasms can produce plantar flexion and inversion of the feet, sometimes with torsion of the trunk. In

www.ketabpezeshki.com (021) 66485457 - 66485438

autoimmune stiff-person syndrome, exaggerated lordosis of the lumbar spine and overactivation of antagonist muscles restrict trunk and lower-limb movement and result in a wooden or fixed posture.

PARKINSONISM AND FREEZING GAIT

Parkinson's disease **(Chap. 36)** is common, affecting 1% of the population >55 years of age. T e stooped posture and shuf ing gait are characteristic and distinctive features. Patients sometimes accelerate (festinate) with walking, display retropulsion, or exhibit a tendency to turn en bloc. A National Institutes of Health workshop defined freezing of gait as "brief, episodic absence of forward progression of the feet, despite the intention to walk." Gait freezing occurs in 26% of Parkinson's patients by the end of 5 years and develops in most such patients eventually. Postural instability and falling occur as the disease progresses; some falls are precipitated by freezing of gait.

Freezing of gait is even more common in some Parkinson's-related neurodegenerative disorders, such as progressive supranuclear palsy, multiple-system atrophy, and corticobasal degeneration. Patients with these disorders frequently present with axial stiffness, postural instability, and a shuf ing, freezing gait while lacking the characteristic pill-rolling tremor of Parkinson's disease. Falls within the first year suggest the possibility of progressive supranuclear palsy.

Hyperkinetic movement disorders also produce characteristic and recognizable disturbances in gait. In Huntington's disease **(Chap. 36)**, the unpredictable occurrence of choreic movements gives the gait a dancing quality. Tardive dyskinesia is the cause of many odd, stereotypic gait disorders seen in patients chronically exposed to antipsychotics and other drugs that block the D_2 dopamine receptor.

FRONTAL GAIT DISORDER

Frontal gait disorder, sometimes known as gait apraxia, is common in the elderly and has a variety of causes. T e term is used to describe a shuf ing, freezing gait with imbalance and other signs of higher cerebral dysfunction. Typical features include a wide base of support, a short stride, shuf ing along the floor, and difficulty with starts and turns. Many patients exhibit a difficulty with gait initiation that is descriptively characterized as the "slipping clutch" syndrome or gait ignition failure. T e term lower-body parkinsonism is also used to describe such patients. Strength is generally preserved, and patients are able to make stepping movements when not standing and maintaining their balance at the same time. T is disorder is best considered a higher-level motor control disorder, as opposed to an apraxia **(Chap. 22)**.

T e most common cause of frontal gait disorder is vascular disease, particularly subcortical small-vessel disease. Lesions are frequently found in the deep frontal white matter and centrum ovale. Gait disorder may be the salient feature in hypertensive patients with ischemic lesions of the deep-hemisphere white matter (Binswanger's disease). T e clinical syndrome includes mental changes (variable in degree), dysarthria, pseudobulbar affect (emotional disinhibition), increased tone, and hyperreflexia in the lower limbs.

Communicating hydrocephalus in adults also presents with a gait disorder of this type. Other features of the diagnostic triad (mental changes, incontinence) may be absent in the initial stages. MRI demonstrates ventricular enlargement, an enlarged flow void about the aqueduct, and a variable degree of periventricular white-matter change. A lumbar puncture or dynamic test is necessary to confirm hydrocephalus.

CEREBELLAR GAIT ATAXIA

Disorders of the cerebellum have a dramatic impact on gait and balance. Cerebellar gait ataxia is characterized by a wide base of support, lateral instability of the trunk, erratic foot placement, and decompensation of balance when attempting to walk on a narrow base. Difficulty maintaining balance when turning is often an early feature. Patients are unable to walk tandem heel to toe and display truncal sway in narrow-based or tandem stance. T ey show considerable variation in their tendency to fall in daily life.

Causes of cerebellar ataxia in older patients include stroke, trauma, tumor, and neurodegenerative disease such as multiple-system atrophy **(Chaps. 36 and 41)** and various forms of hereditary cerebellar degeneration **(Chap. 37)**. A short expansion at the site of the fragile X mutation (*f*ragile X pre-mutation) has been associated with gait ataxia in older men. Alcoholic cerebellar degeneration can be screened by history and often confirmed by MRI. In patients with ataxia, MRI demonstrates the extent and topography of cerebellar atrophy.

SENSORY ATAXIA

As reviewed earlier in this chapter, balance depends on high-quality afferent information from the visual and the vestibular systems and proprioception. When this information is lost or degraded, balance during locomotion is impaired and instability results. T e sensory ataxia of tabetic neurosyphilis is a classic example. T e contemporary equivalent is the patient with neuropathy affecting large fibers. Vitamin B_{12} deficiency is a treatable cause of large-fiber sensory loss in the spinal cord and peripheral nervous system. Joint position and vibration sense are diminished in the lower limbs. T e stance

www.ketabpezeshki.com (021) 66485457 - 66485438

in such patients is destabilized by eye closure; they often look down at their feet when walking and do poorly in the dark. **Table 16-2** compares sensory ataxia with cerebellar ataxia and frontal gait disorder. Some frail older patients exhibit a syndrome of imbalance from the combined effect of multiple sensory deficits. Such patients have disturbances in proprioception, vision, and vestibular sense that impair postural support.

NEUROMUSCULAR DISEASE

Patients with neuromuscular disease often have an abnormal gait, occasionally as a presenting feature. With distal weakness (peripheral neuropathy), the step height is increased to compensate for footdrop, and the sole of the foot may slap on the floor during weight acceptance. Neuropathy may be associated with a degree of sensory imbalance, as described earlier. Patients with myopathy or muscular dystrophy more typically exhibit proximal weakness. Weakness of the hip girdle may result in some degree of excess pelvic sway during locomotion.

TOXIC AND METABOLIC DISORDERS

Alcohol intoxication is the most common cause of acute walking difficulty. Chronic toxicity from medications and metabolic disturbances can impair motor function and gait. Mental status changes may be found, and examination may reveal asterixis or myoclonus. Static equilibrium is disturbed, and such patients are easily thrown off balance. Disequilibrium is particularly evident in patients with chronic renal disease and those with hepatic failure, in whom asterixis may impair postural support. Sedative drugs, especially neuroleptics and long-acting benzodiazepines, affect postural control and increase the risk for falls. T ese disorders are especially important to recognize because they are often treatable.

PSYCHOGENIC GAIT DISORDER

Psychogenic disorders are common in neurologic practice, and the presentation often involves gait. Some patients with extreme anxiety or phobia walk with exaggerated caution with abduction of the arms, as if walking on ice. T is inappropriately overcautious gait differs in degree from the gait of the patient who is insecure and making adjustments for imbalance. Depressed patients exhibit primarily slowness, a manifestation of psychomotor retardation, and lack of purpose in their stride. Hysterical gait disorders are among the most spectacular encountered. Odd gyrations of posture with wastage of muscular energy (astasia–abasia), extreme slow motion, and dramatic fluctuations over time may be observed in patients with somatoform disorders and conversion reactions.

TABLE 16-2

FEATURES OF CEREBELLAR ATAXIA, SENSORY ATAXIA, AND FRONTAL GAIT DISORDERS

FEATURE	CEREBELLAR ATAXIA	SENSORY ATAXIA	FRONTAL GAIT
Base of support	Wide-based	Narrow base, looks down	Wide-based
Velocity	Variable	Slow	Very slow
Stride	Irregular, lurching	Regular with path deviation	Short, shuf ing
Romberg test	+/−	Unsteady, falls	+/−
Heel → shin	Abnormal	+/−	Normal
Initiation	Normal	Normal	Hesitant
Turns	Unsteady	+/−	Hesitant, multistep
Postural instability	+	+++	++++ Poor postural synergies rising from a chair
Falls	Late event	Frequent	Frequent

APPROACH TO THE PATIENT: Slowly Progressive Disorder of Gait

When reviewing the history, it is helpful to inquire about the onset and progression of disability. Initial awareness of an unsteady gait often follows a fall. Stepwise evolution or sudden progression suggests vascular disease. Gait disorder may be associated with urinary urgency and incontinence, particularly in patients with cervical spine disease or hydrocephalus. It is always important to review the use of alcohol and medications that affect gait and balance. Information on localization derived from the neurologic examination can be helpful in narrowing the list of possible diagnoses.

Gait observation provides an immediate sense of the patient's degree of disability. Arthritic and antalgic gaits are recognized by observation, though neurologic and orthopedic problems may coexist. Characteristic patterns of abnormality are sometimes seen, though, as stated previously, failing gaits often look fundamentally similar. Cadence (steps per minute), velocity, and stride length can be recorded by timing a patient over a fixed distance. Watching the patient rise from a chair provides a good functional assessment of balance.

Brain imaging studies may be informative in patients with an undiagnosed disorder of gait. MRI is sensitive for cerebral lesions of vascular or demyelinating disease and is a good screening test for occult hydrocephalus. Patients

www.ketabpezeshki.com (021) 66485457 - 66485438

with recurrent falls are at risk for subdural hematoma. As mentioned earlier, many elderly patients with gait and balance difficulty have white matter abnormalities in the periventricular region and centrum semiovale. While these lesions may be an incidental finding, a substantial burden of white matter disease will ultimately impact cerebral control of locomotion.

DISORDERS OF BALANCE

DEFINITION, ETIOLOGY, AND MANIFESTATIONS

Balance is the ability to maintain equilibrium—a state in which opposing physical forces cancel one another out. In physiology, this term is taken to mean the ability to control the center of mass with respect to gravity and the support surface. In reality, people are not consciously aware of their center of mass, but everyone (particularly gymnasts, figure skaters, and platform divers, for example) move so as to manage it. Disorders of balance present as difficulty maintaining posture while standing and walking and as a subjective sense of disequilibrium, which is a form of dizziness.

T e cerebellum and vestibular system organize antigravity responses needed to maintain an upright posture. T ese responses are physiologically complex, and the anatomic representation they entail is not well understood. Failure, resulting in disequilibrium, can occur at several levels: cerebellar, vestibular, somatosensory, and higher-level disequilibrium.

Patients with cerebellar ataxia do not generally complain of dizziness, though balance is visibly impaired. Neurologic examination reveals a variety of cerebellar signs. Postural compensation may prevent falls early on, but falls are inevitable with disease progression. T e progression of neurodegenerative ataxia is often measured by the number of years to loss of stable ambulation.

Vestibular disorders **(Chap. 12)** have symptoms and signs that fall into three categories: (1) vertigo (the subjective inappropriate perception or illusion of movement); (2) nystagmus (involuntary eye movements); and (3) impaired standing balance. Not every patient has all manifestations. Patients with vestibular deficits related to ototoxic drugs may lack vertigo or obvious nystagmus, but their balance is impaired on standing and walking, and they cannot navigate in the dark. Laboratory testing is available to investigate vestibular deficits.

Somatosensory deficits also produce imbalance and falls. T ere is often a subjective sense of insecure balance and fear of falling. Postural control is compromised by eye closure (Romberg's sign); these patients also have difficulty navigating in the dark. A dramatic example is provided by the patient with autoimmune subacute sensory neuropathy, which is sometimes a paraneoplastic disorder **(Chap. 50)**. Compensatory strategies enable such patients to walk in the virtual absence of proprioception, but the task requires active visual monitoring.

Patients with higher-level disorders *of* equilibrium have difficulty maintaining balance in daily life and may present with falls. T eir awareness of balance impairment may be reduced. Patients taking sedating medications are in this category. In prospective studies, dementia and sedating medications substantially increase the risk for falls.

FALLS

Falls are common in the elderly; 30% of people older than 65 who are living in the community fall each year. Modest changes in balance function have been described in fit older individuals as a result of normal aging. Subtle deficits in sensory systems, attention, and motor reaction time contribute to the risk, and environmental hazards abound. Many falls by older adults are episodes of tripping or slipping, often designated mechanical *f*alls. A fall is not a neurologic problem per se, but there are events for which neurologic evaluation is appropriate. It is important to distinguish falls associated with loss of consciousness (syncope, seizure), which require appropriate evaluation and intervention **(Chaps. 11 and 31)**. In most prospective studies, a small subset of individuals experience a large number of fall events. T ese individuals with recurrent falls often have gait and balance issues that need to be addressed.

Fall patterns: the event description

T e history of a fall is often problematic or incomplete, and the underlying mechanism or cause may be difficult to establish in retrospect. T e patient and family may have limited information about what triggered the fall. Injuries can complicate the physical examination. While there is no standard nosology of falls, some common clinical patterns may emerge and provide a clue.

Drop attacks and collapsing falls

Drop attacks are sudden collapsing falls without loss of consciousness. Patients who collapse from lack of postural tone present a diagnostic challenge. Patients may report that their legs just "gave out" underneath them; their families may describe these patients as "collapsing in a heap." Orthostatic hypotension may be a factor in some such falls, and this possibility should be thoroughly evaluated. Rarely, a colloid cyst of the third ventricle can present with intermittent obstruction of the foramen of Monro, with a consequent drop attack. While collapsing falls are more common among older patients with vascular risk factors, they should not be confused with vertebrobasilar ischemic attacks.

www.ketabpezeshki.com (021) 66485457 - 66485438

Toppling falls

Some patients maintain tone in antigravity muscles but fall over like a tree trunk, as if postural defenses had disengaged. T ere may be a consistent direction to such falls. T e patient with cerebellar pathology may lean and topple over toward the side of the lesion. Patients with lesions of the vestibular system or its central pathways may experience lateral pulsion and toppling falls. Patients with progressive supranuclear palsy often fall over backward. Falls of this nature occur in patients with advanced Parkinson's disease once postural instability has developed.

Falls due to gait freezing

Another fall pattern in Parkinson's disease and related disorders is the fall due to freezing of gait. T e feet stick to the floor and the center of mass keeps moving, resulting in a disequilibrium from which the patient has difficulty recovering. T is sequence of events can result in a forward fall. Gait freezing can also occur as the patient attempts to turn and change direction. Similarly, patients with Parkinson's disease and festinating gait may find their feet unable to keep up and may thus fall forward.

Falls related to sensory loss

Patients with somatosensory, visual, or vestibular deficits are prone to falls. T ese patients have particular difficulty dealing with poor illumination or walking on uneven ground. T ey often report subjective imbalance, apprehension, and fear of falling. Deficits in joint position and vibration sense are apparent on physical examination. T ese patients may be especially responsive to a rehabilitation-based intervention.

Weakness and frailty

Patients who lack strength in antigravity muscles have difficulty rising from a chair, tire easily when walking, and have difficulty maintaining their balance after a perturbation. T ese patients are often unable to get up after a fall and may have to remain on the floor for a prolonged period until help arrives. Deconditioning of this sort is often treatable. Resistance strength training can increase muscle mass and leg strength, even for people in their eighties and nineties.

Risk factors for falls

T e most productive approach is to identify the high-risk patient prospectively, before there is a serious injury. Patients at particular risk include hospitalized patients with mental status changes, nursing home residents, patients with dementia, and those taking medications that compromise attention and alertness. Patients with Parkinson's disease and other gait disorders are also at increased risk. **(Table 16-3)** summarizes a meta-analysis of prospective studies establishing the principal risk factors for falls. It is often possible to address and mitigate some of the major risk factors. Medication overuse may be the most important remediable risk factor for falls.

TABLE 16-3

META-ANALYSIS OF RISK FACTORS FOR FALLS: SUMMARY OF 16 CONTROLLED STUDIES

RISK FACTOR	MEAN RR (OR)	RANGE
Weakness	4.9	1.9–10.3
Balance deficit	3.2	1.6–5.4
Gait disorder	3.0	1.7–4.8
Visual deficit	2.8	1.1–7.4
Mobility limitation	2.5	1.0–5.3
Cognitive impairment	2.4	2.0–4.7
Impaired functional status	2.0	1.0–3.1
Postural hypotension	1.9	1.0–3.4

Abbreviations: OR, odds ratio from retrospective studies; RR, relative risk from prospective studies.
Source: Reproduced with permission from J Masdeu, L Sudarsky, L Wolfson: Gait Disorders of Aging. Lippincott Raven, 1997.

TREATMENT Interventions to Reduce the Risk of Falls and Injury

Efforts should be made to define the etiology of the gait disorder and the mechanism underlying the falls by a given patient. Orthostatic changes in blood pressure and pulse should be recorded. Rising from a chair and walking should be evaluated for safety. Specific treatment may be possible once a diagnosis is established. T erapeutic intervention is often recommended for older patients at substantial risk for falls, even if no neurologic disease is identified. A home visit to look for environmental hazards can be helpful. A variety of modifications may be recommended to improve safety, including improved lighting and the installation of grab bars and nonslip surfaces.

Rehabilitative interventions aim to improve muscle strength and balance stability and to make the patient more resistant to injury. High-intensity resistance strength training with weights and machines is useful to improve muscle mass, even in frail older patients. Improvements realized in posture and gait should translate to reduced risk of falls and injury. Sensory balance training is another approach to improving balance stability. Measurable gains can be made in a few weeks of training, and benefits can be maintained over 6 months by a 10- to 20-min home exercise program. T is strategy is particularly successful in patients with vestibular and somatosensory balance disorders. A Tai Chi exercise program has been demonstrated to reduce the risk of falls and injury in patients with Parkinson's disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 17

VIDEO LIBRARY OF GAIT DISORDERS

Gail Kang ■ Nicholas B. Galifanakis ■ Michael D. Geschwind

Problems with gait and balance are major causes of falls, accidents, and resulting disability, especially in later life, and are often harbingers of neurologic disease. Early diagnosis is essential, especially for treatable conditions, because it may permit the institution of prophylactic measures to prevent dangerous falls and also to reverse or ameliorate the underlying cause. In this video, examples of gait disorders due to Parkinson's disease, other extrapyramidal disorders, and ataxias, as well as other common gait disorders, are presented.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 17–1. Video library of gait disorders

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 18

CONFUSION AND DELIRIUM

S. Andrew Josephson ■ Bruce L. Miller

Confusion, a mental and behavioral state of reduced comprehension, coherence, and capacity to reason, is one of the most common problems encountered in medicine, accounting for a large number of emergency department visits, hospital admissions, and inpatient consultations. Delirium, a term used to describe an acute confusional state, remains a major cause of morbidity and mortality, costing over $150 billion yearly in health care costs in the United States alone. Despite increased efforts targeting awareness of this condition, delirium often goes unrecognized in the face of evidence that it is usually the cognitive manifestation of serious underlying medical or neurologic illness.

CLINICAL FEATURES OF DELIRIUM

A multitude of terms are used to describe patients with delirium, including encephalopathy, acute brain failure, acute confusional state, and postoperative or intensive care unit (ICU) psychosis. Delirium has many clinical manifestations, but is defined as a relatively acute decline in cognition that fluctuates over hours or days. T e hallmark of delirium is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are variably involved. Associated symptoms that may be present in some cases include altered sleep-wake cycles, perceptual disturbances such as hallucinations or delusions, affect changes, and autonomic findings that include heart rate and blood pressure instability.

Delirium is a clinical diagnosis that is made only at the bedside. Two subtypes have been described—hyperactive and hypoactive—based on differential psychomotor features. T e cognitive syndrome associated with severe alcohol withdrawal (i.e., "delirium tremens") remains the classic example of the hyperactive subtype, featuring prominent hallucinations, agitation, and hyperarousal, often accompanied by life-threatening autonomic instability. In striking contrast is the hypoactive subtype, exemplified by benzodiazepine intoxication, in which patients are withdrawn and quiet, with prominent apathy and psychomotor slowing.

T is dichotomy between subtypes of delirium is a useful construct, but patients often fall somewhere along a spectrum between the hyperactive and hypoactive extremes, sometimes fluctuating from one to the other. T erefore, clinicians must recognize this broad range of presentations of delirium to identify all patients with this potentially reversible cognitive disturbance. Hyperactive patients are often easily recognized by their characteristic severe agitation, tremor, hallucinations, and autonomic instability. Patients who are quietly hypoactive are more often overlooked on the medical wards and in the ICU.

T e reversibility of delirium is emphasized because many etiologies, such as systemic infection and medication effects, can be treated easily. T e long-term cognitive effects of delirium remain largely unknown. Some episodes of delirium continue for weeks, months, or even years. T e persistence of delirium in some patients and its high recurrence rate may be due to inadequate initial treatment of the underlying etiology. In other instances, delirium appears to cause permanent neuronal damage and cognitive decline. Even if an episode of delirium completely resolves, there may be lingering effects of the disorder; a patient's recall of events after delirium varies widely, ranging from complete amnesia to repeated re-experiencing of the frightening period of confusion, similar to what is seen in patients with posttraumatic stress disorder.

RISK FACTORS

An effective primary prevention strategy for delirium begins with identification of patients at high risk for this disorder, including those preparing for elective

www.ketabpezeshki.com (021) 66485457 - 66485438

surgery or being admitted to the hospital. Although no single validated scoring system has been widely accepted as a screen for asymptomatic patients, there are multiple well-established risk factors for delirium.

T e two most consistently identified risks are older age and baseline cognitive dysfunction. Individuals who are over age 65 or exhibit low scores on standardized tests of cognition develop delirium upon hospitalization at a rate approaching 50%. Whether age and baseline cognitive dysfunction are truly independent risk factors is uncertain. Other predisposing factors include sensory deprivation, such as preexisting hearing and visual impairment, as well as indices for poor overall health, including baseline immobility, malnutrition, and underlying medical or neurologic illness.

In-hospital risks for delirium include the use of bladder catheterization, physical restraints, sleep and sensory deprivation, and the addition of three or more new medications. Avoiding such risks remains a key component of delirium prevention as well as treatment. Surgical and anesthetic risk factors for the development of postoperative delirium include specific procedures such as those involving cardiopulmonary bypass, inadequate or excessive treatment of pain in the immediate postoperative period, and perhaps specific agents such as inhalational anesthetics.

T e relationship between delirium and dementia **(Chap. 35)** is complicated by significant overlap between the two conditions, and it is not always simple to distinguish between them. Dementia and preexisting cognitive dysfunction serve as major risk factors for delirium, and at least two-thirds of cases of delirium occur in patients with coexisting underlying dementia. A form of dementia with parkinsonism, termed dementia with Lewy bodies, is characterized by a fluctuating course, prominent visual hallucinations, parkinsonism, and an attentional deficit that clinically resembles hyperactive delirium; patients with this condition are particularly vulnerable to delirium. Delirium in the elderly often reflects an insult to the brain that is vulnerable due to an underlying neurodegenerative condition. T erefore, the development of delirium sometimes heralds the onset of a previously unrecognized brain disorder.

EPIDEMIOLOGY

Delirium is common, but its reported incidence has varied widely with the criteria used to define this disorder. Estimates of delirium in hospitalized patients range from 18 to 64%, with higher rates reported for elderly patients and patients undergoing hip surgery. Older patients in the ICU have especially high rates of delirium that approach 75%. T e condition is not recognized in up to one-third of delirious inpatients, and the diagnosis is especially problematic in the ICU environment, where cognitive dysfunction is often difficult to appreciate in the setting of serious systemic illness and sedation. Delirium in the ICU should be viewed as an important manifestation of organ dysfunction not unlike liver, kidney, or heart failure. Outside the acute hospital setting, delirium occurs in nearly one-quarter of patients in nursing homes and in 50 to 80% of those at the end of life. T ese estimates emphasize the remarkably high frequency of this cognitive syndrome in older patients, a population expected to grow in the upcoming decades.

Until recently, an episode of delirium was viewed as a transient condition that carried a benign prognosis. It is now recognized as a disorder with a substantial morbidity rate and increased mortality rate and often represents the first manifestation of a serious underlying illness. Recent estimates of in-hospital mortality rates among delirious patients have ranged from 25 to 33%, a rate similar to that of patients with sepsis. Patients with an in-hospital episode of delirium have a fivefold higher mortality rate in the months after their illness compared with age-matched nondelirious hospitalized patients. Delirious hospitalized patients have a longer length of stay, are more likely to be discharged to a nursing home, and are more likely to experience subsequent episodes of delirium and cognitive decline; as a result, this condition has enormous economic implications.

PATHOGENESIS

T e pathogenesis and anatomy of delirium are incompletely understood. T e attentional deficit that serves as the neuropsychological hallmark of delirium has a diffuse localization within the brainstem, thalamus, prefrontal cortex, and parietal lobes. Rarely, focal lesions such as ischemic strokes have led to delirium in otherwise healthy persons; right parietal and medial dorsal thalamic lesions have been reported most commonly, pointing to the importance of these areas to delirium pathogenesis. In most cases, delirium results from widespread disturbances in cortical and subcortical regions rather than a focal neuroanatomic cause. Electroencephalogram (EEG) data in persons with delirium usually show symmetric slowing, a nonspecific finding that supports diffuse cerebral dysfunction.

Multiple neurotransmitter abnormalities, proinflammatory factors, and specific genes likely play a role in the pathogenesis of delirium. Deficiency of acetylcholine may play a key role, and medications with anticholinergic properties also can precipitate delirium. Dementia patients are susceptible to episodes of delirium, and those with Alzheimer's pathology and dementia with Lewy bodies or Parkinson's disease dementia are known to have a chronic cholinergic deficiency

www.ketabpezeshki.com (021) 66485457 - 66485438

state due to degeneration of acetylcholine-producing neurons in the basal forebrain. Additionally, other neurotransmitters are also likely to be involved in this diffuse cerebral disorder. For example, increases in dopamine can also lead to delirium. Patients with Parkinson's disease treated with dopaminergic medications can develop a delirium-like state that features visual hallucinations, fluctuations, and confusion.

Not all individuals exposed to the same insult will develop signs of delirium. A low dose of an anticholinergic medication may have no cognitive effects on a healthy young adult but produce a florid delirium in an elderly person with known underlying dementia, although even healthy young persons develop delirium with very high doses of anticholinergic medications. T is concept of delirium developing as the result of an insult in predisposed individuals is currently the most widely accepted pathogenic construct. T erefore, if a previously healthy individual with no known history of cognitive illness develops delirium in the setting of a relatively minor insult such as elective surgery or hospitalization, an unrecognized underlying neurologic illness such as a neurodegenerative disease, multiple previous strokes, or another diffuse cerebral cause should be considered. In this context, delirium can be viewed as a "stress test for the brain" whereby exposure to known inciting factors such as systemic infection and offending drugs can unmask a decreased cerebral reserve and herald a serious underlying and potentially treatable illness.

TABLE 18-1

THE CONFUSION ASSESSMENT METHOD (CAM) DIAGNOSTIC ALGORITHM[a]

The diagnosis of delirium requires the presence of features 1 and 2 and of either feature 3 or 4.

FEATURE 1. ACUTE ONSET AND FLUCTUATING COURSE

This feature is satisfied by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or did it increase and decrease in severity?

FEATURE 2. INATTENTION

This feature is satisfied by a positive response to the following question: Did the patient have dif culty focusing attention, for example, being easily distractible, or have dif culty keeping track of what was being said?

FEATURE 3. DISORGANIZED THINKING

This feature is satisfied by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

FEATURE 4. ALTERED LEVEL OF CONSCIOUSNESS

This feature is satisfied by any answer other than "alert" to the following question: Overall, how would you rate the patient's level of consciousness: alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (dif cult to arouse), or coma (unarousable)?

[a]Information is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse.

Source: Modified from SK Inouye et al: Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med 113:941, 1990.

APPROACH TO THE PATIENT: Delirium

Because the diagnosis of delirium is clinical and is made at the bedside, a careful history and physical examination are necessary in evaluating patients with possible confusional states. Screening tools can aid physicians and nurses in identifying patients with delirium, including the Confusion Assessment Method (CAM) **(Table 18-1)**; the Organic Brain Syndrome Scale; the Delirium Rating Scale; and, in the ICU, the ICU version of the CAM and the Delirium Detection Score. Using the well-validated CAM, a diagnosis of delirium is made if there is (1) an acute onset and fluctuating course and (2) inattention accompanied by either (3) disorganized thinking or (4) an altered level of consciousness. T ese scales may not identify the full spectrum of patients with delirium, and all patients who are acutely confused should be presumed delirious regardless of their presentation due to the wide variety of possible clinical features. A course that fluctuates over hours or days and may worsen at night (termed sundowning) is typical but not essential for the diagnosis. Observation of the patient usually will reveal an altered level of consciousness or a deficit of attention. Other features that are sometimes present include alteration of sleep-wake cycles, thought disturbances such as hallucinations or delusions, autonomic instability, and changes in affect.

HISTORY It may be dif cult to elicit an accurate history in delirious patients who have altered levels of consciousness or impaired attention. Information from a collateral source such as a spouse or another family member is therefore invaluable. T e three most important pieces of history are the patient's baseline cognitive function, the time course of the present illness, and current medications.

Premorbid cognitive function can be assessed through the collateral source or, if needed, via a review of outpatient records. Delirium by definition represents a change that is relatively acute, usually over hours to days, from a cognitive baseline. As a result, an acute confusional state is nearly impossible to diagnose without some knowledge of baseline cognitive function. Without this information, many patients with dementia or depression may be mistaken as delirious during a single initial

www.ketabpezeshki.com (021) 66485457 - 66485438

evaluation. Patients with a more hypoactive, apathetic presentation with psychomotor slowing may be identified as being different from baseline only through conversations with family members. A number of validated instruments have been shown to diagnose cognitive dysfunction accurately using a collateral source, including the modified Blessed Dementia Rating Scale and the Clinical Dementia Rating (CDR). Baseline cognitive impairment is common in patients with delirium. Even when no such history of cognitive impairment is elicited, there should still be a high suspicion for a previously unrecognized underlying neurologic disorder.

Establishing the time course of cognitive change is important not only to make a diagnosis of delirium but also to correlate the onset of the illness with potentially treatable etiologies such as recent medication changes or symptoms of systemic infection.

Medications remain a common cause of delirium, especially compounds with anticholinergic or sedative properties. It is estimated that nearly one-third of all cases of delirium are secondary to medications, especially in the elderly. Medication histories should include all prescription as well as over-the-counter and herbal substances taken by the patient and any recent changes in dosing or formulation, including substitution of generics for brand-name medications.

Other important elements of the history include screening for symptoms of organ failure or systemic infection, which often contributes to delirium in the elderly. A history of illicit drug use, alcoholism, or toxin exposure is common in younger delirious patients. Finally, asking the patient and collateral source about other symptoms that may accompany delirium, such as depression, may help identify potential therapeutic targets.

PHYSICAL EXAMINATION T e general physical examination in a delirious patient should include careful screening for signs of infection such as fever, tachypnea, pulmonary consolidation, heart murmur, and stiff neck. T e patient's fluid status should be assessed; both dehydration and fluid overload with resultant hypoxemia have been associated with delirium, and each is usually easily rectified. T e appearance of the skin can be helpful, showing jaundice in hepatic encephalopathy, cyanosis in hypoxemia, or needle tracks in patients using intravenous drugs.

T e neurologic examination requires a careful assessment of mental status. Patients with delirium often present with a fluctuating course; therefore, the diagnosis can be missed when one relies on a single time point of evaluation. Some but not all patients exhibit the characteristic pattern of sundowning, a worsening of their condition in the evening. In these cases, assessment only during morning rounds may be falsely reassuring.

An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be assessed easily at the bedside. In a patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, because this deficit is the classic neuropsychological hallmark of delirium. Attention can be assessed while taking a history from the patient. Tangential speech, a fragmentary flow of ideas, or inability to follow complex commands often signifies an attentional problem. T ere are formal neuropsychological tests to assess attention, but a simple bedside test of digit span forward is quick and fairly sensitive. In this task, patients are asked to repeat successively longer random strings of digits beginning with two digits in a row, said to the patient at 1-second intervals. Healthy adults can repeat a string of five to seven digits before faltering; a digit span of four or less usually indicates an attentional deficit unless hearing or language barriers are present, and many patients with delirium have digit spans of three or fewer digits.

More formal neuropsychological testing can be helpful in assessing a delirious patient, but it is usually too cumbersome and time-consuming in the inpatient setting. A Mini-Mental State Examination (MMSE) provides information regarding orientation, language, and visuospatial skills; however, performance of many tasks on the MMSE, including the spelling of "world" backward and serial subtraction of digits, will be impaired by delirious patients' attentional deficits, rendering the test unreliable.

T e remainder of the screening neurologic examination should focus on identifying new focal neurologic deficits. Focal strokes or mass lesions in isolation are rarely the cause of delirium, but patients with underlying extensive cerebrovascular disease or neurodegenerative conditions may not be able to cognitively tolerate even relatively small new insults. Patients should be screened for other signs of neurodegenerative conditions such as parkinsonism, which is seen not only in idiopathic Parkinson's disease but also in other dementing conditions such as Alzheimer's disease, dementia with Lewy bodies, and progressive supranuclear palsy. T e presence of multifocal myoclonus or asterixis on the motor examination is nonspecific but usually indicates a metabolic or toxic etiology of the delirium.

ETIOLOGY Some etiologies can be easily discerned through a careful history and physical examination, whereas others require confirmation with laboratory studies, imaging, or other ancillary tests. A large, diverse group of insults can lead to delirium, and the cause in many patients is often multifactorial. Common etiologies are listed in **Table 18-2**.

Prescribed, over-the-counter, and herbal medications all can precipitate delirium. Drugs with anticholinergic properties, narcotics, and benzodiazepines are particularly common offenders, but nearly any compound can lead to cognitive dysfunction in a predisposed patient. Whereas an elderly patient with baseline dementia may become

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 18-2

COMMON ETIOLOGIES OF DELIRIUM
Toxins
Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines
Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, "bath salts," marijuana and its synthetic forms
Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic conditions
Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia
Hypothermia and hyperthermia
Pulmonary failure: hypoxemia and hypercarbia
Liver failure/hepatic encephalopathy
Renal failure/uremia
Cardiac failure
Vitamin deficiencies: B_{12}, thiamine, folate, niacin
Dehydration and malnutrition
Anemia
Infections
Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis
CNS infections: meningitis, encephalitis, brain abscess
Endocrine conditions
Hyperthyroidism, hypothyroidism
Hyperparathyroidism
Adrenal insufficiency
Cerebrovascular disorders
Global hypoperfusion states
Hypertensive encephalopathy
Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune disorders
CNS vasculitis
Cerebral lupus
Neurologic paraneoplastic syndromes
Seizure-related disorders
Nonconvulsive status epilepticus
Intermittent seizures with prolonged postictal states
Neoplastic disorders
Dif use metastases to the brain
Gliomatosis cerebri
Carcinomatous meningitis
CNS lymphoma
Hospitalization
Terminal end-of-life delirium

Abbreviations: CNS, central nervous system; GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.

delirious upon exposure to a relatively low dose of a medication, less susceptible individuals may become delirious only with very high doses of the same medication. T is observation emphasizes the importance of correlating the timing of recent medication changes, including dose and formulation, with the onset of cognitive dysfunction.

In younger patients, illicit drugs and toxins are common causes of delirium. In addition to more classic drugs of abuse, the recent rise in availability of methylenedioxymethamphetamine (MDMA, ecstasy), γ-hydroxybutyrate (GHB), "bath salts," synthetic cannabis, and the phencyclidine (PCP)-like agent ketamine, has led to an increase in delirious young persons presenting to acute care settings **(Chap. 65)**. Many common prescription drugs such as oral narcotics and benzodiazepines are often abused and readily available on the street. Alcohol abuse leading to high serum levels causes confusion, but more commonly, it is withdrawal from alcohol that leads to a hyperactive delirium. Alcohol and benzodiazepine withdrawal should be considered in all cases of delirium because even patients who drink only a few servings of alcohol every day can experience relatively severe withdrawal symptoms upon hospitalization.

Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and mild derangements can lead to substantial cognitive disturbances in susceptible individuals. Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxemia, vitamin deficiencies of thiamine and B_{12}, autoimmune disorders including central nervous system (CNS) vasculitis, and endocrinopathies such as thyroid and adrenal disorders.

Systemic infections often cause delirium, especially in the elderly. A common scenario involves the development of an acute cognitive decline in the setting of a urinary tract infection in a patient with baseline dementia. Pneumonia, skin infections such as cellulitis, and frank sepsis also lead to delirium. T is so-called septic encephalopathy, often seen in the ICU, is probably due to the release of proinflammatory cytokines and their diffuse cerebral effects. CNS infections such as meningitis, encephalitis, and abscess are less common etiologies of delirium; however, in light of the high mortality rates associated with these conditions when they are not treated quickly, clinicians must always maintain a high index of suspicion.

In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can lead to delirium. T is etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated. Many primary prevention and treatment strategies for delirium involve relatively simple methods to address the aspects of the inpatient setting that are most confusing.

www.ketabpezeshki.com (021) 66485457 - 66485438

Cerebrovascular etiologies of delirium are usually due to global hypoperfusion in the setting of systemic hypotension from heart failure, septic shock, dehydration, or anemia. Focal strokes in the right parietal lobe and medial dorsal thalamus rarely can lead to a delirious state. A more common scenario involves a new focal stroke or hemorrhage causing confusion in a patient who has decreased cerebral reserve. In these individuals, it is sometimes difficult to distinguish between cognitive dysfunction resulting from the new neurovascular insult itself and delirium due to the infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

Because a fluctuating course often is seen in delirium, intermittent seizures may be overlooked when one is considering potential etiologies. Both nonconvulsive status epilepticus and recurrent focal or generalized seizures followed by postictal confusion can cause delirium; EEG remains essential for this diagnosis. Seizure activity spreading from an electrical focus in a mass or infarct can explain global cognitive dysfunction caused by relatively small lesions.

It is very common for patients to experience delirium at the end of life in palliative care settings. This condition, sometimes described as terminal restlessness, must be identified and treated aggressively because it is an important cause of patient and family discomfort at the end of life. It should be remembered that these patients also may be suffering from more common etiologies of delirium such as systemic infection.

LABORATORY AND DIAGNOSTIC EVALUATION A cost-effective approach to the diagnostic evaluation of delirium allows the history and physical examination to guide further tests. No established algorithm for workup will fit all delirious patients due to the staggering number of potential etiologies, but one stepwise approach is detailed in **Table 18-3**. If a clear precipitant is identified, such as an offending medication, further testing may not be required. If, however, no likely etiology is uncovered with initial evaluation, an aggressive search for an underlying cause should be initiated.

Basic screening labs, including a complete blood count, electrolyte panel, and tests of liver and renal function, should be obtained in all patients with delirium. In elderly patients, screening for systemic infection, including chest radiography, urinalysis and culture, and possibly blood cultures, is important. In younger individuals, serum and urine drug and toxicology screening may be appropriate early in the workup. Additional laboratory tests addressing other autoimmune, endocrinologic, metabolic, and infectious etiologies should be reserved for patients in whom the diagnosis remains unclear after initial testing.

Multiple studies have demonstrated that brain imaging in patients with delirium is often unhelpful. If, however, the initial workup is unrevealing, most clinicians quickly move toward imaging of the brain to exclude structural causes. A noncontrast computed tomography (CT) scan can identify large masses and hemorrhages but is otherwise unlikely to help determine an etiology of delirium. The ability of magnetic resonance imaging (MRI) to identify most acute ischemic strokes as well as to provide neuroanatomic detail that gives clues to possible infectious, inflammatory, neurodegenerative, and neoplastic

TABLE 18-3

STEPWISE EVALUATION OF A PATIENT WITH DELIRIUM
Initial evaluation
History with special attention to medications (including over-the-counter and herbals)
General physical examination and neurologic examination
Complete blood count
Electrolyte panel including calcium, magnesium, phosphorus
Liver function tests, including albumin
Renal function tests
First-tier further evaluation guided by initial evaluation
Systemic infection screen
Urinalysis and culture
Chest radiograph
Blood cultures
Electrocardiogram
Arterial blood gas
Serum and/or urine toxicology screen (perform earlier in young persons)
Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
Suspected CNS infection: lumbar puncture after brain imaging
Suspected seizure-related etiology: electroencephalogram (EEG) (if high suspicion, should be performed immediately)
Second-tier further evaluation
Vitamin levels: B_{12}, folate, thiamine
Endocrinologic laboratories: thyroid-stimulating hormone (TSH) and free T_4; cortisol
Serum ammonia
Sedimentation rate
Autoimmune serologies: antinuclear antibodies (ANA), complement levels; p-ANCA, c-ANCA. consider paraneoplastic serologies
Infectious serologies: rapid plasmin reagin (RPR); fungal and viral serologies if high suspicion; HIV antibody
Lumbar puncture (if not already performed)
Brain MRI with and without gadolinium (if not already performed)

Abbreviations: c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.

www.ketabpezeshki.com (021) 66485457 - 66485438

conditions makes it the test of choice. Because MRI techniques are limited by availability, speed of imaging, patient cooperation, and contraindications, many clinicians begin with CT scanning and proceed to MRI if the etiology of delirium remains elusive.

Lumbar puncture (LP) must be obtained immediately after appropriate neuroimaging in all patients in whom CNS infection is suspected. Spinal fluid examination can also be useful in identifying inflammatory and neoplastic conditions. As a result, LP should be considered in any delirious patient with a negative workup. EEG does not have a routine role in the workup of delirium, but it remains invaluable if seizure-related etiologies are considered.

TREATMENT Delirium

Management of delirium begins with treatment of the underlying inciting factor (e.g., patients with systemic infections should be given appropriate antibiotics, and underlying electrolyte disturbances judiciously corrected). T ese treatments often lead to prompt resolution of delirium. Blindly targeting the symptoms of delirium pharmacologically only serves to prolong the time patients remain in the confused state and may mask important diagnostic information.

Relatively simple methods of supportive care can be highly effective in treating patients with delirium. Reorientation by the nursing staff and family combined with visible clocks, calendars, and outside-facing windows can reduce confusion. Sensory isolation should be prevented by providing glasses and hearing aids to patients who need them. Sundowning can be addressed to a large extent through vigilance to appropriate sleep-wake cycles. During the day, a well-lit room should be accompanied by activities or exercises to prevent napping. At night, a quiet, dark environment with limited interruptions by staff can assure proper rest. T ese sleep-wake cycle interventions are especially important in the ICU setting as the usual constant 24-h activity commonly provokes delirium. Attempting to mimic the home environment as much as possible also has been shown to help treat and even prevent delirium. Visits from friends and family throughout the day minimize the anxiety associated with the constant flow of new faces of staff and physicians. Allowing hospitalized patients to have access to home bedding, clothing, and nightstand objects makes the hospital environment less foreign and therefore less confusing. Simple standard nursing practices such as maintaining proper nutrition and volume status as well as managing incontinence and skin breakdown also help alleviate discomfort and resulting confusion.

In some instances, patients pose a threat to their own safety or to the safety of staff members, and acute management is required. Bed alarms and personal sitters are more effective and much less disorienting than physical restraints. Chemical restraints should be avoided, but only when necessary, very-low-dose typical or atypical antipsychotic medications administered on an as-needed basis are effective. T e recent association of antipsychotic use in the elderly with increased mortality rates underscores the importance of using these medications judiciously and only as a last resort. Benzodiazepines often worsen confusion through their sedative properties. Although many clinicians still use benzodiazepines to treat acute confusion, their use should be limited to cases in which delirium is caused by alcohol or benzodiazepine withdrawal.

PREVENTION

In light of the high morbidity associated with delirium and the tremendously increased health care costs that accompany it, development of an effective strategy to prevent delirium in hospitalized patients is extremely important. Successful identification of high-risk patients is the first step, followed by initiation of appropriate interventions. Simple standardized protocols used to manage risk factors for delirium, including sleep-wake cycle reversal, immobility, visual impairment, hearing impairment, sleep deprivation, and dehydration, have been shown to be effective. Recent trials in the ICU have focused both on identifying sedatives, such as dexmedetomidine, that are less likely to lead to delirium in critically ill patients and on developing protocols for daily awakenings in which infusions of sedative medications are interrupted and the patient is reorientated by the staff. All hospitals and health care systems should work toward decreasing the incidence of delirium.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 19

COMA

Allan H. Ropper

Coma is among the most common and striking problems in general medicine. It accounts for a substantial portion of admissions to emergency wards and occurs on all hospital services. It demands immediate attention and requires an organized approach.

There is a continuum of states of reduced alertness, the most severe form being coma, defined as a deep sleeplike state from which the patient cannot be aroused. Stupor refers to a higher degree of arousability in which the patient can be transiently awakened by vigorous stimuli, accompanied by motor behavior that leads to avoidance of uncomfortable or aggravating stimuli. Drowsiness, which is familiar to all persons, simulates light sleep and is characterized by easy arousal and the persistence of alertness for brief periods. Drowsiness and stupor are usually accompanied by some degree of confusion **(Chap. 18)**. A precise narrative description of the level of arousal and of the type of responses evoked by various stimuli as observed at the bedside is preferable to ambiguous terms such as lethargy, semicoma, or obtundation.

Several conditions that render patients unresponsive and simulate coma are considered separately because of their special significance. The vegetative state signifies an awake-appearing but nonresponsive state in a patient who has emerged from coma. In the vegetative state, the eyelids may open, giving the appearance of wakefulness. Respiratory and autonomic functions are retained. Yawning, coughing, swallowing, and limb and head movements persist, and the patient may follow visually presented objects, but there are few, if any, meaningful responses to the external and internal environment—in essence, an "awake coma." The term vegetative is unfortunate because it is subject to misinterpretation. There are always accompanying signs that indicate extensive damage in both cerebral hemispheres, e.g., decerebrate or decorticate limb posturing and absent responses to visual stimuli (see below). In the closely related but less severe minimally conscious state, the patient displays rudimentary vocal or motor behaviors, often spontaneous, but some in response to touch, visual stimuli, or command. Cardiac arrest with cerebral hypoperfusion and head injuries are the most common causes of the vegetative and minimally conscious states **(Chap. 33)**. The prognosis for regaining mental faculties once the vegetative state has supervened for several months is very poor, and after a year, almost nil; hence the term persistent vegetative state. Most reports of dramatic recovery, when investigated carefully, are found to yield to the usual rules for prognosis, but there have been rare instances in which recovery has occurred to a severely disabled condition and, in rare childhood cases, to an even better state. The possibility of incorrectly attributing meaningful behavior to patients in the vegetative and minimally conscious states creates inordinate problems and anguish. On the other hand, the question of whether these patients lack any capability for cognition has been reopened by functional imaging studies that have demonstrated, in a small proportion of posttraumatic cases, meaningful cerebral activation in response to verbal and other stimuli.

Apart from the above conditions, several syndromes that affect alertness are prone to be misinterpreted as stupor or coma. Akinetic mutism refers to a partially or fully awake state in which the patient is able to form impressions and think, as demonstrated by later recounting of events, but remains virtually immobile and mute. The condition results from damage in the regions of the medial thalamic nuclei or the frontal lobes (particularly lesions situated deeply or on the orbitofrontal surfaces) or from extreme hydrocephalus. The term abulia describes a milder form of akinetic mutism characterized by mental and physical slowness and diminished ability to initiate activity. It is also usually the result of damage to the frontal lobes and its connections **(Chap. 22)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

Catatonia is a curious hypomobile and mute syndrome that occurs as part of a major psychosis, usually schizophrenia or major depression. Catatonic patients make few voluntary or responsive movements, although they blink, swallow, and may not appear distressed. There are nonetheless signs that the patient is responsive, although it may take ingenuity on the part of the examiner to demonstrate them. For example, eyelid elevation is actively resisted, blinking occurs in response to a visual threat, and the eyes move concomitantly with head rotation, all of which are inconsistent with the presence of a brain lesion causing unresponsiveness. It is characteristic but not invariable in catatonia for the limbs to retain the postures in which they have been placed by the examiner ("waxy flexibility," or catalepsy). With recovery, patients often have some memory of events that occurred during their catatonic stupor. Catatonia is superficially similar to akinetic mutism, but clinical evidence of cerebral damage such as Babinski signs and hypertonicity of the limbs is lacking. The special problem of coma in brain death is discussed below.

The locked-in state describes yet another type of pseudocoma in which an awake patient has no means of producing speech or volitional movement but retains voluntary vertical eye movements and lid elevation, thus allowing the patient to signal with a clear mind. The pupils are normally reactive. Such individuals have written entire treatises using Morse code. The usual cause is an infarction or hemorrhage of the ventral pons that transects all descending motor (corticospinal and corticobulbar) pathways. A similar awake but deefferented state occurs as a result of total paralysis of the musculature in severe cases of Guillain-Barré syndrome **(Chap. 54)**, critical illness neuropathy **(Chap. 33)**, and pharmacologic neuromuscular blockade.

THE ANATOMY AND PHYSIOLOGY OF COMA

Almost all instances of diminished alertness can be traced to widespread abnormalities of the cerebral hemispheres or to reduced activity of a special thalamocortical alerting system termed the reticular activating system (RAS). The proper functioning of this system, its ascending projections to the cortex, and the cortex itself are required to maintain alertness and coherence of thought. It follows that the principal causes of coma are (1) lesions that damage the RAS in the upper midbrain or its projections; (2) destruction of large portions of both cerebral hemispheres; or (3) suppression of reticulocerebral function by drugs, toxins, or metabolic derangements such as hypoglycemia, anoxia, uremia, and hepatic failure.

The proximity of the RAS to midbrain structures that control pupillary function and eye movements permits clinical localization of the cause of coma in many cases. Pupillary enlargement with loss of light reaction and loss of vertical and adduction movements of the eyes suggests that the lesion is in the upper brainstem where the nuclei subserving these functions reside. Conversely, preservation of pupillary light reactivity and of eye movements absolves the upper brainstem and indicates that widespread structural lesions or metabolic suppression of the cerebral hemispheres is responsible for coma.

Coma due to cerebral mass lesions and herniations

In addition to the fixed restriction of the skull, the cranial cavity is separated into compartments by infoldings of the dura. The two cerebral hemispheres are separated by the falx, and the anterior and posterior fossae by the tentorium. Herniation refers to displacement of brain tissue by an overlying or adjacent mass into a contiguous compartment that it normally does not occupy. Coma and many of its associated signs can be attributed to these tissue shifts, and certain clinical features are characteristic of specific configurations of herniation **(Fig. 19-1)**. They are in essence "false localizing" signs because they derive from compression of brain structures at a distance from the mass.

In the most common form of herniation, brain tissue is displaced from the supratentorial to the infratentorial compartment through the tentorial opening; this is referred to as transtentorial herniation. Uncal transtentorial herniation refers to impaction of the anterior

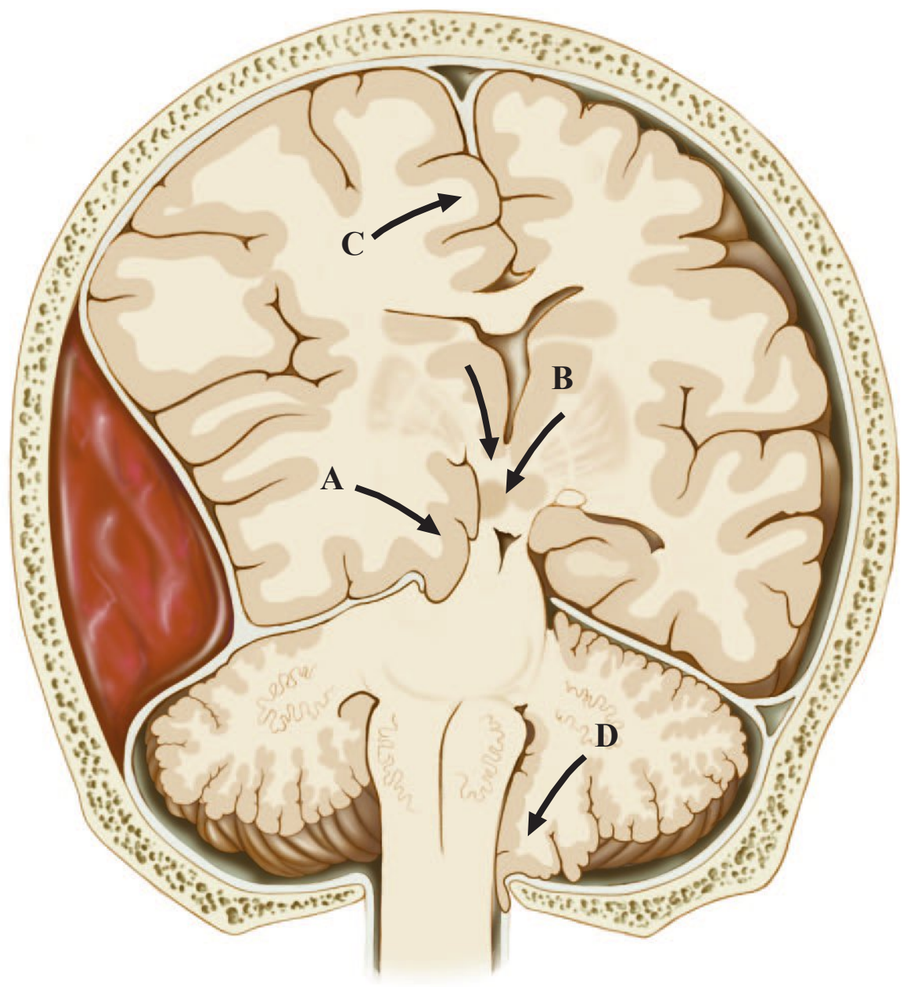


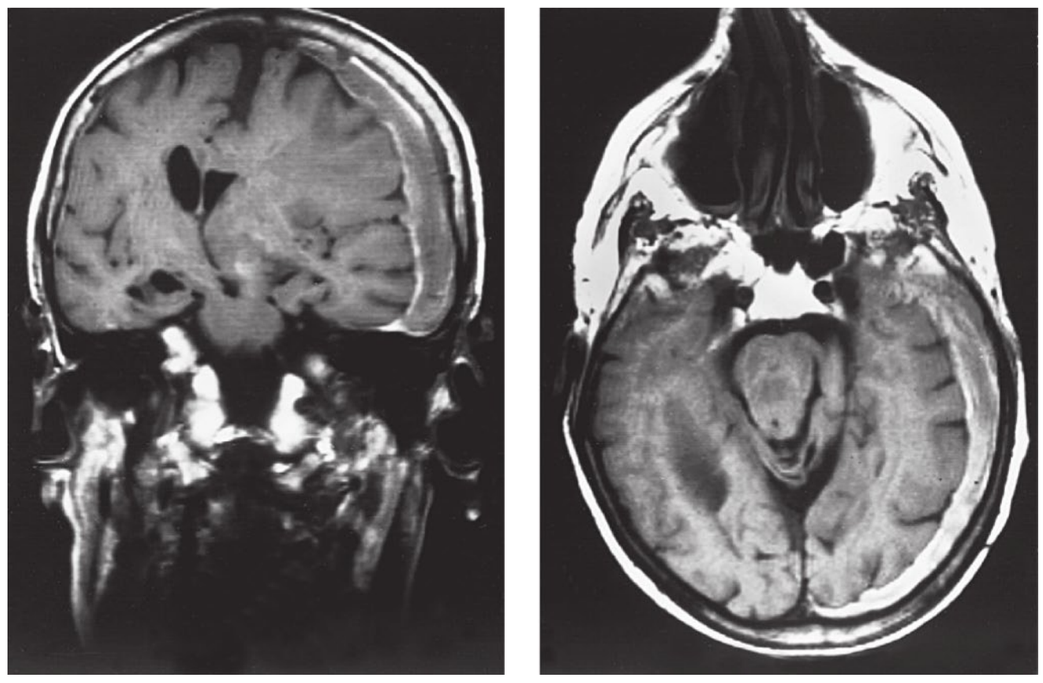
FIGURE 19-1
Types of cerebral herniation: (A) uncal; (B) central; (C) transfalcial; and (D) foraminal.

www.ketabpezeshki.com (021) 66485457 - 66485438

medial temporal gyrus (the uncus) into the tentorial opening just anterior to and adjacent to the midbrain **(Fig. 19-1A)**. The uncus compresses the third nerve as the nerve traverses the subarachnoid space, causing enlargement of the ipsilateral pupil (the fibers subserving parasympathetic pupillary function are located peripherally in the nerve). The coma that follows is due to compression of the midbrain against the opposite tentorial edge by the displaced parahippocampal gyrus **(Fig. 19-2)**. Lateral displacement of the midbrain may compress the opposite cerebral peduncle against the tentorial edge, producing a Babinski sign and hemiparesis contralateral to the hemiparesis that resulted from the mass (the Kernohan-Woltman sign). Herniation may also compress the anterior and posterior cerebral arteries as they pass over the tentorial reflections, with resultant brain infarction. The distortions may also entrap portions of the ventricular system, resulting in hydrocephalus.

Central transtentorial herniation denotes a symmetric downward movement of the thalamic structures through the tentorial opening with compression of the upper midbrain **(Fig. 19-1B)**. Miotic pupils and drowsiness are the heralding signs, in contrast to a unilaterally enlarged pupil of the uncal syndrome. Both uncal and central transtentorial herniations cause progressive compression of the brainstem, with initial damage to the midbrain, then the pons, and finally the medulla. The result is an approximate sequence of neurologic signs that corresponds to each affected level. Other forms of herniation are transfalcial herniation (displacement of the cingulate gyrus under the falx and across the midline, **Fig. 19-1C**) and foraminal herniation (downward forcing of the cerebellar tonsils into the foramen magnum, **Fig. 19-1D**), which causes compression of the medulla, respiratory arrest, and death.

A direct relationship between the various configurations of transtentorial herniation and coma is not always found. Drowsiness and stupor can occur with moderate horizontal displacement of the diencephalon (thalamus), before transtentorial herniation is evident. This lateral shift may be quantified on axial images of computed tomography (CT) and magnetic resonance imaging (MRI) scans (Fig. 19-2). In cases of acutely enlarging masses, horizontal displacement of the pineal calcification of 3–5 mm is generally associated with drowsiness, 6–8 mm with stupor, and >9 mm with coma. Intrusion of the medial temporal lobe into the tentorial opening is also apparent on MRI and CT scans as obliteration of the cisterna that surrounds the upper brainstem.



A B

FIGURE 19-2
Coronal (A) and axial (B) magnetic resonance images from a stuporous patient with a left third nerve palsy as a result of a large left-sided subdural hematoma (seen as a gray-white rim). The upper midbrain and lower thalamic regions are compressed and displaced horizontally away from the mass, and there is transtentorial herniation of the medial temporal lobe structures, including the uncus anteriorly. The lateral ventricle opposite to the hematoma has become enlarged as a result of compression of the third ventricle.

Coma due to metabolic disorders

Many systemic metabolic abnormalities cause coma by interrupting the delivery of energy substrates (e.g., oxygen, glucose) or by altering neuronal excitability (drugs and alcohol, anesthesia, and epilepsy). The metabolic abnormalities that produce coma may, in milder forms, induce an acute confusional state. Thus, in metabolic encephalopathies, clouded consciousness and coma are in a continuum.

Cerebral neurons are fully dependent on cerebral blood flow (CBF) and the delivery of oxygen and glucose. CBF is ~75 mL per 100 g/min in gray matter and 30 mL per 100 g/min in white matter (mean ~55 mL per 100 g/min); oxygen consumption is 3.5 mL per 100 g/min, and glucose utilization is 5 mg per 100 g/min. Brain stores of glucose are able to provide energy for ~2 min after blood flow is interrupted, and oxygen stores last 8–10 s after the cessation of blood flow. Simultaneous hypoxia and ischemia exhaust glucose more rapidly. The electroencephalogram (EEG) rhythm in these circumstances becomes diffusely slowed, typical of metabolic encephalopathies, and as substrate delivery worsens, eventually brain electrical activity ceases.

Unlike hypoxia-ischemia, which causes neuronal destruction, most metabolic disorders such as hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and hepatic and renal failure cause only minor neuropathologic changes. The reversible effects of these conditions on the brain are not understood but may result from impaired energy supplies, changes in ion fluxes across neuronal membranes, and neurotransmitter abnormalities. For example, the high ammonia concentration of hepatic coma interferes with cerebral energy metabolism and with the Na^+, K^+-ATPase pump,

www.ketabpezeshki.com (021) 66485457 - 66485438

increases the number and size of astrocytes, and causes increased concentrations of potentially toxic products of ammonia metabolism; it may also affect neurotransmitters, including the production of putative "false" neurotransmitters that are active at receptor sites. Apart from hyperammonemia, which of these mechanisms is of critical importance is not clear. T e mechanism of the encephalopathy of renal failure is also not known. Unlike ammonia, urea does not produce central nervous system (CNS) toxicity, and a multifactorial causation has been proposed for the encephalopathy, including increased permeability of the blood-brain barrier to toxic substances such as organic acids and an increase in brain calcium and cerebrospinal fluid (CSF) phosphate content.

Coma and seizures are common accompaniments of large shifts in sodium and water balance in the brain. T ese changes in osmolarity arise from systemic medical disorders, including diabetic ketoacidosis, the nonketotic hyperosmolar state, and hyponatremia from any cause (e.g., water intoxication, excessive secretion of antidiuretic hormone, or atrial natriuretic peptides). Sodium levels <125 mmol/L induce confusion, and levels <115 mmol/L are typically associated with coma and convulsions. In hyperosmolar coma, the serum osmolarity is generally >350 mosmol/L. Hypercapnia depresses the level of consciousness in proportion to the rise in carbon dioxide (CO_2) tension in the blood. In all of these metabolic encephalopathies, the degree of neurologic change depends to a large extent on the rapidity with which the serum changes occur. T e pathophysiology of other metabolic encephalopathies such as those due to hypercalcemia, hypothyroidism, vitamin B_{12} deficiency, and hypothermia are incompletely understood but must reflect derangements of CNS biochemistry, membrane function, or neurotransmitters.

Epileptic coma

Generalized electrical seizures are associated with coma, even in the absence of motor convulsions (nonconvulsive status epilepticus). T e self-limited coma that follows a seizure, the postictal state, may be due to exhaustion of energy reserves or effects of locally toxic molecules that are the by-product of seizures. T e postictal state produces continuous, generalized slowing of the background EEG activity similar to that of metabolic encephalopathies.

Toxic (including drug-induced) coma

T is common class of encephalopathy is in large measure reversible and leaves no residual damage provided there has not been cardiorespiratory failure. Many drugs and toxins are capable of depressing nervous system function. Some produce coma by affecting both the brainstem nuclei, including the RAS, and the cerebral cortex. T e combination of cortical and brainstem signs, which occurs in certain drug overdoses, may lead to an incorrect diagnosis of structural brainstem disease. Overdose of medications that have atropinic actions produces signs such as dilated pupils, tachycardia, and dry skin; opiate overdose produces pinpoint pupils <1 mm in diameter.

Coma due to widespread damage to the cerebral hemispheres

T is category, comprising a number of unrelated disorders, results from widespread structural cerebral damage that simulates a metabolic disorder of the cortex. Hypoxia-ischemia is perhaps the best characterized and one in which it is not possible initially to distinguish the acute reversible effects of oxygen deprivation of the brain from the subsequent effects of anoxic neuronal damage. Similar widespread cerebral damage may be produced by disorders that occlude small blood vessels throughout the brain; examples include cerebral malaria, thrombotic thrombocytopenic purpura, and hyperviscosity. Diffuse white matter damage from cranial trauma or inflammatory demyelinating diseases can cause a similar coma syndrome.

APPROACH TO THE PATIENT: Coma

A video examination of the comatose patient is shown in Chap. 20.

Acute respiratory and cardiovascular problems should be attended to prior to neurologic assessment. In most instances, a complete medical evaluation, except for vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma. **T e approach to the patient with coma from cranial trauma is discussed in Chap. 44.**

HISTORY T e cause of coma may be immediately evident as in cases of trauma, cardiac arrest, or observed drug ingestion. In the remainder, certain points are useful: (1) the circumstances and rapidity with which neurologic symptoms developed; (2) the antecedent symptoms (confusion, weakness, headache, fever, seizures, dizziness, double vision, or vomiting); (3) the use of medications, drugs, or alcohol; and (4) chronic liver, kidney, lung, heart, or other medical disease. Direct interrogation of family, observers, and ambulance technicians on the scene, in person or by telephone, is an important part of the evaluation when possible.

www.ketabpezeshki.com (021) 66485457 - 66485438

GENERAL PHYSICAL EXAMINATION Fever suggests a systemic infection, bacterial meningitis, encephalitis, heat stroke, neuroleptic malignant syndrome, malignant hyperthermia due to anesthetics, or anticholinergic drug intoxication. Only rarely is fever attributable to a lesion that has disturbed hypothalamic temperature-regulating centers ("central fever"). A slight elevation in temperature may follow vigorous convulsions. Hypothermia is observed with exposure that attends alcohol, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; or extreme hypothyroidism. Hypothermia itself causes coma when the temperature is <31°C (87.8°F). Tachypnea may indicate systemic acidosis or pneumonia or, rarely, infiltration of the brain with lymphoma. Aberrant respiratory patterns that reflect brainstem disorders are discussed below. Marked hypertension suggests hypertensive encephalopathy or cerebral hemorrhage or head injury. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage, myocardial infarction, sepsis, profound hypothyroidism, or Addisonian crisis. The funduscopic examination can detect subarachnoid hemorrhage (subhyaloid hemorrhages), hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes, papilledema), and increased intracranial pressure (ICP) (papilledema). Cutaneous petechiae suggest thrombotic thrombocytopenic purpura, meningococcemia, or a bleeding diathesis associated with an intracerebral hemorrhage. Cyanosis and reddish or anemic skin coloration are other indications of an underlying systemic disease or carbon monoxide as responsible for the coma.

NEUROLOGIC EXAMINATION The patient should be observed without intervention by the examiner. Tossing about in the bed, reaching up toward the face, crossing legs, yawning, swallowing, coughing, or moaning reflect a drowsy state that is close to normal awakeness. Lack of restless movements on one side or an outturned leg suggests a hemiplegia. Intermittent twitching movements of a foot, finger, or facial muscle may be the only sign of seizures. Multifocal myoclonus almost always indicates a metabolic disorder, particularly uremia, anoxia, drug intoxication (especially with lithium or haloperidol), or a prion disease **(Chap. 40)**. In a drowsy and confused patient, bilateral asterixis is a certain sign of metabolic encephalopathy or drug intoxication.

Decorticate rigidity and decerebrate rigidity, or "posturing," describe stereotyped arm and leg movements occurring spontaneously or elicited by sensory stimulation. Flexion of the elbows and wrists and supination of the arm (decorticate posturing) suggests bilateral damage rostral to the midbrain, whereas extension of the elbows and wrists with pronation (decerebrate posturing) indicates damage to motor tracts in the midbrain or caudal diencephalon. The less frequent combination of arm extension with leg flexion or flaccid legs is associated with lesions in the pons. These concepts have been adapted from animal work and cannot be applied with precision to coma in humans. In fact, acute and widespread disorders of any type, regardless of location, frequently cause limb extension, and almost all extensor posturing becomes predominantly flexor as time passes.

LEVEL OF AROUSAL A sequence of increasingly intense stimuli is used to determine the threshold for arousal and the motor response of each side of the body. The results of testing may vary from minute to minute, and serial examinations are useful. Tickling the nostrils with a cotton wisp is a moderate stimulus to arousal—all but deeply stuporous and comatose patients will move the head away and arouse to some degree. An even greater degree of responsiveness is present if the patient uses his hand to remove an offending stimulus. Pressure on the knuckles or bony prominences and pinprick stimulation are humane forms of noxious stimuli; pinching the skin causes unsightly ecchymoses and is generally not necessary but may be useful in eliciting abduction withdrawal movements of the limbs. Posturing in response to noxious stimuli indicates severe damage to the corticospinal system, whereas abduction-avoidance movement of a limb is usually purposeful and denotes an intact corticospinal system. Posturing may also be unilateral and coexist with purposeful limb movements, reflecting incomplete damage to the motor system.

BRAINSTEM REFLEXES Assessment of brainstem function is essential to localization of the lesion in coma **(Fig. 19-3)**. The brainstem reflexes that are examined are pupillary size and reaction to light, spontaneous and elicited eye movements, corneal responses, and the respiratory pattern. As a rule, coma due to bilateral hemispheral disease preserves these brainstem activities, particularly the pupillary reactions and eye movements. However, the presence of abnormal brainstem signs does not always indicate that the primary lesion is in the brainstem because hemispheral masses can cause secondary brainstem damage by the earlier described transtentorial herniations.

Pupillary signs Pupillary reactions are examined with a bright, diffuse light (preferably not an ophthalmoscope, which illuminates only a limited part of the retina). Reactive and round pupils of midsize (2.5–5 mm) essentially exclude midbrain damage, either primary or secondary to compression. A response to light may be difficult to appreciate in pupils <2 mm in diameter, and bright room lighting mutes pupillary reactivity. One enlarged and poorly reactive pupil (>6 mm) signifies compression or stretching of the third nerve from the effects of a cerebral mass above. Enlargement of the pupil contralateral to a hemispheral mass may occur but is infrequent. An oval and slightly eccentric pupil is a transitional sign that accompanies early midbrain–third nerve compression.

www.ketabpezeshki.com (021) 66485457 - 66485438

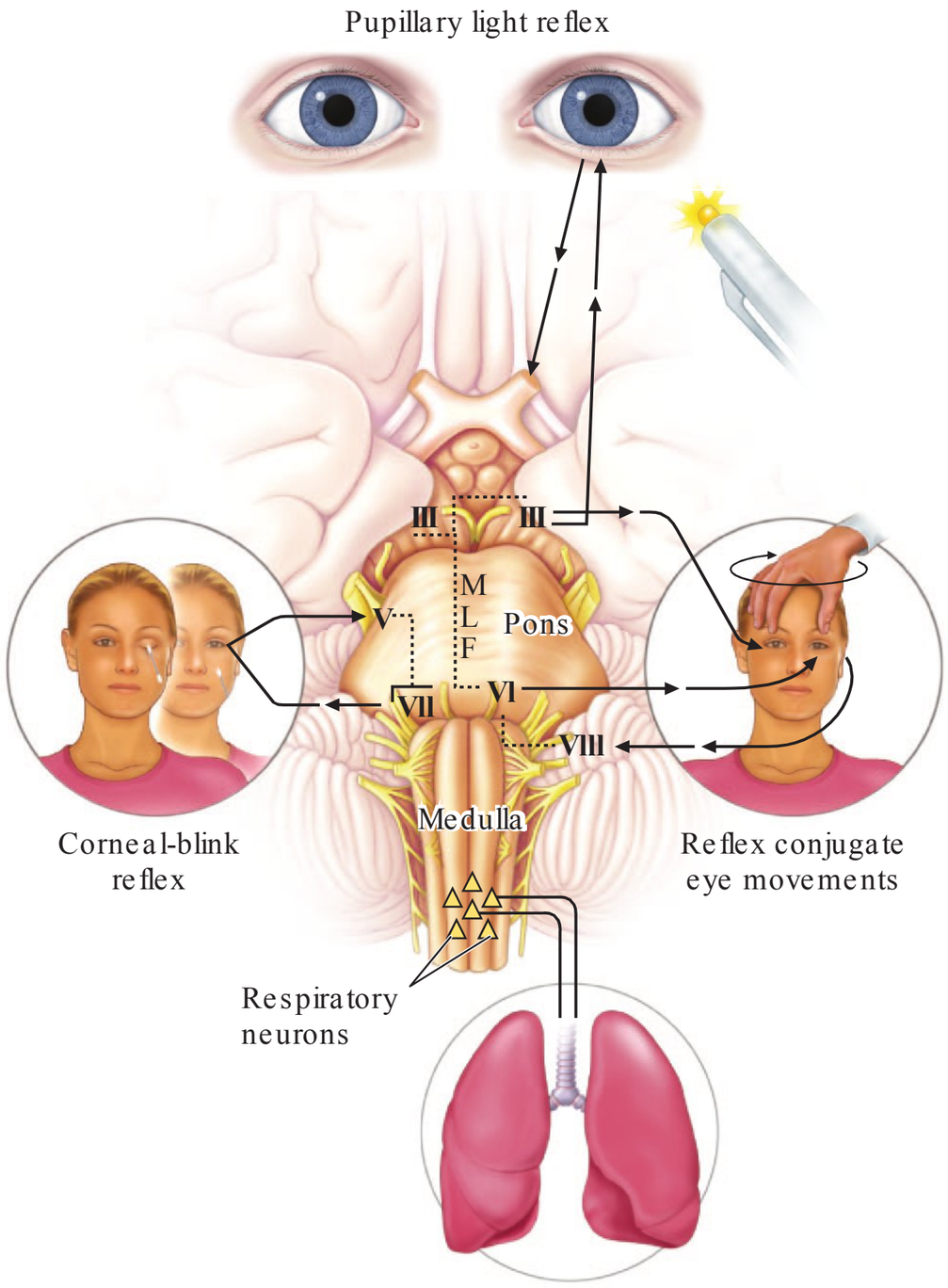


FIGURE 19-3
Examination of brainstem reflexes in coma. Midbrain and third nerve function are tested by pupillary reaction to light, pontine function by spontaneous and reflex eye movements and corneal responses, and medullary function by respiratory and pharyngeal responses. Reflex conjugate, horizontal eye movements are dependent on the medial longitudinal fasciculus (MLF) interconnecting the sixth and contralateral third nerve nuclei. Head rotation (oculocephalic reflex) or caloric stimulation of the labyrinths (oculovestibular reflex) elicits contraversive eye movements (for details see text).

The most extreme pupillary sign, bilaterally dilated and unreactive pupils, indicates severe midbrain damage, usually from compression by a supratentorial mass. Ingestion of drugs with anticholinergic activity, the use of mydriatic eye drops, and direct ocular trauma are among the causes of misleading pupillary enlargement.

Unilateral miosis in coma has been attributed to dysfunction of sympathetic efferents originating in the posterior hypothalamus and descending in the tegmentum of the brainstem to the cervical cord. It is therefore of limited localizing value but is an occasional finding in patients with a large cerebral hemorrhage that affects the thalamus. Reactive and bilaterally small (1–2.5 mm) but not pinpoint pupils are seen in metabolic encephalopathies or in deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage. Even smaller reactive pupils (<1 mm) characterize narcotic or barbiturate overdoses but also occur with extensive pontine hemorrhage. The response to naloxone and the presence of reflex eye movements (see below) assist in distinguishing between these.

Ocular movements The eyes are first observed by elevating the lids and observing the resting position and spontaneous movements of the globes. Lid tone, tested by lifting the eyelids and noting their resistance to opening and the speed of closure, is progressively reduced as unresponsiveness progresses. Horizontal divergence of the eyes at rest is normal in drowsiness. As coma deepens, the ocular axes may become parallel again.

Spontaneous eye movements in coma often take the form of conjugate horizontal roving. This finding alone exonerates damage in the midbrain and pons and has the same significance as normal reflex eye movements (see below). Conjugate horizontal ocular deviation to one side indicates damage to the pons on the opposite side or, alternatively, to the frontal lobe on the same side. This phenomenon is summarized by the following maxim: The eyes look toward a hemispheral lesion and away from a brainstem lesion. Seizures also drive the eyes to one side but usually with superimposed clonic movements of the globes. The eyes may occasionally turn paradoxically away from the side of a deep hemispheral lesion ("wrong-way eyes"). The eyes turn down and inward with thalamic and upper midbrain lesions, typically thalamic hemorrhage. "Ocular bobbing" describes brisk downward and slow upward movements of the eyes associated with loss of horizontal eye movements and is diagnostic of bilateral pontine damage, usually from thrombosis of the basilar artery. "Ocular dipping" is a slower, arrhythmic downward movement followed by a faster upward movement in patients with normal reflex horizontal gaze; it usually indicates diffuse cortical anoxic damage.

The oculocephalic reflexes, elicited by moving the head from side to side or vertically and observing eye movements in the direction opposite to the head movement, depend on the integrity of the ocular motor nuclei and their interconnecting tracts that extend from the midbrain to the pons and medulla (Fig. 19-3). The movements, called somewhat inappropriately "doll's eyes" (which refers more accurately to the reflex elevation of the eyelids with flexion of the neck), are normally suppressed in the awake patient. The ability to elicit them therefore reflects both reduced cortical influence on the brainstem and intact brainstem pathways, indicating that coma is caused by a lesion or dysfunction in the cerebral hemispheres. The opposite, an absence of reflex eye movements, usually signifies damage within the brainstem but can result from overdoses of certain drugs. In this circumstance, normal pupillary size and light reaction distinguishes most drug-induced comas from structural brainstem damage.

www.ketabpezeshki.com (021) 66485457 - 66485438

Thermal, or "caloric," stimulation of the vestibular apparatus (oculovestibular response) provides a more intense stimulus for the oculocephalic reflex but provides essentially the same information. The test is performed by irrigating the external auditory canal with cool water in order to induce convection currents in the labyrinths. After a brief latency, the result is tonic deviation of both eyes to the side of cool-water irrigation and nystagmus in the opposite direction. (The acronym "COWS" has been used to remind generations of medical students of the direction of nystagmus—"cold water opposite, warm water same.") The loss of induced conjugate ocular movements indicates brainstem damage. The presence of corrective nystagmus indicates that the frontal lobes are functioning and connected to the brainstem; thus catatonia or hysterical coma is likely.

By touching the cornea with a wisp of cotton, a response consisting of brief bilateral lid closure is normally observed. The corneal reflex depends on the integrity of pontine pathways between the fifth (afferent) and both seventh (efferent) cranial nerves; in conjunction with reflex eye movements, it is a useful test of pontine function. CNS-depressant drugs diminish or eliminate the corneal responses soon after reflex eye movements are paralyzed but before the pupils become unreactive to light. The corneal (and pharyngeal) response may be lost for a time on the side of an acute hemiplegia.

Respiratory patterns These are of less localizing value in comparison to other brainstem signs. Shallow, slow, but regular breathing suggests metabolic or drug depression. Cheyne-Stokes respiration in its typical cyclic form, ending with a brief apneic period, signifies bihemispheral damage or metabolic suppression and commonly accompanies light coma. Rapid, deep (Kussmaul) breathing usually implies metabolic acidosis but may also occur with pontomesencephalic lesions. Agonal gasps are the result of lower brainstem (medullary) damage and are recognized as the terminal respiratory pattern of severe brain damage. A number of other cyclic breathing variations have been described but are of lesser significance.

LABORATORY STUDIES AND IMAGING

The studies that are most useful in the diagnosis of coma are chemical-toxicologic analysis of blood and urine, cranial CT or MRI, EEG, and CSF examination. Arterial blood gas analysis is helpful in patients with lung disease and acid-base disorders. The metabolic aberrations commonly encountered in clinical practice are usually exposed by measurement of electrolytes, glucose, calcium, osmolarity, and renal (blood urea nitrogen) and hepatic (NH_3) function. Toxicologic analysis may be necessary in any case of acute coma where the diagnosis is not immediately clear. However, the presence of exogenous drugs or toxins, especially alcohol, does not exclude the possibility that other factors, particularly head trauma, are also contributing to the clinical state. An ethanol level of 43 mmol/L (0.2 g/dL) in nonhabituated patients generally causes impaired mental activity; a level of >65 mmol/L (0.3 g/dL) is associated with stupor. The development of tolerance may allow the chronic alcoholic to remain awake at levels >87 mmol/L (0.4 g/dL).

The availability of CT and MRI has focused attention on causes of coma that are detectable by imaging (e.g., hemorrhage, tumor, or hydrocephalus). Resorting primarily to this approach, although at times expedient, is imprudent because most cases of coma (and confusion) are metabolic or toxic in origin. Furthermore, the notion that a normal CT scan excludes an anatomic lesion as the cause of coma is erroneous. Bilateral hemisphere infarction, acute brainstem infarction, encephalitis, meningitis, mechanical shearing of axons as a result of closed head trauma, sagittal sinus thrombosis, and subdural hematoma isodense to adjacent brain are some of the disorders that may not be detected. Nevertheless, if the source of coma remains unknown, a scan should be obtained.

The EEG **(Chap. 6)** is useful in metabolic or drug-induced states but is rarely diagnostic. However, it is the essential test to reveal coma that is due to clinically unrecognized, nonconvulsive seizures, and shows fairly characteristic patterns in herpesvirus encephalitis and prion (Creutzfeldt-Jakob) disease. The EEG may be further helpful in disclosing generalized slowing of the background activity, a reflection of the severity of an encephalopathy. Predominant high-voltage slowing (δ or triphasic waves) in the frontal regions is typical of metabolic coma, as from hepatic failure, and widespread fast (β) activity implicates sedative drugs (e.g., benzodiazepines). A special pattern of "alpha coma," defined by widespread, variable 8- to 12-Hz activity, superficially resembles the normal α rhythm of waking but, unlike normal α activity, is not altered by environmental stimuli. Alpha coma results from pontine or diffuse cortical damage and is associated with a poor prognosis. Normal α activity on the EEG, which is suppressed by stimulating the patient, also alerts the clinician to the locked-in syndrome or to hysteria or catatonia. Still, the most important use of EEG recordings in coma is to reveal clinically inapparent epileptic discharges.

Lumbar puncture is performed less frequently than in the past for coma diagnosis because neuroimaging effectively excludes intracerebral and extensive subarachnoid hemorrhage. However, examination of the CSF remains indispensable in the diagnosis of meningitis and encephalitis. For patients with an altered level of consciousness, it is generally recommended that an imaging study be performed prior to lumbar puncture to exclude a large intracranial mass lesion. Blood culture and antibiotic administration usually precede the imaging study if meningitis is suspected **(Chap. 46)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

DIFFERENTIAL DIAGNOSIS OF COMA

(Table 19-1) The causes of coma can be divided into three broad categories: those cases without focal neurologic signs (e.g., metabolic and toxic encephalopathies); meningitis syndromes, characterized by fever or stiff neck and an excess of cells in the spinal fluid (e.g., bacterial meningitis, subarachnoid hemorrhage, encephalitis); and diseases associated with prominent focal signs (e.g., stroke, cerebral hemorrhage). Conditions that cause sudden coma include drug ingestion, cerebral hemorrhage, trauma, cardiac arrest, epilepsy, and basilar artery occlusion from an embolism. Coma that appears subacutely is usually related to a preexisting medical or neurologic problem or, less often, to secondary brain swelling surrounding a mass such as tumor or cerebral infarction.

The diagnosis of coma due to cerebrovascular disease can be difficult **(Chap. 32)**. The most common diseases are (1) basal ganglia and thalamic hemorrhage (acute but not instantaneous onset, vomiting, headache, hemiplegia, and characteristic eye signs); (2) pontine hemorrhage (sudden onset, pinpoint pupils, loss of reflex eye movements and corneal responses, ocular bobbing, posturing, and hyperventilation); (3) cerebellar hemorrhage (occipital headache, vomiting, gaze paresis, and inability to stand and walk); (4) basilar artery thrombosis (neurologic prodrome or warning spells, diplopia, dysarthria, vomiting, eye movement and corneal response abnormalities, and asymmetric limb paresis); and (5) subarachnoid hemorrhage (precipitous coma after sudden severe headache and vomiting). The most common stroke, infarction in the territory of the middle cerebral artery, does not cause coma, but edema surrounding large infarctions may expand over several days and cause coma from mass effect.

The syndrome of acute hydrocephalus accompanies many intracranial diseases, particularly subarachnoid hemorrhage. It is characterized by headache and sometimes vomiting that may progress quickly to coma with extensor posturing of the limbs, bilateral Babinski signs, small unreactive pupils, and impaired oculocephalic movements in the vertical direction.

The majority of medical causes of coma can be established without a neuroimaging study but if the history and examination do not indicate the cause of coma, CT or MRI is needed. Sometimes imaging results can be misleading such as when small subdural hematomas or old strokes are found, but the patient's coma is due to intoxication.

TABLE 19-1

DIFFERENTIAL DIAGNOSIS OF COMA

1. Diseases that cause no focal or lateralizing neurologic signs, usually with normal brainstem functions; CT scan and cellular content of the CSF are normal
   a. Intoxications: alcohol, sedative drugs, opiates, etc.
   b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
   c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
   d. Shock from any cause
   e. Postseizure states, status epilepticus, nonconvulsive status epilepticus
   f. Hypertensive encephalopathy, eclampsia
   g. Severe hyperthermia, hypothermia
   h. Concussion
   i. Acute hydrocephalus
2. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF, usually without focal or lateralizing cerebral or brainstem signs; CT or MRI shows no mass lesion
   a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
   b. Acute bacterial meningitis
   c. Viral encephalitis
   d. Miscellaneous: fat embolism, cholesterol embolism, carcinomatous and lymphomatous meningitis, etc.
3. Diseases that cause focal brainstem or lateralizing cerebral signs, with or without changes in the CSF; CT and MRI are abnormal
   a. Hemispheral hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
   b. Brainstem infarction due to basilar artery thrombosis or embolism
   c. Brain abscess, subdural empyema
   d. Epidural and subdural hemorrhage, brain contusion
   e. Brain tumor with surrounding edema
   f. Cerebellar and pontine hemorrhage and infarction
   g. Widespread traumatic brain injury
   h. Metabolic coma (see above) with preexisting focal damage
   i. Miscellaneous: Cortical vein thrombosis, herpes simplex encephalitis, multiple cerebral emboli due to bacterial endocarditis, acute hemorrhagic leukoencephalitis, acute disseminated (postinfectious) encephalomyelitis, thrombotic thrombocytopenic purpura, cerebral vasculitis, gliomatosis cerebri, pituitary apoplexy, intravascular lymphoma, etc.

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; RBCs, red blood cells; WBCs, white blood cells.

BRAIN DEATH

This is a state of irreversible cessation of all cerebral function with preservation of cardiac activity and maintenance of respiratory and somatic function by artificial means. It is the only type of brain damage recognized as equivalent to death. Criteria have been advanced for the diagnosis of brain death, and it is essential to adhere to standards endorsed by the local medical community. Ideal criteria are simple, can be assessed at the bedside, and allow no chance of diagnostic error. They

www.ketabpezeshki.com (021) 66485457 - 66485438

contain three essential elements: (1) widespread cortical destruction that is reflected by deep coma and unresponsiveness to all forms of stimulation; (2) global brainstem damage demonstrated by absent pupillary light reaction and by the loss of oculovestibular and corneal reflexes; and (3) destruction of the medulla, manifested by complete and irreversible apnea. T e heart rate is invariant and does not accelerate to atropine. Diabetes insipidus is usually present but may only develop hours or days after the other clinical signs of brain death. T e pupils are usually midsized but may be enlarged; they should not, however, be small. Loss of deep tendon reflexes is not required because the spinal cord remains functional. Babinski signs are generally absent and the toe response is instead, often flexor.

Demonstration that apnea is due to structural medullary damage requires that the Pco_2 be high enough to stimulate respiration during a test of spontaneous breathing. Apnea testing can be done safely by the use of diffusion oxygenation prior to removing the ventilator. T is is accomplished by preoxygenation with 100% oxygen, which is then sustained during the test by oxygen administered through a tracheal cannula. CO_2 tension increases ~0.3–0.4 kPa/min (2–3 mmHg/min) during apnea. At the end of a period of observation, typically several minutes, arterial Pco_2 should be at least >6.6–8.0 kPa (50–60 mmHg) for the test to be valid. Apnea is confirmed if no respiratory effort has been observed in the presence of a suf ciently elevated Pco_2. Other techniques, including the administration of CO_2 to accelerate the test, are used in special circumstances. T e apnea test is usually stopped if there is serious cardiovascular instability.

An isoelectric EEG may be used as a confirmatory test for total cerebral damage. Radionuclide brain scanning, cerebral angiography, or transcranial Doppler measurements may also be included to demonstrate the absence of CBF, but they have not been as extensively correlated with pathologic changes.

T e possibility of profound drug-induced or hypothermic depression of the nervous system must be excluded, and some period of observation, usually 6–24 h, is desirable, during which the clinical signs of brain death are sustained. It is advisable to delay clinical testing for at least 24 h if a cardiac arrest has caused brain death or if the inciting disease is not known.

Although it is largely accepted in Western society that the respirator can be disconnected from a brain-dead patient and that organ donation is subsequently possible, problems frequently arise because of poor communication and inadequate preparation of the family by the physician. Reasonable medical practice, ideally with the agreement of the family, also allows the removal of support or transfer out of an intensive care unit of patients who are not brain dead but whose neurologic conditions are nonetheless hopeless.

TREATMENT Coma

T e immediate goal in a comatose patient is prevention of further nervous system damage. Hypotension, hypoglycemia, hypercalcemia, hypoxia, hypercapnia, and hyperthermia should be corrected rapidly. An oropharyngeal airway is adequate to keep the pharynx open in a drowsy patient who is breathing normally. Tracheal intubation is indicated if there is apnea, upper airway obstruction, hypoventilation, or emesis, or if the patient is liable to aspirate because of coma. Mechanical ventilation is required if there is hypoventilation or a need to induce hypocapnia in order to lower ICP. IV access is established, and naloxone and dextrose are administered if narcotic overdose or hypoglycemia is a possibility; thiamine is given along with glucose to avoid provoking Wernicke's disease in malnourished patients. In cases of suspected basilar thrombosis with brainstem ischemia, IV heparin or a thrombolytic agent is often used, after cerebral hemorrhage has been excluded by a neuroimaging study. Physostigmine may awaken patients with anticholinergic-type drug overdose but should be used only with careful monitoring; many physicians believe that it should only be used to treat anticholinergic overdose–associated cardiac arrhythmias. T e use of benzodiazepine antagonists offers some prospect of improvement after overdose of soporific drugs and has transient benefit in hepatic encephalopathy. Certain other toxic and drug-induced comas have specific treatments such as fomepizole for ethylene glycol ingestion.

Administration of hypotonic intravenous solutions should be monitored carefully in any serious acute brain illness because of the potential for exacerbating brain swelling. Cervical spine injuries must not be overlooked, particularly before attempting intubation or evaluation of oculocephalic responses. Fever and meningismus indicate an urgent need for examination of the CSF to diagnose meningitis. If the lumbar puncture in a case of suspected meningitis is delayed, an antibiotic such as a third-generation cephalosporin may be administered, preferably after obtaining blood cultures. **T e management of raised ICP is discussed in Chap. 33.**

PROGNOSIS

One hopes to avoid the dif cult outcome of a patient who is left severely disabled or vegetative. Children and young adults may have ominous early clinical findings such as abnormal brainstem reflexes and yet recover; temporization in offering a prognosis in this group of patients is wise. Metabolic comas have a far better prognosis than traumatic ones. All systems for estimating prognosis in adults should be taken as approximations, and medical judgments must be tempered by factors such as age, underlying systemic disease, and general medical condition. In an attempt to collect prognostic information from large numbers of patients with head injury, the Glasgow Coma Scale was devised; empirically,

www.ketabpezeshki.com (021) 66485457 - 66485438

it has predictive value in cases of brain trauma (see Table 44-1). For anoxic and metabolic coma, clinical signs such as the pupillary and motor responses after 1 day, 3 days, and 1 week have been shown to have predictive value. Other studies suggest that the absence of corneal responses may have the most discriminative value. T e absence of the cortical waves of the somatosensory evoked potentials has also proved a strong indicator of poor outcome in coma from any cause.

T e uniformly poor outcome of the prolonged vegetative state has already been mentioned, but recent reports that a small number of such patients display consistent cortical activation on functional MRI in response to salient stimuli have begun to alter the perception of the possible internal mental milieu of such individuals. T ese findings do not change the poor prognosis. For example, in one series, about 10% of vegetative patients after traumatic brain injury could activate their frontal or temporal lobes in response to requests by an examiner to imagine certain visuospatial tasks. In one case, a rudimentary form of communication could be established. T ere are also reports in exceptional patients of improvement in cognitive function with the implantation of thalamic-stimulating electrodes. It is prudent to avoid generalizations from these findings.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 20

EXAMINATION OF THE COMATOSE PATIENT

S. Andrew Josephson

T is chapter features a video illustrating the examination of a comatose patient. Proper techniques are demonstrated and supplemented with a discussion of interpretation of f ndings and implications for management. Also included is an overview of coma and its anatomic basis.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 20–1. Examination of the comatose patient

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 21

DEMENTIA

William W. Seeley ■ Bruce L. Miller

Dementia, a syndrome with many causes, affects >5 million people in the United States and results in a total annual health care cost between $157 and $215 billion. Dementia is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Episodic memory, the ability to recall events specific in time and place, is the cognitive function most commonly lost; 10% of persons age >70 years and 20–40% of individuals age >85 years have clinically identifiable memory loss. In addition to memory, dementia may erode other mental faculties, including language, visuospatial, praxis, calculation, judgment, and problem-solving abilities. Neuropsychiatric and social deficits also arise in many dementia syndromes, manifesting as depression, apathy, anxiety, hallucinations, delusions, agitation, insomnia, sleep disturbances, compulsions, or disinhibition. T e clinical course may be slowly progressive, as in Alzheimer's disease (AD); static, as in anoxic encephalopathy; or may fluctuate from day to day or minute to minute, as in dementia with Lewy bodies. Most patients with AD, the most prevalent form of dementia, begin with episodic memory impairment, although in other dementias, such as frontotemporal dementia, memory loss is not typically a presenting feature. **Focal cerebral disorders are discussed in Chap. 22 and illustrated in a video library in Chap. 23; the pathogenesis of AD and related disorders is discussed in Chap. 35**.

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementia syndromes result from the disruption of specific large-scale neuronal networks; the location and severity of synaptic and neuronal loss combine to produce the clinical features **(Chap. 22)**. Behavior, mood, and attention are modulated by ascending noradrenergic, serotonergic, and dopaminergic pathways, whereas cholinergic signaling is critical for attention and memory functions. T e dementias differ in the relative neurotransmitter deficit profiles; accordingly, accurate diagnosis guides effective pharmacologic therapy.

AD begins in the entorhinal region of the medial temporal lobe, spreads to the hippocampus, and then moves to lateral and posterior temporal and parietal neocortex, eventually causing a more widespread degeneration. Vascular dementia is associated with focal damage in a variable patchwork of cortical and subcortical regions or white matter tracts that disconnect nodes within distributed networks. In keeping with its anatomy, AD typically presents with episodic memory loss accompanied later by aphasia or navigational problems. In contrast, dementias that begin in frontal or subcortical regions, such as frontotemporal dementia (FTD) or Huntington's disease (HD), are less likely to begin with memory problems and more likely to present with difficulties with judgment, mood, executive control, movement, and behavior.

Lesions of frontal-striatal[1] pathways produce specific and predictable effects on behavior. T e dorsolateral prefrontal cortex has connections with a central band of the caudate nucleus. Lesions of either the caudate or dorsolateral prefrontal cortex, or their connecting white matter pathways, may result in executive dysfunction, manifesting as poor organization and planning, decreased cognitive flexibility, and impaired working memory. T e lateral orbital frontal cortex connects with the ventromedial caudate, and lesions of this system cause impulsiveness, distractibility, and disinhibition. T e anterior cingulate cortex and adjacent medial prefrontal cortex project to the nucleus accumbens, and

[1]T e striatum comprises the caudate/putamen.

www.ketabpezeshki.com (021) 66485457 - 66485438

interruption of this system produces apathy, poverty of speech, emotional blunting, or even akinetic mutism. All corticostriatal systems also include topographically organized projections through the globus pallidus and thalamus, and damage to these nodes can likewise reproduce the clinical syndrome of cortical or striatal injury.

THE CAUSES OF DEMENTIA

The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade over age 50 and is usually associated with the microscopic changes of AD at autopsy. Yet some centenarians have intact memory function and no evidence of clinically significant dementia. Whether dementia is an inevitable consequence of normal human aging remains controversial.

The many causes of dementia are listed in **Table 21-1**. The frequency of each condition depends on the age group under study, access of the group to medical care, country of origin, and perhaps racial or ethnic background. AD is the most common cause of dementia in Western countries, accounting for more than half of all patients. Vascular disease is considered the second most frequent cause for dementia and is particularly common in elderly patients or populations with limited access to medical care, where vascular risk factors are undertreated. Often, vascular brain injury is mixed with neurodegenerative disorders, making it difficult, even for the neuropathologist, to estimate the contribution of cerebrovascular disease to the cognitive disorder in an individual patient. Dementias associated with Parkinson's disease (PD) **(Chap. 36)** are common and may develop years after onset of a parkinsonian disorder, as seen with PD-related dementia (PDD), or can occur concurrently with or preceding the motor syndrome, as in dementia with Lewy bodies (DLB). In patients under the age of 65, FTD rivals AD as the most common cause of dementia. Chronic intoxications, including those resulting from alcohol and prescription drugs, are an important and often treatable cause of dementia. Other disorders listed in Table 21-1 are uncommon but important because many are reversible. The classification of dementing illnesses into reversible and irreversible disorders is a useful approach to differential diagnosis. When effective treatments for the neurodegenerative conditions emerge, this dichotomy will become obsolete.

In a study of 1000 persons attending a memory disorders clinic, 19% had a potentially reversible cause of the cognitive impairment and 23% had a potentially reversible concomitant condition that may have contributed to the patient's impairment. The three most common potentially reversible diagnoses were depression, normal pressure hydrocephalus (NPH), and alcohol dependence; medication side effects are also

TABLE 21-1

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism[a]
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication[a]
Diffuse white matter disease (Binswanger's)	
Less Common Causes of Dementia	
Vitamin deficiencies	Toxic disorders
Thiamine (B_1): Wernicke's encephalopathy[a]	Drug, medication, and narcotic poisoning[a]
B_{12} (subacute combined degeneration)[a]	Heavy metal intoxication[a]
Nicotinic acid (pellagra)[a]	Organic toxins
Endocrine and other organ failure	Psychiatric
Hypothyroidism[a]	Depression (pseudodementia)[a]
Adrenal insufficiency and Cushing's syndrome[a]	Schizophrenia[a]
Hypo- and hyperparathyroidism[a]	Conversion disorder[a]
Renal failure[a]	Degenerative disorders
Liver failure[a]	Huntington's disease
Pulmonary failure[a]	Multisystem atrophy
Chronic infections	Hereditary ataxias (some forms)
HIV	Frontotemporal lobar degeneration spectrum
Neurosyphilis[a]	Multiple sclerosis
Papovavirus (JC virus) (progressive multifocal leukoencephalopathy)	Adult Down's syndrome with Alzheimer's disease
Tuberculosis, fungal, and protozoal[a]	ALS-parkinsonism-dementia complex of Guam
Whipple's disease[a]	Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
Head trauma and diffuse brain damage	Miscellaneous
Chronic traumatic encephalopathy	Sarcoidosis[a]
Chronic subdural hematoma[a]	Vasculitis[a]
Postanoxia	CADASIL, etc.
Postencephalitis	Acute intermittent porphyria[a]
Normal-pressure hydrocephalus[a]	Recurrent nonconvulsive seizures[a]
Intracranial hypotension	Additional conditions in children or adolescents
Neoplastic	Pantothenate kinase–associated neurodegeneration
Primary brain tumor[a]	Subacute sclerosing panencephalitis
Metastatic brain tumor[a]	Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)
Paraneoplastic/autoimmune limbic encephalitis[a]	

[a]Potentially reversible dementia.

Abbreviations: ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

www.ketabpezeshki.com (021) 66485457 - 66485438

common and should be considered in every patient (Table 21-1).

Subtle cumulative decline in episodic memory is a common part of aging. T is frustrating experience, of en the source of jokes and humor, is referred to as benign forgetfulness of the elderly. Benign means that it is not so progressive or serious that it impairs reasonably successful and productive daily functioning, although the distinction between benign and more significant memory loss can be difficult to make. At age 85, the average person is able to learn and recall approximately one-half of the items (e.g., words on a list) that he or she could at age 18. A measurable cognitive problem that does not seriously disrupt daily activities is of en referred to as mild cognitive impairment (MCI). Factors that predict progression from MCI to an AD dementia include a prominent memory deficit, family history of dementia, presence of an apolipoprotein ε4 (Apo ε4) allele, small hippocampal volumes, an AD-like signature of cortical atrophy, low cerebrospinal fluid Aβ, and elevated tau or evidence of brain amyloid deposition on positron emission tomography (PET) imaging.

T e major degenerative dementias include AD, DLB, FTD and related disorders, HD, and prion diseases, including Creutzfeldt-Jakob disease (CJD). T ese disorders are all associated with the abnormal aggregation of a specific protein: $A\beta_{42}$ and tau in AD; α-synuclein in DLB; tau, TAR DNA-binding protein of 43 kDa (TDP-43), or fused in sarcoma (FUS) in FTD; huntingtin in HD; and misfolded prion protein (PrP^{sc}) in CJD **(Table 21-2)**.

APPROACH TO THE PATIENT: Dementias

T ree major issues should be kept at the forefront: (1) What is the best fit for a clinical diagnosis? (2) What component of the dementia syndrome is treatable or reversible? (3) Can the physician help to alleviate the burden on caregivers? A broad overview of the approach to dementia is shown in **Table 21-3**. T e major degenerative dementias can usually be distinguished by the initial symptoms; neuropsychological, neuropsychiatric, and neurologic findings; and neuroimaging features **(Table 21-4)**.

HISTORY T e history should concentrate on the onset, duration, and tempo of progression. An acute or subacute onset of confusion may be due to delirium **(Chap. 18)** and should trigger the search for intoxication, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include difficulty with managing money, driving, shopping, following instructions, finding words, or navigating. Personality change, disinhibition, and weight gain or compulsive eating suggest FTD, not AD. FTD is also suggested by prominent apathy, compulsivity, loss of empathy for others, or progressive loss of speech fluency or single-word comprehension and by a relative sparing of memory and visuospatial abilities. T e diagnosis of DLB is suggested by early visual hallucinations; parkinsonism; proneness to delirium or sensitivity to psychoactive medications; rapid

TABLE 21-2

THE MOLECULAR BASIS FOR DEGENERATIVE DEMENTIA

DEMENTIA	MOLECULAR BASIS	CAUSAL GENES (CHROMOSOME)	SUSCEPTIBILITY GENES	PATHOLOGIC FINDINGS
AD	Aβ/tau	APP (21), PS-1 (14), PS-2 (1) (<2% carry these mutations, most often in PS-1)	Apo ε4 (19)	Amyloid plaques, neurofibrillary tangles, and neuropil threads
FTD	Tau	MAPT exon and intron mutations (17) (about 10% of familial cases)	H1 MAPT haplotype	Tau neuronal and glial inclusions varying in morphology and distribution
	TDP-43	GRN (10% of familial cases), C9ORF72 (20–30% of familial cases), rare VCP, very rare TARDBP		TDP-43 neuronal and glial inclusions varying in morphology and distribution
	FUS	Very rare FUS		FUS neuronal and glial inclusions varying in morphology and distribution
DLB	α-Synuclein	Very rare SNCA (4)	Unknown	α-Synuclein neuronal inclusions (Lewy bodies)
CJD	PrP^{SC}	PRNP (20) (up to 15% of patients carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	PrP^{SC} deposition, panlaminar spongiosis

Abbreviations: AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 21-3

ROUTINE EVALUATION	OPTIONAL FOCUSED TESTS	OCCASIONALLY HELPFUL TESTS
History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B_{12}	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
		Lab screen for autoantibodies
DIAGNOSTIC CATEGORIES		
REVERSIBLE CAUSES	**IRREVERSIBLE/DEGENERATIVE DEMENTIAS**	**PSYCHIATRIC DISORDERS**
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Autoimmune encephalopathy		
ASSOCIATED TREATABLE CONDITIONS		
	Depression	Agitation
	Seizures	Caregiver "burnout"
	Insomnia	Drug side effects

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

eye movement (REM) behavior disorder (RBD; the loss of skeletal muscle paralysis during dreaming); or Capgras syndrome, the delusion that a familiar person has been replaced by an impostor.

A history of stroke with irregular stepwise progression suggests vascular dementia. Vascular dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. In patients suffering from cerebrovascular disease, it can be difficult to determine whether the dementia is due to AD, vascular disease, or a mixture of the two because many of the risk factors for vascular dementia, including diabetes, high cholesterol, elevated homocysteine, and low exercise, are also putative risk factors for AD. Moreover, many patients with a major vascular contribution to their dementia lack a history of stepwise decline. Rapid progression with motor rigidity and myoclonus suggests CJD **(Chap. 40)**. Seizures may indicate strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD. Gait disturbance is common in vascular dementia, PD/DLB, or NPH. A history of high-risk sexual behaviors or intravenous drug use should trigger a search for central nervous system (CNS) infection, especially HIV or syphilis. A history of recurrent head trauma could indicate chronic subdural hematoma, chronic traumatic encephalopathy (a progressive dementia best characterized in contact sport athletes such as boxers and American football players), intracranial hypotension, or NPH. Subacute onset of severe amnesia and psychosis with mesial temporal T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities on magnetic resonance imaging (MRI) should raise concern for paraneoplastic limbic encephalitis, especially in a long-term smoker or other patients at risk for cancer. Related autoimmune conditions, such as voltage-gated potassium channel (VGKC)- or N-methyl-d-aspartate (NMDA)-receptor antibody-mediated encephalopathy, can present with a similar tempo and imaging signature with or without characteristic motor manifestations such as myokymia (anti-VGKC) and faciobrachial dystonic seizures (anti-NMDA). Alcohol abuse creates risk for malnutrition and thiamine deficiency. Veganism, bowel irradiation, an autoimmune diathesis, a remote history of gastric surgery, and chronic antihistamine therapy for dyspepsia or gastroesophageal reflux predispose to B_{12}

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 21-4

CLINICAL DIFFERENTIATION OF THE MAJOR DEMENTIAS

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confuent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fuid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement.

deficiency. Certain occupations, such as working in a battery or chemical factory, might indicate heavy metal intoxication. Careful review of medication intake, especially for sedatives and analgesics, may raise the issue of chronic drug intoxication. An autosomal dominant family history is found in HD and in familial forms of AD, FTD, DLB, or prion disorders. A history of mood disorders, the recent death of a loved one, or depressive signs, such as insomnia or weight loss, raise the possibility of depression-related cognitive impairments.

PHYSICAL AND NEUROLOGIC EXAMINATION A thorough general and neurologic examination is essential to document dementia, to look for other signs of nervous system involvement, and to search for clues suggesting a systemic disease that might be responsible for the cognitive disorder. Typical AD spares motor systems until later in the course. In contrast, FTD patients of en develop axial rigidity, supranuclear gaze palsy, or a motor neuron disease reminiscent of amyotrophic lateral sclerosis (ALS). In DLB, the initial symptoms may include the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinating gait), but DLB of en starts with visual hallucinations or dementia. Symptoms referable to the lower brainstem (RBD, gastrointestinal or autonomic problems) may arise years or even decades before parkinsonism or dementia. Corticobasal syndrome (CBS) features asymmetric akinesia and rigidity, dystonia, myoclonus, alien limb phenomena, pyramidal signs, and prefrontal deficits such as nonfluent aphasia with or without motor speech impairment, executive dysfunction, apraxia, or a behavioral disorder. Progressive supranuclear palsy (PSP) is associated with unexplained falls, axial rigidity, dysphagia, and vertical gaze deficits. CJD is suggested by the presence of diffuse rigidity, an akinetic-mute state, and prominent, of en startle-sensitive myoclonus.

Hemiparesis or other focal neurologic deficits suggest vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B_{12} deficiency. Peripheral neuropathy could also indicate another vitamin deficiency, heavy metal intoxication, thyroid dysfunction, Lyme disease, or vasculitis. Dry, cool skin, hair loss, and bradycardia suggest hypothyroidism. Fluctuating confusion associated with repetitive stereotyped movements may indicate ongoing limbic, temporal, or frontal seizures. In the elderly, hearing impairment or visual loss

www.ketabpezeshki.com (021) 66485457 - 66485438

may produce confusion and disorientation misinterpreted as dementia. Profound bilateral sensorineural hearing loss in a younger patient with short stature or myopathy, however, should raise concern for a mitochondrial disorder.

COGNITIVE AND NEUROPSYCHIATRIC EXAMINATION Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and Cognistat can be used to capture dementia and follow progression. None of these tests is highly sensitive to early-stage dementia or discriminates between dementia syndromes. The MMSE is a 30 point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 minutes later); and language (e.g., name pencil and watch; repeat "no if's and's or but's"; follow a 3-step command; obey a written command; and write a sentence and copy a design). In most patients with MCI and some with clinically apparent AD, bedside screening tests may be normal, and a more challenging and comprehensive set of neuropsychological tests will be required. When the etiology for the dementia syndrome remains in doubt, a specially tailored evaluation should be performed that includes tasks of working and episodic memory, executive function, language, and visuospatial and perceptual abilities. In AD, the early deficits involve episodic memory, category generation ("name as many animals as you can in 1 minute"), and visuoconstructive ability. Usually deficits in verbal or visual episodic memory are the first neuropsychological abnormalities detected, and tasks that require the patient to recall a long list of words or a series of pictures after a predetermined delay will demonstrate deficits in most patients. In FTD, the earliest deficits on cognitive testing involve executive control or language (speech or naming) function, but some patients lack either finding despite profound social-emotional deficits. PDD or DLB patients have more severe deficits in visuospatial function but do better on episodic memory tasks than patients with AD. Patients with vascular dementia often demonstrate a mixture of executive control and visuospatial deficits, with prominent psychomotor slowing. In delirium, the most prominent deficits involve attention, working memory, and executive function, making the assessment of other cognitive domains challenging and often uninformative.

A functional assessment should also be performed to help the physician determine the day-to-day impact of the disorder on the patient's memory, community affairs, hobbies, judgment, dressing, and eating. Knowledge of the patient's functional abilities will help the clinician and the family to organize a therapeutic approach.

Neuropsychiatric assessment is important for diagnosis, prognosis, and treatment. In the early stages of AD, mild depressive features, social withdrawal, and irritability or anxiety are the most prominent psychiatric changes, but patients often maintain core social graces into the middle or late stages, when delusions, agitation, and sleep disturbance may emerge. In FTD, dramatic personality change with apathy, overeating, compulsions, disinhibition, euphoria, and loss of empathy are early and common. DLB is associated with visual hallucinations, delusions related to person or place identity, RBD, and excessive daytime sleepiness. Dramatic fluctuations occur not only in cognition but also in arousal. Vascular dementia can present with psychiatric symptoms such as depression, anxiety, delusions, disinhibition, or apathy.

LABORATORY TESTS The choice of laboratory tests in the evaluation of dementia is complex and should be tailored to the individual patient. The physician must take measures to avoid missing a reversible or treatable cause, yet no single treatable etiology is common; thus, a screen must use multiple tests, each of which has a low yield. Cost/benefit ratios are difficult to assess, and many laboratory screening algorithms for dementia discourage multiple tests. Nevertheless, even a test with only a 1–2% positive rate is worth undertaking if the alternative is missing a treatable cause of dementia. Table 21-3 lists most screening tests for dementia. The American Academy of Neurology recommends the routine measurement of a complete blood count, electrolytes, renal and thyroid function, a vitamin B_{12} level, and a neuroimaging study (computed tomography [CT] or MRI).

Neuroimaging studies, especially MRI, help to rule out primary and metastatic neoplasms, locate areas of infarction or inflammation, detect subdural hematomas, and suggest NPH or diffuse white matter disease. They also help to establish a regional pattern of atrophy. Support for the diagnosis of AD includes hippocampal atrophy in addition to posterior-predominant cortical atrophy **(Fig. 21-1)**. Focal frontal, insular, and/or anterior temporal atrophy suggests FTD **(Chap. 35)**. DLB often features less prominent atrophy, with greater involvement of amygdala than hippocampus. In CJD, magnetic resonance (MR) diffusion-weighted imaging reveals restricted diffusion within the cortical ribbon and basal ganglia in most patients. Extensive white matter abnormalities correlate with a vascular etiology **(Fig. 21-2)**. Communicating hydrocephalus with vertex effacement (crowding of dorsal convexity gyri/sulci), gaping Sylvian fissures despite minimal cortical atrophy, and additional features shown in **Fig. 21-3** suggest NPH. Single-photon emission computed tomography (SPECT) and PET scanning show temporal-parietal hypoperfusion or hypometabolism in AD and frontotemporal deficits in FTD, but these changes often reflect atrophy and can therefore be detected with MRI alone in many patients. Recently, amyloid imaging has shown promise for the diagnosis of AD, and Pittsburgh Compound-B (PiB)

www.ketabpezeshki.com (021) 66485457 - 66485438

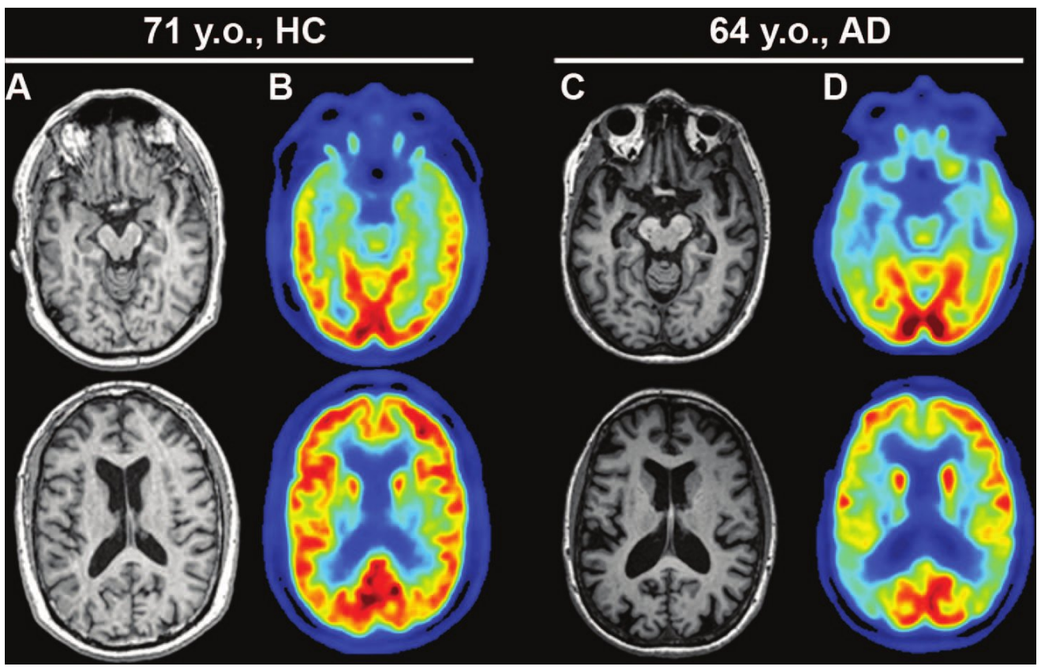


FIGURE 21-1
Alzheimer's disease (AD). Axial T1-weighted magnetic resonance images of a healthy 71-year-old (A) and a 64-year-old with AD (C). Note the reduction in medial temporal lobe volume in the patient with AD. Fluorodeoxyglucose positron emission tomography scans of the same individuals (B and D) demonstrate reduced glucose metabolism in the posterior temporoparietal regions bilaterally in AD, a typical finding in this condition. HC, healthy control. (Images courtesy of Gil Rabinovici, University of California, San Francisco and William Jagust, University of California, Berkeley.)

(not available outside of research settings) and ^{18}F-AV-45 (florbetapir; approved by the U.S. Food and Drug Administration in 2013) are reliable radioligands for detecting brain amyloid associated with amyloid angiopathy or neuritic plaques of AD (**Fig. 21-4**). Because these abnormalities can be seen in cognitively normal older persons, however (~25% of individuals at age 65), amyloid imaging may also detect preclinical or incidental AD in patients lacking an AD-like dementia syndrome. Currently, the main clinical value of amyloid imaging is to exclude AD as the likely cause of dementia in patients who have negative scans. Once disease-modifying therapies become available, use of these biomarkers may help to identify treatment candidates before irreversible brain injury has occurred. In the meantime, the significance of detecting brain amyloid in an asymptomatic elder remains a topic of vigorous investigation. Similarly, MRI perfusion and structural/functional connectivity methods are being explored as potential treatment-monitoring strategies.

Lumbar puncture need not be done routinely in the evaluation of dementia, but it is indicated when CNS infection or inflammation are credible diagnostic possibilities. Cerebrospinal fluid (CSF) levels of $A\beta_{42}$ and tau proteins show differing patterns with the various dementias, and the presence of low $A\beta_{42}$ and mildly elevated CSF tau is highly suggestive of AD. T e routine use of lumbar puncture in the diagnosis of dementia is debated, but the sensitivity and specificity of AD diagnostic measures are not yet high enough to warrant routine use. Formal psychometric testing helps to document the severity of cognitive disturbance, suggest psychogenic causes, and provide a more

FIGURE 21-2
Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (arrows) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in patients with dementia of a vascular etiology.

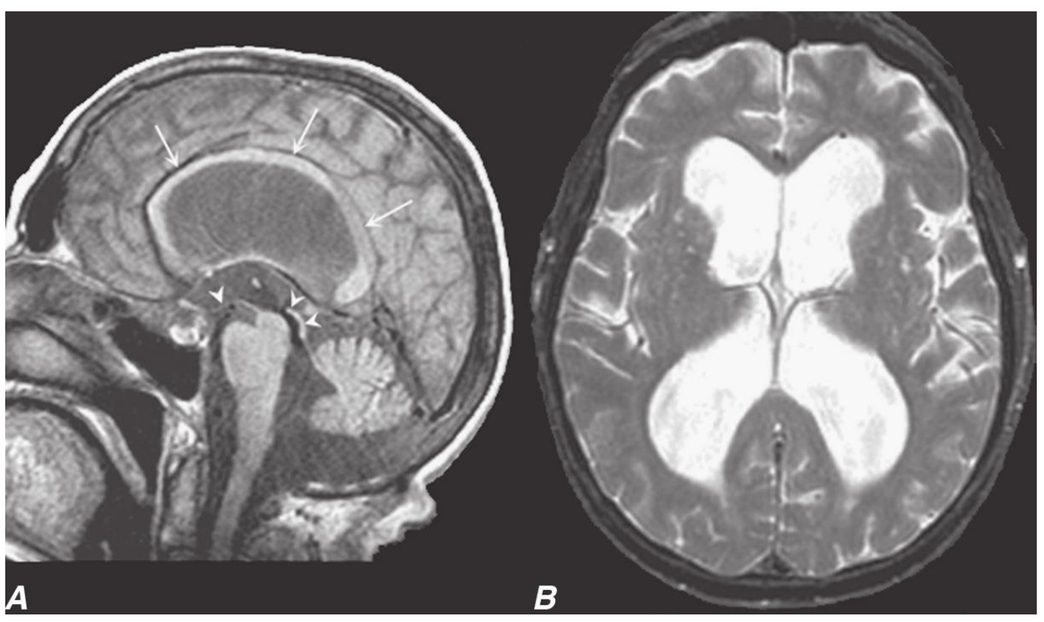


FIGURE 21-3
Normal-pressure hydrocephalus. A. Sagittal T1-weighted magnetic resonance image (MRI) demonstrates dilation of the lateral ventricle and stretching of the corpus callosum (arrows), depression of the floor of the third ventricle (single arrowhead), and enlargement of the aqueduct (double arrowheads). Note the diffuse dilation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. B. Axial T2-weighted MRIs demonstrate dilation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting.

www.ketabpezeshki.com (021) 66485457 - 66485438

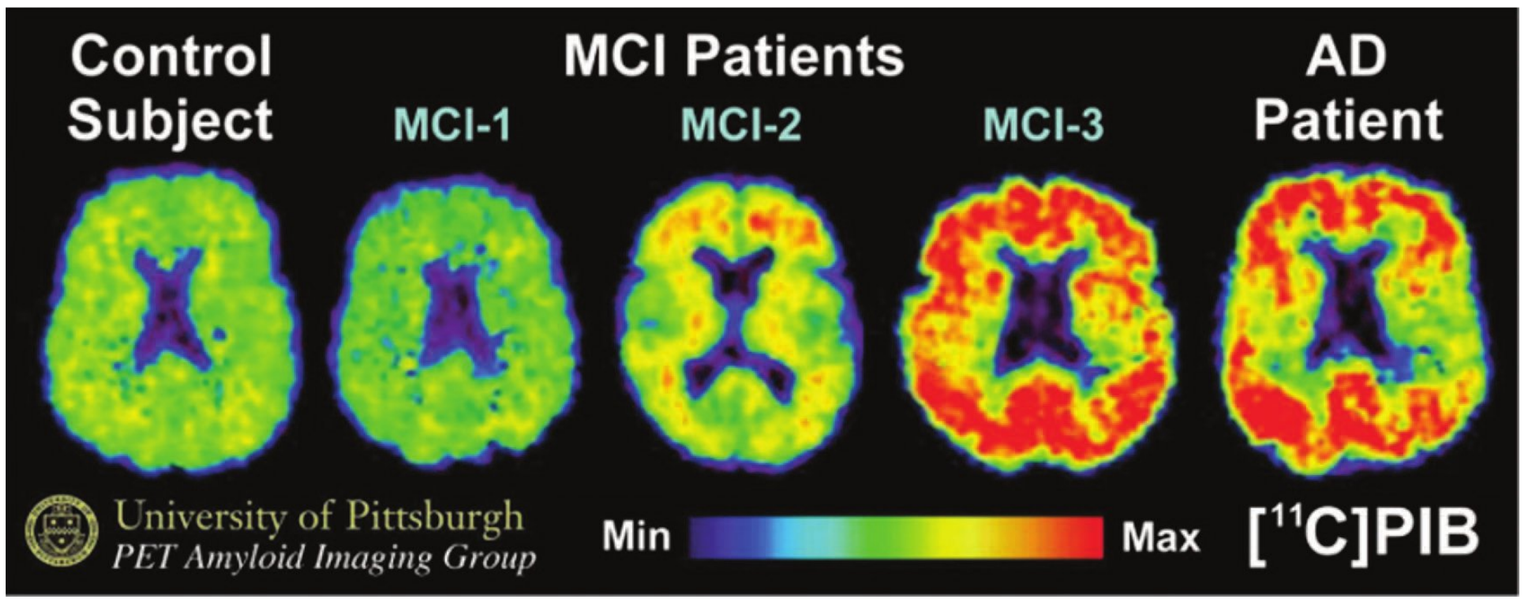


FIGURE 21-4
Positron emission tomography (PET) images obtained with the amyloid-imaging agent Pittsburgh Compound-B ([^{11}C]PIB) in a normal control (left); three different patients with mild cognitive impairment (MCI; center); and a patient with mild Alzheimer's disease (AD; right). Some MCI patients have control-like levels of amyloid, some have AD-like levels of amyloid, and some have intermediate levels. (Images courtesy of William Klunk and Chester Mathis, University of Pittsburgh.)

formal method for following the disease course. Electroencephalogram (EEG) is not routinely used but can help to suggest CJD (repetitive bursts of diffuse high-amplitude sharp waves, or "periodic complexes") or an underlying nonconvulsive seizure disorder (epileptiform discharges). Brain biopsy (including meninges) is not advised except to diagnose vasculitis, potentially treatable neoplasms, or unusual infections when the diagnosis is uncertain. Systemic disorders with CNS manifestations, such as sarcoidosis, can usually be confirmed through biopsy of lymph node or solid organ rather than brain. MR angiography should be considered when cerebral vasculitis or cerebral venous thrombosis is a possible cause of the dementia.

TREATMENT Dementia

The major goals of dementia management are to treat reversible causes and to provide comfort and support to the patient and caregivers. Treatment of underlying causes includes thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B_{12} deficiency or for elevated serum homocysteine; antimicrobials for opportunistic infections or antiretrovirals for HIV; ventricular shunting for NPH; or appropriate surgical, radiation, and/or chemotherapeutic treatment for CNS neoplasms. Removal of cognition-impairing drugs or medications is frequently useful. If the patient's cognitive complaints stem from a psychiatric disorder, vigorous treatment of this condition should seek to eliminate the cognitive complaint or confirm that it persists despite adequate resolution of the mood or anxiety symptoms. Patients with degenerative diseases may also be depressed or anxious, and those aspects of their condition often respond to therapy. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) **(Chap. 60)**, which feature anxiolytic properties but few cognitive side effects, provide the mainstay of treatment when necessary. Anticonvulsants are used to control seizures. Levetiracetam may be particularly useful, but there have as yet been no randomized trials for treatment of AD-associated seizures.

Agitation, hallucinations, delusions, and confusion are difficult to treat. These behavioral problems represent major causes for nursing home placement and institutionalization. Before treating these behaviors with medications, the clinician should aggressively seek out modifiable environmental or metabolic factors. Hunger, lack of exercise, toothache, constipation, urinary tract or respiratory infection, electrolyte imbalance, and drug toxicity all represent easily correctable causes that can be remedied without psychoactive drugs. Drugs such as phenothiazines and benzodiazepines may ameliorate the behavior problems but have untoward side effects such as sedation, rigidity, dyskinesia, and occasionally paradoxical disinhibition (benzodiazepines). Despite their unfavorable side effect profile, second-generation antipsychotics such as quetiapine (starting dose, 12.5–25 mg daily) can be used for patients with agitation, aggression, and psychosis, although the risk profile for these compounds is significant. When patients do not respond to treatment, it is usually a mistake to advance to higher doses or to use anticholinergic drugs or sedatives (such as barbiturates or benzodiazepines). It is important to recognize and treat depression; treatment can begin with a low dose of an SSRI (e.g., escitalopram, starting dose 5 mg daily, target dose 5–10 mg daily) while monitoring for efficacy and toxicity. Sometimes apathy, visual hallucinations, depression, and other psychiatric symptoms respond to the cholinesterase inhibitors, especially in DLB, obviating the need for other more toxic therapies.

Cholinesterase inhibitors are being used to treat AD (donepezil, rivastigmine, galantamine) and PDD (rivastigmine). Recent work has focused on developing antibodies against $A\beta_{42}$ as a treatment for AD. Although the initial randomized controlled trials failed, there was some evidence for efficacy in the mildest patient groups. Therefore, researchers have begun

www.ketabpezeshki.com (021) 66485457 - 66485438

to focus on patients with very mild disease and asymptomatic individuals at risk for AD, such as those who carry autosomal dominantly inherited genetic mutations or healthy elders with CSF or amyloid imaging biomarker evidence supporting presymptomatic AD. Memantine proves useful when treating some patients with moderate to severe AD; its major benefit relates to decreasing caregiver burden, most likely by decreasing resistance to dressing and grooming support. In moderate to severe AD, the combination of memantine and a cholinesterase inhibitor delayed nursing home placement in several studies, although other studies have not supported the efficacy of adding memantine to the regimen.

A proactive strategy has been shown to reduce the occurrence of delirium in hospitalized patients. T is strategy includes frequent orientation, cognitive activities, sleep-enhancement measures, vision and hearing aids, and correction of dehydration.

Nondrug behavior therapy has an important place in dementia management. T e primary goals are to make the patient's life comfortable, uncomplicated, and safe. Preparing lists, schedules, calendars, and labels can be helpful in the early stages. It is also useful to stress familiar routines, walks, and simple physical exercises. For many demented patients, memory for events is worse than their ability to carry out routine activities, and they may still be able to take part in activities such as walking, bowling, dancing, singing, bingo, and golf. Demented patients of en object to losing control over familiar tasks such as driving, cooking, and handling finances. Attempts to help or take over may be greeted with complaints, depression, or anger. Hostile responses on the part of the caregiver are counterproductive and sometimes even harmful. Reassurance, distraction, and calm positive statements are more productive in this setting. Eventually, tasks such as finances and driving must be assumed by others, and the patient will conform and adjust. Safety is an important issue that includes not only driving but controlling the kitchen, bathroom, and sleeping area environments, as well as stairways. T ese areas need to be monitored, supervised, and made as safe as possible. A move to a retirement complex, assisted-living center, or nursing home can initially increase confusion and agitation. Repeated reassurance, reorientation, and careful introduction to the new personnel will help to smooth the process. Providing activities that are known to be enjoyable to the patient can be of considerable benefit.

T e clinician must pay special attention to frustration and depression among family members and caregivers. Caregiver guilt and burnout are common. Family members of en feel overwhelmed and helpless and may vent their frustrations on the patient, each other, and health care providers. Caregivers should be encouraged to take advantage of day-care facilities and respite services. Education and counseling about dementia are important. Local and national support groups, such as the Alzheimer's Association (www.alz.org), can provide considerable help.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 22

APHASIA, MEMORY LOSS, AND OTHER FOCAL CEREBRAL DISORDERS

M.-Marsel Mesulam

The cerebral cortex of the human brain contains approximately 20 billion neurons spread over an area of 2.5 m^2. The primary sensory and motor areas constitute 10% of the cerebral cortex. The rest is subsumed by modality-selective, heteromodal, paralimbic, and limbic areas collectively known as the association cortex **(Fig. 22-1)**. The association cortex mediates the integrative processes that subserve cognition, emotion, and comportment. A systematic testing of these mental functions is necessary for the effective clinical assessment of the association cortex and its diseases. According to current thinking, there are no centers for "hearing words," "perceiving space," or "storing memories." Cognitive and behavioral functions (domains) are coordinated by intersecting large-scale neural networks that contain interconnected cortical and subcortical components. Five anatomically defined large-scale networks are most relevant to clinical practice: (1) a perisylvian network for language, (2) a parietofrontal network for spatial orientation, (3) an occipitotemporal network for face and object recognition, (4) a limbic network for retentive memory, and (5) a prefrontal network for the executive control of cognition and comportment.

THE LEFT PERISYLVIAN NETWORK FOR APHASIAS

The areas that are critical for language make up a distributed network located along the perisylvian region of the l*eft* hemisphere. One hub, located in the inferior frontal gyrus, is known as Broca's area. Damage to this region impairs phonology, fluency, and the grammatical structure of sentences. The location of a second hub, known as Wernicke's area, is less clearly settled but is traditionally thought to include the posterior parts of the temporal lobe. Cerebrovascular accidents that damage this area interfere with the ability to understand spoken or written sentences as well as the ability to express thoughts through meaningful words and statements. These two hubs are interconnected with each other and with surrounding parts of the frontal, parietal, and temporal lobes. Damage to this network gives rise to language impairments known as aphasia. Aphasia should be diagnosed only when there are deficits in the formal aspects of language, such as word finding, word choice, comprehension, spelling, or grammar. Dysarthria and mutism do not by themselves lead to a diagnosis of aphasia. In approximately 90% of right-handers and 60% of left-handers, aphasia occurs only after lesions of the left hemisphere.

CLINICAL EXAMINATION

The clinical examination of language should include the assessment of naming, spontaneous speech, comprehension, repetition, reading, and writing. A deficit of naming (anomia) is the single most common finding in aphasic patients. When asked to name a common object, the patient may fail to come up with the appropriate word, may provide a circumlocutious description of the object ("the thing for writing"), or may come up with the wrong word (paraphasia). If the patient offers an incorrect but related word ("pen" for "pencil"), the naming error is known as a semantic paraphasia; if the word approximates the correct answer but is phonetically inaccurate ("plentil" for "pencil"), it is known as a phonemic paraphasia. In most anomias, the patient cannot retrieve the appropriate name when shown an object but can point to the appropriate object when the name is provided by the examiner. This is known as a

www.ketabpezeshki.com (021) 66485457 - 66485438

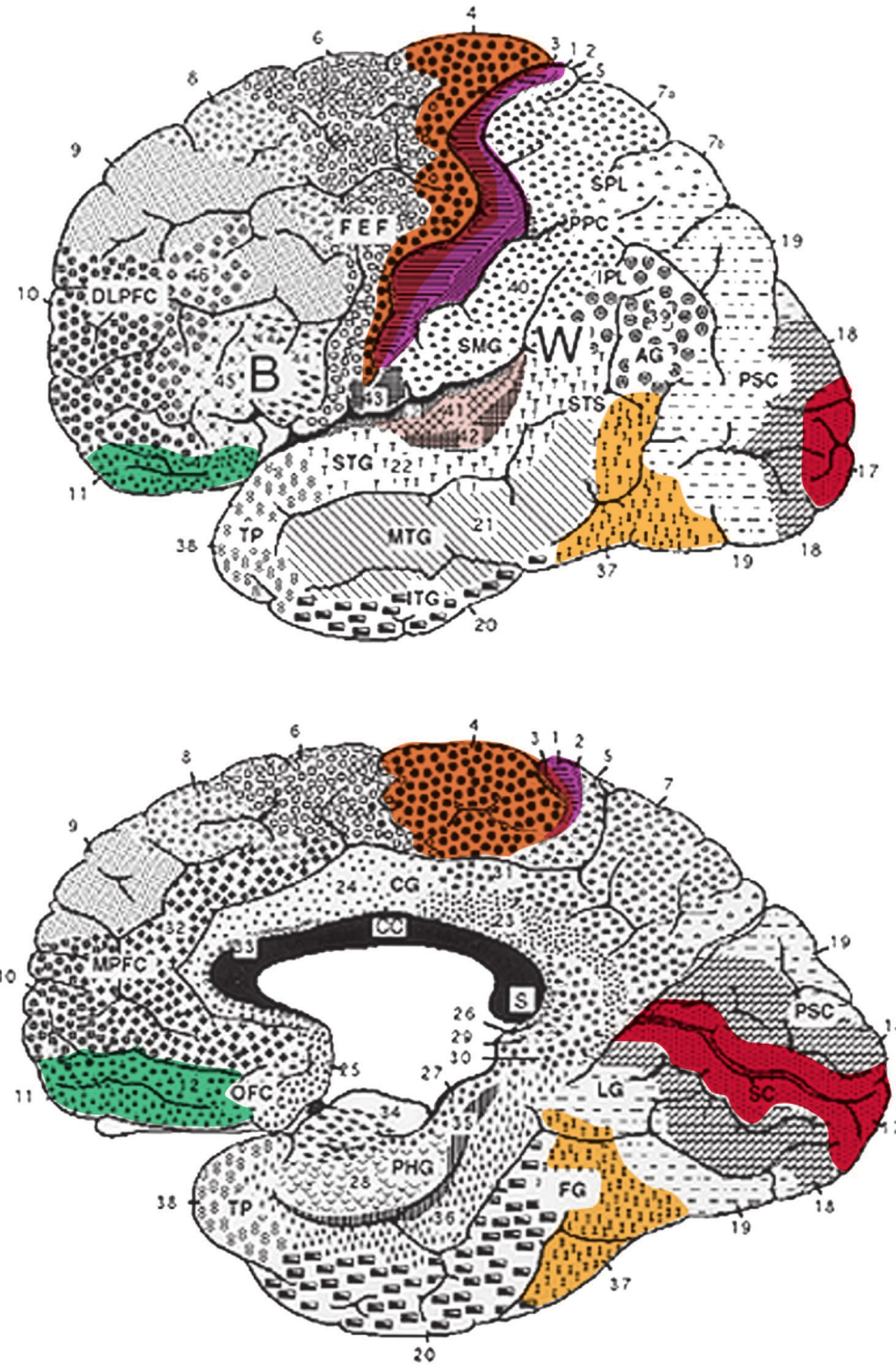


FIGURE 22-1

Lateral (top**) and medial (**bottom**) views of the cerebral hemispheres**. The numbers refer to the Brodmann cytoarchitectonic designations. Area 17 corresponds to the primary visual cortex, 41–42 to the primary auditory cortex, 1–3 to the primary somatosensory cortex, and 4 to the primary motor cortex. The rest of the cerebral cortex contains association areas. AG, angular gyrus; B, Broca's area; CC, corpus callosum; CG, cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields (premotor cortex); FG, fusiform gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LG, lingual gyrus; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PPC, posterior parietal cortex; PSC, peristriate cortex; SC, striate cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; TP, temporopolar cortex; W, Wernicke's area.

one-way (or retrieval-based) naming deficit. A two-way (comprehension-based) naming deficit exists if the patient can neither provide nor recognize the correct name. Spontaneous speech is described as "fluent" if it maintains appropriate output volume, phrase length, and melody or as "nonfluent" if it is sparse and halting and average utterance length is below four words. T e examiner also should note the integrity of grammar as manifested by word order (syntax), tenses, suf xes, prefixes, plurals, and possessives. Comprehension can be tested by assessing the patient's ability to follow conversation, asking yes-no questions ("Can a dog fly?" "Does it snow in summer?"), asking the patient to point to appropriate objects ("Where is the source of illumination in this room?"), or asking for verbal definitions of single words. Repetition is assessed by asking the patient to repeat single words, short sentences, or strings of words such as "No ifs, ands, or buts." T e testing of repetition with tongue twisters such as "hippopotamus" and "Irish constabulary" provides a better assessment of dysarthria and palilalia than of aphasia. It is important to make sure that the number of words does not exceed the patient's attention span. Otherwise, the failure of repetition becomes a reflection of the narrowed attention span (working memory) rather than an indication of an aphasic deficit. Reading should be assessed for deficits in reading aloud as well as comprehension. Alexia describes an inability to either read aloud or comprehend single words and simple sentences; agraphia (or dysgraphia) is used to describe an acquired deficit in spelling.

Aphasias can arise acutely in cerebrovascular accidents (CVAs) or gradually in neurodegenerative diseases. T e syndromes listed in **Table 22-1** are most applicable to the former group, where gray matter and white matter at the lesion site are abruptly and jointly destroyed. Progressive neurodegenerative diseases can have cellular, laminar, and regional specificity, giving rise to a different set of aphasias that will be described separately. T e syndromes outlined below are idealizations and rarely occur in pure form.

Wernicke's aphasia

Comprehension is impaired for spoken and written words and sentences. Language output is fluent but is highly paraphasic and circumlocutious. Paraphasic errors may lead to strings of neologisms, which lead to "jargon aphasia." Speech contains few substantive nouns. T e output is therefore voluminous but uninformative. For example, a patient attempts to describe how his wife accidentally threw away something important, perhaps his dentures: "We don't need it anymore, she says. And with it when that was downstairs was my teeth-tick … a … den … dentith … my dentist. And they happened to be in that bag … see? …Where my two … two little pieces of dentist that I use … that I … all gone. If she throws the whole thing away … visit some friends of hers and she can't throw them away."

Gestures and pantomime do not improve communication. T e patient may not realize that his or her language is incomprehensible and may appear angry and impatient when the examiner fails to decipher the meaning of a severely paraphasic statement. In some patients this type of aphasia can be associated

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 22-1

CLINICAL FEATURES OF APHASIAS AND RELATED CONDITIONS COMMONLY SEEN IN CEREBROVASCULAR ACCIDENTS

	COMPREHENSION	REPETITION OF SPOKEN LANGUAGE	NAMING	FLUENCY
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

with severe agitation and paranoia. The ability to follow commands aimed at axial musculature may be preserved. The dissociation between the failure to understand simple questions ("What is your name?") in a patient who rapidly closes his or her eyes, sits up, or rolls over when asked to do so is characteristic of Wernicke's aphasia and helps differentiate it from deafness, psychiatric disease, or malingering. Patients with Wernicke's aphasia cannot express their thoughts in meaning-appropriate words and cannot decode the meaning of words in any modality of input. This aphasia therefore has expressive as well as receptive components. Repetition, naming, reading, and writing also are impaired.

The lesion site most commonly associated with Wernicke's aphasia is the posterior portion of the language network. An embolus to the inferior division of the middle cerebral artery, to the posterior temporal or angular branches in particular, is the most common etiology **(Chap. 32)**. Intracerebral hemorrhage, head trauma, and neoplasm are other causes of Wernicke's aphasia. A coexisting right hemianopia or superior quadrantanopia is common, and mild right nasolabial flattening may be found, but otherwise, the examination is often unrevealing. The paraphasic, neologistic speech in an agitated patient with an otherwise unremarkable neurologic examination may lead to the suspicion of a primary psychiatric disorder such as schizophrenia or mania, but the other components characteristic of acquired aphasia and the absence of prior psychiatric disease usually settle the issue. Prognosis for recovery of language function is guarded.

Broca's aphasia

Speech is nonfluent, labored, interrupted by many word-finding pauses, and usually dysarthric. It is impoverished in function words but enriched in meaning-appropriate nouns. Abnormal word order and the inappropriate deployment of bound morphemes (word endings used to denote tenses, possessives, or plurals) lead to a characteristic agrammatism. Speech is telegraphic and pithy but quite informative. In the following passage, a patient with Broca's aphasia describes his medical history: "I see … the dotor, dotor sent me … Bosson. Go to hospital. Dotor … kept me beside. Two, tee days, doctor send me home."

Output may be reduced to a grunt or single word ("yes" or "no"), which is emitted with different intonations in an attempt to express approval or disapproval. In addition to fluency, naming and repetition are impaired. Comprehension of spoken language is intact except for syntactically difficult sentences with a passive voice structure or embedded clauses, indicating that Broca's aphasia is not just an "expressive" or "motor" disorder and that it also may involve a comprehension deficit in decoding syntax. Patients with Broca's aphasia can be tearful, easily frustrated, and profoundly depressed. Insight into their condition is preserved, in contrast to Wernicke's aphasia. Even when spontaneous speech is severely dysarthric, the patient may be able to display a relatively normal articulation of words when singing. This dissociation has been used to develop specific therapeutic approaches (melodic intonation therapy) for Broca's aphasia. Additional neurologic deficits include right facial weakness,

www.ketabpezeshki.com (021) 66485457 - 66485438

hemiparesis or hemiplegia, and a buccofacial apraxia characterized by an inability to carry out motor commands involving oropharyngeal and facial musculature (e.g., patients are unable to demonstrate how to blow out a match or suck through a straw). The cause is most often infarction of Broca's area (the inferior frontal convolution; "B" in Fig. 22-1) and surrounding anterior perisylvian and insular cortex due to occlusion of the superior division of the middle cerebral artery **(Chap. 32)**. Mass lesions, including tumor, intracerebral hemorrhage, and abscess, also may be responsible. When the cause of Broca's aphasia is stroke, recovery of language function generally peaks within 2 to 6 months, after which time further progress is limited. Speech therapy is more successful than in Wernicke's aphasia.

Conduction aphasia

Speech output is fluent but contains many phonemic paraphasias, comprehension of spoken language is intact, and repetition is severely impaired. Naming elicits phonemic paraphasias, and spelling is impaired. Reading aloud is impaired, but reading comprehension is preserved. The lesion sites spare the functionality of Broca's and Wernicke's areas but may induce a disconnection between the two. Occasionally, a transient Wernicke's aphasia may rapidly resolve into a conduction aphasia. The paraphasic output in conduction aphasia interferes with the ability to express meaning, but this deficit is not nearly as severe as the one displayed by patients with Wernicke's aphasia. Associated neurologic signs in conduction aphasia vary according to the primary lesion site.

Transcortical aphasias: fluent and nonfluent

Clinical features of *fl*uent (posterior) transcortical aphasia are similar to those of Wernicke's aphasia, but repetition is intact. The lesion site disconnects the intact core of the language network from other temporoparietal association areas. Associated neurologic findings may include hemianopia. Cerebrovascular lesions (e.g., infarctions in the posterior watershed zone) and neoplasms that involve the temporoparietal cortex posterior to Wernicke's area are common causes. The features of non*fl*uent (anterior) transcortical aphasia are similar to those of Broca's aphasia, but repetition is intact and agrammatism is less pronounced. The neurologic examination may be otherwise intact, but a right hemiparesis also can exist. The lesion site disconnects the intact language network from prefrontal areas of the brain and usually involves the anterior watershed zone between anterior and middle cerebral artery territories or the supplementary motor cortex in the territory of the anterior cerebral artery.

Global and isolation aphasias

Global aphasia represents the combined dysfunction of Broca's and Wernicke's areas and usually results from strokes that involve the entire middle cerebral artery distribution in the left hemisphere. Speech output is nonfluent, and comprehension of language is severely impaired. Related signs include right hemiplegia, hemisensory loss, and homonymous hemianopia. Isolation aphasia represents a combination of the two transcortical aphasias. Comprehension is severely impaired, and there is no purposeful speech output. The patient may parrot fragments of heard conversations (echolalia), indicating that the neural mechanisms for repetition are at least partially intact. This condition represents the pathologic function of the language network when it is isolated from other regions of the brain. Broca's and Wernicke's areas tend to be spared, but there is damage to the surrounding frontal, parietal, and temporal cortex. Lesions are patchy and can be associated with anoxia, carbon monoxide poisoning, or complete watershed zone infarctions.

Anomic aphasia

This form of aphasia may be considered the "minimal dysfunction" syndrome of the language network. Articulation, comprehension, and repetition are intact, but confrontation naming, word finding, and spelling are impaired. Word-finding pauses are uncommon, so language output is fluent but paraphasic, circumlocutious, and uninformative. The lesion sites can be anywhere within the left hemisphere language network, including the middle and inferior temporal gyri. Anomic aphasia is the single most common language disturbance seen in head trauma, metabolic encephalopathy, and Alzheimer's disease.

Pure word deafness

The most common causes are either bilateral or left-sided middle cerebral artery (MCA) strokes affecting the superior temporal gyrus. The net effect of the underlying lesion is to interrupt the flow of information from the auditory association cortex to the language network. Patients have no difficulty understanding written language and can express themselves well in spoken or written language. They have no difficulty interpreting and reacting to environmental sounds since primary auditory cortex and auditory association areas of the right hemisphere are spared. Because auditory information cannot be conveyed to the language network, however, it cannot be decoded into neural word representations, and the patient reacts to speech as if it were in an alien tongue that cannot be deciphered. Patients cannot repeat spoken language but have no difficulty

www.ketabpezeshki.com (021) 66485457 - 66485438

naming objects. In time, patients with pure word deafness teach themselves lipreading and may appear to have improved. There may be no additional neurologic findings, but agitated paranoid reactions are common in the acute stages. Cerebrovascular lesions are the most common cause.

Pure alexia without agraphia

This is the visual equivalent of pure word deafness. The lesions (usually a combination of damage to the left occipital cortex and to a posterior sector of the corpus callosum—the splenium) interrupt the flow of visual input into the language network. There is usually a right hemianopia, but the core language network remains unaffected. The patient can understand and produce spoken language, name objects in the left visual hemifield, repeat, and write. However, the patient acts as if illiterate when asked to read even the simplest sentence because the visual information from the written words (presented to the intact left visual hemifield) cannot reach the language network. Objects in the left hemifield may be named accurately because they activate nonvisual associations in the right hemisphere, which in turn can access the language network through transcallosal pathways anterior to the splenium. Patients with this syndrome also may lose the ability to name colors, although they can match colors. This is known as a color anomia. The most common etiology of pure alexia is a vascular lesion in the territory of the posterior cerebral artery or an infiltrating neoplasm in the left occipital cortex that involves the optic radiations as well as the crossing fibers of the splenium. Because the posterior cerebral artery also supplies medial temporal components of the limbic system, a patient with pure alexia also may experience an amnesia, but this is usually transient because the limbic lesion is unilateral.

Apraxia and aphemia

Apraxia designates a complex motor deficit that cannot be attributed to pyramidal, extrapyramidal, cerebellar, or sensory dysfunction and that does not arise from the patient's failure to understand the nature of the task. Apraxia *of* speech is used to designate articulatory abnormalities in the duration, fluidity, and stress of syllables that make up words. Intoning the words may improve articulation. It can arise with CVAs in the posterior part of Broca's area or in the course of frontotemporal lobar degeneration (FTLD) with tauopathy. Aphemia is a severe form of acute speech apraxia that presents with severely impaired fluency (often mutism). Recovery is the rule and involves an intermediate stage of hoarse whispering. Writing, reading, and comprehension are intact, and so this is not a true aphasic syndrome. CVAs in parts of Broca's area or subcortical lesions that undercut its connections with other parts of the brain may be present. Occasionally, the lesion site is on the medial aspects of the frontal lobes and may involve the supplementary motor cortex of the left hemisphere. Ideomotor apraxia is diagnosed when commands to perform a specific motor act ("cough," "blow out a match") or pantomime the use of a common tool (a comb, hammer, straw, or toothbrush) in the absence of the real object cannot be followed. The patient's ability to comprehend the command is ascertained by demonstrating multiple movements and establishing that the correct one can be recognized. Some patients with this type of apraxia can imitate the appropriate movement (when it is demonstrated by the examiner) and show no impairment when handed the real object, indicating that the sensorimotor mechanisms necessary for the movement are intact. Some forms of ideomotor apraxia represent a disconnection of the language network from pyramidal motor systems so that commands to execute complex movements are understood but cannot be conveyed to the appropriate motor areas. Bucco*f*acial apraxia involves apraxic deficits in movements of the face and mouth. Limb apraxia encompasses apraxic deficits in movements of the arms and legs. Ideomotor apraxia almost always is caused by lesions in the left hemisphere and is commonly associated with aphasic syndromes, especially Broca's aphasia and conduction aphasia. Because the handling of real objects is not impaired, ideomotor apraxia by itself causes no major limitation of daily living activities. Patients with lesions of the anterior corpus callosum can display ideomotor apraxia confined to the left side of the body, a sign known as sympathetic dyspraxia. A severe form of sympathetic dyspraxia, known as the alien hand syndrome, is characterized by additional features of motor disinhibition on the left hand. Ideational apraxia refers to a deficit in the sequencing of goal-directed movements in patients who have no difficulty executing the individual components of the sequence. For example, when the patient is asked to pick up a pen and write, the sequence of uncapping the pen, placing the cap at the opposite end, turning the point toward the writing surface, and writing may be disrupted, and the patient may be seen trying to write with the wrong end of the pen or even with the removed cap. These motor sequencing problems usually are seen in the context of confusional states and dementias rather than focal lesions associated with aphasic conditions. Limb-kinetic apraxia involves clumsiness in the use of tools or objects that cannot be attributed to sensory, pyramidal, extrapyramidal, or cerebellar dysfunction. This condition can emerge in the context of focal premotor cortex lesions or corticobasal degeneration.

www.ketabpezeshki.com (021) 66485457 - 66485438

Gerstmann's syndrome

The combination of acalculia (impairment of simple arithmetic), dysgraphia (impaired writing), finger anomia (an inability to name individual fingers such as the index and thumb), and right-left confusion (an inability to tell whether a hand, foot, or arm of the patient or examiner is on the right or left side of the body) is known as Gerstmann's syndrome. In making this diagnosis, it is important to establish that the finger and left-right naming deficits are not part of a more generalized anomia and that the patient is not otherwise aphasic. When Gerstmann's syndrome arises acutely and in isolation, it is commonly associated with damage to the inferior parietal lobule (especially the angular gyrus) in the left hemisphere.

Pragmatics and prosody

Pragmatics refers to aspects of language that communicate attitude, affect, and the figurative rather than literal aspects of a message (e.g., "green thumb" does not refer to the actual color of the finger). One component of pragmatics, prosody, refers to variations of melodic stress and intonation that influence attitude and the inferential aspect of verbal messages. For example, the two statements "He is clever." and "He is clever?" contain an identical word choice and syntax but convey vastly different messages because of differences in the intonation with which the statements are uttered. Damage to right hemisphere regions corresponding to Broca's area impairs the ability to introduce meaning-appropriate prosody into spoken language. The patient produces grammatically correct language with accurate word choice, but the statements are uttered in a monotone that interferes with the ability to convey the intended stress and affect. Patients with this type of aprosodia give the mistaken impression of being depressed or indifferent. Other aspects of pragmatics, especially the ability to infer the figurative aspect of a message, become impaired by damage to the right hemisphere or frontal lobes.

Subcortical aphasia

Damage to subcortical components of the language network (e.g., the striatum and thalamus of the left hemisphere) also can lead to aphasia. The resulting syndromes contain combinations of deficits in the various aspects of language but rarely fit the specific patterns described in Table 22-1. In a patient with a CVA, an anomic aphasia accompanied by dysarthria or a fluent aphasia with hemiparesis should raise the suspicion of a subcortical lesion site.

Progressive aphasias

Aphasias caused by major cerebrovascular accidents start suddenly and display maximal deficits at the onset. These are the "classic" aphasias described above. Aphasias caused by neurodegenerative diseases have an insidious onset and relentless progression. The neuropathology can be selective not only for gray matter but also for specific layers and cell types. The clinicoanatomic patterns are therefore different from those described in Table 22-1.

Clinical presentation and diagnosis of primary progressive aphasia (PPA)

Several neurodegenerative syndromes, such as typical Alzheimer-type (amnestic) and frontal-type (behavioral) dementias, can also undermine language as the disease progresses. In these cases, the aphasia is an ancillary component of the overall syndrome. When a neurodegenerative language disorder arises in relative isolation and becomes the primary concern that brings the patient to medical attention, a diagnosis of PPA is made.

Language in PPA

The impairments of language in PPA have slightly different patterns from those seen in CVA-caused aphasias. Three major subtypes of PPA can be recognized. The agrammatic variant is characterized by consistently low fluency and impaired grammar but intact word comprehension. It most closely resembles Broca's aphasia or anterior transcortical aphasia but usually lacks the right hemiparesis or dysarthria and has more profound impairments of grammar. Peak sites of neuronal loss (gray matter atrophy) include the left inferior frontal gyrus where Broca's area is located. The neuropathology is usually an FTLD with tauopathy but can also be an atypical form of Alzheimer's disease (AD) pathology. The semantic variant is characterized by preserved fluency and syntax but poor single-word comprehension and profound two-way naming impairments. This kind of aphasia is not seen with CVAs. It differs from Wernicke's aphasia or posterior transcortical aphasia because speech is usually informative, repetition is intact, and comprehension of conversation is relatively preserved, as long as the meaning is not too dependent on words that the patient fails to understand. Peak atrophy sites are located in the left anterior temporal lobe, indicating that this part of the brain plays a critical role in the comprehension of words, especially words that denote concrete objects. The neuropathology is frequently an FTLD with abnormal precipitates of the 43-kDa transactive response DNA-binding protein TDP-43. The logopenic variant is characterized by preserved syntax and comprehension but frequent and severe word-finding pauses, anomia, circumlocutions, and simplifications during spontaneous speech. Peak atrophy sites are located in the temporoparietal junction and posterior temporal lobe, partially overlapping with traditional location of Wernicke's area. However,

www.ketabpezeshki.com (021) 66485457 - 66485438

the comprehension impairment of Wernicke's aphasia is absent, perhaps because the underlying white matter, frequently damaged by cerebrovascular accidents, remains relatively intact in PPA. In contrast to Broca's aphasia or agrammatic PPA, the interruption of fluency is variable so that speech may appear entirely normal if the patient is allowed to engage in small talk. Logopenic PPA resembles the anomic aphasia of Table 22-1 but usually has longer and more frequent word-finding pauses. Patients may also have poor phrase and word repetition, in which case the aphasia resembles the conduction aphasia in Table 22-1. Of all PPA subtypes, this is the one most commonly associated with the pathology of AD, but FTLD can also be the cause. In addition to these three major subtypes, PPA can also present in the form of pure word deafness or Gerstmann's syndrome.

THE PARIETOFRONTAL NETWORK FOR NEGLECT AND RELATED CONDITIONS

Adaptive spatial orientation is subserved by a large-scale network containing three major cortical components. The cingulate cortex provides access to a motivational mapping of the extrapersonal space, the posterior parietal cortex to a sensorimotor representation of salient extrapersonal events, and the frontal eye fields to motor strategies for attentional behaviors **(Fig. 22-2)**. Subcortical components of this network include the striatum and the thalamus. Damage to this network can undermine the distribution of attention within the extrapersonal space, giving rise to hemispatial neglect, simultanagnosia and object finding failures. The integration of egocentric (self-centered) with allocentric (object-centered) coordinates can also be disrupted, giving rise to impairments in route finding, the ability to avoid obstacles, and the ability to dress.

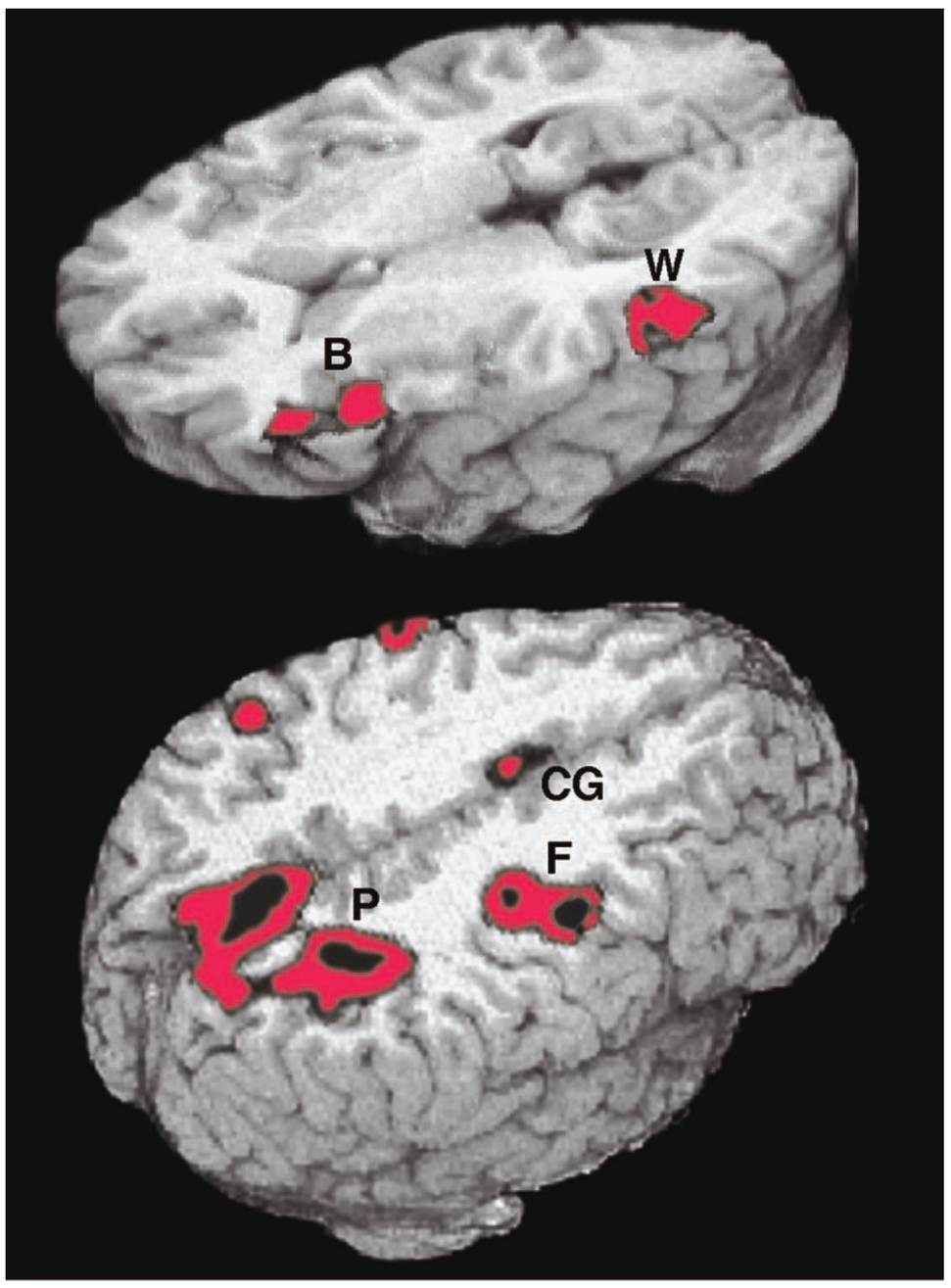


FIGURE 22-2

Functional magnetic resonance imaging of language and spatial attention in neurologically intact subjects. The red and black areas show regions of task-related significant activation. (Top) The subjects were asked to determine if two words were synonymous. This language task led to the simultaneous activation of the two epicenters of the language network, Broca's area (B) and Wernicke's area (W). The activations are exclusively in the left hemisphere. (Bottom) The subjects were asked to shift spatial attention to a peripheral target. This task led to the simultaneous activation of the three epicenters of the attentional network: the posterior parietal cortex (P), the frontal eye fields (F), and the cingulate gyrus (CG). The activations are predominantly in the right hemisphere. (Courtesy of Darren Gitelman, MD; with permission.)

HEMISPATIAL NEGLECT

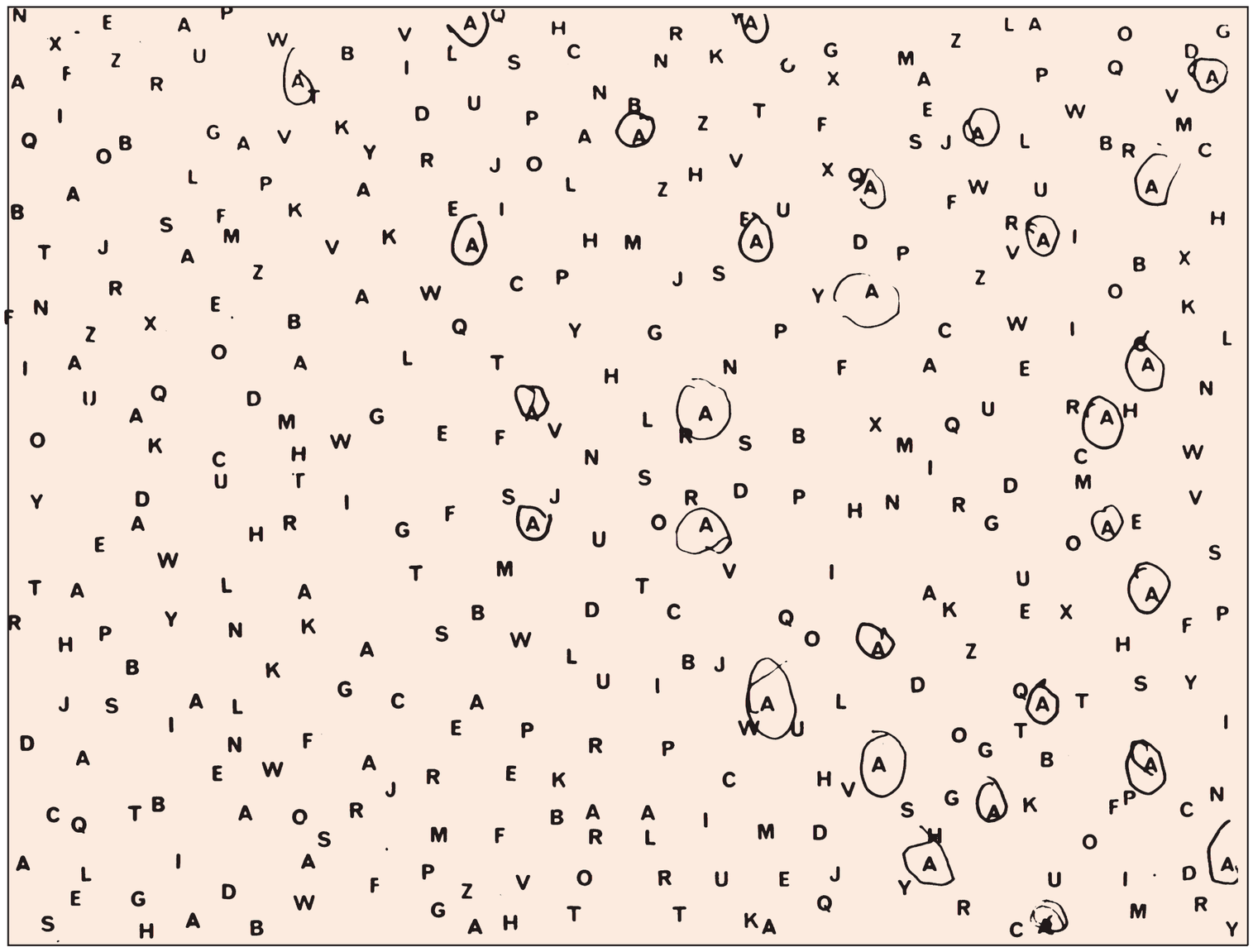
Contralesional hemispatial neglect represents one outcome of damage to the cortical or subcortical components of this network. The traditional view that hemispatial neglect always denotes a parietal lobe lesion is inaccurate. According to one model of spatial cognition, the right hemisphere directs attention within the entire extrapersonal space, whereas the left hemisphere directs attention mostly within the contralateral right hemispace. Consequently, left hemisphere lesions do not give rise to much contralesional neglect because the global attentional mechanisms of the right hemisphere can compensate for the loss of the contralaterally directed attentional functions of the left hemisphere. Right hemisphere lesions, however, give rise to severe contralesional left hemispatial neglect because the unaffected left hemisphere does not contain ipsilateral attentional mechanisms. This model is consistent with clinical experience, which shows that contralesional neglect is more common, more severe, and longer lasting after damage to the right hemisphere than after damage to the left hemisphere. Severe neglect for the right hemispace is rare, even in left-handers with left hemisphere lesions.

Clinical examination

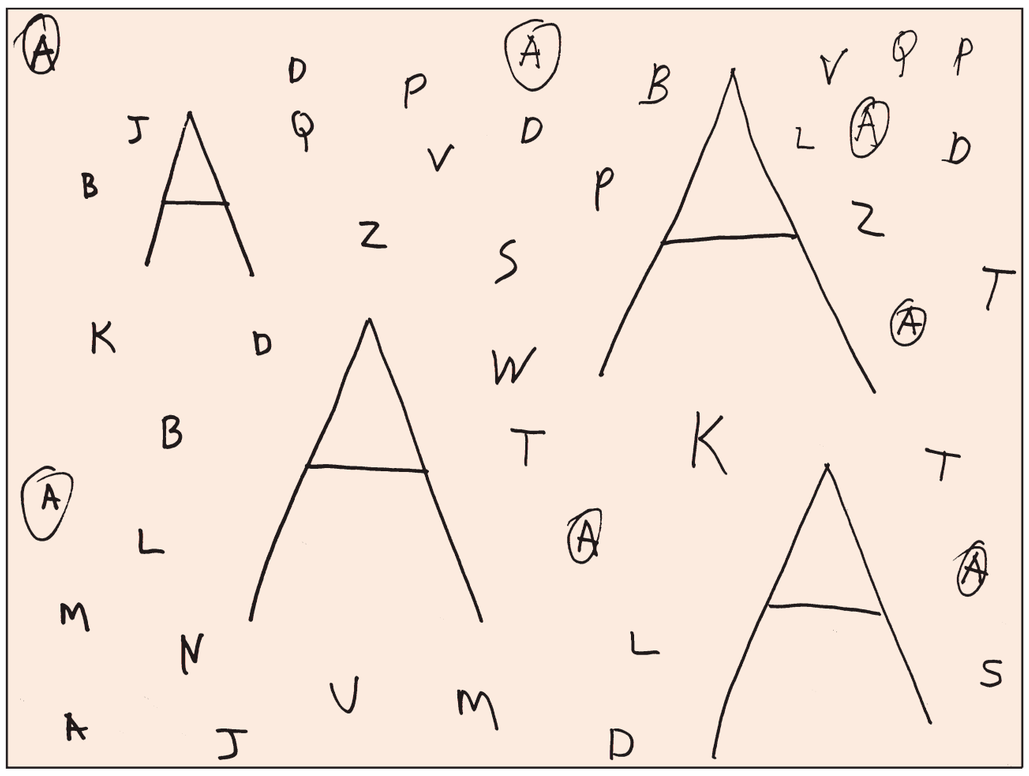
Patients with severe neglect may fail to dress, shave, or groom the left side of the body; fail to eat food placed on the left side of the tray; and fail to read the left half

www.ketabpezeshki.com (021) 66485457 - 66485438

of sentences. When asked to copy a simple line drawing, the patient fails to copy detail on the left, and when the patient is asked to write, there is a tendency to leave an unusually wide margin on the left. Two bedside tests that are useful in assessing neglect are simultaneous bilateral stimulation and visual target cancellation. In the former, the examiner provides either unilateral or simultaneous bilateral stimulation in the visual, auditory, and tactile modalities. After right hemisphere injury, patients who have no dif culty detecting unilateral stimuli on either side experience the bilaterally presented stimulus as coming only from the right. T is phenomenon is known as extinction and is a manifestation of the sensory-representational aspect of hemispatial neglect. In the target detection task, targets (e.g., A's) are interspersed with foils (e.g., other letters of the alphabet) on a 21.5- to 28.0-cm (8.5 to 11 in.) sheet of paper, and the patient is asked to circle all the targets. A failure to detect targets on the left is a manifestation of the exploratory (motor) deficit in hemispatial neglect **(Fig. 22-3A)**. Hemianopia is not by itself suf cient to cause the target detection failure because the patient is



A



B

FIGURE 22-3

A. A 47-year-old man with a large frontoparietal lesion in the right hemisphere was asked to circle all the A's. Only targets on the right are circled. This is a manifestation of left hemispatial neglect.

B. A 70-year-old woman with a 2-year history of degenerative dementia was able to circle most of the small targets but ignored the larger ones. This is a manifestation of simultanagnosia.

www.ketabpezeshki.com (021) 66485457 - 66485438

free to turn the head and eyes to the left. Target detection failures therefore reflect a distortion of spatial attention, not just of sensory input. Some patients with neglect also may deny the existence of hemiparesis and may even deny ownership of the paralyzed limb, a condition known as anosognosia.

BÁLINT'S SYNDROME, SIMULTANAGNOSIA, DRESSING APRAXIA, CONSTRUCTION APRAXIA, AND ROUTE FINDING

Bilateral involvement of the network for spatial attention, especially its parietal components, leads to a state of severe spatial disorientation known as Bálint's syndrome. Bálint's syndrome involves deficits in the orderly visuomotor scanning of the environment (oculomotor apraxia), accurate manual reaching toward visual targets (optic ataxia), and the ability to integrate visual information in the center of gaze with more peripheral information (simultanagnosia). A patient with simultanagnosia "misses the forest for the trees." For example, a patient who is shown a table lamp and asked to name the object may look at its circular base and call it an ashtray. Some patients with simultanagnosia report that objects they look at may vanish suddenly, probably indicating an inability to look back at the original point of gaze after brief saccadic displacements. Movement and distracting stimuli greatly exacerbate the dif culties of visual perception. Simultanagnosia can occur without the other two components of Bálint's syndrome.

A modification of the letter cancellation task described above can be used for the bedside diagnosis of simultanagnosia. In this modification, some of the targets (e.g., A's) are made to be much larger than the others (7.5 to 10 cm vs 2.5 cm [3 to 4 in. vs 1 in.] in height), and all targets are embedded among foils. Patients with simultanagnosia display a counterintuitive but characteristic tendency to miss the larger targets **(Fig. 22-3B)**. T is occurs because the information needed for the identification of the larger targets cannot be confined to the immediate line of gaze and requires the integration of visual information across multiple fixation points. T e greater dif culty in the detection of the larger targets also indicates that poor acuity is not responsible for the impairment of visual function and that the problem is central rather than peripheral. T e test shown in Fig. 22-3B is not by itself suf cient to diagnose simultanagnosia because some patients with a frontal network syndrome may omit the large letters, perhaps because they lack the mental flexibility needed to realize that the two types of targets are symbolically identical despite being superficially different.

Bilateral parietal lesions can impair the integration of egocentric with allocentric spatial coordinates. One manifestation is dressing apraxia. A patient with this condition is unable to align the body axis with the axis of the garment and can be seen struggling as he or she holds a coat from its bottom or extends his or her arm into a fold of the garment rather than into its sleeve. Lesions that involve the posterior parietal cortex also lead to severe dif culties in copying simple line drawings. T is is known as a construction apraxia and is much more severe if the lesion is in the right hemisphere. In some patients with right hemisphere lesions, the drawing dif culties are confined to the left side of the figure and represent a manifestation of hemispatial neglect; in others, there is a more universal deficit in reproducing contours and three-dimensional perspective. Impairments of route finding can be included in this group of disorders, which reflect an inability to orient the self with respect to external objects and landmarks.

Causes of spatial disorientation

Cerebrovascular lesions and neoplasms in the right hemisphere are common causes of hemispatial neglect. Depending on the site of the lesion, a patient with neglect also may have hemiparesis, hemihypesthesia, and hemianopia on the left, but these are not invariant findings. T e majority of these patients display considerable improvement of hemispatial neglect, usually within the first several weeks. Bálint's syndrome, dressing apraxia, and route finding impairments are more likely to result from bilateral dorsal parietal lesions; common settings for acute onset include watershed infarction between the middle and posterior cerebral artery territories, hypoglycemia, and sagittal sinus thrombosis.

A progressive form of spatial disorientation, known as the posterior cortical atrophy syndrome, most commonly represents a variant of AD with unusual concentrations of neurofibrillary degeneration in the parieto-occipital cortex and the superior colliculus. T e patient displays a progressive hemispatial neglect or Bálint's syndrome, usually accompanied by dressing and construction apraxia. T e corticobasal syndrome, which can be caused by AD or FTLD pathology, can also lead to a progressive left hemineglect syndrome. Both syndromes can impair route finding.

THE OCCIPITOTEMPORAL NETWORK FOR FACE AND OBJECT RECOGNITION

A patient with prosopagnosia cannot recognize familiar faces, including, sometimes, the reflection of his or her own face in the mirror. T is is not a perceptual deficit because prosopagnosic patients easily can tell whether two faces are identical. Furthermore, a prosopagnosic patient who cannot recognize a familiar face

www.ketabpezeshki.com (021) 66485457 - 66485438

by visual inspection alone can use auditory cues to reach appropriate recognition if allowed to listen to the person's voice. T e deficit in prosopagnosia is therefore modality-specific and reflects the existence of a lesion that prevents the activation of otherwise intact multimodal templates by relevant visual input. Prosopagnosic patients characteristically have no dif culty with the generic identification of a face as a face or a car as a car, but may not recognize the identity of an individual face or the make of an individual car. T is reflects a visual recognition deficit for proprietary features that characterize individual members of an object class. When recognition problems become more generalized and extend to the generic identification of common objects, the condition is known as visual object agnosia. A patient with anomia cannot name the object but can describe its use. In contrast, a patient with visual agnosia is unable either to name a visually presented object or to describe its use. Face and object recognition disorders also can result from the simultanagnosia of Bálint's syndrome, in which case they are known as apperceptive agnosias as opposed to the associative agnosias that result from inferior temporal lobe lesions.

CAUSES

T e characteristic lesions in prosopagnosia and visual object agnosia of acute onset consist of bilateral infarctions in the territory of the posterior cerebral arteries. Associated deficits can include visual field defects (especially superior quadrantanopias) and a centrally based color blindness known as achromatopsia. Rarely, the responsible lesion is unilateral. In such cases, prosopagnosia is associated with lesions in the right hemisphere, and object agnosia with lesions in the left. Degenerative diseases of anterior and inferior temporal cortex can cause progressive associative prosopagnosia and object agnosia. T e combination of progressive associative agnosia and a fluent aphasia is known as semantic dementia. Patients with semantic dementia fail to recognize faces and objects and cannot understand the meaning of words denoting objects. T is needs to be differentiated from the semantic type of PPA where there is severe impairment in understanding words that denote objects and in naming faces and objects but a relative preservation of face and object recognition.

LIMBIC NETWORK FOR MEMORY AND AMNESIA

Limbic and paralimbic areas (such as the hippocampus, amygdala, and entorhinal cortex), the anterior and medial nuclei of the thalamus, the medial and basal parts of the striatum, and the hypothalamus collectively constitute a distributed network known as the limbic system. T e behavioral af liations of this network include the coordination of emotion, motivation, autonomic tone, and endocrine function. An additional area of specialization for the limbic network and the one that is of most relevance to clinical practice is that of declarative (explicit) memory for recent episodes and experiences. A disturbance in this function is known as an amnestic state. In the absence of deficits in motivation, attention, language, or visuospatial function, the clinical diagnosis of a persistent global amnestic state is always associated with bilateral damage to the limbic network, usually within the hippocampo-entorhinal complex or the thalamus. Damage to the limbic network does not necessarily destroy memories but interferes with their conscious recall in coherent form. T e individual fragments of information remain preserved despite the limbic lesions and can sustain what is known as implicit memory. For example, patients with amnestic states can acquire new motor or perceptual skills even though they may have no conscious knowledge of the experiences that led to the acquisition of these skills.

T e memory disturbance in the amnestic state is multimodal and includes retrograde and anterograde components. T e retrograde amnesia involves an inability to recall experiences that occurred before the onset of the amnestic state. Relatively recent events are more vulnerable to retrograde amnesia than are more remote and more extensively consolidated events. A patient who comes to the emergency room complaining that he cannot remember his or her identity but can remember the events of the previous day almost certainly does not have a neurologic cause of memory disturbance. T e second and most important component of the amnestic state is the anterograde amnesia, which indicates an inability to store, retain, and recall new knowledge. Patients with amnestic states cannot remember what they ate a few hours ago or the details of an important event they may have experienced in the recent past. In the acute stages, there also may be a tendency to fill in memory gaps with inaccurate, fabricated, and often implausible information. T is is known as con*f*abulation. Patients with the amnestic syndrome forget that they forget and tend to deny the existence of a memory problem when questioned. Confabulation is more common in cases where the underlying lesion also interferes with parts of the frontal network, as in the case of the Wernicke-Korsakoff syndrome or traumatic head injury.

CLINICAL EXAMINATION

A patient with an amnestic state is almost always disoriented, especially to time, and has little knowledge of current news. T e anterograde component of an amnestic state can be tested with a list of four to five

www.ketabpezeshki.com (021) 66485457 - 66485438

words read aloud by the examiner up to five times or until the patient can immediately repeat the entire list without an intervening delay. T e next phase of the recall occurs after a period of 5 to 10 min during which the patient is engaged in other tasks. Amnestic patients fail this phase of the task and may even forget that they were given a list of words to remember. Accurate recognition of the words by multiple choice in a patient who cannot recall them indicates a less severe memory disturbance that affects mostly the retrieval stage of memory. T e retrograde component of an amnesia can be assessed with questions related to autobiographical or historic events. T e anterograde component of amnestic states is usually much more prominent than the retrograde component. In rare instances, occasionally associated with temporal lobe epilepsy or herpes simplex encephalitis, the retrograde component may dominate. Confusional states caused by toxic-metabolic encephalopathies and some types of frontal lobe damage lead to secondary memory impairments, especially at the stages of encoding and retrieval, even in the absence of limbic lesions. T is sort of memory impairment can be differentiated from the amnestic state by the presence of additional impairments in the attention-related tasks described below in the section on the frontal lobes.

CAUSES, INCLUDING ALZHEIMER'S DISEASE

Neurologic diseases that give rise to an amnestic state include tumors (of the sphenoid wing, posterior corpus callosum, thalamus, or medial temporal lobe), infarctions (in the territories of the anterior or posterior cerebral arteries), head trauma, herpes simplex encephalitis, Wernicke-Korsakoff encephalopathy, paraneoplastic limbic encephalitis, and degenerative dementias such as AD and Pick's disease. T e one common denominator of all these diseases is the presence of bilateral lesions within one or more components in the limbic network. Occasionally, unilateral left-sided hippocampal lesions can give rise to an amnestic state, but the memory disorder tends to be transient. Depending on the nature and distribution of the underlying neurologic disease, the patient also may have visual field deficits, eye movement limitations, or cerebellar findings. AD and its prodromal state of mild cognitive impairment (MCI) are the most common causes of progressive memory impairments. T e predilection of the entorhinal cortex and hippocampus for early neurofibrillary degeneration by typical AD pathology is responsible for the initially selective impairment of episodic memory. In time, additional impairments in language, attention, and visuospatial skills emerge as the neurofibrillary degeneration spreads to additional neocortical areas.

*T*ransient global amnesia is a distinctive syndrome usually seen in late middle age. Patients become acutely disoriented and repeatedly ask who they are, where they are, and what they are doing. T e spell is characterized by anterograde amnesia (inability to retain new information) and a retrograde amnesia for relatively recent events that occurred before the onset. T e syndrome usually resolves within 24 to 48 h and is followed by the filling in of the period affected by the retrograde amnesia, although there is persistent loss of memory for the events that occurred during the ictus. Recurrences are noted in approximately 20% of patients. Migraine, temporal lobe seizures, and perfusion abnormalities in the posterior cerebral territory have been postulated as causes of transient global amnesia. T e absence of associated neurologic findings occasionally may lead to the incorrect diagnosis of a psychiatric disorder.

THE PREFRONTAL NETWORK FOR EXECUTIVE FUNCTION AND BEHAVIOR

T e frontal lobes can be subdivided into motor-premotor, dorsolateral prefrontal, medial prefrontal, and orbitofrontal components. T e terms *f*rontal lobe syndrome and pre*f*rontal cortex refer only to the last three of these four components. T ese are the parts of the cerebral cortex that show the greatest phylogenetic expansion in primates, especially in humans. T e dorsolateral prefrontal, medial prefrontal, and orbitofrontal areas, along with the subcortical structures with which they are interconnected (i.e., the head of the caudate and the dorsomedial nucleus of the thalamus), collectively make up a large-scale network that coordinates exceedingly complex aspects of human cognition and behavior.

T e prefrontal network plays an important role in behaviors that require multitasking and the integration of thought with emotion. Cognitive operations impaired by prefrontal cortex lesions often are referred to as "executive functions." T e most common clinical manifestations of damage to the prefrontal network take the form of two relatively distinct syndromes. In the *f*rontal abulic syndrome, the patient shows a loss of initiative, creativity, and curiosity and displays a pervasive emotional blandness, apathy, and lack of empathy. In the *f*rontal disinhibition syndrome, the patient becomes socially disinhibited and shows severe impairments of judgment, insight, foresight, and the ability to mind rules of conduct. T e dissociation between intact intellectual function and a total lack of even rudimentary common sense is striking. Despite the preservation of all essential memory functions, the patient cannot learn from experience and continues to display inappropriate behaviors without appearing to feel emotional pain, guilt, or regret when those behaviors repeatedly

www.ketabpezeshki.com (021) 66485457 - 66485438

lead to disastrous consequences. T e impairments may emerge only in real-life situations when behavior is under minimal external control and may not be apparent within the structured environment of the medical of ce. Testing judgment by asking patients what they would do if they detected a fire in a theater or found a stamped and addressed envelope on the road is not very informative because patients who answer these questions wisely in the of ce may still act very foolishly in real-life settings. T e physician must therefore be prepared to make a diagnosis of frontal lobe disease based on historic information alone even when the mental state is quite intact in the of ce examination.

CLINICAL EXAMINATION

T e emergence of developmentally primitive reflexes, also known as frontal release signs, such as grasping (elicited by stroking the palm) and sucking (elicited by stroking the lips) are seen primarily in patients with large structural lesions that extend into the premotor components of the frontal lobes or in the context of metabolic encephalopathies. T e vast majority of patients with prefrontal lesions and frontal lobe behavioral syndromes do not display these reflexes. Damage to the frontal lobe disrupts a variety of attention-related functions, including working memory (the transient online holding and manipulation of information), concentration span, the scanning and retrieval of stored information, the inhibition of immediate but inappropriate responses, and mental flexibility. Digit span (which should be seven forward and five reverse) is decreased, reflecting poor working memory; the recitation of the months of the year in reverse order (which should take less than 15 s) is slowed as another indication of poor working memory; and the fluency in producing words starting with the letter a, f, or s that can be generated in 1 min (normally ≥12 per letter) is diminished even in nonaphasic patients, indicating an impairment in the ability to search and retrieve information from long-term stores. In "go–no go" tasks (where the instruction is to raise the finger upon hearing one tap but keep it still upon hearing two taps), the patient shows a characteristic inability to inhibit the response to the "no go" stimulus. Mental flexibility (tested by the ability to shift from one criterion to another in sorting or matching tasks) is impoverished; distractibility by irrelevant stimuli is increased; and there is a pronounced tendency for impersistence and perseveration. T e ability for abstracting similarities and interpreting proverbs is also undermined.

T e attentional deficits disrupt the orderly registration and retrieval of new information and lead to secondary memory deficits. T e distinction of the underlying neural mechanisms is illustrated by the observation that severely amnestic patients who cannot remember events that occurred a few minutes ago may have intact if not superior working memory capacity as shown in tests of digit span.

CAUSES: TRAUMA, NEOPLASM, AND FRONTOTEMPORAL DEMENTIA

T e abulic syndrome tends to be associated with damage in dorsolateral or dorsomedial prefrontal cortex, and the disinhibition syndrome with damage in orbitofrontal or ventromedial cortex. T ese syndromes tend to arise almost exclusively after bilateral lesions. Unilateral lesions confined to the prefrontal cortex may remain silent until the pathology spreads to the other side; this explains why thromboembolic CVA is an unusual cause of the frontal lobe syndrome. Common settings for frontal lobe syndromes include head trauma, ruptured aneurysms, hydrocephalus, tumors (including metastases, glioblastoma, and falx or olfactory groove meningiomas), and focal degenerative diseases. A major clinical form of FTLD known as the behavioral variant of frontotemporal dementia (bvFTD) causes a progressive frontal lobe syndrome. T e behavioral changes can range from apathy to shoplifting, compulsive gambling, sexual indiscretions, remarkable lack of common sense, new ritualistic behaviors, and alterations in dietary preferences, usually leading to increased taste for sweets or rigid attachment to specific food items. In many patients with AD, neurofibrillary degeneration eventually spreads to prefrontal cortex and gives rise to components of the frontal lobe syndrome, but almost always on a background of severe memory impairment. Rarely, the bvFTD syndrome can arise in isolation in the context of an atypical form of AD pathology.

Lesions in the caudate nucleus or in the dorsomedial nucleus of the thalamus (subcortical components of the prefrontal network) also can produce a frontal lobe syndrome. T is is one reason why the changes in mental state associated with degenerative basal ganglia diseases such as Parkinson's disease and Huntington's disease display components of the frontal lobe syndrome. Bilateral multifocal lesions of the cerebral hemispheres, none of which are individually large enough to cause specific cognitive deficits such as aphasia and neglect, can collectively interfere with the connectivity and therefore integrating (executive) function of the prefrontal cortex. A frontal lobe syndrome is therefore the single most common behavioral profile associated with a variety of bilateral multifocal brain diseases, including metabolic encephalopathy, multiple sclerosis, and vitamin B_{12} deficiency, among others. Many patients with the clinical diagnosis of a frontal lobe syndrome tend to have lesions that do not involve prefrontal cortex

www.ketabpezeshki.com (021) 66485457 - 66485438

but involve either the subcortical components of the prefrontal network or its connections with other parts of the brain. To avoid making a diagnosis of "frontal lobe syndrome" in a patient with no evidence of frontal cortex disease, it is advisable to use the diagnostic term *f*rontal network syndrome, with the understanding that the responsible lesions can lie anywhere within this distributed network. A patient with frontal lobe disease raises potential dilemmas in differential diagnosis: the abulia and blandness may be misinterpreted as depression, and the disinhibition as idiopathic mania or acting out. Appropriate intervention may be delayed while a treatable tumor keeps expanding.

CARING FOR PATIENTS WITH DEFICITS OF HIGHER CEREBRAL FUNCTION

Brain damage may cause a dissociation between feeling states and their expression so that a patient who may superficially appear jocular could still be suffering from an underlying depression that needs to be treated. If neuroleptics become absolutely necessary for the control of agitation, atypical neuroleptics are preferable because of their lower extrapyramidal side effects. Treatment with neuroleptics in elderly patients with dementia requires weighing the potential benefits against the potentially serious side effects.

Spontaneous improvement of cognitive deficits due to acute neurologic lesions is common. It is most rapid in the first few weeks but may continue for up to 2 years, especially in young individuals with single brain lesions. Some of the initial deficits appear to arise from remote dysfunction (diaschisis) in parts of the brain that are interconnected with the site of initial injury. Improvement in these patients may reflect, at least in part, a normalization of the remote dysfunction. Other mechanisms may involve functional reorganization in surviving neurons adjacent to the injury or the compensatory use of homologous structures, e.g., the right superior temporal gyrus with recovery from Wernicke's aphasia. Cognitive rehabilitation procedures have been used in the treatment of higher cortical deficits. T ere are few controlled studies, but some show a benefit of rehabilitation in the recovery from hemispatial neglect and aphasia. Determining driving competence is challenging, especially in the early stages of dementing diseases. T e diagnosis of a neurodegenerative disease is not by itself suf cient for asking the patient to stop driving. An on-the-road driving test and reports from family members may help time decisions related to this very important activity.

Some of the deficits described in this chapter are so complex that they may bewilder not only the patient and family but also the physician. It is imperative to carry out a systematic clinical evaluation to characterize the nature of the deficits and explain them in lay terms to the patient and family. An enlightened approach to patients with damage to the cerebral cortex requires an understanding of the principles that link neural networks to higher cerebral functions in health and disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 23

PRIMARY PROGRESSIVE APHASIA, MEMORY LOSS, AND OTHER FOCAL CEREBRAL DISORDERS

Maria Luisa Gorno-Tempini ■ Jennifer Ogar ■ Joel Kramer
Bruce L. Miller ■ Gil Rabinovici ■ Maria Carmela Tartaglia

Language and memory are essential human functions. For the experienced clinician, the recognition of different types of language and memory disturbances of en provides essential clues to the anatomic localization and diagnosis of neurologic disorders. T is video illustrates classic disorders of language and speech (including the aphasias), memory (the amnesias), and other disorders of cognition that are commonly encountered in clinical practice.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 23–1 primary progressive aphasia, memory loss, and other focal cerebral disorders.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 24

SLEEP DISORDERS

Charles A. Czeisler ■ Thomas E. Scammell ■ Clif ord B. Saper

Disturbed sleep is among the most frequent health complaints that physicians encounter. More than one-half of adults in the United States experience at least intermittent sleep disturbance, and only 30% of adult Americans report consistently obtaining a sufficient amount of sleep. T e Institute of Medicine has estimated that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, which can adversely affect daytime functioning as well as physical and mental health. Over the last 20 years, the field of sleep medicine has emerged as a distinct specialty in response to the impact of sleep disorders and sleep deficiency on overall health.

PHYSIOLOGY OF SLEEP AND WAKEFULNESS

Given the opportunity, most healthy young adults will sleep 7–8 h per night, although the timing, duration, and internal structure of sleep vary among individuals. In the United States, adults tend to have one consolidated sleep episode each night, although in some cultures sleep may be divided into a mid-afternoon nap and a shortened night sleep. T is pattern changes considerably over the life span, as infants and young children sleep considerably more than older people.

T e stages of human sleep are defined on the basis of characteristic patterns in the electroencephalogram (EEG), the electrooculogram (EOG—a measure of eye-movement activity), and the surface electromyogram (EMG) measured on the chin, neck, and legs. T e continuous recording of these electrophysiologic parameters to define sleep and wakefulness is termed polysomnography.

Polysomnographic profiles define two basic states of sleep: (1) rapid eye movement (REM) sleep and (2) non–rapid eye movement (NREM) sleep. NREM sleep is further subdivided into three stages: N1, N2, and N3, characterized by increasing arousal threshold and slowing of the cortical EEG. REM sleep is characterized by a low-amplitude, mixed-frequency EEG similar to that of NREM stage N1 sleep. T e EOG shows bursts of rapid eye movements similar to those seen during eyes-open wakefulness. EMG activity is absent in nearly all skeletal muscles, reflecting the brainstem-mediated muscle atonia that is characteristic of REM sleep.

ORGANIZATION OF HUMAN SLEEP

Normal nocturnal sleep in adults displays a consistent organization from night to night **(Fig. 24-1)**. After sleep onset, sleep usually progresses through NREM stages N1–N3 sleep within 45–60 min. NREM stage N3 sleep (also known as slow-wave sleep) predominates in the first third of the night and comprises 15–25% of total nocturnal sleep time in young adults. Sleep deprivation increases the rapidity of sleep onset and both the intensity and amount of slow-wave sleep.

T e first REM sleep episode usually occurs in the second hour of sleep. NREM and REM sleep alternate through the night with an average period of 90–110 min (the "ultradian" sleep cycle). Overall, in a healthy young adult, REM sleep constitutes 20–25% of total sleep, and NREM stages N1 and N2 constitute 50–60%.

Age has a profound impact on sleep state organization (Fig. 24-1). N3 sleep is most intense and prominent during childhood, decreasing with puberty and across the second and third decades of life. N3 sleep declines during adulthood to the point where it may be completely absent in older adults. T e remaining NREM sleep becomes more fragmented, with many more frequent awakenings from NREM sleep. It is the increased frequency of awakenings, rather than a decreased ability to fall back asleep, that accounts for the increased wakefulness during the sleep episode in older people.

www.ketabpezeshki.com (021) 66485457 - 66485438

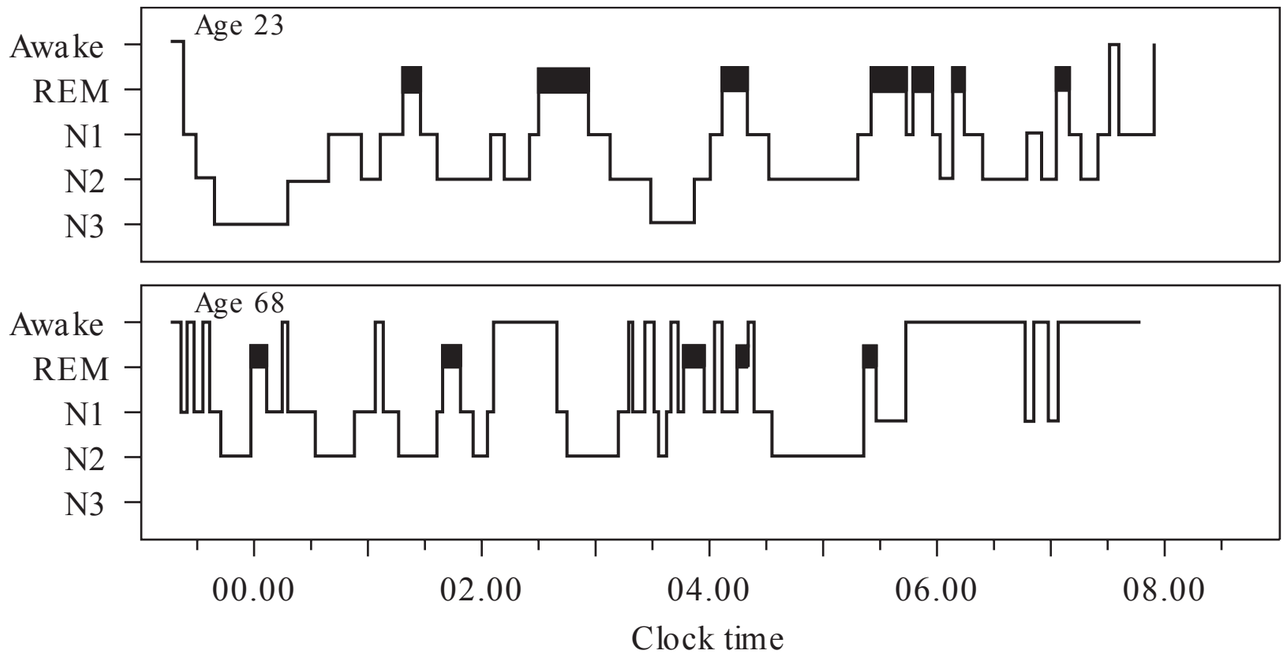


FIGURE 24-1
Wake-sleep architecture. Alternating stages of wakefulness, the three stages of NREM sleep (N1–N3), and REM sleep (solid bars) occur over the course of the night for representative young and older adult men. Characteristic features of sleep in older people include reduction of N3 slow-wave sleep, frequent spontaneous awakenings, early sleep onset, and early morning awakening. NREM, non–rapid eye movement; REM, rapid eye movement. (From the Division of Sleep and Circadian Disorders, Brigham and Women's Hospital.)

While REM sleep may account for 50% of total sleep time in infancy, the percentage falls off sharply over the first postnatal year as a mature REM-NREM cycle develops; thereafter, REM sleep occupies about 25% of total sleep time.

Sleep deprivation degrades cognitive performance, particularly on tests that require continual vigilance. Paradoxically, older people are less vulnerable to the neurobehavioral performance impairment induced by acute sleep deprivation than young adults, maintaining their reaction time and sustaining vigilance with fewer lapses of attention. However, it is more difficult for older adults to obtain recovery sleep after staying awake all night, as the ability to sleep during the daytime declines with age.

After sleep deprivation, NREM sleep is generally recovered first, followed by REM sleep. However, because REM sleep tends to be most prominent in the second half of the night, sleep truncation (e.g., by an alarm clock) results in selective REM sleep deprivation. T is may increase REM sleep pressure to the point where the first REM sleep may occur much earlier in the nightly sleep episode. Because several disorders (see below) also cause sleep fragmentation, it is important that the patient have sufficient sleep opportunity (at least 8 h per night) for several nights prior to a diagnostic polysomnogram.

T ere is growing evidence that sleep deficiency in humans may cause glucose intolerance and contribute to the development of diabetes, obesity, and the metabolic syndrome, as well as impaired immune responses, accelerated atherosclerosis, and increased risk of cardiac disease and stroke. For these reasons, the Institute of Medicine declared sleep deficiency and sleep disorders "an unmet public health problem."

WAKE AND SLEEP ARE REGULATED BY BRAIN CIRCUITS

Two principal neural systems govern the expression of the sleep and wakefulness. T e ascending arousal system, illustrated in green in **Fig. 24-2**, consists of clusters of nerve cells extending from the upper pons to the hypothalamus and basal forebrain that activate the cerebral cortex, thalamus (which is necessary to relay sensory information to the cortex), and other forebrain regions. T e ascending arousal neurons use monoamines (norepinephrine, dopamine, serotonin, and histamine), glutamate, or acetylcholine as neurotransmitters to activate their target neurons. Additional arousal-promoting neurons in the hypothalamus use the peptide neurotransmitter orexin (also known as hypocretin, shown in blue) to reinforce activity in the other arousal cell groups.

Damage to the arousal system at the level of the rostral pons and lower midbrain causes coma, indicating that the ascending arousal influence from this level is critical in maintaining wakefulness. Damage to the hypothalamic branch of the arousal system causes profound sleepiness, but usually not coma. Specific loss of the orexin neurons produces the sleep disorder narcolepsy (see below).

T e arousal system is turned off during sleep by inhibitory inputs from cell groups in the sleep-promoting system, shown in Fig. 24-2 in red. T ese neurons in the preoptic area, lateral hypothalamus, and pons use γ-aminobutyric acid (GABA) to inhibit the arousal system. Many sleep-promoting neurons are themselves inhibited by inputs from the arousal system. T is mutual inhibition between the arousal- and sleep-promoting systems forms a neural circuit akin to what electrical engineers call a "flip-flop switch." A switch of this type tends to promote rapid transitions between the on (wake) and off (sleep) states, while avoiding intermediate states. T e relatively rapid transitions between waking and sleeping states, as seen in the EEG of humans and animals, is consistent with this model.

Neurons in the ventrolateral preoptic nucleus, one of the key sleep-promoting sites, are lost during normal human aging, correlating with reduced ability to maintain sleep (sleep fragmentation). T e ventrolateral preoptic neurons are also injured in Alzheimer's disease, which may in part account for the poor sleep quality in those patients.

www.ketabpezeshki.com (021) 66485457 - 66485438

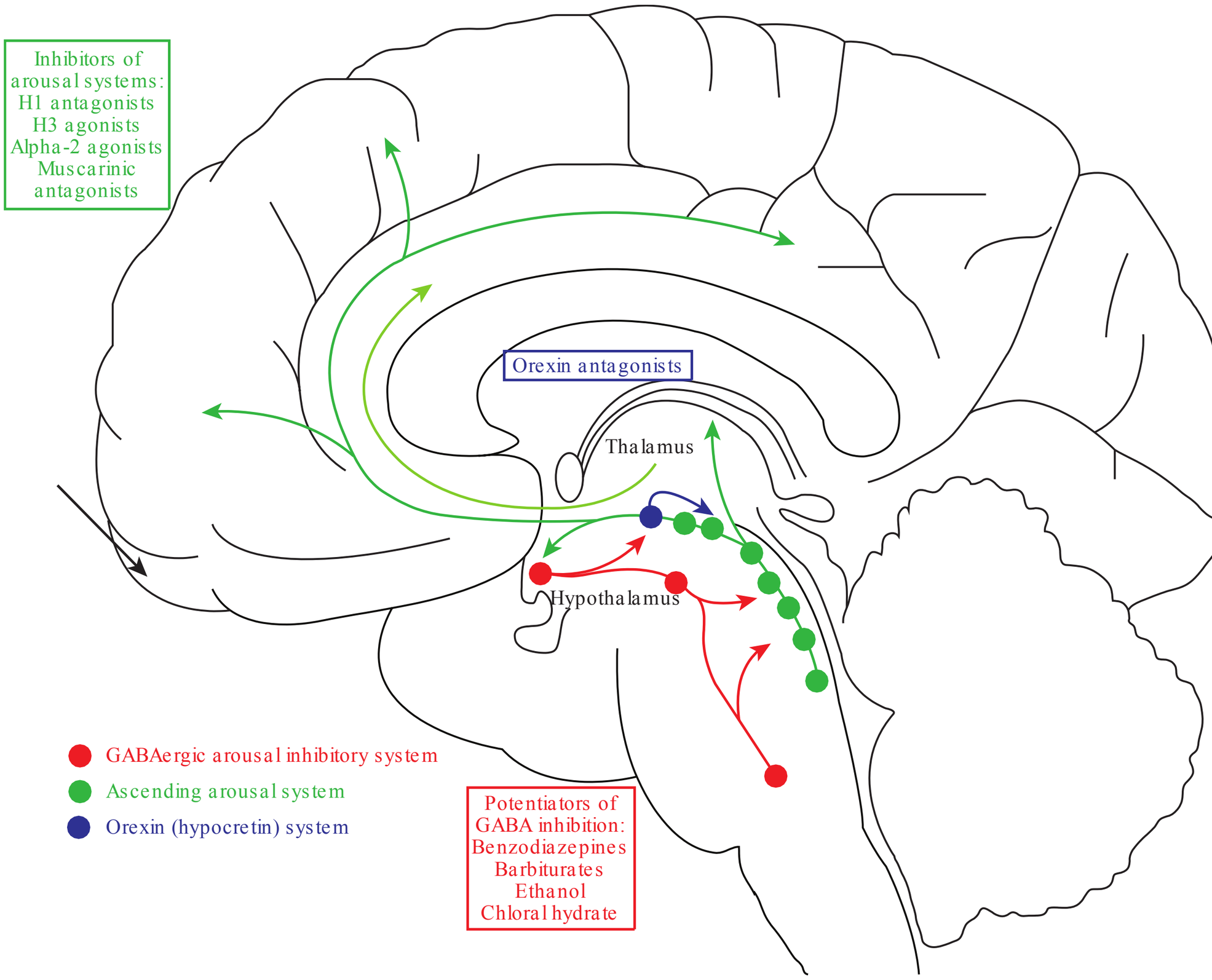


FIGURE 24-2

Relationship of drugs for insomnia with wake-sleep systems. The arousal system in the brain (green) includes monoaminergic, glutamatergic, and cholinergic neurons in the brainstem that activate neurons in the hypothalamus, thalamus, basal forebrain, and cerebral cortex. Orexin neurons (blue) in the hypothalamus, which are lost in narcolepsy, reinforce and stabilize arousal by activating other components of the arousal system. The sleep-promoting system (red) consists of GABAergic neurons in the preoptic area, lateral hypothalamus, and brainstem that inhibit the components of the arousal system, thus allowing sleep to occur. Drugs used to treat insomnia include those that block the effects of arousal system neurotransmitters (green and blue) and those that enhance the effects of γ-aminobutyric acid (GABA) produced by the sleep system (red).

Transitions between NREM and REM sleep appear to be governed by a similar switch in the brainstem. GABAergic REM-Off neurons have been identified in the lower midbrain that inhibit REM-On neurons in the upper pons. T e REM-On group contains both GABAergic neurons that inhibit the REM-Off group (thus satisfying the conditions for a REM flip-flop switch) as well as glutamatergic neurons that project widely in the central nervous system (CNS) to cause the key phenomena associated with REM sleep. REM-On neurons that project to the medulla and spinal cord activate inhibitory (GABA and glycine-containing) interneurons, which in turn hyperpolarize the motor neurons, producing the atonia of REM sleep. REM-On neurons that project to the forebrain may be important in producing dreams.

T e REM sleep switch receives cholinergic input, which favors transitions to REM sleep, and monoaminergic (norepinephrine and serotonin) input that prevents REM sleep. As a result, drugs that increase monoamine tone (e.g., serotonin or norepinephrine reuptake inhibitors) tend to reduce the amount of REM sleep. Damage to the neurons that promote REM sleep atonia can produce REM sleep behavior disorder, a condition in which patients act out their dreams (see below).

www.ketabpezeshki.com (021) 66485457 - 66485438

SLEEP-WAKE CYCLES ARE DRIVEN BY HOMEOSTATIC, ALLOSTATIC, AND CIRCADIAN INPUTS

T e gradual increase in sleep drive with prolonged wakefulness, followed by deeper slow-wave sleep and prolonged sleep episodes, demonstrates that there is a homeostatic mechanism that regulates sleep. T e neurochemistry of sleep homeostasis is only partially understood, but with prolonged wakefulness, adenosine levels rise in parts of the brain. Adenosine may act through A1 receptors to directly inhibit many arousal-promoting brain regions. In addition, adenosine promotes sleep through A2a receptors; inhibition of these receptors by caffeine is one of the chief ways in which people fight sleepiness. Other humoral factors, such as prostaglandin D_2, have also been implicated in this process. Both adenosine and prostaglandin D_2 activate the sleep-promoting neurons in the ventrolateral preoptic nucleus.

Allostasis is the physiologic response to a threat that cannot be managed by homeostatic mechanisms (e.g., the presence of physical danger or psychological threat). T ese stress responses can severely impact the need for and ability to sleep. For example, insomnia is very common in patients with anxiety and other psychiatric disorders. Stress-induced insomnia is even more common, affecting most people at some time in their lives. Positron emission tomography (PET) studies in patients with chronic insomnia show hyperactivation of the components of the ascending arousal system, as well as their targets in the limbic system in the forebrain (e.g., cingulate cortex and amygdala). T e limbic areas are not only targets for the arousal system, but they also send excitatory outputs back to the arousal system, which contributes to a vicious cycle of anxiety about wakefulness that makes it more difficult to sleep. Approaches to treating insomnia rely on drugs that either inhibit the output of the ascending arousal system (green and blue in Fig. 24-2) or potentiate the output of the sleep-promoting system (red in Fig. 24-2). However, behavioral approaches (cognitive behavioral therapy and sleep hygiene) that may reduce forebrain limbic activity at bedtime are often equally or more successful.

Sleep is also regulated by a strong circadian timing signal, driven by the suprachiasmatic nuclei (SCN) of the hypothalamus, as described below. T e SCN sends outputs to key sites in the hypothalamus, which impose 24-h rhythms on a wide range of behaviors and body systems, including the wake-sleep cycle.

PHYSIOLOGY OF CIRCADIAN RHYTHMICITY

T e wake-sleep cycle is the most evident of many 24-h rhythms in humans. Prominent daily variations also occur in endocrine, thermoregulatory, cardiac, pulmonary, renal, immune, gastrointestinal, and neurobehavioral functions. At the molecular level, endogenous circadian rhythmicity is driven by self-sustaining transcriptional/translational feedback loops. In evaluating daily rhythms in humans, it is important to distinguish between diurnal components passively evoked by periodic environmental or behavioral changes (e.g., the increase in blood pressure and heart rate that occurs upon assumption of the upright posture) and circadian rhythms actively driven by an endogenous oscillatory process (e.g., the circadian variations in adrenal cortisol and pineal melatonin secretion that persist across a variety of environmental and behavioral conditions).

While it is now recognized that most cells in the body have circadian clocks that regulate diverse physiologic processes, most of these disparate clocks are unable to maintain the synchronization with each other that is required to produce useful 24-h rhythms aligned with the external light-dark cycle. T e neurons in the SCN are interconnected with one another in such a way as to produce a near-24-h synchronous rhythm of neural activity that is then transmitted to the rest of the body. Bilateral destruction of the SCN results in a loss of most endogenous circadian rhythms including wake-sleep behavior and rhythms in endocrine and metabolic systems. T e genetically determined period of this endogenous neural oscillator, which averages ~24.15 h in humans, is normally synchronized to the 24-h period of the environmental light-dark cycle through direct input from intrinsically photosensitive ganglion cells in the retina to the SCN. Humans are exquisitely sensitive to the resetting effects of light, particularly the shorter wavelengths (~460–500 nm) of the visible spectrum. Small differences in circadian period contribute to variations in diurnal preference in young adults (with the circadian period shorter in those who typically go to bed and rise earlier compared to those who typically go to bed and wake up later), whereas changes in homeostatic sleep regulation may underlie the age-related tendency toward earlier sleep-wake timing.

T e timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Paradoxically, the endogenous circadian rhythm for wake propensity peaks just before the habitual bedtime, whereas that of sleep propensity peaks near the habitual wake time. T ese rhythms are thus timed to oppose the rise of sleep tendency throughout the usual waking day and the decline of sleep propensity during the habitual sleep episode, respectively. Misalignment of the endogenous circadian pacemaker with the desired wake-sleep cycle can, therefore, induce insomnia, decreased alertness, and impaired performance evident in night-shift workers and airline travelers.

www.ketabpezeshki.com (021) 66485457 - 66485438

BEHAVIORAL AND PHYSIOLOGIC CORRELATES OF SLEEP STATES AND STAGES

Polysomnographic staging of sleep correlates with behavioral changes during specific states and stages. During the transitional state (stage N1) between wakefulness and deeper sleep, individuals may respond to faint auditory or visual signals. Formation of short-term memories is inhibited at the onset of NREM stage N1 sleep, which may explain why individuals aroused from that transitional sleep stage frequently lack situational awareness. After sleep deprivation, such transitions may intrude upon behavioral wakefulness notwithstanding attempts to remain continuously awake (see "Shift-Work Disorder," below).

Awakenings from REM sleep are associated with recall of vivid dream imagery over 80% of the time, especially later in the night. Imagery may also be reported after NREM sleep interruptions. Certain disorders may occur during specific sleep stages and are described below under "Parasomnias." T ese include sleepwalking, night terrors, and enuresis (bed wetting), which occur most commonly in children during deep (N3) NREM sleep, and REM sleep behavior disorder, which occurs mainly among older men who fail to maintain full atonia during REM sleep, and often call out, thrash around, or even act out entire dreams.

All major physiologic systems are influenced by sleep. Blood pressure and heart rate decrease during NREM sleep, particularly during N3 sleep. During REM sleep, bursts of eye movements are associated with large variations in both blood pressure and heart rate mediated by the autonomic nervous system. Cardiac dysrhythmias may occur selectively during REM sleep. Respiratory function also changes. In comparison to relaxed wakefulness, respiratory rate becomes slower but more regular during NREM sleep (especially N3 sleep) and becomes irregular during bursts of eye movements in REM sleep. Decreases in minute ventilation during NREM sleep are out of proportion to the decrease in metabolic rate, resulting in a slightly higher Pco_2.

Endocrine function also varies with sleep. N3 sleep is associated with secretion of growth hormone in men, while sleep in general is associated with augmented secretion of prolactin in both men and women. Sleep has a complex effect on the secretion of luteinizing hormone (LH): during puberty, sleep is associated with increased LH secretion, whereas sleep in the postpubertal female inhibits LH secretion in the early follicular phase of the menstrual cycle. Sleep onset (and probably N3 sleep) is associated with inhibition of thyroid-stimulating hormone and of the adrenocorticotropic hormone–cortisol axis, an effect that is superimposed on the prominent circadian rhythms in the two systems.

T e pineal hormone melatonin is secreted predominantly at night in both day- and night-active species, reflecting the direct modulation of pineal activity by a circuitous neural pathway that links the SCN to the sympathetic nervous system, which innervates the pineal gland. Melatonin secretion does not require sleep, but melatonin secretion is inhibited by ambient light, an effect mediated by the neural connection from the retina to the pineal gland via the SCN. Sleep efficiency is highest when the sleep episode coincides with endogenous melatonin secretion. Administration of exogenous melatonin can hasten sleep onset and increase sleep efficiency when administered at a time when endogenous melatonin levels are low, such as in the afternoon or evening or at the desired bedtime in patients with delayed sleep-wake phase disorder, but it does not increase sleep efficiency if administered when endogenous melatonin levels are elevated. T is may explain why melatonin is often ineffective in the treatment of patients with primary insomnia.

Sleep is accompanied by alterations of thermoregulatory function. NREM sleep is associated with an increase in the firing of warm-responsive neurons in the preoptic area and a fall in body temperature; conversely, skin warming without increasing core body temperature has been found to increase NREM sleep. REM sleep is associated with reduced thermoregulatory responsiveness.

DISORDERS OF SLEEP AND WAKEFULNESS

APPROACH TO THE PATIENT: Sleep Disorders

Patients may seek help from a physician because of: (1) sleepiness or tiredness during the day; (2) difficulty initiating or maintaining sleep at night (insomnia); or (3) unusual behaviors during sleep itself (parasomnias).

Obtaining a careful history is essential. In particular, the duration, severity, and consistency of the symptoms are important, along with the patient's estimate of the consequences of the sleep disorder on waking function. Information from a bed partner or family member is often helpful because some patients may be unaware of symptoms such as heavy snoring or may underreport symptoms such as falling asleep at work or while driving. Physicians should inquire about when the patient typically goes to bed, when they fall asleep and wake up, whether they awaken during sleep, whether they feel rested in the morning, and whether they nap during the day. Depending on the primary complaint, it may be useful to

www.ketabpezeshki.com (021) 66485457 - 66485438

ask about snoring, witnessed apneas, restless sensations in the legs, movements during sleep, depression, anxiety, and behaviors around the sleep episode. T e physical exam may provide evidence of a small airway, large tonsils, or a neurologic or medical disorder that contributes to the main complaint.

It is important to remember that, rarely, seizures may occur exclusively during sleep, mimicking a primary sleep disorder; such sleep-related seizures typically occur during episodes of NREM sleep and may take the form of generalized tonic-clonic movements (sometimes with urinary incontinence or tongue biting) or stereotyped movements in partial complex epilepsy **(Chap. 31)**.

It is often helpful for the patient to complete a daily sleep log for 1–2 weeks to define the timing and amounts of sleep. When relevant, the log can also include information on levels of alertness, work times, and drug and alcohol use, including caffeine and hypnotics.

Polysomnography is necessary for the diagnosis of several disorders such as sleep apnea, narcolepsy, and periodic limb movement disorder. A conventional polysomnogram performed in a clinical sleep laboratory allows measurement of sleep stages, respiratory effort and airflow, oxygen saturation, limb movements, heart rhythm, and additional parameters. A home sleep test usually focuses on just respiratory measures and is helpful in patients with a moderate to high likelihood of having obstructive sleep apnea. T e multiple sleep latency test (MSLT) is used to measure a patient's propensity to sleep during the day and can provide crucial evidence for diagnosing narcolepsy and some other causes of sleepiness. T e maintenance of wakefulness test is used to measure a patient's ability to sustain wakefulness during the daytime and can provide important evidence for evaluating the efficacy of therapies for improving sleepiness in conditions such as narcolepsy and obstructive sleep apnea.

EVALUATION OF DAYTIME SLEEPINESS

Up to 25% of the adult population has persistent daytime sleepiness that impairs an individual's ability to perform optimally in school, at work, while driving, and in other conditions that require alertness. Sleepy students often have trouble staying alert and performing well in school, and sleepy adults struggle to stay awake and focused on their work. More than half of Americans have fallen asleep while driving. An estimated 1.2 million motor vehicle crashes per year are due to drowsy drivers, causing about 20% of all serious crash injuries and deaths. One needn't fall asleep to have an accident, as the inattention and slowed responses of drowsy drivers are a major contributor. Reaction time is equally impaired by 24 h of sleep loss as by a blood alcohol concentration of 0.10 g/dL.

Identifying and quantifying sleepiness can be challenging. First, patients may describe themselves as "sleepy," "fatigued," or "tired," and the meanings of these words may differ between patients. For clinical purposes, it is best to use the term "sleepiness" to describe a propensity to fall asleep; whereas "fatigue" is best used to describe a feeling of low physical or mental energy but without a tendency to actually sleep. Sleepiness is usually most evident when the patient is sedentary, whereas fatigue may interfere with more active pursuits. Sleepiness generally occurs with disorders that reduce the quality or quantity of sleep or that interfere with the neural mechanisms of arousal, whereas fatigue is more common in inflammatory disorders such as cancer, multiple sclerosis **(Chap. 45)**, fibromyalgia, chronic fatigue syndrome **(Chap. 59)**, or endocrine deficiencies such as hypothyroidism or Addison's disease. Second, sleepiness can affect judgment in a manner analogous to ethanol, such that patients may have limited insight into the condition and the extent of their functional impairment. Finally, patients may be reluctant to admit that sleepiness is a problem because they may have become unfamiliar with feeling fully alert and because sleepiness is sometimes viewed pejoratively as reflecting poor motivation or bad sleep habits.

Table 24-1 outlines the diagnostic and therapeutic approach to the patient with a complaint of excessive daytime sleepiness.

To determine the extent and impact of sleepiness on daytime function, it is helpful to ask patients about the occurrence of sleep episodes during normal waking hours, both intentional and unintentional. Specific areas to be addressed include the occurrence of inadvertent sleep episodes while driving or in other safety-related settings, sleepiness while at work or school (and the relationship of sleepiness to work and school performance), and the effect of sleepiness on social and family life. Standardized questionnaires such as the Epworth Sleepiness Scale are often used clinically to measure sleepiness.

Eliciting a history of daytime sleepiness is usually adequate, but objective quantification is sometimes necessary. T e MSLT measures a patient's propensity to sleep under quiet conditions. T e test is performed after an overnight polysomnogram to establish that the patient has had an adequate amount of good-quality nighttime sleep. T e MSLT consists of five 20-min nap opportunities every 2 h across the day. T e patient is instructed to try to fall asleep, and the major endpoints are the average latency to sleep and the occurrence of REM sleep during the naps. An average sleep latency across the naps of less than 8 min is considered objective evidence of excessive daytime sleepiness. REM sleep normally occurs only during the nighttime sleep episode, and the occurrence of REM sleep in two or

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 24-1

EVALUATION OF THE PATIENT WITH EXCESSIVE DAYTIME SLEEPINESS

FINDINGS ON HISTORY AND PHYSICAL EXAMINATION	DIAGNOSTIC EVALUATION	DIAGNOSIS	THERAPY
Difficulty waking in the morning, rebound sleep on weekends and vacations with improvement in sleepiness	Sleep log	Insufficient sleep	Sleep education and behavioral modification to increase amount of sleep
Obesity, snoring, hypertension	Polysomnogram	Obstructive sleep apnea	Continuous positive airway pressure; upper airway surgery (e.g., uvulopalatopharyngoplasty); dental appliance; weight loss
Cataplexy, hypnogogic hallucinations, sleep paralysis	Polysomnogram and multiple sleep latency test	Narcolepsy	Stimulants (e.g., modafinil, methylphenidate); REM sleep-suppressing antidepressants (e.g., venlafaxine); sodium oxybate
Restless legs, kicking movements during sleep	Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure)	Restless legs syndrome with or without periodic limb movements	Treatment of predisposing condition if possible; dopamine agonists (e.g., pramipexole, ropinirole)
Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson's disease and other neurodegenerative disorders, hypothyroidism, encephalopathy	Thorough medical history and exam including detailed neurologic exam	Sleepiness due to a drug or medical condition	Change medications, treat underlying condition, consider stimulants

more of the MSLT naps provides support for the diagnosis of narcolepsy.

For the safety of the individual and the general public, physicians have a responsibility to help manage issues around driving in patients with sleepiness. Legal reporting requirements vary from state to state, but at a minimum, physicians should inform sleepy patients about their increased risk of having an accident and advise such patients not to drive a motor vehicle until the sleepiness has been treated effectively. T is discussion is especially important for professional drivers, and it should be documented in the patient's medical record.

INSUFFICIENT SLEEP

Insufficient sleep is probably the most common cause of excessive daytime sleepiness. T e average adult needs 7.5–8 h of sleep, but on weeknights, the average U.S. adult gets only 6.75 h of sleep. Only 30% of the U.S. adult population reports consistently obtaining sufficient sleep. Insufficient sleep is especially common among shift workers, individuals working multiple jobs, and people in lower socioeconomic groups. Most teenagers need ≥9 h of sleep, but many fail to get enough sleep because of circadian phase delay, or social pressures to stay up late coupled with early school start times. Late evening light exposure, television viewing, video-gaming, social media, texting, and smartphone use often delay bedtimes despite the fixed, early wake times required for work or school. As is typical with any disorder that causes sleepiness, individuals with chronically insufficient sleep may feel inattentive, irritable, unmotivated, and depressed, and have difficulty with school, work, and driving. Individuals differ in their optimal amount of sleep, and it can be helpful to ask how much sleep the patient obtains on a quiet vacation when he or she can sleep without restrictions. Some patients may think that a short amount of sleep is normal or advantageous, and they may not appreciate their biological need for more sleep, especially if coffee and other stimulants mask the sleepiness. A 2-week sleep log documenting the timing of sleep and daily level of alertness is diagnostically useful and provides helpful feedback for the patient. Extending sleep to the optimal amount on a regular basis can resolve the sleepiness and other symptoms. As with any lifestyle change, extending sleep requires commitment and adjustments, but the improvements in daytime alertness make this change worthwhile.

www.ketabpezeshki.com (021) 66485457 - 66485438

SLEEP APNEA SYNDROMES

Respiratory dysfunction during sleep is a common, serious cause of excessive daytime sleepiness as well as of disturbed nocturnal sleep. At least 24% of middle-aged men and 9% of middle-aged women in the United States have a reduction or cessation of breathing dozens or more times each night during sleep, with 9% of men and 4% of women doing so more than a hundred times per night. These episodes may be due to an occlusion of the airway (obstructive sleep apnea), absence of respiratory effort (central sleep apnea), or a combination of these factors (mixed sleep apnea). Failure to recognize and treat these conditions appropriately may lead to impairment of daytime alertness, increased risk of sleep-related motor vehicle crashes, depression, hypertension, myocardial infarction, diabetes, stroke, and increased mortality. Sleep apnea is particularly prevalent in overweight men and in the elderly, yet it is estimated to go undiagnosed in most affected individuals. This is unfortunate because several effective treatments are available.

NARCOLEPSY

Narcolepsy is characterized by difficulty sustaining wakefulness, poor regulation of REM sleep, and disturbed nocturnal sleep. All patients with narcolepsy have excessive daytime sleepiness. This sleepiness is often severe, but in some, it is mild. In contrast to patients with disrupted sleep (e.g., sleep apnea), people with narcolepsy usually feel well rested upon awakening and then feel tired throughout much of the day. In addition, they often experience symptoms related to an intrusion of REM sleep characteristics. REM sleep is characterized by dreaming and muscle paralysis, and people with narcolepsy can have: (1) sudden muscle weakness without a loss of consciousness, which is usually triggered by strong emotions (cataplexy; **Video 24-1**); (2) dream-like hallucinations at sleep onset (hypnagogic hallucinations) or upon awakening (hypnopompic hallucinations); and (3) muscle paralysis upon awakening (sleep paralysis). With severe cataplexy, an individual may be laughing at a joke and then suddenly collapse to the ground, immobile but awake for 1–2 min. With milder episodes, patients may have mild weakness of the face or neck. Narcolepsy is one of the more common causes of chronic sleepiness and affects about 1 in 2000 people in the United States. Narcolepsy typically begins between age 10 and 20; once established, the disease persists for life.

Video can be accessed via the following link: https://www.mhprofessional.com/mediacenter/

Video 24-1. A typical episode of severe cataplexy.

The patient is joking and then falls to the ground with an abrupt loss of muscle tone. The electromyogram recordings (four lower traces on the right) show reductions in muscle activity during the period of paralysis. The electroencephalogram (top two traces) shows wakefulness throughout the episode. (Video courtesy of Giuseppe Plazzi, University of Bologna.)

Narcolepsy is caused by loss of the hypothalamic neurons that produce the orexin neuropeptides (also known as hypocretins). Research in mice and dogs first demonstrated that a loss of orexin signaling due to null mutations of either the orexin neuropeptides or one of the orexin receptors causes sleepiness and cataplexy nearly identical to that seen in people with narcolepsy. Although genetic mutations rarely cause human narcolepsy, researchers soon discovered that patients with narcolepsy had very low or undetectable levels of orexins in their cerebrospinal fluid, and autopsy studies showed a nearly complete loss of the orexin-producing neurons in the hypothalamus. The orexins normally promote long episodes of wakefulness and suppress REM sleep, and thus, loss of orexin signaling results in frequent intrusions of sleep during the usual waking episode, with REM sleep and fragments of REM sleep at any time of day **(Fig. 24-3)**.

Extensive evidence suggests that an autoimmune process likely causes this selective loss of the orexin-producing neurons. Certain human leukocyte antigens (HLAs) can increase the risk of autoimmune disorders, and narcolepsy has the strongest known HLA association. HLA DQB1*06:02 is found in about 90% of people with narcolepsy, whereas it occurs in only 12–25% of the general population. Researchers now hypothesize that in people with DQB1*06:02, an immune response against influenza, Streptococcus, or other infections may also damage the orexin-producing neurons through a process of molecular mimicry. This mechanism may account for the 8- to 12-fold increase in new cases of narcolepsy among children in Europe who received a particular brand of H1N1 influenza A vaccine (Pandemrix).

On rare occasions, narcolepsy can occur with neurologic disorders such as tumors or strokes that directly damage the orexin-producing neurons in the hypothalamus or their projections.

Diagnosis

Narcolepsy is most commonly diagnosed by the history of chronic sleepiness plus cataplexy or other symptoms. Many disorders can cause feelings of weakness, but with true cataplexy, patients will describe definite functional weakness (e.g., slurred speech, dropping a cup, slumping into a chair) that has consistent emotional triggers such as heartfelt mirth when laughing at a great joke, happy surprise at unexpectedly seeing a friend, or intense anger. Cataplexy occurs in about half of all narcolepsy patients and is diagnostically very helpful because it occurs in almost no other disorder.

www.ketabpezeshki.com (021) 66485457 - 66485438

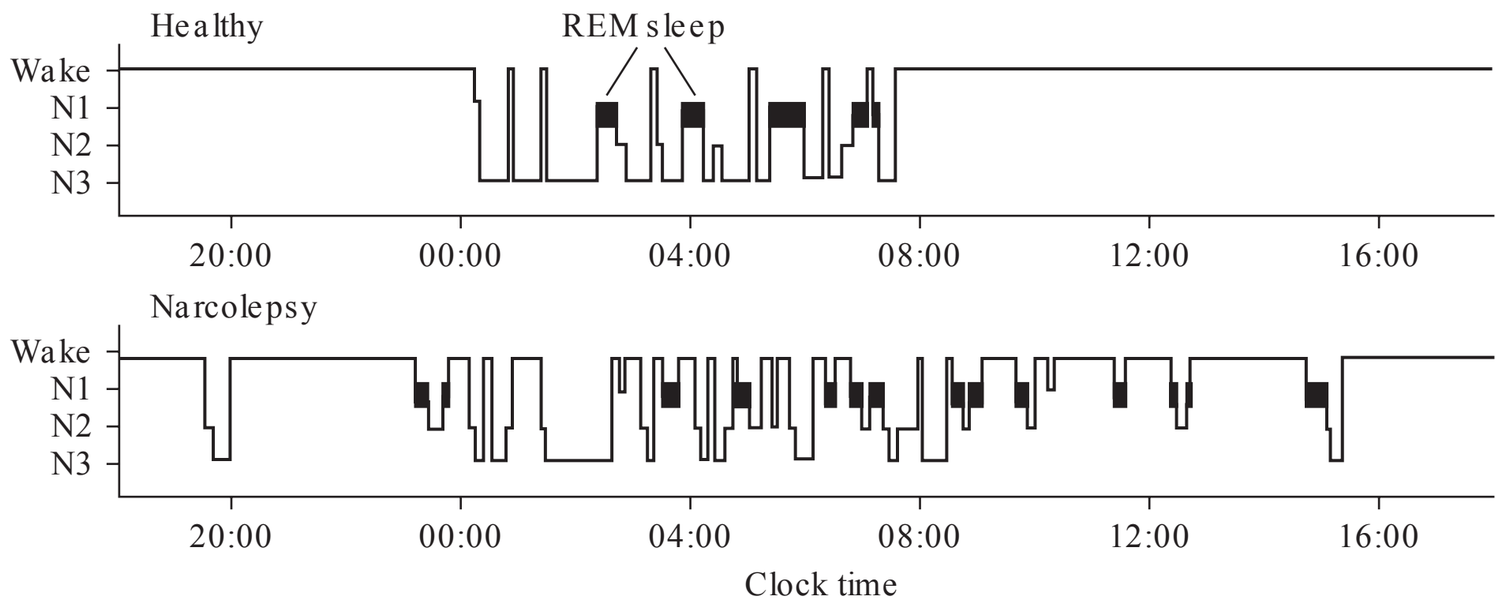


FIGURE 24-3
Polysomnographic recordings of a healthy individual and a patient with narcolepsy. The individual with narcolepsy enters rapid eye movement (REM) sleep quickly at night and has moderately fragmented sleep. During the day, the healthy subject stays awake from 8:00 am until midnight, but the patient with narcolepsy dozes off frequently, with many daytime naps that include REM sleep.

In contrast, occasional hypnagogic hallucinations and sleep paralysis occur in about 20% of the general population, and these symptoms are not as diagnostically specific.

When narcolepsy is suspected, the diagnosis should be firmly established with a polysomnogram followed by an MSLT. The polysomnogram helps rule out other possible causes of sleepiness such as sleep apnea, and the MSLT provides essential, objective evidence of sleepiness plus REM sleep dysregulation. Across the five naps of the MSLT, most patients with narcolepsy will fall asleep in less than 8 min on average, and they will have episodes of REM sleep in at least two of the naps. Abnormal regulation of REM sleep is also manifested by the appearance of REM sleep within 15 min of sleep onset at night, which is rare in healthy individuals sleeping at their habitual bedtime. Stimulants should be stopped 1 week before the MSLT and antidepressants should be stopped 3 weeks prior, because these medications can affect the MSLT. In addition, patients should be encouraged to obtain a fully adequate amount of sleep each night for the week prior to the test to eliminate any effects of insufficient sleep.

TREATMENT Narcolepsy

The treatment of narcolepsy is symptomatic. Most patients with narcolepsy feel more alert after sleep, and they should be encouraged to get adequate sleep each night and to take a 15- to 20-min nap in the afternoon. This nap may be sufficient for some patients with mild narcolepsy, but most also require treatment with wake-promoting medications. Modafinil is used quite often because it has fewer side effects than amphetamines and a relatively long half-life; for most patients, 200–400 mg each morning is very effective. Methylphenidate (10–20 mg bid) or dextroamphetamine (10 mg bid) are often effective, but sympathomimetic side effects, anxiety, and the potential for abuse can be concerns. These medications are available in slow-release formulations, extending their duration of action and allowing easier dosing. Sodium oxybate (gamma hydroxybutyrate) is given twice each night and is often very valuable in improving alertness, but it can produce excessive sedation, nausea, and confusion.

Cataplexy is usually much improved with antidepressants that increase noradrenergic or serotonergic tone because these medications strongly suppress REM sleep and cataplexy. Venlafaxine (37.5–150 mg each morning) and fluoxetine (10–40 mg each morning) are often quite effective. The tricyclic antidepressants, such as protriptyline (10–40 mg/d) or clomipramine (25–50 mg/d) are potent suppressors of cataplexy, but their anticholinergic effects, including sedation and dry mouth, make them less attractive.[1] Sodium oxybate, given at bedtime and 3–4 h later, is also very helpful in reducing cataplexy.

EVALUATION OF INSOMNIA

Insomnia is the complaint of poor sleep and usually presents as difficulty initiating or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel that it impairs their ability to function well in work, school, and social situations. Affected individuals often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment.

Chronic insomnia, lasting more than 3 months, occurs in about 10% of adults and is more common in women, older adults, people of lower socioeconomic

[1]No antidepressant has been approved by the U.S. Food and Drug Administration (FDA) for treating narcolepsy.

www.ketabpezeshki.com (021) 66485457 - 66485438

status, and individuals with medical, psychiatric, and substance abuse disorders. Acute or short-term insomnia affects over 30% of adults and is often precipitated by stressful life events such as a major illness or loss, change of occupation, medications, and substance abuse. If the acute insomnia triggers maladaptive behaviors such as increased nocturnal light exposure, frequently checking the clock, or attempting to sleep more by napping, it can lead to chronic insomnia.

Most insomnia begins in adulthood, but many patients may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual. Clinical studies and animal models indicate that insomnia is associated with activation during sleep of brain areas normally active only during wakefulness. T e polysomnogram is rarely used in the evaluation of insomnia, as it typically confirms the patient's subjective report of long latency to sleep and numerous awakenings but usually adds little new information. Many patients with insomnia have increased fast (beta) activity in the EEG during sleep; this fast activity is normally present only during wakefulness, which may explain why some patients report feeling awake for much of the night. T e MSLT is rarely used in the evaluation of insomnia because, despite their feelings of low energy, most people with insomnia do not easily fall asleep during the day, and on the MSLT, their average sleep latencies are usually longer than normal.

Many factors can contribute to insomnia, and obtaining a careful history is essential so one can select therapies targeting the underlying factors. T e assessment should focus on identifying predisposing, precipitating, and perpetuating factors.

Psychophysiologic factors

Many patients with insomnia have negative expectations and conditioned arousal that interfere with sleep. T ese individuals may worry about their insomnia during the day and have increasing anxiety as bedtime approaches if they anticipate a poor night of sleep. While attempting to sleep, they may frequently check the clock, which only heightens anxiety and frustration. T ey may find it easier to sleep in a new environment rather than their bedroom, as it lacks the negative associations.

Inadequate sleep hygiene

Patients with insomnia sometimes develop counterproductive behaviors that contribute to their insomnia. T ese can include daytime napping that reduces sleep drive at night; an irregular sleep-wake schedule that disrupts their circadian rhythms; use of wake-promoting substances (e.g., caffeine, tobacco) too close to bedtime; engaging in alerting or stressful activities close to bedtime (e.g., arguing with a partner, work-related emailing and texting while in bed, sleeping with a smartphone or tablet at the bedside); and routinely using the bedroom for activities other than sleep or sex (e.g., TV, work), so the bedroom becomes associated with arousing or stressful feelings.

Psychiatric conditions

About 80% of patients with psychiatric disorders have sleep complaints, and about half of all chronic insomnia occurs in association with a psychiatric disorder. Depression is classically associated with early morning awakening, but it can also interfere with the onset and maintenance of sleep. Mania and hypomania can disrupt sleep and often are associated with substantial reductions in the total amount of sleep. Anxiety disorders can lead to racing thoughts and rumination that interfere with sleep and can be very problematic if the patient's mind becomes active midway through the night. Panic attacks can occur during sleep and need to be distinguished from other parasomnias. Insomnia is common in schizophrenia and other psychoses, often resulting in fragmented sleep, less deep NREM sleep, and sometimes reversal of the day-night sleep pattern.

Medications and drugs of abuse

A wide variety of psychoactive drugs can interfere with sleep. Caffeine, which has a half-life of 6–9 h, can disrupt sleep for up to 8–14 h, depending on the dose, variations in metabolism, and an individual's caffeine sensitivity. Insomnia can also result from use of prescription medications too close to bedtime (e.g., theophylline, stimulants, antidepressants, glucocorticoids). Conversely, withdrawal of sedating medications such as alcohol, narcotics, or benzodiazepines can cause insomnia. Alcohol taken just before bed can shorten sleep latency, but it often produces rebound insomnia 2–3 h later as it wears off. T is same problem with sleep maintenance can occur with short-acting benzodiazepines such as alprazolam.

Medical conditions

A large number of medical conditions disrupt sleep. Pain from rheumatologic disorders or a painful neuropathy commonly disrupts sleep. Some patients may sleep poorly because of respiratory conditions such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, congestive heart failure, or restrictive lung disease, and some of these disorders are worse at night in bed due to circadian variations in airway resistance and

www.ketabpezeshki.com (021) 66485457 - 66485438

postural changes that can result in paroxysmal nocturnal dyspnea. Many women experience poor sleep with the hormonal changes of menopause. Gastroesophageal reflux is also a common cause of difficulty sleeping.

Neurologic disorders

Dementia **(Chap. 21)** is often associated with poor sleep, probably due to a variety of factors, including napping during the day, altered circadian rhythms, and perhaps a weakened output of the brain's sleep-promoting mechanisms. In fact, insomnia and nighttime wandering are some of the most common causes for institutionalization of patients with dementia, because they place a larger burden on caregivers. Conversely, in cognitively intact elderly men, fragmented sleep and poor sleep quality are associated with subsequent cognitive decline. Patients with Parkinson's disease may sleep poorly due to rigidity, dementia, and other factors. Fatal familial insomnia is a very rare neurodegenerative condition caused by mutations in the prion protein gene, and although insomnia is a common early symptom, most patients present with other obvious neurologic signs such dementia, myoclonus, dysarthria, or autonomic dysfunction.

TREATMENT Insomnia

Treatment of insomnia improves quality of life and can promote long-term health. With improved sleep, patients often report less daytime fatigue, improved cognition, and more energy. Treating the insomnia can also improve the comorbid disease. For example, management of insomnia at the time of diagnosis of major depression often improves the response to antidepressants and reduces the risk of relapse. Sleep loss can heighten the perception of pain, so a similar approach is warranted in acute and chronic pain management.

The treatment plan should target all putative contributing factors: establish good sleep hygiene, treat medical disorders, use behavioral therapies for anxiety and negative conditioning, and use pharmacotherapy and/or psychotherapy for psychiatric disorders. Behavioral therapies should be the first-line treatment, followed by judicious use of sleep-promoting medications if needed.

TREATMENT OF MEDICAL AND PSYCHIATRIC DISEASE If the history suggests that a medical or psychiatric disease contributes to the insomnia, then it should be addressed by, for example, treating the pain, improving breathing, and switching or adjusting the timing of medications.

IMPROVE SLEEP HYGIENE Attention should be paid to improving sleep hygiene and avoiding counterproductive, arousing behaviors before bedtime. Patients should establish a regular bedtime and wake time, even on weekends, to help synchronize their circadian rhythms and sleep patterns. The amount of time allocated for sleep should not be more than their actual total amount of sleep. In the 30 min before bedtime, patients should establish a relaxing "wind-down" routine that can include a warm bath, listening to music, meditation, or other relaxation techniques. The bedroom should be off-limits to computers, televisions, radios, smartphones, videogames, and tablets. Once in bed, patients should try to avoid thinking about anything stressful or arousing such as problems with relationships or work. If they cannot fall asleep within 20 min, it often helps to get out of bed and read or listen to relaxing music in dim light as a form of distraction from any anxiety, but artificial light, including light from a television, cell phone, or computer, should be avoided, because light itself suppresses melatonin secretion and is arousing.

Table 24-2 outlines some of the key aspects of good sleep hygiene to improve insomnia.

COGNITIVE BEHAVIORAL THERAPY Cognitive behavioral therapy (CBT) uses a combination of the techniques above plus additional methods to improve insomnia. A trained therapist may use cognitive psychology techniques to reduce excessive worrying about sleep and to reframe faulty beliefs about the insomnia and its daytime consequences. The therapist may also teach the patient relaxation techniques, such as progressive muscle relaxation or meditation, to reduce autonomic arousal, intrusive thoughts, and anxiety.

MEDICATIONS FOR INSOMNIA If insomnia persists after treatment of these contributing factors, pharmacotherapy is often used on a nightly or intermittent basis. A variety of sedatives can improve sleep.

TABLE 24-2

METHODS TO IMPROVE SLEEP HYGIENE IN INSOMNIA PATIENTS

HELPFUL BEHAVIORS	BEHAVIORS TO AVOID
Use the bed only for sleep and sex • If you cannot sleep within 20 min, get out of bed and read or do other relaxing activities in dim light before returning to bed	Avoid behaviors that interfere with sleep physiology, including: • Napping, especially after 3:00 pm • Attempting to sleep too early • Caffeine after lunchtime
Make quality sleep a priority • Go to bed and get up at the same time each day • Ensure a restful environment (comfortable bed, bedroom quiet and dark)	In the 2–3 h before bedtime, avoid: • Heavy eating • Smoking or alcohol • Vigorous exercise
Develop a consistent bedtime routine. For example: • Prepare for sleep with 20–30 min of relaxation (e.g., soft music, meditation, yoga, pleasant reading) • Take a warm bath	When trying to fall asleep, avoid: • Solving problems • Thinking about life issues • Reviewing events of the day

www.ketabpezeshki.com (021) 66485457 - 66485438

Antihistamines, such as diphenhydramine, are the primary active ingredient in most over-the-counter sleep aids. T ese may be of benefit when used intermittently, but often produce rapid tolerance and can produce anticholinergic side effects such as dry mouth and constipation, which limit their use, particularly in the elderly.

Benzodiazepine receptor agonists (BzRAs) are an effective and well-tolerated class of medications for insomnia. BzRAs bind to the $GABA_A$ receptor and potentiate the postsynaptic response to GABA. $GABA_A$ receptors are found throughout the brain, and BzRAs may globally reduce neural activity and may enhance the activity of specific sleep-promoting GABAergic pathways. Classic BzRAs include lorazepam, triazolam, and clonazepam, whereas newer agents such as zolpidem and zaleplon have more selective affinity for the α_1 subunit of the $GABA_A$ receptor.

Specific BzRAs are often chosen based on the desired duration of action. T e most commonly prescribed agents in this family are zaleplon (5–20 mg), with a half-life of 1–2 h; zolpidem (5–10 mg) and triazolam (0.125–0.25 mg), with half-lives of 2–4 h; eszopiclone (1–3 mg), with a half-life of 5–8 h; and temazepam (15–30 mg), with a half-life of 8–20 h. Generally, side effects are minimal when the dose is kept low and the serum concentration is minimized during the waking hours (by using the shortest-acting effective agent). For chronic insomnia, intermittent use is recommended, unless the consequences of untreated insomnia outweigh concerns regarding chronic use.

T e heterocyclic antidepressants (trazodone, amitriptyline,[2] and doxepin) are the most commonly prescribed alternatives to BzRAs due to their lack of abuse potential and lower cost. Trazodone (25–100 mg) is used more commonly than the tricyclic antidepressants, because it has a much shorter half-life (5–9 h) and less anticholinergic activity.

Medications for insomnia are now among the most commonly prescribed medications, but they should be used cautiously. All sedatives increase the risk of injurious falls and confusion in the elderly, and therefore if needed, these medications should be used at the lowest effective dose. Morning sedation can interfere with driving and judgment, and when selecting a medication, one should consider the duration of action. Benzodiazepines carry a risk of addiction and abuse, especially in patients with a history of alcohol or sedative abuse. Like alcohol, some sleep-promoting medications can worsen sleep apnea. Sedatives can also produce complex behaviors during sleep, such as sleep walking and sleep eating, although this seems more likely at higher doses.

RESTLESS LEGS SYNDROME

Patients with restless legs syndrome (RLS) report an irresistible urge to move the legs. Many patients report a creepy-crawly or unpleasant deep ache within the thighs or calves, and those with more severe RLS may have discomfort in the arms as well. For most patients with RLS, these dysesthesias and restlessness are much worse in the evening and first half of the night. T e symptoms appear with inactivity and can make sitting still in an airplane or when watching a movie a miserable experience. T e sensations are temporarily relieved by movement, stretching, or massage. T is nocturnal discomfort usually interferes with sleep, and patients may report daytime sleepiness as a consequence. RLS is very common, affecting 5–10% of adults and is more common in women and older adults.

A variety of factors can cause RLS. Iron deficiency is the most common treatable cause, and iron replacement should be considered if the ferritin level is less than 50 ng/mL. RLS can also occur with peripheral neuropathies and uremia and can be worsened by pregnancy, caffeine, alcohol, antidepressants, lithium, neuroleptics, and antihistamines. Genetic factors contribute to RLS, and polymorphisms in a variety of genes (BTBD9, MEIS1, MAP2K5/LBXCOR, and PTPRD) have been linked to RLS, although as yet, the mechanism through which they cause RLS remains unknown. Roughly one-third of patients (particularly those with an early age of onset) have multiple affected family members.

RLS is treated by addressing the underlying cause such as iron deficiency if present. Otherwise, treatment is symptomatic, and dopamine agonists are used most frequently. Agonists of dopamine $D_{2/3}$ receptors such as pramipexole (0.25–0.5 mg q7PM) or ropinirole (0.5–4 mg q7PM) are considered first-line agents. Augmentation is a worsening of RLS such that symptoms begin earlier in the day and can spread to other body regions, and it can occur in about 25% of patients taking dopamine agonists. Other possible side effects of dopamine agonists include nausea, morning sedation, and increases in rewarding behavior such as gambling and sex. Opioids, benzodiazepines, pregabalin, and gabapentin may also be of therapeutic value. Most patients with restless legs also experience periodic limb movement disorder, although the reverse is not the case.

PERIODIC LIMB MOVEMENT DISORDER

Periodic limb movement disorder (PLMD) involves rhythmic twitches of the legs that disrupt sleep. T e movements resemble a triple flexion reflex with extensions of the great toe and dorsiflexion of the foot for 0.5 to 5.0 s, which recur every 20–40 s during NREM sleep, in episodes lasting from minutes to hours. PLMD is diagnosed by a polysomnogram that includes recordings of the anterior tibialis and sometimes other muscles. T e EEG shows that the movements of PLMD frequently cause brief arousals that disrupt sleep and can cause insomnia and daytime sleepiness.

[2]Trazodone and amitriptyline have not been approved by the FDA for treating insomnia.

www.ketabpezeshki.com (021) 66485457 - 66485438

PLMD can be caused by the same factors that cause RLS (see above), and the frequency of leg movements improves with the same medications as used for RLS, including dopamine agonists. Recent genetic studies identified polymorphisms associated with RLS/PLMD, suggesting that they may have a common pathophysiology.

PARASOMNIAS

Parasomnias are abnormal behaviors or experiences that arise from or occur during sleep. A variety of parasomnias can occur during NREM sleep, from brief confusional arousals to sleepwalking and night terrors. T e presenting complaint is usually related to the behavior itself, but the parasomnias can disturb sleep continuity or lead to mild impairments in daytime alertness. Two main parasomnias occur in REM sleep: REM sleep behavior disorder (RBD) and nightmares.

Sleepwalking (somnambulism)

Patients affected by this disorder carry out automatic motor activities that range from simple to complex. Individuals may walk, urinate inappropriately, eat, exit the house, or drive a car with minimal awareness. Full arousal may be difficult, and occasional individuals may respond to attempted awakening with agitation or violence. Sleepwalking arises from NREM stage N3 sleep, usually in the first few hours of the night, and the EEG usually shows the slow cortical activity of deep NREM sleep even when the patient is moving about. Sleepwalking is most common in children and adolescents, when these sleep stages are most robust. About 15% of children have occasional sleepwalking, and it persists in about 1% of adults. Episodes are usually isolated but may be recurrent in 1–6% of patients. T e cause is unknown, although it has a familial basis in roughly one-third of cases. Sleepwalking can be worsened by insufficient sleep, which subsequently causes an increase in deep NREM sleep; alcohol; and stress. T ese should be addressed if present. Small studies have shown some efficacy of antidepressants and benzodiazepines; relaxation techniques and hypnosis can also be helpful. Patients and their families should improve home safety (e.g., replace glass doors, remove low tables to avoid tripping) to minimize the chance of injury if sleepwalking occurs.

Sleep terrors

T is disorder occurs primarily in young children during the first few hours of sleep during NREM stage N3 sleep. T e child often sits up during sleep and screams, exhibiting autonomic arousal with sweating, tachycardia, large pupils, and hyperventilation. T e individual may be difficult to arouse and rarely recalls the episode on awakening in the morning. Treatment usually consists of reassuring the parents that the condition is self-limited and benign, and like sleepwalking, it may improve by avoiding insufficient sleep.

Sleep bruxism

Bruxism is an involuntary, forceful grinding of teeth during sleep that affects 10–20% of the population. T e patient is usually unaware of the problem. T e typical age of onset is 17–20 years, and spontaneous remission usually occurs by age 40. Sex distribution appears to be equal. In many cases, the diagnosis is made during dental examination, damage is minor, and no treatment is indicated. In more severe cases, treatment with a tooth guard is necessary to prevent tooth injury. Stress management or, in some cases, biofeedback can be useful when bruxism is a manifestation of psychological stress. T ere are anecdotal reports of benefit with benzodiazepines.

Sleep enuresis

Bedwetting, like sleepwalking and night terrors, is another parasomnia that occurs during sleep in the young. Before age 5 or 6 years, nocturnal enuresis should be considered a normal feature of development. T e condition usually improves spontaneously by puberty, has a prevalence in late adolescence of 1–3%, and is rare in adulthood. Treatment consists of bladder training exercises and behavioral therapy. Symptomatic pharmacotherapy is usually accomplished in adults with desmopressin (0.2 mg qhs), oxybutynin chloride (5 mg qhs), or imipramine (10–25 mg qhs). Important causes of nocturnal enuresis in patients who were previously continent for 6–12 months include urinary tract infections or malformations, cauda equina lesions, emotional disturbances, epilepsy, sleep apnea, and certain medications.

REM sleep behavior disorder

REM sleep behavior disorder (RBD) **(Video 24-2)** is distinct from other parasomnias in that it occurs during REM sleep. T e patient or the bed partner usually reports agitated or violent behavior during sleep, and upon awakening, the patient can often report a dream that accompanied the movements. During normal REM sleep, nearly all skeletal muscles are paralyzed, but in patients with RBD, the polysomnogram often shows limb movements during REM sleep, lasting for seconds to minutes. T e movements can be dramatic, and it is not uncommon for the patient or the bed partner to be injured.

www.ketabpezeshki.com (021) 66485457 - 66485438

Video can be accessed via the following link: https://www.mhprofessional.com/mediacenter/

Video 24-2. Typical aggressive movements in rapid eye movement (REM) sleep behavior disorder.

(Video courtesy of Dr. Carlos Schenck, University of Minnesota Medical School.)

RBD primarily af icts older men, and most either have or will develop a neurodegenerative disorder. In longitudinal studies of RBD, half of the patients developed a synucleinopathy such as Parkinson's disease **(Chap. 36)** or dementia with Lewy bodies **(Chap. 35)**, or occasionally multiple system atrophy **(Chap. 41)**, within 12 years, and over 80% developed a synucleinopathy by 20 years. RBD can occur in patients taking antidepressants, and in some, these medications may unmask this early indicator of neurodegeneration. Synucleinopathies probably cause neuronal loss in brainstem regions that regulate muscle atonia during REM sleep, and loss of these neurons permits movements to break through during REM sleep. RBD also occurs in about 30% of patients with narcolepsy, but the underlying cause is probably different, as they seem to be at no increased risk of a neurodegenerative disorder.

Many patients with RBD have sustained improvement with clonazepam (0.5–2.0 mg qhs).[3] Melatonin at doses up to 9 mg nightly may also prevent attacks.

CIRCADIAN RHYTHM SLEEP DISORDERS

A subset of patients presenting with either insomnia or hypersomnia may have a disorder of sleep timing rather than sleep generation. Disorders of sleep timing can be either organic (i.e., due to an abnormality of circadian pacemaker[s]) or environmental/behavioral (i.e., due to a disruption of environmental synchronizers). Effective therapies aim to entrain the circadian rhythm of sleep propensity to an appropriate phase.

Delayed sleep-wake phase disorder

Delayed sleep-wake phase disorder (DSWPD) is characterized by: (1) reported sleep onset and wake times intractably later than desired; (2) actual sleep times at nearly the same clock hours daily; and (3) if conducted at the habitual delayed sleep time, essentially normal sleep on polysomnography (except for delayed sleep onset). Patients with DSWPD exhibit an abnormally delayed endogenous circadian phase, which can be assessed by measuring, in a dimly lit environment, the onset of secretion of the endogenous circadian rhythm of pineal melatonin in either the blood or saliva, as light suppresses melatonin secretion. Dim-light melatonin onset (DLMO) in DSWPD patients typically occurs later in the evening than normal, which is about 8:00–9:00 pm (i.e., about 1–2 h before habitual bedtime). Patients tend to be young adults. T e delayed circadian phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) reduced phase-advancing capacity of the pacemaker; (3) slower rate of buildup of homeostatic sleep drive during wakefulness; or (4) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake while exposed to artificial light well past midnight (for personal, social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, as patients with either a behaviorally induced or biologically driven circadian phase delay may both exhibit a similar circadian phase delay in DLMO, making it difficult for both to fall asleep at the desired hour. DSWPD is a self-perpetuating condition that can persist for years and may not respond to attempts to reestablish normal bedtime hours. Treatment methods involving phototherapy with blue-enriched light during the morning hours and/or melatonin administration in the evening hours show promise in these patients, although the relapse rate is high. Patients with this circadian rhythm sleep disorder can be distinguished from those who have sleep-onset insomnia because DSWPD patients show late onset of dim-light melatonin secretion.

Advanced sleep-wake phase disorder

Advanced sleep-wake phase disorder (ASWPD) is the converse of DSWPD. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5:00 am, with twice that number complaining that they wake up too early at least several times per week. Patients with ASWPD are sleepy during the evening hours, even in social settings. Sleep-wake timing in ASWPD patients can interfere with a normal social life. Patients with this circadian rhythm sleep disorder can be distinguished from those who have early wakening due to insomnia because ASWPD patients show early onset of dim-light melatonin secretion.

In addition to age-related ASWPD, an early-onset familial variant of this condition has also been reported. In two families in which ASWPD was inherited in an autosomal dominant pattern, the syndrome was due to missense mutations in a circadian clock component (in the casein kinase binding domain of PER2 in one family, and in casein kinase I delta in the other) that altered the circadian period. Patients with ASWPD may benefit from bright-light and/or blue enriched phototherapy during the evening hours to reset the circadian pacemaker to a later hour.

Non-24-h sleep-wake rhythm disorder

Non-24-h sleep-wake rhythm disorder (N24SWRD) can occur when the primary synchronizing input (i.e., the

[3]No medications have been approved by the FDA for the treatment of RBD.

www.ketabpezeshki.com (021) 66485457 - 66485438

light-dark cycle) from the environment to the circadian pacemaker is compromised (as occurs in many blind people with no light perception) or when the maximal phase-advancing capacity of the circadian pacemaker cannot accommodate the difference between the 24-h geophysical day and the intrinsic period of the patient's circadian pacemaker, resulting in loss of entrainment to the 24-h day. Rarely, self-selected exposure to artificial light may, in some sighted patients, inadvertently entrain the circadian pacemaker to a >24-h schedule. Affected patients with N24SWRD have difficulty maintaining a stable phase relationship between the output of the pacemaker and the 24-h day. Such patients typically present with an incremental pattern of successive delays in sleep propensity, progressing in and out of phase with local time. When the N24SWRD patient's endogenous circadian rhythms are out of phase with the local environment, nighttime insomnia coexists with excessive daytime sleepiness. Conversely, when the endogenous circadian rhythms are in phase with the local environment, symptoms remit. T e interval between symptomatic phases may last several weeks to several months in N24SWRD, depending on the period of the underlying nonentrained rhythm and the 24-h day. Nightly low-dose (0.5 mg) melatonin administration may improve sleep and, in some cases, induce synchronization of the circadian pacemaker.

Shift-work disorder

More than 7 million workers in the United States regularly work at night, either on a permanent or rotating schedule. Many more begin the commute to work or school between 4:00 am and 7:00 am, requiring them to commute and then work during the time of day that they would otherwise be asleep. In addition, each week, millions of "day" workers and students elect to remain awake at night or awaken very early in the morning to work or study to meet work or school deadlines, drive long distances, compete in sporting events, or participate in recreational activities. Such schedules can result in both sleep loss and misalignment of circadian rhythms with respect to the sleep-wake cycle.

T e circadian timing system usually fails to adapt successfully to the inverted schedules required by overnight work or the phase advance required by early morning (4:00 am to 7:00 am) start times. T is leads to a misalignment between the desired work-rest schedule and the output of the pacemaker and to disturbed daytime sleep in most individuals. Excessive work hours (per day or per week), insufficient time off between consecutive days of work or school, and transmeridian travel may be contributing factors. Sleep deficiency, increased length of time awake prior to work, and misalignment of circadian phase produce decreased alertness and performance, increased reaction time, and increased risk of performance lapses, thereby resulting in greater safety hazards among night workers and other sleep-deprived individuals. Sleep disturbance nearly doubles the risk of a fatal work accident. Long-term night shift workers have higher rates of breast, colorectal, and prostate cancer and of cardiac, gastrointestinal, and reproductive disorders. T e World Health Organization has added night-shift work to its list of probable carcinogens.

Sleep onset begins in local brain regions before gradually sweeping over the entire brain as sensory thresholds rise and consciousness is lost. A sleepy individual struggling to remain awake may attempt to continue performing routine and familiar motor tasks during the transition state between wakefulness and stage N1 sleep, while unable to adequately process sensory input from the environment. Motor vehicle operators who fail to heed the warning signs of sleepiness are especially vulnerable to sleep-related accidents, as sleep processes can intrude involuntarily upon the waking brain, causing catastrophic consequences. Such sleep-related attentional failures typically last only seconds but are known on occasion to persist for longer durations. T ere is a significant increase in the risk of sleep-related, fatal-to-the-driver highway crashes in the early morning and late afternoon hours, coincident with bimodal peaks in the daily rhythm of sleep tendency.

Resident physicians constitute another group of workers at greater risk for accidents and other adverse consequences of lack of sleep and misalignment of the circadian rhythm. Recurrent scheduling of resident physicians to work shifts of ≥24 consecutive hours impairs psychomotor performance to a degree that is comparable to alcohol intoxication, doubles the risk of attentional failures among intensive care unit resident physicians working at night, and significantly increases the risk of serious medical errors in intensive care units, including a fivefold increase in the risk of serious diagnostic mistakes. Some 20% of hospital resident physicians report making a fatigue-related mistake that injured a patient, and 5% admit making a fatigue-related mistake that resulted in the death of a patient. Moreover, working for >24 consecutive hours increases the risk of percutaneous injuries and more than doubles the risk of motor vehicle crashes on the commute home. For these reasons, in 2008, the Institute of Medicine concluded that the practice of scheduling resident physicians to work for more than 16 consecutive hours without sleep is hazardous for both resident physicians and their patients.

From 5 to 15% of individuals scheduled to work at night or in the early morning hours have much greater-than-average difficulties remaining awake during night work and sleeping during the day; these individuals are diagnosed with chronic and severe shift-work disorder (SWD). Patients with this disorder have a level of excessive sleepiness during work at night or in the early morning and insomnia during day sleep that the

www.ketabpezeshki.com (021) 66485457 - 66485438

physician judges to be clinically significant; the condition is associated with an increased risk of sleep-related accidents and with some of the illnesses associated with night-shift work. Patients with chronic and severe SWD are profoundly sleepy at work. In fact, their sleep latencies during night work average just 2 min, comparable to mean daytime sleep latency durations of patients with narcolepsy or severe sleep apnea.

TREATMENT Shift-Work Disorder

Caffeine is frequently used by night workers to promote wakefulness. However, it cannot forestall sleep indefinitely, and it does not shield users from sleep-related performance lapses. Postural changes, exercise, and strategic placement of nap opportunities can sometimes temporarily reduce the risk of fatigue-related performance lapses. Properly timed exposure to blue-enriched light or bright white light can directly enhance alertness and facilitate more rapid adaptation to night-shift work.

Modafinil (200 mg) or armodafinil (150 mg) 30–60 min before the start of each night shift is an effective treatment for the excessive sleepiness during night work in patients with SWD. Although treatment with modafinil or armodafinil significantly improves performance and reduces sleep propensity and the risk of lapses of attention during night work, affected patients remain excessively sleepy.

Fatigue risk management programs for night shift workers should promote education about sleep, increase awareness of the hazards associated with sleep deficiency and night work, and screen for common sleep disorders. Work schedules should be designed to minimize: (1) exposure to night work; (2) the frequency of shift rotations; (3) the number of consecutive night shifts; and (4) the duration of night shifts.

Jet lag disorder

Each year, more than 60 million people fly from one time zone to another, often resulting in excessive daytime sleepiness, sleep-onset insomnia, and frequent arousals from sleep, particularly in the latter half of the night. T e syndrome is transient, typically lasting 2–14 d depending on the number of time zones crossed, the direction of travel, and the traveler's age and phase-shifting capacity. Travelers who spend more time outdoors at their destination reportedly adapt more quickly than those who remain in hotel rooms, presumably due to brighter (outdoor) light exposure. Avoidance of antecedent sleep loss and obtaining naps on the afternoon prior to overnight travel can reduce the difficulties associated with extended wakefulness. Laboratory studies suggest that low doses of melatonin can enhance sleep efficiency, but only if taken when endogenous melatonin concentrations are low (i.e., during the biologic daytime).

In addition to jet lag associated with travel across time zones, many patients report a behavioral pattern that has been termed social jet lag, in which bedtimes and wake times on weekends or days off occur 4–8 h later than during the week. Such recurrent displacement of the timing of the sleep-wake cycle is common in adolescents and young adults and is associated with sleep-onset insomnia, poorer academic performance, increased risk of depressive symptoms, and excessive daytime sleepiness.

MEDICAL IMPLICATIONS OF CIRCADIAN RHYTHMICITY

Prominent circadian variations have been reported in the incidence of acute myocardial infarction, sudden cardiac death, and stroke, the leading causes of death in the United States. Platelet aggregability is increased in the early morning hours, coincident with the peak incidence of these cardiovascular events. Recurrent circadian disruption combined with chronic sleep deficiency, such as occurs during night-shift work, is associated with increased plasma glucose concentrations after a meal due to inadequate pancreatic insulin secretion. Night shift workers with elevated fasting glucose have an increased risk of progressing to diabetes. Blood pressure of night workers with sleep apnea is higher than that of day workers. A better understanding of the possible role of circadian rhythmicity in the acute destabilization of a chronic condition such as atherosclerotic disease could improve the understanding of its pathophysiology.

Diagnostic and therapeutic procedures may also be affected by the time of day at which data are collected. Examples include blood pressure, body temperature, the dexamethasone suppression test, and plasma cortisol levels. T e timing of chemotherapy administration has been reported to have an effect on the outcome of treatment. In addition, both the toxicity and effectiveness of drugs can vary with time of day. For example, more than a fivefold difference has been observed in mortality rates following administration of toxic agents to experimental animals at different times of day. Anesthetic agents are particularly sensitive to time-of-day effects. Finally, the physician must be aware of the public health risks associated with the ever-increasing demands made by the 24/7 schedules in our round-the-clock society.

Acknowledgment

John W. Winkelman, MD, PhD and Gary S. Richardson, MD contributed to this chapter in the prior edition and some material from that chapter has been retained here.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 25

DISORDERS OF THE EYE

Jonathan C. Horton

THE HUMAN VISUAL SYSTEM

T e visual system provides a supremely efficient means for the rapid assimilation of information from the environment to aid in the guidance of behavior. T e act of seeing begins with the capture of images focused by the cornea and lens on a light-sensitive membrane in the back of the eye called the retina. T e retina is actually part of the brain, banished to the periphery to serve as a transducer for the conversion of patterns of light energy into neuronal signals. Light is absorbed by pigment in two types of photoreceptors: rods and cones. In the human retina there are 100 million rods and 5 million cones. T e rods operate in dim (scotopic) illumination. T e cones function under daylight (photopic) conditions. T e cone system is specialized for color perception and high spatial resolution. T e majority of cones are within the macula, the portion of the retina that serves the central 10° of vision. In the middle of the macula a small pit termed the *f*ovea, packed exclusively with cones, provides the best visual acuity.

Photoreceptors hyperpolarize in response to light, activating bipolar, amacrine, and horizontal cells in the inner nuclear layer. After processing of photoreceptor responses by this complex retinal circuit, the flow of sensory information ultimately converges on a final common pathway: the ganglion cells. T ese cells translate the visual image impinging on the retina into a continuously varying barrage of action potentials that propagates along the primary optic pathway to visual centers within the brain. T ere are a million ganglion cells in each retina and hence a million fibers in each optic nerve.

Ganglion cell axons sweep along the inner surface of the retina in the nerve fiber layer, exit the eye at the optic disc, and travel through the optic nerve, optic chiasm, and optic tract to reach targets in the brain. T e majority of fibers synapse on cells in the lateral geniculate body, a thalamic relay station. Cells in the lateral geniculate body project in turn to the primary visual cortex. T is af erent retinogeniculocortical sensory pathway provides the neural substrate for visual perception. Although the lateral geniculate body is the main target of the retina, separate classes of ganglion cells project to other subcortical visual nuclei involved in dif erent functions. Ganglion cells that mediate pupillary constriction and circadian rhythms are light sensitive owing to a novel visual pigment, melanopsin. Pupil responses are mediated by input to the pretectal olivary nuclei in the midbrain. T e pretectal nuclei send their output to the Edinger-Westphal nuclei, which in turn provide parasympathetic innervation to the iris sphincter via an interneuron in the ciliary ganglion. Circadian rhythms are timed by a retinal projection to the suprachiasmatic nucleus. Visual orientation and eye movements are served by retinal input to the superior colliculus. Gaze stabilization and optokinetic reflexes are governed by a group of small retinal targets known collectively as the brainstem accessory optic system.

T e eyes must be rotated constantly within their orbits to place and maintain targets of visual interest on the fovea. T is activity, called *f*oveation, or looking, is governed by an elaborate ef erent motor system. Each eye is moved by six extraocular muscles that are supplied by cranial nerves from the oculomotor (III), trochlear (IV), and abducens (VI) nuclei. Activity in these ocular motor nuclei is coordinated by pontine and midbrain mechanisms for smooth pursuit, saccades, and gaze stabilization during head and body movements. Large regions of the frontal and parietooccipital cortex control these brainstem eye movement centers by providing descending supranuclear input.

www.ketabpezeshki.com (021) 66485457 - 66485438

CLINICAL ASSESSMENT OF VISUAL FUNCTION

REFRACTIVE STATE

In approaching a patient with reduced vision, the first step is to decide whether refractive error is responsible. In emmetropia, parallel rays from infinity are focused perfectly on the retina. Sadly, this condition is enjoyed by only a minority of the population. In myopia, the globe is too long, and light rays come to a focal point in front of the retina. Near objects can be seen clearly, but distant objects require a diverging lens in front of the eye. In hyperopia, the globe is too short, and hence a converging lens is used to supplement the refractive power of the eye. In astigmatism, the corneal surface is not perfectly spherical, necessitating a cylindrical corrective lens. As an alternative to eyeglasses or contact lenses, refractive error can be corrected by performing laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) to alter the curvature of the cornea.

With the onset of middle age, presbyopia develops as the lens within the eye becomes unable to increase its refractive power to accommodate on near objects. To compensate for presbyopia an emmetropic patient must use reading glasses. A patient already wearing glasses for distance correction usually switches to bifocals. T e only exception is a myopic patient, who may achieve clear vision at near simply by removing glasses containing the distance prescription.

Refractive errors usually develop slowly and remain stable after adolescence, except in unusual circumstances. For example, the acute onset of diabetes mellitus can produce sudden myopia because of lens edema induced by hyperglycemia. Testing vision through a pinhole aperture is a useful way to screen quickly for refractive error. If visual acuity is better through a pinhole than it is with the unaided eye, the patient needs refraction to obtain best corrected visual acuity.

FIGURE 25-1
The Rosenbaum card is a miniature, scale version of the Snellen chart for testing visual acuity at near. When the visual acuity is recorded, the Snellen distance equivalent should bear a notation indicating that vision was tested at near, not at 6 m (20 ft), or else the Jaeger number system should be used to report the acuity.

VISUAL ACUITY

T e Snellen chart is used to test acuity at a distance of 6 m (20 ft). For convenience, a scale version of the Snellen chart called the Rosenbaum card is held at 36 cm (14 in.) from the patient **(Fig. 25-1)**. All subjects should be able to read the 6/6 m (20/20 ft) line with each eye using their refractive correction, if any. Patients who need reading glasses because of presbyopia must wear them for accurate testing with the Rosenbaum card. If 6/6 (20/20) acuity is not present in each eye, the deficiency in vision must be explained. If it is worse than 6/240 (20/800), acuity should be recorded in terms of counting fingers, hand motions, light perception, or no light perception. Legal blindness is defined by the Internal Revenue Service as a best corrected acuity of 6/60 (20/200) or less in the better eye or a binocular visual field subtending 20° or less. For driving the laws vary by state, but most states require a corrected acuity of 6/12 (20/40) in at least one eye for unrestricted privileges. Patients with a homonymous hemianopia should not drive.

PUPILS

T e pupils should be tested individually in dim light with the patient fixating on a distant target. T ere is no need to check the near response if the pupils respond briskly to light, because isolated loss of constriction (miosis) to accommodation does not occur. For this reason, the ubiquitous abbreviation PERRLA (pupils equal, round, and reactive to light and accommodation)

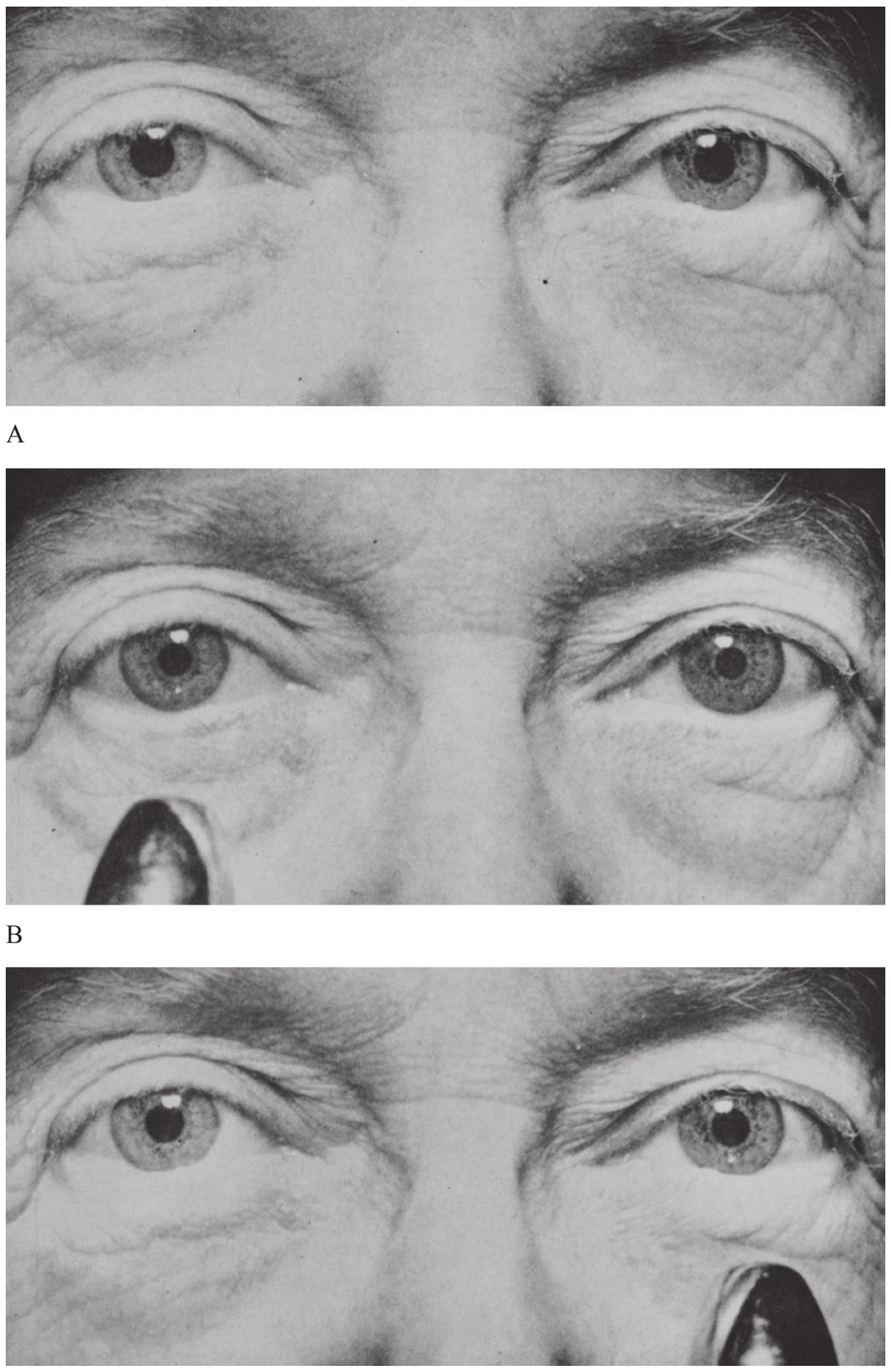
www.ketabpezeshki.com (021) 66485457 - 66485438

implies a wasted effort with the last step. However, it is important to test the near response if the light response is poor or absent. Light-near dissociation occurs with neurosyphilis (Argyll Robertson pupil), with lesions of the dorsal midbrain (Parinaud's syndrome), and after aberrant regeneration (oculomotor nerve palsy, Adie's tonic pupil).

An eye with no light perception has no pupillary response to direct light stimulation. If the retina or optic nerve is only partially injured, the direct pupillary response will be weaker than the consensual pupillary response evoked by shining a light into the healthy fellow eye. A relative afferent pupillary defect (Marcus Gunn pupil) can be elicited with the swinging flashlight test **(Fig. 25-2)**. It is an extremely useful sign in retrobulbar optic neuritis and other optic nerve diseases, in which it may be the sole objective evidence for disease. In bilateral optic neuropathy, no afferent pupil defect is present if the optic nerves are affected equally.

Subtle inequality in pupil size, up to 0.5 mm, is a fairly common finding in normal persons. The diagnosis of essential or physiologic anisocoria is secure as long as the relative pupil asymmetry remains constant as ambient lighting varies. Anisocoria that increases in dim light indicates a sympathetic paresis of the iris dilator muscle. The triad of miosis with ipsilateral ptosis and anhidrosis constitutes Horner's syndrome, although anhidrosis is an inconstant feature. Brainstem stroke, carotid dissection, and neoplasm impinging on the sympathetic chain occasionally are identified as the cause of Horner's syndrome, but most cases are idiopathic.

Anisocoria that increases in bright light suggests a parasympathetic palsy. The first concern is an oculomotor nerve paresis. This possibility is excluded if the eye movements are full and the patient has no ptosis or diplopia. Acute pupillary dilation (mydriasis) can result from damage to the ciliary ganglion in the orbit. Common mechanisms are infection (herpes zoster, influenza), trauma (blunt, penetrating, surgical), and ischemia (diabetes, temporal arteritis). After denervation of the iris sphincter the pupil does not respond well to light, but the response to near is often relatively intact. When the near stimulus is removed, the pupil redilates very slowly compared with the normal pupil, hence the term tonic pupil. In Adie's syndrome a tonic pupil is present, sometimes in conjunction with weak or absent tendon reflexes in the lower extremities. This is benign disorder, which occurs predominantly in healthy young women, is assumed to represent a mild dysautonomia. Tonic pupils are also associated with Shy-Drager syndrome, segmental hypohidrosis, diabetes, and amyloidosis. Occasionally, a tonic pupil is discovered incidentally in an otherwise completely normal, asymptomatic individual. The diagnosis is confirmed by placing a drop of dilute (0.125%) pilocarpine into each eye. Denervation hypersensitivity produces pupillary constriction in a tonic pupil, whereas the normal pupil shows no response. Pharmacologic dilatation from accidental or deliberate instillation of anticholinergic agents (atropine, scopolamine drops) into the eye also can produce pupillary mydriasis. In this situation, normal strength (1%) pilocarpine causes no constriction.



A

B

C

FIGURE 25-2

Demonstration of a relative afferent pupil defect (Marcus Gunn pupil) in the left eye, done with the patient fixating on a distant target. A. With dim background lighting, the pupils are equal and relatively large. B. Shining a flashlight into the right eye evokes equal, strong constriction of both pupils. C. Swinging the flashlight over to the damaged left eye causes dilation of both pupils, although they remain smaller than in A. Swinging the flashlight back over to the healthy right eye would result in symmetric constriction back to the appearance shown in B. Note that the pupils always remain equal; the damage to the left retina/optic nerve is revealed by weaker bilateral pupil constriction to a flashlight in the left eye compared with the right eye. (From P Levatin: Arch Ophthalmol 62:768, 1959. Copyright © 1959 American Medical Association. All rights reserved.)

www.ketabpezeshki.com (021) 66485457 - 66485438

Both pupils are affected equally by systemic medications. They are small with narcotic use (morphine, heroin) and large with anticholinergics (scopolamine). Parasympathetic agents (pilocarpine, demecarium bromide) used to treat glaucoma produce miosis. In any patient with an unexplained pupillary abnormality, a slit-lamp examination is helpful to exclude surgical trauma to the iris, an occult foreign body, perforating injury, intraocular inflammation, adhesions (synechia), angle-closure glaucoma, and iris sphincter rupture from blunt trauma.

EYE MOVEMENTS AND ALIGNMENT

Eye movements are tested by asking the patient, with both eyes open, to pursue a small target such as a penlight into the cardinal fields of gaze. Normal ocular versions are smooth, symmetric, full, and maintained in all directions without nystagmus. Saccades, or quick refixation eye movements, are assessed by having the patient look back and forth between two stationary targets. The eyes should move rapidly and accurately in a single jump to their target. Ocular alignment can be judged by holding a penlight directly in front of the patient at about 1 m. If the eyes are straight, the corneal light reflex will be centered in the middle of each pupil. To test eye alignment more precisely, the cover test is useful. The patient is instructed to look at a small fixation target in the distance. One eye is covered suddenly while the second eye is observed. If the second eye shifts to fixate on the target, it was misaligned. If it does not move, the first eye is uncovered and the test is repeated on the second eye. If neither eye moves the eyes are aligned orthotropically. If the eyes are orthotropic in primary gaze but the patient complains of diplopia, the cover test should be performed with the head tilted or turned in whatever direction elicits diplopia. With practice, the examiner can detect an ocular deviation (heterotropia) as small as 1–2° with the cover test. In a patient with vertical diplopia, a small deviation can be difficult to detect and easy to dismiss. The magnitude of the deviation can be measured by placing a prism in front of the misaligned eye to determine the power required to neutralize the fixation shift evoked by covering the other eye. Temporary press-on plastic Fresnel prisms, prism eyeglasses, or eye muscle surgery can be used to restore binocular alignment.

STEREOPSIS

Stereoacuity is determined by presenting targets with retinal disparity separately to each eye by using polarized images. The most popular office tests measure a range of thresholds from 800–40 seconds of arc. Normal stereoacuity is 40 seconds of arc. If a patient achieves this level of stereoacuity, one is assured that the eyes are aligned orthotropically and that vision is intact in each eye. Random dot stereograms have no monocular depth cues and provide an excellent screening test for strabismus and amblyopia in children.

COLOR VISION

The retina contains three classes of cones, with visual pigments of differing peak spectral sensitivity: red (560 nm), green (530 nm), and blue (430 nm). The red and green cone pigments are encoded on the X chromosome, and the blue cone pigment on chromosome 7. Mutations of the blue cone pigment are exceedingly rare. Mutations of the red and green pigments cause congenital X-linked color blindness in 8% of males. Affected individuals are not truly color blind; rather, they differ from normal subjects in the way they perceive color and how they combine primary monochromatic lights to match a particular color. Anomalous trichromats have three cone types, but a mutation in one cone pigment (usually red or green) causes a shift in peak spectral sensitivity, altering the proportion of primary colors required to achieve a color match. Dichromats have only two cone types and therefore will accept a color match based on only two primary colors. Anomalous trichromats and dichromats have 6/6 (20/20) visual acuity, but their hue discrimination is impaired. Ishihara color plates can be used to detect red-green color blindness. The test plates contain a hidden number that is visible only to subjects with color confusion from red-green color blindness. Because color blindness is almost exclusively X-linked, it is worth screening only male children.

The Ishihara plates often are used to detect acquired defects in color vision, although they are intended as a screening test for congenital color blindness. Acquired defects in color vision frequently result from disease of the macula or optic nerve. For example, patients with a history of optic neuritis often complain of color desaturation long after their visual acuity has returned to normal. Color blindness also can result from bilateral strokes involving the ventral portion of the occipital lobe (cerebral achromatopsia). Such patients can perceive only shades of gray and also may have difficulty recognizing faces (prosopagnosia). Infarcts of the dominant occipital lobe sometimes give rise to color anomia. Affected patients can discriminate colors but cannot name them.

VISUAL FIELDS

Vision can be impaired by damage to the visual system anywhere from the eyes to the occipital lobes. One can localize the site of the lesion with considerable accuracy

www.ketabpezeshki.com (021) 66485457 - 66485438

by mapping the visual field deficit by finger confrontation and then correlating it with the topographic anatomy of the visual pathway **(Fig. 25-3)**. Quantitative visual field mapping is performed by computer-driven perimeters that present a target of variable intensity at fixed positions in the visual field **(Fig. 25-3A)**. By generating an automated printout of light thresholds, these static perimeters provide a sensitive means of detecting scotomas in the visual field. T ey are exceedingly useful for serial assessment of visual function in chronic diseases such as glaucoma and pseudotumor cerebri.

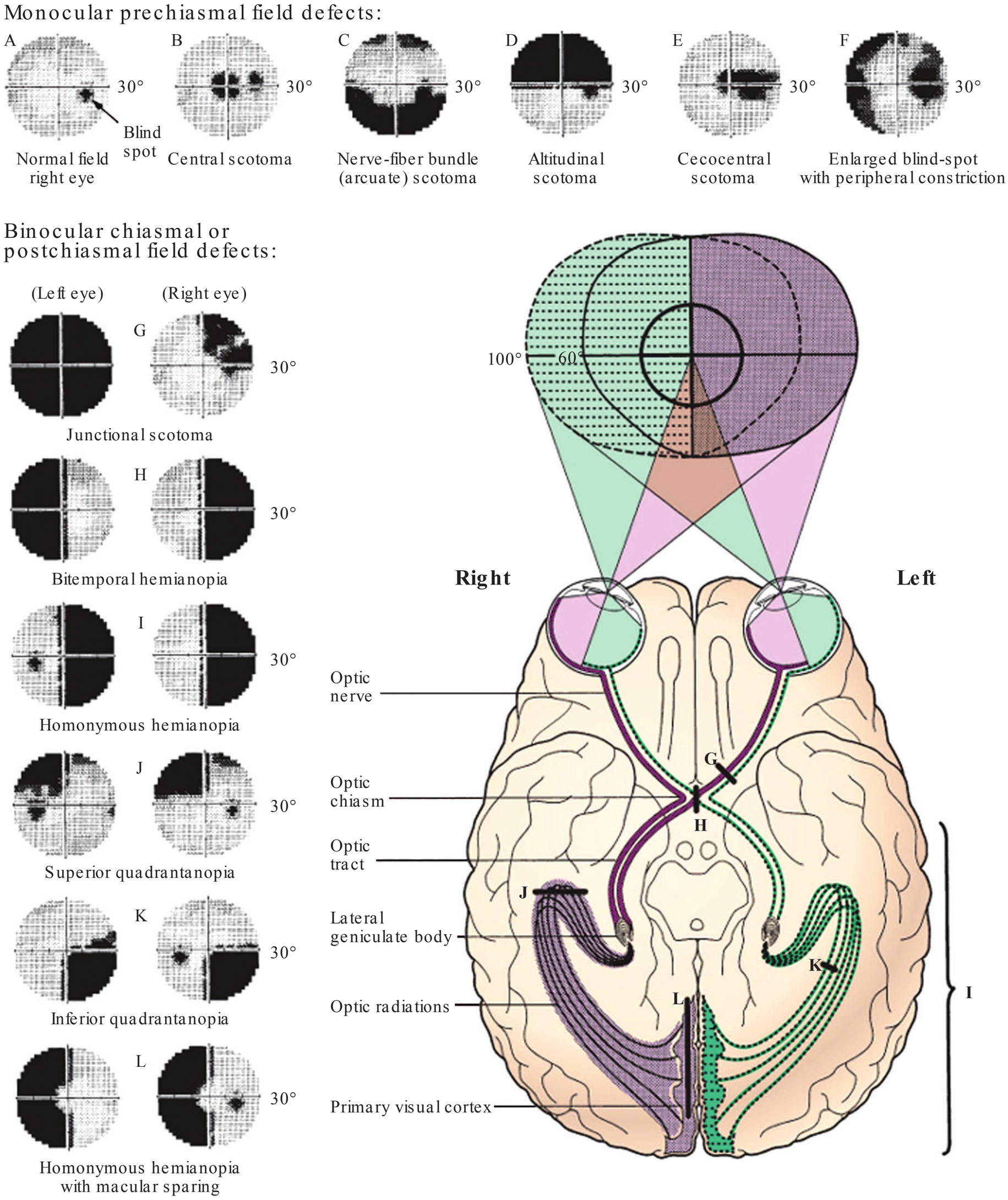


FIGURE 25-3

Ventral view of the brain, correlating patterns of visual field loss with the sites of lesions in the visual pathway. The visual fields overlap partially, creating 120° of central binocular field flanked by a 40° monocular crescent on either side. The visual field maps in this figure were done with a computer-driven perimeter (Humphrey Instruments, Carl Zeiss, Inc.). It plots the retinal sensitivity to light in the central 30° by using a gray scale format. Areas of visual field loss are shown in black. The examples of common monocular, prechiasmal field defects are all shown for the right eye. By convention, the visual fields are always recorded with the left eye's field on the left and the right eye's field on the right, just as the patient sees the world.

www.ketabpezeshki.com (021) 66485457 - 66485438

The crux of visual field analysis is to decide whether a lesion is before, at, or behind the optic chiasm. If a scotoma is confined to one eye, it must be due to a lesion anterior to the chiasm, involving either the optic nerve or the retina. Retinal lesions produce scotomas that correspond optically to their location in the fundus. For example, a superior-nasal retinal detachment results in an inferior-temporal field cut. Damage to the macula causes a central scotoma **(Fig. 25-3B)**.

Optic nerve disease produces characteristic patterns of visual field loss. Glaucoma selectively destroys axons that enter the superotemporal or inferotemporal poles of the optic disc, resulting in arcuate scotomas shaped like a Turkish scimitar, which emanate from the blind spot and curve around fixation to end flat against the horizontal meridian **(Fig. 25-3C)**. This type of field defect mirrors the arrangement of the nerve fiber layer in the temporal retina. Arcuate or nerve fiber layer scotomas also result from optic neuritis, ischemic optic neuropathy, optic disc drusen, and branch retinal artery or vein occlusion.

Damage to the entire upper or lower pole of the optic disc causes an altitudinal field cut that follows the horizontal meridian **(Fig. 25-3D)**. This pattern of visual field loss is typical of ischemic optic neuropathy but also results from retinal vascular occlusion, advanced glaucoma, and optic neuritis.

About half the fibers in the optic nerve originate from ganglion cells serving the macula. Damage to papillomacular fibers causes a cecocentral scotoma that encompasses the blind spot and macula **(Fig. 25-3E)**. If the damage is irreversible, pallor eventually appears in the temporal portion of the optic disc. Temporal pallor from a cecocentral scotoma may develop in optic neuritis, nutritional optic neuropathy, toxic optic neuropathy, Leber's hereditary optic neuropathy, Kjer's dominant optic atrophy, and compressive optic neuropathy. It is worth mentioning that the temporal side of the optic disc is slightly paler than the nasal side in most normal individuals. Therefore, it sometimes can be difficult to decide whether the temporal pallor visible on fundus examination represents a pathologic change. Pallor of the nasal rim of the optic disc is a less equivocal sign of optic atrophy.

At the optic chiasm, fibers from nasal ganglion cells decussate into the contralateral optic tract. Crossed fibers are damaged more by compression than are uncrossed fibers. As a result, mass lesions of the sellar region cause a temporal hemianopia in each eye. Tumors anterior to the optic chiasm, such as meningiomas of the tuberculum sella, produce a junctional scotoma characterized by an optic neuropathy in one eye and a superior-temporal field cut in the other eye **(Fig. 25-3G)**. More symmetric compression of the optic chiasm by a pituitary adenoma **(see Fig. 51-1)**, meningioma, craniopharyngioma, glioma, or aneurysm results in a bitemporal hemianopia **(Fig. 25-3H)**. The insidious development of a bitemporal hemianopia often goes unnoticed by the patient and will escape detection by the physician unless each eye is tested separately.

It is difficult to localize a postchiasmal lesion accurately, because injury anywhere in the optic tract, lateral geniculate body, optic radiations, or visual cortex can produce a homonymous hemianopia (i.e., a temporal hemifield defect in the contralateral eye and a matching nasal hemifield defect in the ipsilateral eye) **(Fig. 25-3I)**. A unilateral postchiasmal lesion leaves the visual acuity in each eye unaffected, although the patient may read the letters on only the left or right half of the eye chart. Lesions of the optic radiations tend to cause poorly matched or incongruous field defects in each eye. Damage to the optic radiations in the temporal lobe (Meyer's loop) produces a superior quadrantic homonymous hemianopia **(Fig. 25-3J)**, whereas injury to the optic radiations in the parietal lobe results in an inferior quadrantic homonymous hemianopia **(Fig. 25-3K)**. Lesions of the primary visual cortex give rise to dense, congruous hemianopic field defects. Occlusion of the posterior cerebral artery supplying the occipital lobe is a common cause of total homonymous hemianopia. Some patients with hemianopia after occipital stroke have macular sparing, because the macular representation at the tip of the occipital lobe is supplied by collaterals from the middle cerebral artery **(Fig. 25-3L)**. Destruction of both occipital lobes produces cortical blindness. This condition can be distinguished from bilateral prechiasmal visual loss by noting that the pupil responses and optic fundi remain normal.

DISORDERS

RED OR PAINFUL EYE

Corneal abrasions

Corneal abrasions are seen best by placing a drop of fluorescein in the eye and looking with the slit lamp, using a cobalt-blue light. A penlight with a blue filter will suffice if a slit lamp is not available. Damage to the corneal epithelium is revealed by yellow fluorescence of the exposed basement membrane underlying the epithelium. It is important to check for foreign bodies. To search the conjunctival fornices, the lower lid should be pulled down and the upper lid everted. A foreign body can be removed with a moistened cotton-tipped applicator after a drop of a topical anesthetic such as proparacaine has been placed in the eye. Alternatively, it may be possible to flush the foreign body from the eye

www.ketabpezeshki.com (021) 66485457 - 66485438

by irrigating copiously with saline or artificial tears. If the corneal epithelium has been abraded, antibiotic ointment and a patch should be applied to the eye. A drop of an intermediate-acting cycloplegic such as cyclopentolate hydrochloride 1% helps reduce pain by relaxing the ciliary body. T e eye should be reexamined the next day. Minor abrasions may not require patching, antibiotics, or cycloplegia.

Subconjunctival hemorrhage

T is results from rupture of small vessels bridging the potential space between the episclera and the conjunctiva. Blood dissecting into this space can produce a spectacular red eye, but vision is not af ected and the hemorrhage resolves without treatment. Subconjunctival hemorrhage is usually spontaneous but can result from blunt trauma, eye rubbing, or vigorous coughing. Occasionally it is a clue to an underlying bleeding disorder.

Pinguecula

Pinguecula is a small, raised conjunctival nodule at the temporal or nasal limbus. In adults such lesions are extremely common and have little significance unless they become inflamed (pingueculitis). T ey are more apt to occur in workers with frequent outdoor exposure. A pterygium resembles a pinguecula but has crossed the limbus to encroach on the corneal surface. Removal is justified when symptoms of irritation or blurring develop, but recurrence is a common problem.

Blepharitis

T is refers to inflammation of the eyelids. T e most common form occurs in association with acne rosacea or seborrheic dermatitis. T e eyelid margins usually are colonized heavily by staphylococci. Upon close inspection, they appear greasy, ulcerated, and crusted with scaling debris that clings to the lashes. Treatment consists of strict eyelid hygiene, using warm compresses and eyelash scrubs with baby shampoo. An external hordeolum (sty) is caused by staphylococcal infection of the superficial accessory glands of Zeis or Moll located in the eyelid margins. An internal hordeolum occurs after suppurative infection of the oil-secreting meibomian glands within the tarsal plate of the eyelid. Topical antibiotics such as bacitracin/polymyxin B ophthalmic ointment can be applied. Systemic antibiotics, usually tetracyclines or azithromycin, sometimes are necessary for treatment of meibomian gland inflammation (meibomitis) or chronic, severe blepharitis. A chalazion is a painless, chronic granulomatous inflammation of a meibomian gland that produces a pealike nodule within the eyelid. It can be incised and drained or injected with glucocorticoids. Basal cell, squamous cell, or meibomian gland carcinoma should be suspected with any nonhealing ulcerative lesion of the eyelids.

Dacryocystitis

An inflammation of the lacrimal drainage system, dacryocystitis can produce epiphora (tearing) and ocular injection. Gentle pressure over the lacrimal sac evokes pain and reflux of mucus or pus from the tear puncta. Dacryocystitis usually occurs after obstruction of the lacrimal system. It is treated with topical and systemic antibiotics, followed by probing, silicone stent intubation, or surgery to reestablish patency. Entropion (inversion of the eyelid) or ectropion (sagging or eversion of the eyelid) can also lead to epiphora and ocular irritation.

Conjunctivitis

Conjunctivitis is the most common cause of a red, irritated eye. Pain is minimal, and visual acuity is reduced only slightly. T e most common viral etiology is adenovirus infection. It causes a watery discharge, a mild foreign-body sensation, and photophobia. Bacterial infection tends to produce a more mucopurulent exudate. Mild cases of infectious conjunctivitis usually are treated empirically with broad-spectrum topical ocular antibiotics such as sulfacetamide 10%, polymyxin-bacitracin, or a trimethoprim-polymyxin combination. Smears and cultures usually are reserved for severe, resistant, or recurrent cases of conjunctivitis. To prevent contagion, patients should be admonished to wash their hands frequently, not to touch their eyes, and to avoid direct contact with others.

Allergic conjunctivitis

T is condition is extremely common and often is mistaken for infectious conjunctivitis. Itching, redness, and epiphora are typical. T e palpebral conjunctiva may become hypertropic with giant excrescences called cobblestone papillae. Irritation from contact lenses or any chronic foreign body also can induce formation of cobblestone papillae. Atopic conjunctivitis occurs in subjects with atopic dermatitis or asthma. Symptoms caused by allergic conjunctivitis can be alleviated with cold compresses, topical vasoconstrictors, antihistamines, and mast cell stabilizers such as cromolyn sodium. Topical glucocorticoid solutions provide dramatic relief of immune-mediated forms of conjunctivitis, but their long-term use is ill advised because of the complications of glaucoma, cataract, and secondary infection. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ketorolac tromethamine) are better alternatives.

www.ketabpezeshki.com (021) 66485457 - 66485438

Keratoconjunctivitis sicca

Also known as dry eye, this produces a burning foreign-body sensation, injection, and photophobia. In mild cases the eye appears surprisingly normal, but tear production measured by wetting of a filter paper (Schirmer strip) is deficient. A variety of systemic drugs, including antihistaminic, anticholinergic, and psychotropic medications, result in dry eye by reducing lacrimal secretion. Disorders that involve the lacrimal gland directly, such as sarcoidosis and Sjögren's syndrome, also cause dry eye. Patients may develop dry eye after radiation therapy if the treatment field includes the orbits. Problems with ocular drying are also common after lesions affecting cranial nerve V or VII. Corneal anesthesia is particularly dangerous, because the absence of a normal blink reflex exposes the cornea to injury without pain to warn the patient. Dry eye is managed by frequent and liberal application of artificial tears and ocular lubricants. In severe cases the tear puncta can be plugged or cauterized to reduce lacrimal outflow.

Keratitis

Keratitis is a threat to vision because of the risk of corneal clouding, scarring, and perforation. Worldwide, the two leading causes of blindness from keratitis are trachoma from chlamydial infection and vitamin A deficiency related to malnutrition. In the United States, contact lenses play a major role in corneal infection and ulceration. They should not be worn by anyone with an active eye infection. In evaluating the cornea, it is important to differentiate between a superficial infection (keratoconjunctivitis) and a deeper, more serious ulcerative process. The latter is accompanied by greater visual loss, pain, photophobia, redness, and discharge. Slit-lamp examination shows disruption of the corneal epithelium, a cloudy infiltrate or abscess in the stroma, and an inflammatory cellular reaction in the anterior chamber. In severe cases, pus settles at the bottom of the anterior chamber, giving rise to a hypopyon. Immediate empirical antibiotic therapy should be initiated after corneal scrapings are obtained for Gram's stain, Giemsa stain, and cultures. Fortified topical antibiotics are most effective, supplemented with subconjunctival antibiotics as required. A fungal etiology should always be considered in a patient with keratitis. Fungal infection is common in warm humid climates, especially after penetration of the cornea by plant or vegetable material.

Herpes simplex

The herpesviruses are a major cause of blindness from keratitis. Most adults in the United States have serum antibodies to herpes simplex, indicating prior viral infection. Primary ocular infection generally is caused by herpes simplex type 1 rather than type 2. It manifests as a unilateral follicular blepharoconjunctivitis that is easily confused with adenoviral conjunctivitis unless telltale vesicles appear on the periocular skin or conjunctiva. A dendritic pattern of corneal epithelial ulceration revealed by fluorescein staining is pathognomonic for herpes infection but is seen in only a minority of primary infections. Recurrent ocular infection arises from reactivation of the latent herpesvirus. Viral eruption in the corneal epithelium may result in the characteristic herpes dendrite. Involvement of the corneal stroma produces edema, vascularization, and iridocyclitis. Herpes keratitis is treated with topical antiviral agents, cycloplegics, and oral acyclovir. Topical glucocorticoids are effective in mitigating corneal scarring but must be used with extreme caution because of the danger of corneal melting and perforation. Topical glucocorticoids also carry the risk of prolonging infection and inducing glaucoma.

Herpes zoster

Herpes zoster from reactivation of latent varicella (chickenpox) virus causes a dermatomal pattern of painful vesicular dermatitis. Ocular symptoms can occur after zoster eruption in any branch of the trigeminal nerve but are particularly common when vesicles form on the nose, reflecting nasociliary (V1) nerve involvement (Hutchinson's sign). Herpes zoster ophthalmicus produces corneal dendrites, which can be difficult to distinguish from those seen in herpes simplex. Stromal keratitis, anterior uveitis, raised intraocular pressure, ocular motor nerve palsies, acute retinal necrosis, and postherpetic scarring and neuralgia are other common sequelae. Herpes zoster ophthalmicus is treated with antiviral agents and cycloplegics. In severe cases, glucocorticoids may be added to prevent permanent visual loss from corneal scarring.

Episcleritis

This is an inflammation of the episclera, a thin layer of connective tissue between the conjunctiva and the sclera. Episcleritis resembles conjunctivitis, but it is a more localized process and discharge is absent. Most cases of episcleritis are idiopathic, but some occur in the setting of an autoimmune disease. Scleritis refers to a deeper, more severe inflammatory process that frequently is associated with a connective tissue disease such as rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis (Wegener's), or relapsing polychondritis. The inflammation and thickening of the sclera can be diffuse or nodular. In anterior forms of scleritis, the globe assumes a

www.ketabpezeshki.com (021) 66485457 - 66485438

violet hue and the patient complains of severe ocular tenderness and pain. With posterior scleritis, the pain and redness may be less marked, but there is often proptosis, choroidal effusion, reduced motility, and visual loss. Episcleritis and scleritis should be treated with NSAIDs. If these agents fail, topical or even systemic glucocorticoid therapy may be necessary, especially if an underlying autoimmune process is active.

Uveitis

Involving the anterior structures of the eye, uveitis also is called iritis or iridocyclitis. The diagnosis requires slit-lamp examination to identify inflammatory cells floating in the aqueous humor or deposited on the corneal endothelium (keratic precipitates). Anterior uveitis develops in sarcoidosis, ankylosing spondylitis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, reactive arthritis, and Behçet's disease. It also is associated with herpes infections, syphilis, Lyme disease, onchocerciasis, tuberculosis, and leprosy. Although anterior uveitis can occur in conjunction with many diseases, no cause is found to explain the majority of cases. For this reason, laboratory evaluation usually is reserved for patients with recurrent or severe anterior uveitis. Treatment is aimed at reducing inflammation and scarring by judicious use of topical glucocorticoids. Dilatation of the pupil reduces pain and prevents the formation of synechiae.

Posterior uveitis

This is diagnosed by observing inflammation of the vitreous, retina, or choroid on fundus examination. It is more likely than anterior uveitis to be associated with an identifiable systemic disease. Some patients have panuveitis, or inflammation of both the anterior and posterior segments of the eye. Posterior uveitis is a manifestation of autoimmune diseases such as sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome, and inflammatory bowel disease. It also accompanies diseases such as toxoplasmosis, onchocerciasis, cysticercosis, coccidioidomycosis, toxocariasis, and histoplasmosis; infections caused by organisms such as Candida, Pneumocystis carinii, Cryptococcus, Aspergillus, herpes, and cytomegalovirus; and other diseases, such as syphilis, Lyme disease, tuberculosis, cat-scratch disease, Whipple's disease, and brucellosis. In multiple sclerosis, chronic inflammatory changes can develop in the extreme periphery of the retina (pars planitis or intermediate uveitis).

Acute angle-closure glaucoma

This is an unusual but frequently misdiagnosed cause of a red, painful eye. Asian populations have a particularly high risk of angle-closure glaucoma. Susceptible eyes have a shallow anterior chamber because the eye has either a short axial length (hyperopia) or a lens enlarged by the gradual development of cataract. When the pupil becomes mid-dilated, the peripheral iris blocks aqueous outflow via the anterior chamber angle and the intraocular pressure rises abruptly, producing pain, injection, corneal edema, obscurations, and blurred vision. In some patients, ocular symptoms are overshadowed by nausea, vomiting, or headache, prompting a fruitless workup for abdominal or neurologic disease. The diagnosis is made by measuring the intraocular pressure during an acute attack or by performing gonioscopy, a procedure that allows one to observe a narrow chamber angle with a mirrored contact lens. Acute angle closure is treated with acetazolamide (PO or IV), topical beta blockers, prostaglandin analogues, α_2-adrenergic agonists, and pilocarpine to induce miosis. If these measures fail, a laser can be used to create a hole in the peripheral iris to relieve pupillary block. Many physicians are reluctant to dilate patients routinely for fundus examination because they fear precipitating an angle-closure glaucoma. The risk is actually remote and more than outweighed by the potential benefit to patients of discovering a hidden fundus lesion visible only through a fully dilated pupil. Moreover, a single attack of angle closure after pharmacologic dilatation rarely causes any permanent damage to the eye and serves as an inadvertent provocative test to identify patients with narrow angles who would benefit from prophylactic laser iridectomy.

Endophthalmitis

This results from bacterial, viral, fungal, or parasitic infection of the internal structures of the eye. It usually is acquired by hematogenous seeding from a remote site. Chronically ill, diabetic, or immunosuppressed patients, especially those with a history of indwelling IV catheters or positive blood cultures, are at greatest risk for endogenous endophthalmitis. Although most patients have ocular pain and injection, visual loss is sometimes the only symptom. Septic emboli from a diseased heart valve or a dental abscess that lodge in the retinal circulation can give rise to endophthalmitis. White-centered retinal hemorrhages known as Roth's spots **(Fig. 25-4)** are considered pathognomonic for subacute bacterial endocarditis, but they also appear in leukemia, diabetes, and many other conditions. Endophthalmitis also occurs as a complication of ocular surgery, especially glaucoma filtering, occasionally months or even years after the operation. An occult penetrating foreign body or unrecognized trauma to the globe should be considered in any patient with unexplained intraocular infection or inflammation.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 25-4
Roth's spot, cotton-wool spot, and retinal hemorrhages in a 48-year-old liver transplant patient with candidemia from immunosuppression.

FIGURE 25-6
Central retinal artery occlusion in a 78-year-old man reducing acuity to counting fingers in the right eye. Note the splinter hemorrhage on the optic disc and the slightly milky appearance to the macula with a cherry-red fovea.

TRANSIENT OR SUDDEN VISUAL LOSS

Amaurosis fugax

This term refers to a transient ischemic attack of the retina **(Chap. 32)**. Because neural tissue has a high rate of metabolism, interruption of blood flow to the retina for more than a few seconds results in transient monocular blindness, a term used interchangeably with amaurosis fugax. Patients describe a rapid fading of vision like a curtain descending, sometimes affecting only a portion of the visual field. Amaurosis fugax usually results from an embolus that becomes stuck within a retinal arteriole **(Fig. 25-5)**. If the embolus breaks up or passes, flow is restored and vision returns quickly to normal without permanent damage. With prolonged interruption of blood flow, the inner retina suffers infarction. Ophthalmoscopy reveals zones of whitened, edematous retina following the distribution of branch retinal arterioles. Complete occlusion of the central retinal artery produces arrest of blood flow and a milky retina with a cherry-red fovea **(Fig. 25-6)**. Emboli are composed of cholesterol (Hollenhorst plaque), calcium, or platelet-fibrin debris. The most common source is an atherosclerotic plaque in the carotid artery or aorta, although emboli also can arise from the heart, especially in patients with diseased valves, atrial fibrillation, or wall motion abnormalities.

FIGURE 25-5
Hollenhorst plaque lodged at the bifurcation of a retinal arteriole proves that a patient is shedding emboli from the carotid artery, great vessels, or heart.

In rare instances, amaurosis fugax results from low central retinal artery perfusion pressure in a patient with a critical stenosis of the ipsilateral carotid artery and poor collateral flow via the circle of Willis. In this situation, amaurosis fugax develops when there is a dip in systemic blood pressure or a slight worsening of the carotid stenosis. Sometimes there is contralateral motor or sensory loss, indicating concomitant hemispheric cerebral ischemia.

Retinal arterial occlusion also occurs rarely in association with retinal migraine, lupus erythematosus, anticardiolipin antibodies, anticoagulant deficiency states (protein S, protein C, and antithrombin deficiency), pregnancy, IV drug abuse, blood dyscrasias, dysproteinemias, and temporal arteritis.

Marked systemic hypertension causes sclerosis of retinal arterioles, splinter hemorrhages, focal infarcts of the nerve fiber layer (cotton-wool spots), and leakage of lipid and fluid (hard exudate) into the macula **(Fig. 25-7)**. In hypertensive crisis, sudden visual loss

www.ketabpezeshki.com (021) 66485457 - 66485438

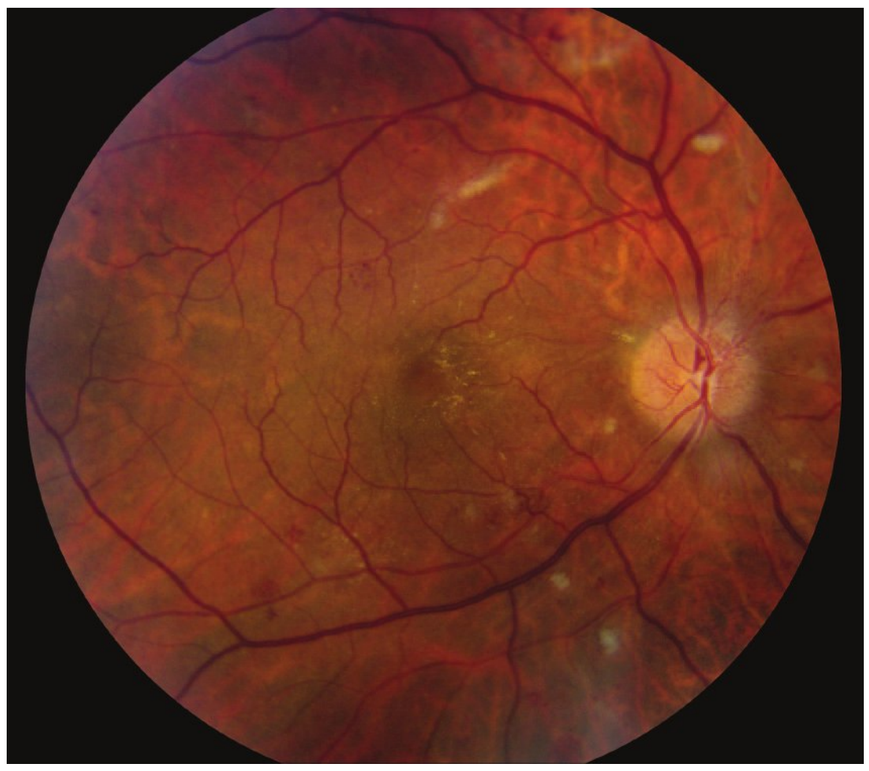


FIGURE 25-7
Hypertensive retinopathy with blurred optic disc, scattered hemorrhages, cotton-wool spots (nerve fiber layer infarcts), and foveal exudate in a 62-year-old man with chronic renal failure and a systolic blood pressure of 220.

can result from vasospasm of retinal arterioles and retinal ischemia. In addition, acute hypertension may produce visual loss from ischemic swelling of the optic disc. Patients with acute hypertensive retinopathy should be treated by lowering the blood pressure. However, the blood pressure should not be reduced precipitously, because there is a danger of optic disc infarction from sudden hypoperfusion.

Impending branch or central retinal vein occlusion can produce prolonged visual obscurations that resemble those described by patients with amaurosis fugax. The veins appear engorged and phlebitic, with numerous retinal hemorrhages **(Fig. 25-8)**. In some patients, venous blood flow recovers spontaneously, whereas others evolve a frank obstruction with extensive retinal bleeding ("blood and thunder" appearance), infarction, and visual loss. Venous occlusion of the retina is often idiopathic, but hypertension, diabetes, and glaucoma are prominent risk factors. Polycythemia, thrombocythemia, or other factors leading to an underlying hypercoagulable state should be corrected; aspirin treatment may be beneficial.

Anterior ischemic optic neuropathy (AION)

This is caused by insufficient blood flow through the posterior ciliary arteries that supply the optic disc. It produces painless monocular visual loss that is sudden in onset, followed sometimes by stuttering progression. The optic disc appears swollen and surrounded by nerve fiber layer splinter hemorrhages **(Fig. 25-9)**. AION is divided into two forms: arteritic and nonarteritic. The nonarteritic form is most common. No specific cause can be identified, although diabetes and hypertension are common risk factors. A crowded disc architecture and small optic cup predispose to the development of nonarteritic AION. No treatment is available. About 5% of patients, especially those age >60, develop the arteritic form of AION in conjunction with giant-cell (temporal) arteritis. It is urgent to recognize arteritic AION so that high doses of glucocorticoids can be instituted immediately to prevent blindness in the second eye. Symptoms of polymyalgia rheumatica may be present; the sedimentation rate and C-reactive protein level are usually elevated. In a patient with visual loss from suspected arteritic AION, temporal artery biopsy is mandatory to confirm the diagnosis. Glucocorticoids should be started immediately, without waiting for the biopsy to be

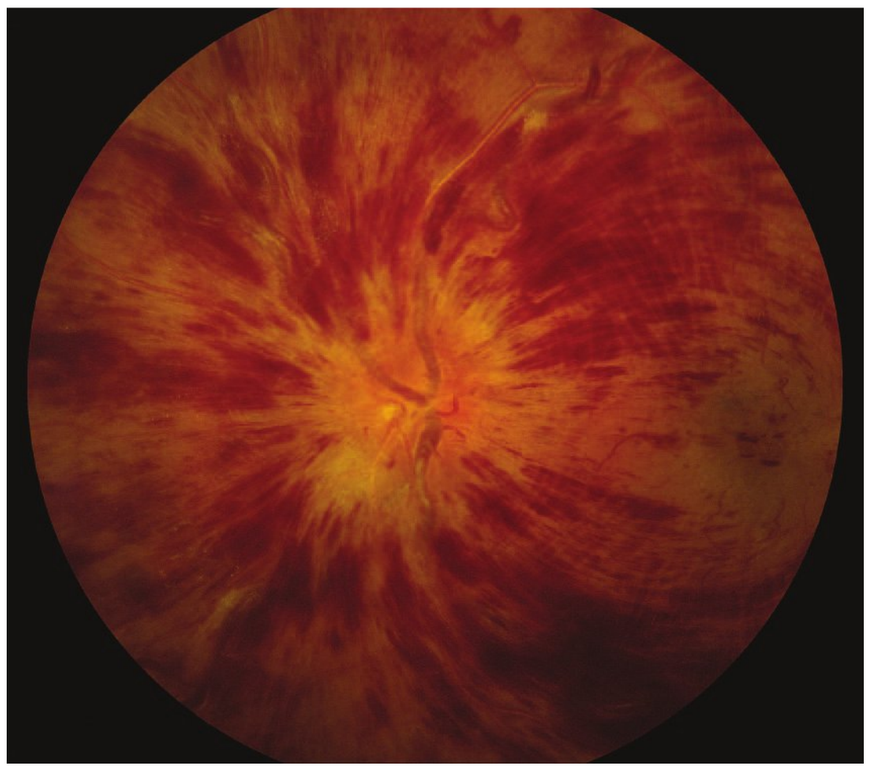


FIGURE 25-8
Central retinal vein occlusion can produce massive retinal hemorrhage ("blood and thunder"), ischemia, and vision loss.

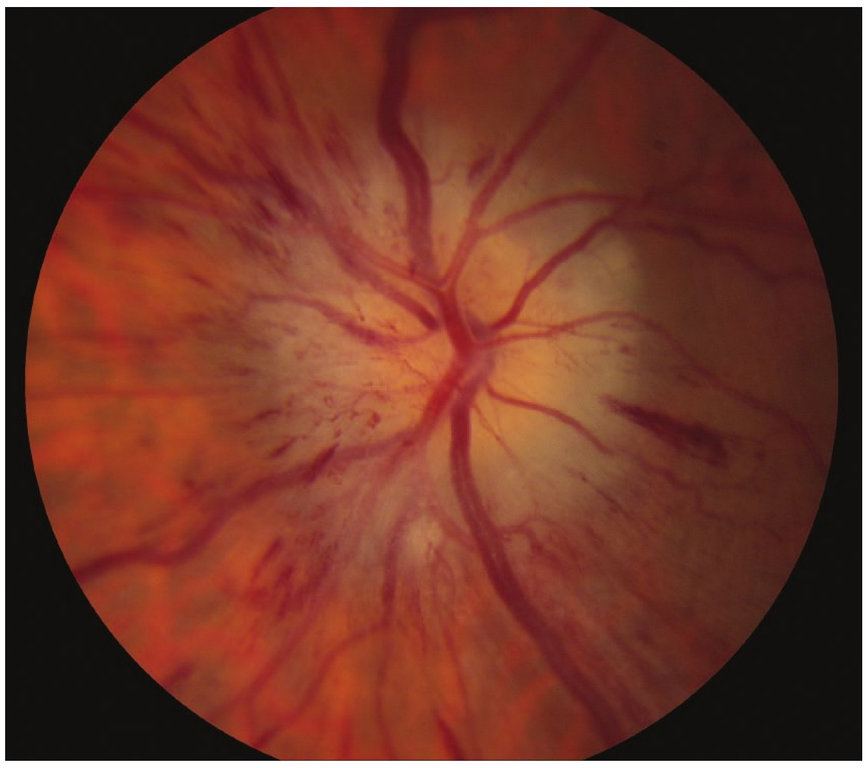


FIGURE 25-9
Anterior ischemic optic neuropathy from temporal arteritis in a 67-year-old woman with acute disc swelling, splinter hemorrhages, visual loss, and an erythrocyte sedimentation rate of 70 mm/h.

www.ketabpezeshki.com (021) 66485457 - 66485438

completed. The diagnosis of arteritic AION is difficult to sustain in the face of a negative temporal artery biopsy, but such cases do occur rarely. It is important to biopsy an arterial segment of at least 3 cm and to examine a sufficient number of tissue sections prepared from the specimen.

Posterior ischemic optic neuropathy

This is an uncommon cause of acute visual loss, induced by the combination of severe anemia and hypotension. Cases have been reported after major blood loss during surgery (especially in patients undergoing cardiac or lumbar spine operations), exsanguinating trauma, gastrointestinal bleeding, and renal dialysis. The fundus usually appears normal, although optic disc swelling develops if the process extends anteriorly far enough to reach the globe. Vision can be salvaged in some patients by prompt blood transfusion and reversal of hypotension.

Optic neuritis

This is a common inflammatory disease of the optic nerve. In the Optic Neuritis Treatment Trial (ONTT), the mean age of patients was 32 years, 77% were female, 92% had ocular pain (especially with eye movements), and 35% had optic disc swelling. In most patients, the demyelinating event was retrobulbar and the ocular fundus appeared normal on initial examination **(Fig. 25-10)**, although optic disc pallor slowly developed over subsequent months.

Virtually all patients experience a gradual recovery of vision after a single episode of optic neuritis, even without treatment. This is rule is so reliable that failure of vision to improve after a first attack of optic neuritis casts doubt on the original diagnosis. Treatment with high-dose IV methylprednisolone (250 mg every 6 h for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days) makes no difference in ultimate acuity 6 months after the attack, but the recovery of visual function occurs more rapidly. Therefore, when visual loss is severe (worse than 20/100), IV followed by PO glucocorticoids are often recommended.

For some patients, optic neuritis remains an isolated event. However, the ONTT showed that the 15-year cumulative probability of developing clinically definite multiple sclerosis after optic neuritis is 50%. A brain magnetic resonance (MR) scan is advisable in every patient with a first attack of optic neuritis. If two or more plaques are present on initial imaging, treatment should be considered to prevent the development of additional demyelinating lesions **(Chap. 45)**.

FIGURE 25-10
Retrobulbar optic neuritis is characterized by a normal fundus examination initially, hence the rubric "the doctor sees nothing, and the patient sees nothing." Optic atrophy develops after severe or repeated attacks.

LEBER'S HEREDITARY OPTIC NEUROPATHY

This disease usually affects young men, causing gradual, painless, severe central visual loss in one eye, followed weeks to years later by the same process in the other eye. Acutely, the optic disc appears mildly plethoric with surface capillary telangiectasias but no vascular leakage on fluorescein angiography. Eventually optic atrophy ensues. Leber's optic neuropathy is caused by a point mutation at codon 11778 in the mitochondrial gene encoding nicotinamide adenine dinucleotide dehydrogenase (NADH) subunit 4. Additional mutations responsible for the disease have been identified, most in mitochondrial genes that encode proteins involved in electron transport. Mitochondrial mutations that cause Leber's neuropathy are inherited from the mother by all her children, but usually only sons develop symptoms.

Toxic optic neuropathy

This can result in acute visual loss with bilateral optic disc swelling and central or cecocentral scotomas. Such cases have been reported to result from exposure to ethambutol, methyl alcohol (moonshine), ethylene glycol (antifreeze), or carbon monoxide. In toxic optic neuropathy, visual loss also can develop gradually and produce optic atrophy **(Fig. 25-11)** without a phase of acute optic disc edema. Many agents have been implicated as a cause of toxic optic neuropathy, but the evidence supporting the association for many is weak. The following is a partial list of potential offending drugs or toxins: disulfiram, ethchlorvynol, chloramphenicol, amiodarone, monoclonal anti-CD3 antibody, ciprofloxacin, digitalis, streptomycin, lead, arsenic, thallium, d-penicillamine, isoniazid, emetine, sildenafil, tadalafil, vardenafil, and sulfonamides. Deficiency states induced

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 25-11
Optic atrophy is not a specific diagnosis but refers to the combination of optic disc pallor, arteriolar narrowing, and nerve fiber layer destruction produced by a host of eye diseases, especially optic neuropathies.

by starvation, malabsorption, or alcoholism can lead to insidious visual loss. Thiamine, vitamin B_{12}, and folate levels should be checked in any patient with unexplained bilateral central scotomas and optic pallor.

Papilledema

Thisconnotes bilateral optic disc swelling from raised intracranial pressure **(Fig. 25-12)**. Headache is a common but not invariable accompaniment. All other forms of optic disc swelling (e.g., from optic neuritis or ischemic optic neuropathy) should be called "optic disc edema". Thisconvention is arbitrary but serves to avoid confusion. Often it is difficult to differentiate papilledema from other forms of optic disc edema by fundus examination alone. Transient visual obscurations are a classic symptom of papilledema. Theycan occur in only one eye or simultaneously in both eyes. Theyusually last seconds but can persist longer. Obscurations follow abrupt shifts in posture or happen spontaneously. When obscurations are prolonged or spontaneous, the papilledema is more threatening. Visual acuity is not affected by papilledema unless the papilledema is severe, long-standing, or accompanied by macular edema and hemorrhage. Visual field testing shows enlarged blind spots and peripheral constriction (Fig. 25-3F). With unremitting papilledema, peripheral visual field loss progresses in an insidious fashion while the optic nerve develops atrophy. In this setting, reduction of optic disc swelling is an ominous sign of a dying nerve rather than an encouraging indication of resolving papilledema.

FIGURE 25-12
Papilledema means optic disc edema from raised intracranial pressure. This young woman developed acute papilledema, with hemorrhages and cotton-wool spots, as a rare side effect of treatment with tetracycline for acne.

Evaluation of papilledema requires neuroimaging to exclude an intracranial lesion. MR angiography is appropriate in selected cases to search for a dural venous sinus occlusion or an arteriovenous shunt. If neuroradiologic studies are negative, the subarachnoid opening pressure should be measured by lumbar puncture. An elevated pressure, with normal cerebrospinal fluid, points by exclusion to the diagnosis of pseudotumor cerebri (idiopathic intracranial hypertension). The majority of patients are young, female, and obese. Treatment with a carbonic anhydrase inhibitor such as acetazolamide lowers intracranial pressure by reducing the production of cerebrospinal fluid. Weight reduction is vital: bariatric surgery should be considered in patients who cannot lose weight by diet control. If vision loss is severe or progressive, a shunt should be performed without delay to prevent blindness. Occasionally, emergency surgery is required for sudden blindness caused by fulminant papilledema.

Optic disc drusen

Theseare refractile deposits within the substance of the optic nerve head **(Fig. 25-13)**. Theyare unrelated to drusen of the retina, which occur in age-related macular degeneration. Optic disc drusen are most common in people of northern European descent. Their diagnosis is obvious when they are visible as glittering particles on the surface of the optic disc. However, in many patients they are hidden beneath the surface, producing pseudopapilledema. It is important to recognize optic disc drusen to avoid an unnecessary evaluation for papilledema. Ultrasound or computed tomography (CT) scanning is sensitive for detection of buried optic disc drusen because they contain calcium. In most patients, optic disc drusen are an incidental, innocuous finding, but they can produce visual obscurations. On perimetry they

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 25-13
Optic disc drusen are calcified, mulberry-like deposits of unknown etiology within the optic disc, giving rise to "pseudopapilledema."

give rise to enlarged blind spots and arcuate scotomas from damage to the optic disc. With increasing age, drusen tend to become more exposed on the disc surface as optic atrophy develops. Hemorrhage, choroidal neovascular membrane, and AION are more likely to occur in patients with optic disc drusen. No treatment is available.

Vitreous degeneration

This occurs in all individuals with advancing age, leading to visual symptoms. Opacities develop in the vitreous, casting annoying shadows on the retina. As the eye moves, these distracting "floaters" move synchronously, with a slight lag caused by inertia of the vitreous gel. Vitreous traction on the retina causes mechanical stimulation, resulting in perception of flashing lights. This photopsia is brief and is confined to one eye, in contrast to the bilateral, prolonged scintillations of cortical migraine. Contraction of the vitreous can result in sudden separation from the retina, heralded by an alarming shower of floaters and photopsia. This process, known as vitreous detachment, is a common involutional event in the elderly. It is not harmful unless it damages the retina. A careful examination of the dilated fundus is important in any patient complaining of floaters or photopsia to search for peripheral tears or holes. If such a lesion is found, laser application can forestall a retinal detachment. Occasionally a tear ruptures a retinal blood vessel, causing vitreous hemorrhage and sudden loss of vision. On attempted ophthalmoscopy the fundus is hidden by a dark haze of blood. Ultrasound is required to examine the interior of the eye for a retinal tear or detachment. If the hemorrhage does not resolve spontaneously, the vitreous can be removed surgically. Vitreous hemorrhage also results from the fragile neovascular vessels that proliferate on the surface of the retina in diabetes, sickle cell anemia, and other ischemic ocular diseases.

Retinal detachment

This produces symptoms of floaters, flashing lights, and a scotoma in the peripheral visual field corresponding to the detachment **(Fig. 25-14)**. If the detachment includes the fovea, there is an afferent pupil defect and the visual acuity is reduced. In most eyes, retinal detachment starts with a hole, flap, or tear in the peripheral retina (rhegmatogenous retinal detachment). Patients with peripheral retinal thinning (lattice degeneration) are particularly vulnerable to this process. Once a break has developed in the retina, liquefied vitreous is free to enter the subretinal space, separating the retina from the pigment epithelium. The combination of vitreous traction on the retinal surface and passage of fluid behind the retina leads inexorably to detachment. Patients with a history of myopia, trauma, or prior cataract extraction are at greatest risk for retinal detachment. The diagnosis is confirmed by ophthalmoscopic examination of the dilated eye.

Classic migraine

(See also Chap. 34) This is usually occurs with a visual aura lasting about 20 min. In a typical attack, a small central disturbance in the field of vision marches toward the periphery, leaving a transient scotoma in its wake. The expanding border of migraine scotoma has a scintillating, dancing, or zigzag edge, resembling the bastions of a fortified city, hence the term *fortification* spectra. Patients' descriptions of fortification spectra vary widely and can be confused with amaurosis

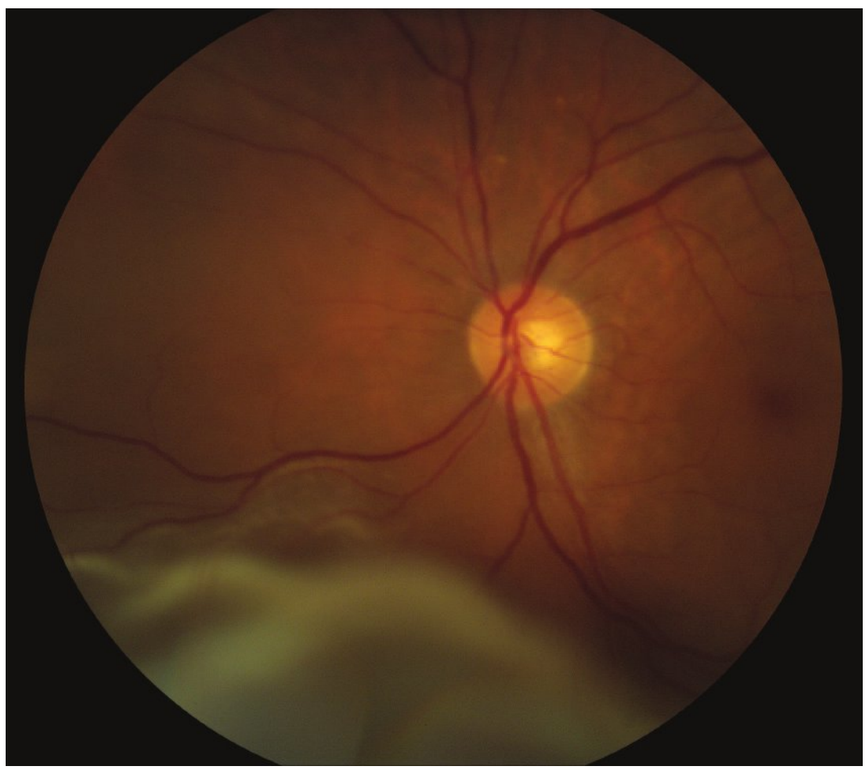


FIGURE 25-14
Retinal detachment appears as an elevated sheet of retinal tissue with folds. In this patient, the fovea was spared, so acuity was normal, but an inferior detachment produced a superior scotoma.

www.ketabpezeshki.com (021) 66485457 - 66485438

fugax. Migraine patterns usually last longer and are perceived in both eyes, whereas amaurosis fugax is briefer and occurs in only one eye. Migraine phenomena also remain visible in the dark or with the eyes closed. Generally they are confined to either the right or the left visual hemifield, but sometimes both fields are involved simultaneously. Patients often have a long history of stereotypic attacks. After the visual symptoms recede, headache develops in most patients.

Transient ischemic attacks

Vertebrobasilar insufficiency may result in acute homonymous visual symptoms. Many patients mistakenly describe symptoms in the left or right eye when in fact the symptoms are occurring in the left or right hemifield of both eyes. Interruption of blood supply to the visual cortex causes a sudden fogging or graying of vision, occasionally with flashing lights or other positive phenomena that mimic migraine. Cortical ischemic attacks are briefer in duration than migraine, occur in older patients, and are not followed by headache. There may be associated signs of brainstem ischemia, such as diplopia, vertigo, numbness, weakness, and dysarthria.

Stroke

Stroke occurs when interruption of blood supply from the posterior cerebral artery to the visual cortex is prolonged. The only finding on examination is a homonymous visual field defect that stops abruptly at the vertical meridian. Occipital lobe stroke usually is due to thrombotic occlusion of the vertebrobasilar system, embolus, or dissection. Lobar hemorrhage, tumor, abscess, and arteriovenous malformation are other common causes of hemianopic cortical visual loss.

Factitious (*f*unctional, nonorganic) visual Loss

This is claimed by hysterics or malingerers. The latter account for the vast majority, seeking sympathy, special treatment, or financial gain by feigning loss of sight. The diagnosis is suspected when the history is atypical, physical findings are lacking or contradictory, inconsistencies emerge on testing, and a secondary motive can be identified. In our litigious society, the fraudulent pursuit of recompense has spawned an epidemic of factitious visual loss.

CHRONIC VISUAL LOSS

Cataract

Cataract is a clouding of the lens sufficient to reduce vision. Most cataracts develop slowly as a result of aging, leading to gradual impairment of vision. The formation of cataract occurs more rapidly in patients with a history of ocular trauma, uveitis, or diabetes mellitus. Cataracts are acquired in a variety of genetic diseases, such as myotonic dystrophy, neurofibromatosis type 2, and galactosemia. Radiation therapy and glucocorticoid treatment can induce cataract as a side effect. The cataracts associated with radiation or glucocorticoids have a typical posterior subcapsular location. Cataract can be detected by noting an impaired red reflex when viewing light reflected from the fundus with an ophthalmoscope or by examining the dilated eye with the slit lamp.

The only treatment for cataract is surgical extraction of the opacified lens. Millions of cataract operations are performed each year around the globe. The operation generally is done under local anesthesia on an outpatient basis. A plastic or silicone intraocular lens is placed within the empty lens capsule in the posterior chamber, substituting for the natural lens and leading to rapid recovery of sight. More than 95% of patients who undergo cataract extraction can expect an improvement in vision. In some patients, the lens capsule remaining in the eye after cataract extraction eventually turns cloudy, causing secondary loss of vision. A small opening, called a posterior capsulotomy, is made in the lens capsule with a laser to restore clarity.

Glaucoma

Glaucoma is a slowly progressive, insidious optic neuropathy that usually is associated with chronic elevation of intraocular pressure. After cataract, it is the most common cause of blindness in the world. It is especially prevalent in people of African descent. The mechanism by which raised intraocular pressure injures the optic nerve is not understood. Axons entering the inferotemporal and superotemporal aspects of the optic disc are damaged first, producing typical nerve fiber bundle or arcuate scotomas on perimetric testing. As fibers are destroyed, the neural rim of the optic disc shrinks and the physiologic cup within the optic disc enlarges **(Fig. 25-15)**. This process is referred to as pathologic "cupping." The cup-to-disc diameter is expressed as a fraction (e.g., 0.2). The cup-to-disc ratio ranges widely in normal individuals, making it difficult to diagnose glaucoma reliably simply by observing an unusually large or deep optic cup. Careful documentation of serial examinations is helpful. In a patient with physiologic cupping the large cup remains stable, whereas in a patient with glaucoma it expands relentlessly over the years. Observation of progressive cupping and detection of an arcuate scotoma or a nasal step on computerized visual field testing is sufficient to establish the diagnosis of glaucoma. Optical coherence tomography reveals corresponding loss of fibers along the arcuate pathways in the nerve fiber layer.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 25-15
Glaucoma results in "cupping" as the neural rim is destroyed and the central cup becomes enlarged and excavated. The cup-to-disc ratio is about 0.8 in this patient.

About 95% of patients with glaucoma have open anterior chamber angles. In most affected individuals the intraocular pressure is elevated. The cause of elevated intraocular pressure is unknown, but it is associated with gene mutations in the heritable forms. Surprisingly, a third of patients with open-angle glaucoma have an intraocular pressure within the normal range of 10–20 mmHg. For this so-called normal or low-tension form of glaucoma, high myopia is a risk factor.

Chronic angle-closure glaucoma and chronic open-angle glaucoma are usually asymptomatic. Only acute angle-closure glaucoma causes a red or painful eye, from abrupt elevation of intraocular pressure. In all forms of glaucoma, foveal acuity is spared until end-stage disease is reached. For these reasons, severe and irreversible damage can occur before either the patient or the physician recognizes the diagnosis. Screening of patients for glaucoma by noting the cup-to-disc ratio on ophthalmoscopy and by measuring intraocular pressure is vital. Glaucoma is treated with topical adrenergic agonists, cholinergic agonists, beta blockers, and prostaglandin analogues. Occasionally, systemic absorption of beta blocker from eyedrops can be sufficient to cause side effects of bradycardia, hypotension, heart block, bronchospasm, or depression. Topical or oral carbonic anhydrase inhibitors are used to lower intraocular pressure by reducing aqueous production. Laser treatment of the trabecular meshwork in the anterior chamber angle improves aqueous outflow from the eye. If medical or laser treatments fail to halt optic nerve damage from glaucoma, a filter must be constructed surgically (trabeculectomy) or a drainage device placed to release aqueous from the eye in a controlled fashion.

Macular degeneration

This is a major cause of gradual, painless, bilateral central visual loss in the elderly. It occurs in a nonexudative (dry) form and an exudative (wet) form. Inflammation may be important in both forms of macular degeneration; susceptibility is associated with variants in the gene for complement factor H, an inhibitor of the alternative complement pathway. The nonexudative process begins with the accumulation of extracellular deposits called drusen underneath the retinal pigment epithelium. On ophthalmoscopy, they are pleomorphic but generally appear as small discrete yellow lesions clustered in the macula **(Fig. 25-16)**. With time they become larger, more numerous, and confluent. The retinal pigment epithelium becomes focally detached and atrophic, causing visual loss by interfering with photoreceptor function. Treatment with vitamins C and E, beta-carotene, and zinc may retard dry macular degeneration.

Exudative macular degeneration, which develops in only a minority of patients, occurs when neovascular vessels from the choroid grow through defects in Bruch's membrane and proliferate underneath the retinal pigment epithelium or the retina. Leakage from these vessels produces elevation of the retina, with distortion (metamorphopsia) and blurring of vision. Although the onset of these symptoms is usually gradual, bleeding from a subretinal choroidal neovascular membrane sometimes causes acute visual loss. Neovascular membranes can be difficult to see on fundus examination because they are located beneath the retina. Fluorescein angiography and optical coherence tomography, a technique for acquiring images of the retina in cross-section, are extremely useful for their detection. Major or repeated hemorrhage under the

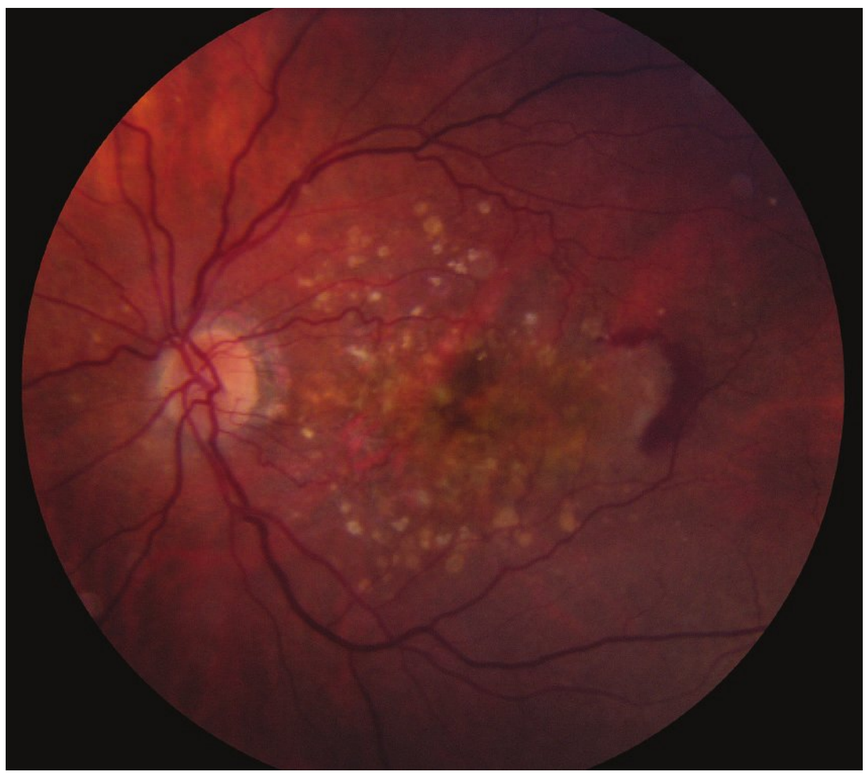


FIGURE 25-16
Age-related macular degeneration consisting of scattered yellow drusen in the macula (dry form) and a crescent of fresh hemorrhage temporal to the fovea from a subretinal neovascular membrane (wet form).

www.ketabpezeshki.com (021) 66485457 - 66485438

retina from neovascular membranes results in fibrosis, development of a round (disciform) macular scar, and permanent loss of central vision.

A major therapeutic advance has occurred with the discovery that exudative macular degeneration can be treated with intraocular injection of antagonists to vascular endothelial growth factor. Bevacizumab, ranibizumab, or aflibercept is administered by direct injection into the vitreous cavity, beginning on a monthly basis. These antibodies cause the regression of neovascular membranes by blocking the action of vascular endothelial growth factor, thereby improving visual acuity.

Central serous chorioretinopathy

This primarily affects males between the ages of 20 and 50 years. Leakage of serous fluid from the choroid causes small, localized detachment of the retinal pigment epithelium and the neurosensory retina. These detachments produce acute or chronic symptoms of metamorphopsia and blurred vision when the macula is involved. They are difficult to visualize with a direct ophthalmoscope because the detached retina is transparent and only slightly elevated. Optical coherence tomography shows fluid beneath the retina, and fluorescein angiography shows dye streaming into the subretinal space. The cause of central serous chorioretinopathy is unknown. Symptoms may resolve spontaneously if the retina reattaches, but recurrent detachment is common. Laser photocoagulation has benefited some patients with this condition.

Diabetic retinopathy

A rare disease until 1921, when the discovery of insulin resulted in a dramatic improvement in life expectancy for patients with diabetes mellitus, diabetic retinopathy is now a leading cause of blindness in the United States. The retinopathy takes years to develop but eventually appears in nearly all cases. Regular surveillance of the dilated fundus is crucial for any patient with diabetes. In advanced diabetic retinopathy, the proliferation of neovascular vessels leads to blindness from vitreous hemorrhage, retinal detachment, and glaucoma **(Fig. 25-17)**. These complications can be avoided in most patients by administration of panretinal laser photocoagulation at the appropriate point in the evolution of the disease.

Retinitis pigmentosa

This is a general term for a disparate group of rod-cone dystrophies characterized by progressive night blindness, visual field constriction with a ring scotoma, loss of acuity, and an abnormal electroretinogram (ERG). It occurs sporadically or in an autosomal recessive, dominant, or X-linked pattern. Irregular black deposits of clumped pigment in the peripheral retina, called bone spicules because of their vague resemblance to the spicules of cancellous bone, give the disease its name **(Fig. 25-18)**. The name is actually a misnomer because retinitis pigmentosa is not an inflammatory process. Most cases are due to a mutation in the gene for rhodopsin, the rod photopigment, or in the gene for peripherin, a glycoprotein located in photoreceptor outer segments. Vitamin A (15,000 IU/d) slightly retards the deterioration of the ERG in patients with retinitis pigmentosa but has no beneficial effect on visual acuity or fields.

Leber's congenital amaurosis, a rare cone dystrophy, has been treated by replacement of the missing RPE65 protein through gene therapy, resulting in modest improvement in visual function. Some forms of retinitis pigmentosa occur in association with rare, hereditary systemic diseases (olivopontocerebellar degeneration, Bassen-Kornzweig disease, Kearns-Sayre syndrome, Refsum's disease). Chronic treatment with chloroquine, hydroxychloroquine, and phenothiazines (especially thioridazine) can produce visual loss from a toxic retinopathy that resembles retinitis pigmentosa.

Epiretinal membrane

This is a fibrocellular tissue that grows across the inner surface of the retina, causing metamorphopsia and reduced visual acuity from distortion of the macula. A crinkled, cellophane-like membrane is visible on the retinal examination. Epiretinal membrane is most common in patients over 50 years of age and is usually

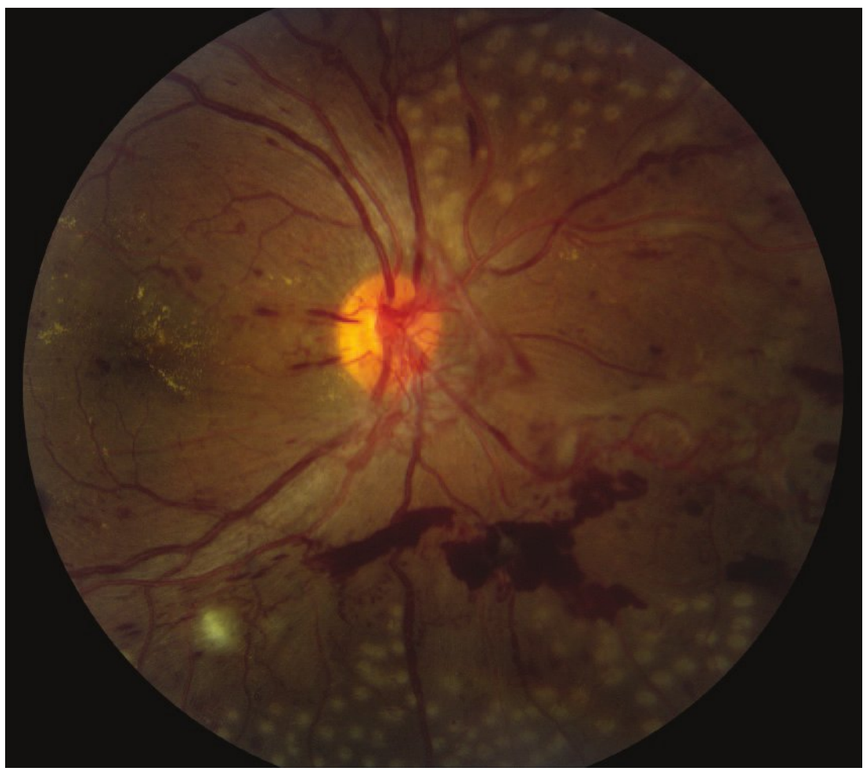


FIGURE 25-17
Proliferative diabetic retinopathy in a 25-year-old man with an 18-year history of diabetes, showing neovascular vessels emanating from the optic disc, retinal and vitreous hemorrhage, cotton-wool spots, and macular exudate. Round spots in the periphery represent recently applied panretinal photocoagulation.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 25-18
Retinitis pigmentosa with black clumps of pigment known as "bone spicules." The patient had peripheral visual field loss with sparing of central (macular) vision.

unilateral. Most cases are idiopathic, but some occur as a result of hypertensive retinopathy, diabetes, retinal detachment, or trauma. When visual acuity is reduced to the level of about 6/24 (20/80), vitrectomy and surgical peeling of the membrane to relieve macular puckering are recommended. Contraction of an epiretinal membrane sometimes gives rise to a macular hole. Most macular holes, however, are caused by local vitreous traction within the fovea. Vitrectomy can improve acuity in selected cases.

Melanoma and other tumors

Melanoma is the most common primary tumor of the eye **(Fig. 25-19)**. It causes photopsia, an enlarging scotoma, and loss of vision. A small melanoma is often difficult to differentiate from a benign choroidal nevus. Serial examinations are required to document a malignant pattern of growth. Treatment of melanoma is controversial. Options include enucleation, local resection, and irradiation. Metastatic tumors to the eye outnumber primary tumors. Breast and lung carcinomas have a special propensity to spread to the choroid or iris. Leukemia and lymphoma also commonly invade ocular tissues. Sometimes their only sign on eye examination is cellular debris in the vitreous, which can masquerade as a chronic posterior uveitis. Retrobulbar tumor of the optic nerve (meningioma, glioma) or chiasmal tumor (pituitary adenoma, meningioma) produces gradual visual loss with few objective findings except for optic disc pallor. Rarely, sudden expansion of a pituitary adenoma from infarction and bleeding (pituitary apoplexy) causes acute retrobulbar visual loss, with headache, nausea, and ocular motor nerve palsies. In any patient with visual field loss or optic atrophy, CT or

FIGURE 25-19
Melanoma of the choroid, appearing as an elevated dark mass in the inferior fundus, with overlying hemorrhage. The black line denotes the plane of the optical coherence tomography scan (below) showing the subretinal tumor.

MR scanning should be considered if the cause remains unknown after careful review of the history and thorough examination of the eye.

PROPTOSIS

When the globes appear asymmetric, the clinician must first decide which eye is abnormal. Is one eye recessed within the orbit (enophthalmos), or is the other eye protuberant (exophthalmos, or proptosis)? A small globe or a Horner's syndrome can give the appearance of enophthalmos. True enophthalmos occurs commonly after trauma, from atrophy of retrobulbar fat, or from fracture of the orbital floor. The position of the eyes within the orbits is measured by using a Hertel exophthalmometer, a handheld instrument that records the position of the anterior corneal surface relative to the lateral orbital rim. If this instrument is not available, relative eye position can be judged by bending the patient's head forward and looking down upon the orbits. A proptosis of only 2 mm in one eye is detectable from this perspective. The development of proptosis implies a space-occupying lesion in the orbit and usually warrants CT or MR imaging.

Graves' ophthalmopathy

This is the leading cause of proptosis in adults. The proptosis is often asymmetric and can even appear to be unilateral. Orbital inflammation and engorgement of

www.ketabpezeshki.com (021) 66485457 - 66485438

the extraocular muscles, particularly the medial rectus and the inferior rectus, account for the protrusion of the globe. Corneal exposure, lid retraction, conjunctival injection, restriction of gaze, diplopia, and visual loss from optic nerve compression are cardinal symptoms. Graves' eye disease is a clinical diagnosis, but laboratory testing can be useful. T e serum level of thyroid-stimulating immunoglobulins is often elevated. Orbital imaging usually reveals enlarged extraocular eye muscles, but not always. Graves' ophthalmopathy can be treated with oral prednisone (60 mg/d) for 1 month, followed by a taper over several months. Worsening of symptoms upon glucocorticoid withdrawal is common. Topical lubricants, taping the eyelids closed at night, moisture chambers, and eyelid surgery are helpful to limit exposure of ocular tissues. Radiation therapy is not ef ective. Orbital decompression should be performed for severe, symptomatic exophthalmos or if visual function is reduced by optic nerve compression. In patients with diplopia, prisms or eye muscle surgery can be used to restore ocular alignment in primary gaze.

Orbital pseudotumor

T is is an idiopathic, inflammatory orbital syndrome that is distinguished from Graves' ophthalmopathy by the prominent complaint of pain. Other symptoms include diplopia, ptosis, proptosis, and orbital congestion. Evaluation for sarcoidosis, granulomatosis with polyangiitis, and other types of orbital vasculitis or collagen-vascular disease is negative. Imaging often shows swollen eye muscles (orbital myositis) with enlarged tendons. By contrast, in Graves' ophthalmopathy, the tendons of the eye muscles usually are spared. T e Tolosa-Hunt syndrome **(Chap. 42)** may be regarded as an extension of orbital pseudotumor through the superior orbital fissure into the cavernous sinus. T e diagnosis of orbital pseudotumor is difficult. Biopsy of the orbit frequently yields nonspecific evidence of fat infiltration by lymphocytes, plasma cells, and eosinophils. A dramatic response to a therapeutic trial of systemic glucocorticoids indirectly provides the best confirmation of the diagnosis.

Orbital cellulitis

T is causes pain, lid erythema, proptosis, conjunctival chemosis, restricted motility, decreased acuity, af erent pupillary defect, fever, and leukocytosis. It often arises from the paranasal sinuses, especially by contiguous spread of infection from the ethmoid sinus through the lamina papyracea of the medial orbit. A history of recent upper respiratory tract infection, chronic sinusitis, thick mucus secretions, or dental disease is significant in any patient with suspected orbital cellulitis. Blood cultures should be obtained, but they are usually negative. Most patients respond to empirical therapy with broad-spectrum IV antibiotics. Occasionally, orbital cellulitis follows an overwhelming course, with massive proptosis, blindness, septic cavernous sinus thrombosis, and meningitis. To avert this disaster, orbital cellulitis should be managed aggressively in the early stages, with immediate imaging of the orbits and antibiotic therapy that includes coverage of methicillin-resistant Staphylococcus aureus (MRSA). Prompt surgical drainage of an orbital abscess or paranasal sinusitis is indicated if optic nerve function deteriorates despite antibiotics.

Tumors

Tumors of the orbit cause painless, progressive proptosis. T e most common primary tumors are cavernous hemangioma, lymphangioma, neurofibroma, schwannoma, dermoid cyst, adenoid cystic carcinoma, optic nerve glioma, optic nerve meningioma, and benign mixed tumor of the lacrimal gland. Metastatic tumor to the orbit occurs frequently in breast carcinoma, lung carcinoma, and lymphoma. Diagnosis by fine-needle aspiration followed by urgent radiation therapy sometimes can preserve vision.

Carotid cavernous fstulas

With anterior drainage through the orbit, these fistulas produce proptosis, diplopia, glaucoma, and corkscrew, arterialized conjunctival vessels. Direct fistulas usually result from trauma. T ey are easily diagnosed because of the prominent signs produced by high-flow, high-pressure shunting. Indirect fistulas, or dural arteriovenous malformations, are more likely to occur spontaneously, especially in older women. T e signs are more subtle, and the diagnosis frequently is missed. T e combination of slight proptosis, diplopia, enlarged muscles, and an injected eye often is mistaken for thyroid ophthalmopathy. A bruit heard upon auscultation of the head or reported by the patient is a valuable diagnostic clue. Imaging shows an enlarged superior ophthalmic vein in the orbits. Carotid cavernous shunts can be eliminated by intravascular embolization.

PTOSIS

Blepharoptosis

T is is an abnormal drooping of the eyelid. Unilateral or bilateral ptosis can be congenital, from dysgenesis of the levator palpebrae superioris, or from abnormal insertion of its aponeurosis into the eyelid. Acquired ptosis can develop so gradually that the patient is unaware of the problem. Inspection of old photographs is helpful in dating the onset. A history of prior trauma, eye surgery, contact lens use, diplopia, systemic symptoms (e.g., dysphagia or peripheral muscle weakness),

www.ketabpezeshki.com (021) 66485457 - 66485438

or a family history of ptosis should be sought. Fluctuating ptosis that worsens late in the day is typical of myasthenia gravis. Examination should focus on evidence for proptosis, eyelid masses or deformities, inflammation, pupil inequality, or limitation of motility. The width of the palpebral fissures is measured in primary gaze to determine the degree of ptosis. The ptosis will be underestimated if the patient compensates by lifting the brow with the frontalis muscle.

Mechanical ptosis

This occurs in many elderly patients from stretching and redundancy of eyelid skin and subcutaneous fat (dermatochalasis). The extra weight of these sagging tissues causes the lid to droop. Enlargement or deformation of the eyelid from infection, tumor, trauma, or inflammation also results in ptosis on a purely mechanical basis.

Aponeurotic ptosis

This is an acquired dehiscence or stretching of the aponeurotic tendon, which connects the levator muscle to the tarsal plate of the eyelid. It occurs commonly in older patients, presumably from loss of connective tissue elasticity. Aponeurotic ptosis is also a common sequela of eyelid swelling from infection or blunt trauma to the orbit, cataract surgery, or contact lens use.

Myogenic ptosis

The causes of myogenic ptosis include myasthenia gravis **(Chap. 55)** and a number of rare myopathies that manifest with ptosis. The term chronic progressive external ophthalmoplegia refers to a spectrum of systemic diseases caused by mutations of mitochondrial DNA. As the name implies, the most prominent findings are symmetric, slowly progressive ptosis and limitation of eye movements. In general, diplopia is a late symptom because all eye movements are reduced equally. In the Kearns-Sayre variant, retinal pigmentary changes and abnormalities of cardiac conduction develop. Peripheral muscle biopsy shows characteristic "ragged-red fibers." Oculopharyngeal dystrophy is a distinct autosomal dominant disease with onset in middle age, characterized by ptosis, limited eye movements, and trouble swallowing. Myotonic dystrophy, another autosomal dominant disorder, causes ptosis, ophthalmoparesis, cataract, and pigmentary retinopathy. Patients have muscle wasting, myotonia, frontal balding, and cardiac abnormalities.

Neurogenic ptosis

This results from a lesion affecting the innervation to either of the two muscles that open the eyelid: Müller's muscle or the levator palpebrae superioris. Examination of the pupil helps distinguish between these two possibilities. In Horner's syndrome, the eye with ptosis has a smaller pupil and the eye movements are full. In an oculomotor nerve palsy, the eye with the ptosis has a larger or a normal pupil. If the pupil is normal but there is limitation of adduction, elevation, and depression, a pupil-sparing oculomotor nerve palsy is likely (see next section). Rarely, a lesion affecting the small, central subnucleus of the oculomotor complex will cause bilateral ptosis with normal eye movements and pupils.

DOUBLE VISION (DIPLOPIA)

The first point to clarify is whether diplopia persists in either eye after the opposite eye is covered. If it does, the diagnosis is monocular diplopia. The cause is usually intrinsic to the eye and therefore has no dire implications for the patient. Corneal aberrations (e.g., keratoconus, pterygium), uncorrected refractive error, cataract, or foveal traction may give rise to monocular diplopia. Occasionally it is a symptom of malingering or psychiatric disease. Diplopia alleviated by covering one eye is binocular diplopia and is caused by disruption of ocular alignment. Inquiry should be made into the nature of the double vision (purely side-by-side versus partial vertical displacement of images), mode of onset, duration, intermittency, diurnal variation, and associated neurologic or systemic symptoms. If the patient has diplopia while being examined, motility testing should reveal a deficiency corresponding to the patient's symptoms. However, subtle limitation of ocular excursions is often difficult to detect. For example, a patient with a slight left abducens nerve paresis may appear to have full eye movements despite a complaint of horizontal diplopia upon looking to the left. In this situation, the cover test provides a more sensitive method for demonstrating the ocular misalignment. It should be conducted in primary gaze and then with the head turned and tilted in each direction. In the above example, a cover test with the head turned to the right will maximize the fixation shift evoked by the cover test.

Occasionally, a cover test performed in an asymptomatic patient during a routine examination will reveal an ocular deviation. If the eye movements are full and the ocular misalignment is equal in all directions of gaze (concomitant deviation), the diagnosis is strabismus. In this condition, which affects about 1% of the population, fusion is disrupted in infancy or early childhood. To avoid diplopia, vision is suppressed from the nonfixating eye. In some children, this leads to impaired vision (amblyopia, or "lazy" eye) in the deviated eye.

Binocular diplopia results from a wide range of processes: infectious, neoplastic, metabolic, degenerative, inflammatory, and vascular. One must decide whether the diplopia is neurogenic in origin or is due to restriction of globe rotation by local disease in the orbit.

www.ketabpezeshki.com (021) 66485457 - 66485438

Orbital pseudotumor, myositis, infection, tumor, thyroid disease, and muscle entrapment (e.g., from a blow-out fracture) cause restrictive diplopia. The diagnosis of restriction is usually made by recognizing other associated signs and symptoms of local orbital disease. Omission of high-resolution orbital imaging is a common mistake in the evaluation of diplopia.

Myasthenia gravis

(See also Chap. 55) This is a major cause of diplopia. The diplopia is often intermittent, variable, and not confined to any single ocular motor nerve distribution. The pupils are always normal. Fluctuating ptosis may be present. Many patients have a purely ocular form of the disease, with no evidence of systemic muscular weakness. The diagnosis can be confirmed by an IV edrophonium injection, which produces a transient reversal of eyelid or eye muscle weakness. Blood tests for antibodies against the acetylcholine receptor or the MuSK protein can establish the diagnosis but are frequently negative in the purely ocular form of myasthenia gravis. Botulism from food or wound poisoning can mimic ocular myasthenia.

After restrictive orbital disease and myasthenia gravis are excluded, a lesion of a cranial nerve supplying innervation to the extraocular muscles is the most likely cause of binocular diplopia.

Oculomotor nerve

The third cranial nerve innervates the medial, inferior, and superior recti; inferior oblique; levator palpebrae superioris; and the iris sphincter. Total palsy of the oculomotor nerve causes ptosis, a dilated pupil, and leaves the eye "down and out" because of the unopposed action of the lateral rectus and superior oblique. This is combination of findings is obvious. More challenging is the diagnosis of early or partial oculomotor nerve palsy. In this setting any combination of ptosis, pupil dilation, and weakness of the eye muscles supplied by the oculomotor nerve may be encountered. Frequent serial examinations during the evolving phase of the palsy help ensure that the diagnosis is not missed. The advent of an oculomotor nerve palsy with a pupil involvement, especially when accompanied by pain, suggests a compressive lesion, such as a tumor or circle of Willis aneurysm. Neuroimaging should be obtained, along with a CT or MR angiogram. Occasionally, a catheter arteriogram must be done to exclude an aneurysm.

A lesion of the oculomotor nucleus in the rostral midbrain produces signs that differ from those caused by a lesion of the nerve itself. There is bilateral ptosis because the levator muscle is innervated by a single central subnucleus. There is also weakness of the contralateral superior rectus, because it is supplied by the oculomotor nucleus on the other side. Occasionally both superior recti are weak. Isolated nuclear oculomotor palsy is rare. Usually neurologic examination reveals additional signs that suggest brainstem damage from infarction, hemorrhage, tumor, or infection.

Injury to structures surrounding fascicles of the oculomotor nerve descending through the midbrain has given rise to a number of classic eponymic designations. In Nothnagel's syndrome, injury to the superior cerebellar peduncle causes ipsilateral oculomotor palsy and contralateral cerebellar ataxia. In Benedikt's syndrome, injury to the red nucleus results in ipsilateral oculomotor palsy and contralateral tremor, chorea, and athetosis. Claude's syndrome incorporates features of both of these syndromes, by injury to both the red nucleus and the superior cerebellar peduncle. Finally, in Weber's syndrome, injury to the cerebral peduncle causes ipsilateral oculomotor palsy with contralateral hemiparesis.

In the subarachnoid space the oculomotor nerve is vulnerable to aneurysm, meningitis, tumor, infarction, and compression. In cerebral herniation, the nerve becomes trapped between the edge of the tentorium and the uncus of the temporal lobe. Oculomotor palsy also can result from midbrain torsion and hemorrhages during herniation. In the cavernous sinus, oculomotor palsy arises from carotid aneurysm, carotid cavernous fistula, cavernous sinus thrombosis, tumor (pituitary adenoma, meningioma, metastasis), herpes zoster infection, and the Tolosa-Hunt syndrome.

The etiology of an isolated, pupil-sparing oculomotor palsy often remains an enigma even after neuroimaging and extensive laboratory testing. Most cases are thought to result from microvascular infarction of the nerve somewhere along its course from the brainstem to the orbit. Usually the patient complains of pain. Diabetes, hypertension, and vascular disease are major risk factors. Spontaneous recovery over a period of months is the rule. If this fails to occur or if new findings develop, the diagnosis of microvascular oculomotor nerve palsy should be reconsidered. Aberrant regeneration is common when the oculomotor nerve is injured by trauma or compression (tumor, aneurysm). Miswiring of sprouting fibers to the levator muscle and the rectus muscles results in elevation of the eyelid upon downgaze or adduction. The pupil also constricts upon attempted adduction, elevation, or depression of the globe. Aberrant regeneration is not seen after oculomotor palsy from microvascular infarct and hence vitiates that diagnosis.

Trochlear nerve

The fourth cranial nerve originates in the midbrain, just caudal to the oculomotor nerve complex. Fibers exit the brainstem dorsally and cross to innervate the contralateral superior oblique. The principal actions of

www.ketabpezeshki.com (021) 66485457 - 66485438

this muscle are to depress and intort the globe. A palsy therefore results in hypertropia and excyclotorsion. The cyclotorsion seldom is noticed by patients. Instead, they complain of vertical diplopia, especially upon reading or looking down. The vertical diplopia also is exacerbated by tilting the head toward the side with the muscle palsy and alleviated by tilting it away. This "head tilt test" is a cardinal diagnostic feature.

Isolated trochlear nerve palsy results from all the causes listed above for the oculomotor nerve except aneurysm. The trochlear nerve is particularly apt to suffer injury after closed head trauma. The free edge of the tentorium is thought to impinge on the nerve during a concussive blow. Most isolated trochlear nerve palsies are idiopathic and hence are diagnosed by exclusion as "microvascular." Spontaneous improvement occurs over a period of months in most patients. A base-down prism (conveniently applied to the patient's glasses as a stick-on Fresnel lens) may serve as a temporary measure to alleviate diplopia. If the palsy does not resolve, the eyes can be realigned by weakening the inferior oblique muscle.

Abducens nerve

The sixth cranial nerve innervates the lateral rectus muscle. A palsy produces horizontal diplopia, worse on gaze to the side of the lesion. A nuclear lesion has different consequences, because the abducens nucleus contains interneurons that project via the medial longitudinal fasciculus to the medial rectus subnucleus of the contralateral oculomotor complex. Therefore, an abducens nuclear lesion produces a complete lateral gaze palsy from weakness of both the ipsilateral lateral rectus and the contralateral medial rectus. Foville's syndrome after dorsal pontine injury includes lateral gaze palsy, ipsilateral facial palsy, and contralateral hemiparesis incurred by damage to descending corticospinal fibers. Millard-Gubler syndrome from ventral pontine injury is similar except for the eye findings. There is lateral rectus weakness only, instead of gaze palsy, because the abducens fascicle is injured rather than the nucleus. Infarct, tumor, hemorrhage, vascular malformation, and multiple sclerosis are the most common etiologies of brainstem abducens palsy.

After leaving the ventral pons, the abducens nerve runs forward along the clivus to pierce the dura at the petrous apex, where it enters the cavernous sinus. Along its subarachnoid course it is susceptible to meningitis, tumor (meningioma, chordoma, carcinomatous meningitis), subarachnoid hemorrhage, trauma, and compression by aneurysm or dolichoectatic vessels. At the petrous apex, mastoiditis can produce deafness, pain, and ipsilateral abducens palsy (Gradenigo's syndrome). In the cavernous sinus, the nerve can be affected by carotid aneurysm, carotid cavernous fistula, tumor (pituitary adenoma, meningioma, nasopharyngeal carcinoma), herpes infection, and Tolosa-Hunt syndrome.

Unilateral or bilateral abducens palsy is a classic sign of raised intracranial pressure. The diagnosis can be confirmed if papilledema is observed on fundus examination. The mechanism is still debated but probably is related to rostral-caudal displacement of the brainstem. The same phenomenon accounts for abducens palsy from Chiari malformation or low intracranial pressure (e.g., after lumbar puncture, spinal anesthesia, or spontaneous dural cerebrospinal fluid leak).

Treatment of abducens palsy is aimed at prompt correction of the underlying cause. However, the cause remains obscure in many instances despite diligent evaluation. As was mentioned above for isolated trochlear or oculomotor palsy, most cases are assumed to represent microvascular infarcts because they often occur in the setting of diabetes or other vascular risk factors. Some cases may develop as a postinfectious mononeuritis (e.g., after a viral flu). Patching one eye, occluding one eyeglass lens with tape, or applying a temporary prism will provide relief of diplopia until the palsy resolves. If recovery is incomplete, eye muscle surgery nearly always can realign the eyes, at least in primary position. A patient with an abducens palsy that fails to improve should be reevaluated for an occult etiology (e.g., chordoma, carcinomatous meningitis, carotid cavernous fistula, myasthenia gravis). Skull base tumors are easily missed even on contrast-enhanced neuroimaging studies.

Multiple ocular motor nerve palsies

These should not be attributed to spontaneous microvascular events affecting more than one cranial nerve at a time. This is remarkable coincidence does occur, especially in diabetic patients, but the diagnosis is made only in retrospect after all other diagnostic alternatives have been exhausted. Neuroimaging should focus on the cavernous sinus, superior orbital fissure, and orbital apex, where all three ocular motor nerves are in close proximity. In a diabetic or immunocompromised host, fungal infection (Aspergillus, Mucorales, Cryptococcus) is a common cause of multiple nerve palsies. In a patient with systemic malignancy, carcinomatous meningitis is a likely diagnosis. Cytologic examination may be negative despite repeated sampling of the cerebrospinal fluid. The cancer-associated Lambert-Eaton myasthenic syndrome also can produce ophthalmoplegia. Giant cell (temporal) arteritis occasionally manifests as diplopia from ischemic palsies of extraocular muscles. Fisher's syndrome, an ocular variant of Guillain-Barré, produces ophthalmoplegia with areflexia and ataxia. Often the ataxia is mild, and the reflexes are normal. Antiganglioside antibodies (GQ1b) can be detected in about 50% of cases.

www.ketabpezeshki.com (021) 66485457 - 66485438

Supranuclear disorders of gaze

These are often mistaken for multiple ocular motor nerve palsies. For example, Wernicke's encephalopathy can produce nystagmus and a partial deficit of horizontal and vertical gaze that mimics a combined abducens and oculomotor nerve palsy. The disorder occurs in malnourished or alcoholic patients and can be reversed by thiamine. Infarct, hemorrhage, tumor, multiple sclerosis, encephalitis, vasculitis, and Whipple's disease are other important causes of supranuclear gaze palsy. Disorders of vertical gaze, especially downward saccades, are an early feature of progressive supranuclear palsy. Smooth pursuit is affected later in the course of the disease. Parkinson's disease, Huntington's disease, and olivopontocerebellar degeneration also can affect vertical gaze.

The *frontal eye field* of the cerebral cortex is involved in generation of saccades to the contralateral side. After hemispheric stroke, the eyes usually deviate toward the lesioned side because of the unopposed action of the frontal eye field in the normal hemisphere. With time, this deficit resolves. Seizures generally have the opposite effect: the eyes deviate conjugately away from the irritative focus. Parietal lesions disrupt smooth pursuit of targets moving toward the side of the lesion. Bilateral parietal lesions produce Bálint's syndrome, which is characterized by impaired eye-hand coordination (optic ataxia), difficulty initiating voluntary eye movements (ocular apraxia), and visuospatial disorientation (simultanagnosia).

Horizontal gaze

Descending cortical inputs mediating horizontal gaze ultimately converge at the level of the pons. Neurons in the paramedian pontine reticular formation are responsible for controlling conjugate gaze toward the same side. They project directly to the ipsilateral abducens nucleus. A lesion of either the paramedian pontine reticular formation or the abducens nucleus causes an ipsilateral conjugate gaze palsy. Lesions at either locus produce nearly identical clinical syndromes, with the following exception: vestibular stimulation (oculocephalic maneuver or caloric irrigation) will succeed in driving the eyes conjugately to the side in a patient with a lesion of the paramedian pontine reticular formation but not in a patient with a lesion of the abducens nucleus.

Internuclear ophthalmoplegia

This results from damage to the medial longitudinal fasciculus ascending from the abducens nucleus in the pons to the oculomotor nucleus in the midbrain (hence, "internuclear"). Damage to fibers carrying the conjugate signal from abducens interneurons to the contralateral medial rectus motoneurons results in a failure of adduction on attempted lateral gaze. For example, a patient with a left internuclear ophthalmoplegia (INO) will have slowed or absent adducting movements of the left eye **(Fig. 25-20)**. A patient with bilateral injury to the medial longitudinal fasciculus will have bilateral INO. Multiple sclerosis is the most common cause, although tumor, stroke, trauma, or any brainstem process may be responsible. One-and-a-half syndrome is due to a combined lesion of the medial longitudinal fasciculus and the abducens nucleus on the same side. The patient's only horizontal eye movement is abduction of the eye on the other side.

Vertical gaze

This is controlled at the level of the midbrain. The neuronal circuits affected in disorders of vertical gaze are not fully elucidated, but lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal cause supranuclear paresis of upgaze, downgaze, or all vertical eye movements. Distal basilar artery ischemia is the most common etiology. Skew deviation refers to a vertical misalignment of the eyes, usually constant in all positions of gaze. The finding has poor localizing value because skew deviation has been reported after lesions in widespread regions of the brainstem and cerebellum.

Parinaud's syndrome

Also known as dorsal midbrain syndrome, this is a distinct supranuclear vertical gaze disorder caused by damage to the posterior commissure. It is a classic sign of hydrocephalus from aqueductal stenosis. Pineal region or midbrain tumors, cysticercosis, and stroke also cause Parinaud's syndrome. Features include loss of upgaze (and sometimes downgaze), convergence-retraction nystagmus on attempted upgaze, downward ocular deviation ("setting sun" sign), lid retraction (Collier's sign), skew deviation, pseudoabducens palsy, and light-near dissociation of the pupils.

Nystagmus

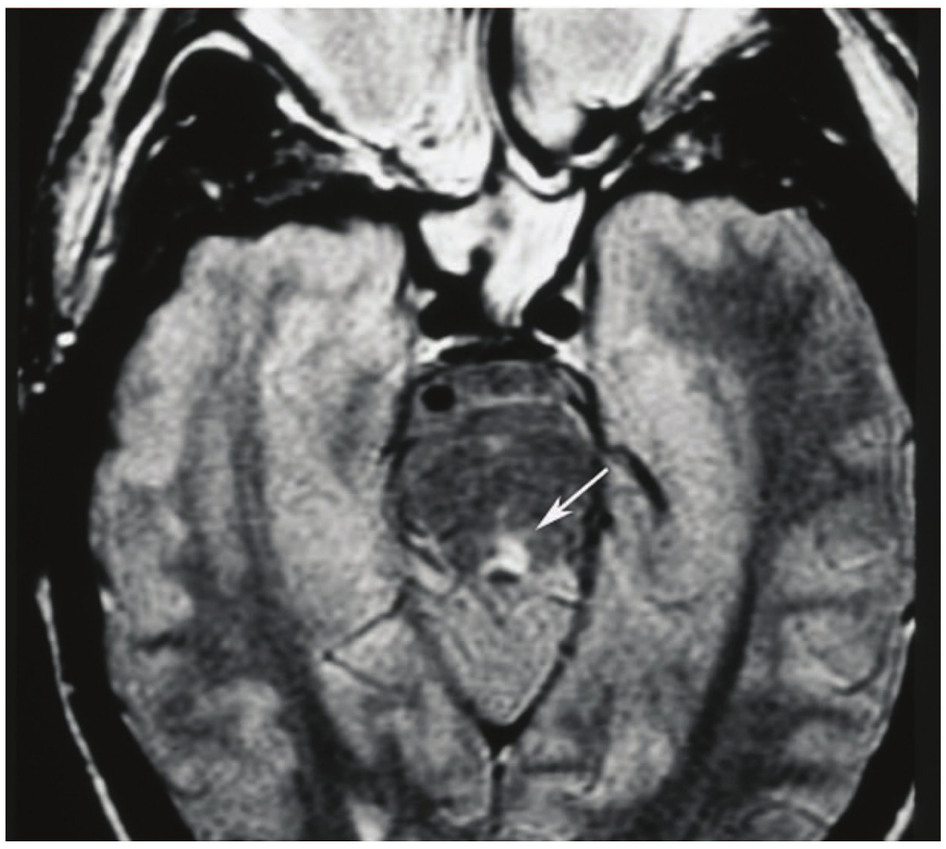
This is a rhythmic oscillation of the eyes, occurring physiologically from vestibular and optokinetic stimulation or pathologically in a wide variety of diseases **(Chap. 12)**. Abnormalities of the eyes or optic nerves, present at birth or acquired in childhood, can produce a complex, searching nystagmus with irregular pendular (sinusoidal) and jerk features. Examples are albinism, Leber's congenital amaurosis, and bilateral cataract. This nystagmus is commonly referred to as congenital sensory nystagmus. This is a poor term because even in children with congenital lesions, the nystagmus does not appear until weeks after birth. Congenital motor nystagmus, which looks similar to congenital sensory nystagmus, develops in the absence of any abnormality of the sensory visual system. Visual acuity also is reduced in congenital motor nystagmus,

www.ketabpezeshki.com (021) 66485457 - 66485438

A

B

C



D

FIGURE 25-20

Left internuclear ophthalmoplegia (INO). A. In primary position of gaze, the eyes appear normal. B. Horizontal gaze to the left is intact. C. On attempted horizontal gaze to the right, the left eye fails to adduct. In mildly affected patients, the eye may adduct partially or more slowly than normal. Nystagmus is usually present in the abducted eye. D. T2-weighted axial magnetic resonance image through the pons showing a demyelinating plaque in the left medial longitudinal fasciculus (arrow).

probably by the nystagmus itself, but seldom below a level of 20/200.

Jerk nystagmus

This is characterized by a slow drift of the target, followed by a fast corrective saccade. By convention, the nystagmus is named after the quick phase. Jerk nystagmus can be downbeat, upbeat, horizontal (left or right), and torsional. The pattern of nystagmus may vary with gaze position. Some patients will be oblivious to their nystagmus. Others will complain of blurred vision or a subjective to-and-fro movement of the environment (oscillopsia) corresponding to the nystagmus. Fine nystagmus may be difficult to see on gross examination of the eyes. Observation of nystagmoid movements of the optic disc on ophthalmoscopy is a sensitive way to detect subtle nystagmus.

Gaze-evoked nystagmus

This is the most common form of jerk nystagmus. When the eyes are held eccentrically in the orbits, they have a natural tendency to drift back to primary position. The subject compensates by making a corrective saccade to maintain the deviated eye position. Many normal patients have mild gaze-evoked nystagmus. Exaggerated gaze-evoked nystagmus can be induced by drugs (sedatives, anticonvulsants, alcohol); muscle paresis; myasthenia gravis; demyelinating disease; and cerebellopontine angle, brainstem, and cerebellar lesions.

Vestibular nystagmus

Vestibular nystagmus results from dysfunction of the labyrinth (Ménière's disease), vestibular nerve, or vestibular nucleus in the brainstem. Peripheral vestibular nystagmus often occurs in discrete attacks, with symptoms of nausea and vertigo. There may be associated tinnitus and hearing loss. Sudden shifts in head position may provoke or exacerbate symptoms.

Downbeat nystagmus

Downbeat nystagmus results from lesions near the craniocervical junction (Chiari malformation, basilar invagination). It also has been reported in brainstem or cerebellar stroke, lithium or anticonvulsant intoxication, alcoholism, and multiple sclerosis. Upbeat nystagmus is associated with damage to the pontine tegmentum from stroke, demyelination, or tumor.

Opsoclonus

This is rare, dramatic disorder of eye movements consists of bursts of consecutive saccades (saccadomania). When the saccades are confined to the horizontal plane, the term ocular flutter is preferred. It can result from viral encephalitis, trauma, or a paraneoplastic effect of neuroblastoma, breast carcinoma, and other malignancies. It has also been reported as a benign, transient phenomenon in otherwise healthy patients.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 26

USE OF THE HAND-HELD OPHTHALMOSCOPE

Homayoun Tabandeh ■ Morton F. Goldberg

Examination of the living human retina provides a unique opportunity for the direct study of nervous, vascular, and connective tissues. Many systemic disorders have retinal manifestations that are valuable for screening, diagnosis, and management of these conditions. Furthermore, retinal involvement in systemic disorders, such as diabetes mellitus, is a major cause of morbidity. Early recognition by ophthalmoscopic screening is a key factor in effective treatment. Ophthalmoscopy has the potential to be one of the most "high-yield" elements of the physical examination. Effective ophthalmoscopy requires a basic understanding of ocular structures and ophthalmoscopic techniques and recognition of abnormal findings.

OVERVIEW OF OCULAR STRUCTURES

T e eye consists of a shell (cornea and sclera), lens, iris diaphragm, ciliary body, choroid, and retina. T e anterior chamber is the space between the cornea and the lens, and it is filled with aqueous humor. T e space between the posterior aspect of the lens and the retina is filled by vitreous gel. T e choroid and the retina cover the posterior two-thirds of the sclera internally. T e cornea and the lens form the focusing system of the eye, while the retina functions as the photoreceptor system, translating light to neuronal signals that are in turn transmitted to the brain via the optic nerve and visual pathways. T e choroid is a layer of highly vascularized tissue that nourishes the retina and is located between the sclera and the retina. T e retinal pigment epithelium (RPE) layer is a monolayer of pigmented cells that are adherent to the overlying retinal photoreceptor cells. RPE plays a major role in retinal photoreceptor metabolism.

NORMAL FUNDUS

T e important areas that are visible by ophthalmoscopy include the macula, optic disc, retinal blood vessels, and retinal periphery **(Fig. 26-1)**.

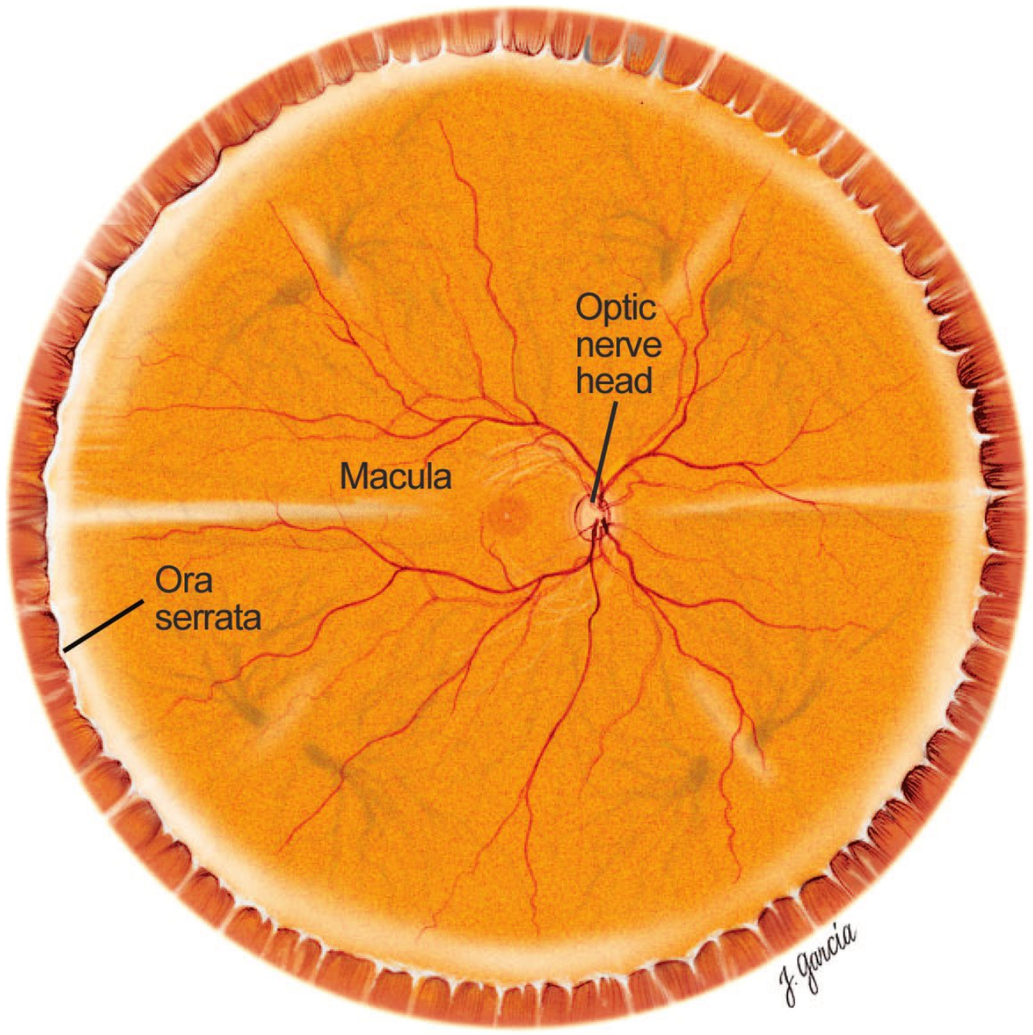


FIGURE 26-1
Diagram showing the landmarks of the normal fundus. The macula is bounded by the superior and inferior vascular arcades and extends for 5 disc diameters (DD) temporal to the optic disc (optic nerve head). The central part of the macula (fovea) is located 2.5 DD temporal to the optic disc. The peripheral fundus is arbitrarily defined as the area extending anteriorly from the opening of the vortex veins to the ora serrata (the juncture between the retina and ciliary body). (Drawing courtesy of Juan R. Garcia. Used with permission from Johns Hopkins University.)

www.ketabpezeshki.com (021) 66485457 - 66485438

THE MACULA

The macula is the central part of the retina and is responsible for detailed vision (acuity) and perception of color. The macula is defined clinically as the area of the retina centered on the posterior pole of the fundus, measuring about 5 disc diameters (DD) (7–8 mm) and bordered by the optic disc nasally and the temporal vascular arcades superiorly and inferiorly. Temporally, the macula extends for about 2.5 DD from its center. The fovea, in the central part of the macula, corresponds to the site of sharpest visual acuity. It is approximately 1 DD in size and appears darker in color than the surrounding area. The center of the fovea, the foveola, has a depressed pit-like configuration measuring about 350 μm.

THE OPTIC DISC

The optic disc measures about 1.5 mm and is located about 4 mm (2.5 DD) nasal to the fovea. It contains the central retinal artery and vein as they branch, a central excavation (cup), and a peripheral neural rim. Normally, the cup-to-disc ratio is less than 0.6. The cup is located temporal to the entry of the disc vessels. The normal optic disc is yellow/pink in color. It has clear and well-defined margins and is in the same plane as the retina **(Fig. 26-2)**. Pathologic findings include pallor (atrophy), swelling, and enlarged cupping.

FIGURE 26-2
Photograph of a normal left optic disc illustrating branching of the central retinal vein and artery, a physiologic cup, surface capillaries, and distinct margin. The cup is located temporal to the entry of the disc vessels. (From H Tabandeh, MF Goldberg: Retina in Systemic Disease: A Color Manual of Ophthalmoscopy. New York, Thieme, 2009.)

THE EQUATOR AND PERIPHERAL RETINA

The equator of the fundus is clinically defined as the area that includes the internal opening of the vortex veins. The peripheral retina extends from the equator anteriorly to the ora serrata.

OPHTHALMOSCOPY

There are a number of ways to visualize the retina, including direct ophthalmoscopy, binocular indirect ophthalmoscopy, and slit-lamp biomicroscopy. Most nonophthalmologists prefer direct ophthalmoscopy, performed with a hand-held ophthalmoscope, because the technique is simple to master and the device is very portable. Ophthalmologists often use slit-lamp biomicroscopy and indirect ophthalmoscopy to obtain a more extensive view of the fundus.

DIRECT OPHTHALMOSCOPE

Direct ophthalmoscopes are simple hand-held devices that include a small light source for illumination, a viewing aperture through which the examiner looks at the retina, and a lens dial used for correction of the examiner's and the patient's refractive errors. A more recent design, the PanOptic ophthalmoscope, provides a wider field of view.

How to use a direct ophthalmoscope

Good alignment is the key. The goal is to align the examiner's eye with the viewing aperture of the ophthalmoscope, the patient's pupil, and the area of interest on the retina. Both the patient and the examiner should be in a comfortable position (sitting or lying for the patient, sitting or standing for the examiner). Dilating the pupil and dimming the room lights make the examination easier. Steps for performing direct ophthalmoscopy are summarized in **Table 26-1**.

PANOPTIC OPHTHALMOSCOPE

The PanOptic ophthalmoscope is a type of direct ophthalmoscope that is designed to provide a wider view of the fundus and has slightly more magnification than the standard direct ophthalmoscope. Steps for using the PanOptic Ophthalmoscope are summarized in **Table 26-2**.

RETINAL SIGNS ASSOCIATED WITH SYSTEMIC DISEASES

AGE-RELATED CHANGES

Common age-related changes include diminished foveal light reflex, drusen (small yellow subretinal deposits), mild RPE atrophy, and pigment clumping.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 26-1

GUIDELINES FOR PERFORMING DIRECT OPHTHALMOSCOPY

- Instruct the patient to remove glasses, keep the head straight, and to look steadily at a distant target straight in front. You may keep or remove your own glasses. Position your head at the same level as the patient's head.
- Use your right eye and right hand to examine the patient's right eye, and use your left eye and left hand to examine the patient's left eye.
- Using the ophthalmoscope light as a pen light, briefly examine the external features of the eye, including lashes, lid margins, conjunctiva, sclera, iris, and pupil shape, size, and reactivity.
- Shine the ophthalmoscope light into the patient's pupil at arm's length and observe the red reflex. Note abnormalities of the red reflex such as an opacity of the media.
- Dialing up a +10 D lens in the lens wheel, while examining the eye from 10 cm, allows magnified viewing of the anterior segment of the eye.
- Reduce the power of the lens in the wheel to zero, and move closer to the patient. Identify the optic disc by pointing the ophthalmoscope about 15° nasally or by following a blood vessel toward the apex of any branching. If the retina is out of focus, turn the lens dial either way, without moving your head. If the disc becomes clearer, keep turning until best focus is achieved; if it becomes more blurred, turn the dial the other way.
- Once you visualize the optic nerve, note its shape, size, color, margins, and the cup. Also note the presence of any venous pulsation or surrounding pigment, such as a choroidal or scleral crescent.
- Next, examine the macula. The macula is the area between the superior and inferior temporal vascular arcades, and its center is the fovea. You can examine the macula by pointing your ophthalmoscope about 15° temporal to the optic disc. Alternatively, ask the patient to look into the center of the light. Note the foveal reflex and the presence of any hemorrhage, exudate, abnormal blood vessels, scars, deposits, or other abnormalities.
- Examine the retinal blood vessels by re-identifying the optic disc and following each of the four main branches away from the disc. The veins are dark red and relatively large. The arteries are narrower and bright red.
- Ask the patient to look in the eight cardinal directions to allow you to view the peripheral fundus. In a patient with a well-dilated pupil, it is possible to visualize as far as the equator.

TABLE 26-2

HOW TO USE A PANOPTIC OPHTHALMOSCOPE

- Focus the ophthalmoscope: Look through the scope at an object that is at least 10 to 15 feet away. Sharpen the image of the object by using the focusing wheel. Set the aperture dial to "small" or home position.
- Turn the scope on, and adjust the light intensity to "Maximum."
- Instruct the patient to look straight ahead. Move the ophthalmoscope close to the patient until the eye-cup touches the patient's brow. The eyecup should be compressed about half its length to optimize the view.
- Visualize the optic disc.
- Examine the fundus as described in Table 26-1.

RETINAL HEMORRHAGES

Retinal hemorrhages may take various shapes and sizes depending on their location within the retina **(Figs. 26-3 and 26-4)**. Flame-shaped hemorrhages are located at the level of the superficial nerve fiber layer and represent bleeding from the inner capillary network of the retina. A white-centered hemorrhage is a superficial flame-shaped hemorrhage with an area of central whitening, often representing edema, focal necrosis, or cellular infiltration. Causes of white-centered hemorrhage include bacterial endocarditis and septicemia (Roth spots), lymphoproliferative disorders, diabetes mellitus, hypertension, anemia, and collagen vascular disorders. Dot hemorrhages are small, round, superficial hemorrhages that also originate from the superficial capillary network of the retina. They resemble microaneurysms. Blot hemorrhages are slightly larger in size, dark, and intraretinal. They represent bleeding from the deep capillary network of the retina. Subhyaloid hemorrhages are variable in shape and size and tend to be larger than other types of hemorrhages. They often have a fluid level ("boat-shaped" hemorrhage) and are located within the space between the vitreous and the retina. Subretinal hemorrhages are located deep (external) to the retina. The retinal vessels can be seen crossing over (internal to) such hemorrhages. Subretinal hemorrhages are variable in size and most commonly are caused by choroidal neovascularization (e.g., wet macular degeneration).

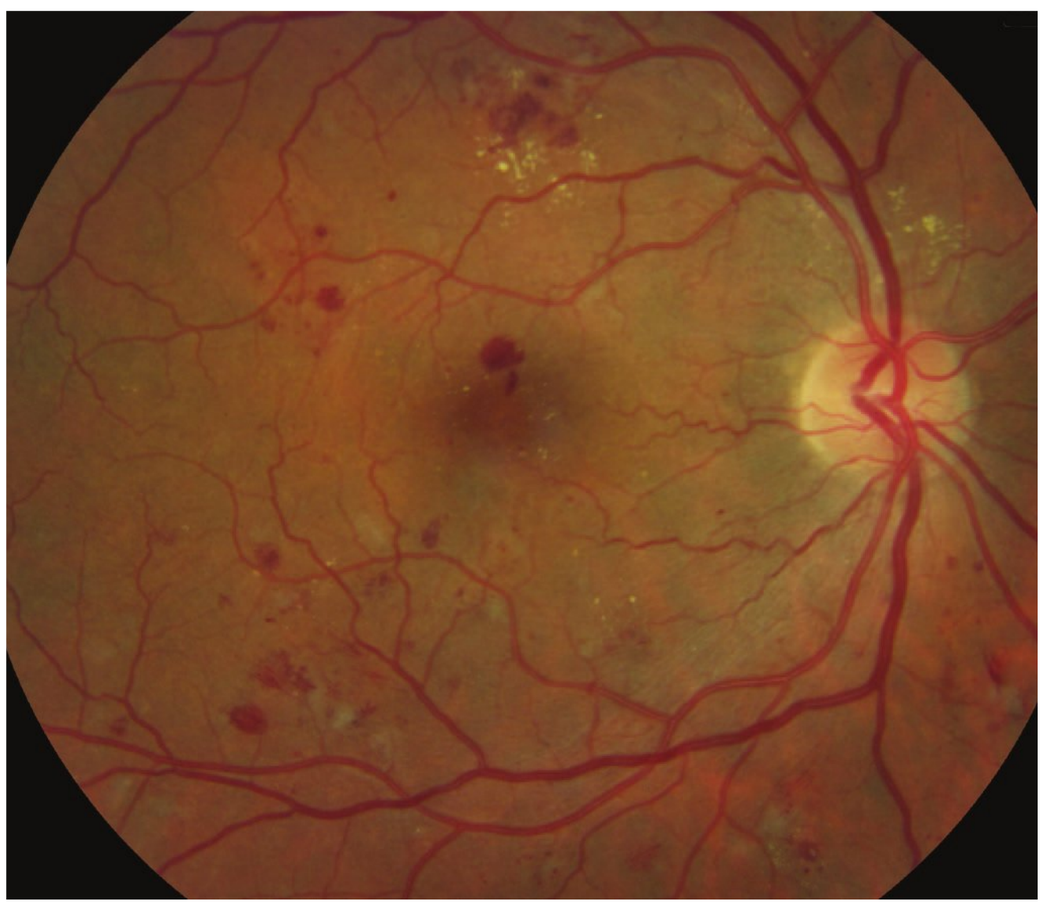


FIGURE 26-3
Superficial flame-shaped hemorrhages, dot hemorrhages, and microaneurysms in a patient with nonproliferative diabetic retinopathy.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 26-4
Deep and superficial retinal hemorrhages in a patient with chronic leukemia.

Conditions associated with retinal hemorrhages include diseases causing retinal microvasculopathy **(Table 26-3)**, retinitis, retinal macroaneurysm, papilledema, subarachnoid hemorrhage (Terson's syndrome), Valsalva retinopathy, trauma (ocular injury, head injury, compression injuries of chest and abdomen, shaken baby syndrome, strangulation), macular degeneration, and posterior vitreous detachment. Hyperviscosity states may produce dot and blot hemorrhages, dilated veins ("string of sausages" appearance), optic disc edema, and exudates; similar changes can occur with adaptation to high altitude in mountain climbers.

TABLE 26-3

DISEASES ASSOCIATED WITH RETINAL MICROVASCULOPATHY
• Diabetes mellitus
• Systemic hypertension
• Retinal vein occlusion
• Retinal artery occlusion
• Multiple microemboli, e.g., talc retinopathy secondary to intravenous drug abuse, septicemia, endocarditis, Purtscher's retinopathy
• Carotid artery disease, carotid-cavernous fistula, aortic arch syndrome
• Sickle cell retinopathy
• Radiation retinopathy, head/neck irradiation
• HIV retinopathy
• Retinal vasculitis
• Anemia
• Thrombocytopenia
• Lymphoproliferative disorders
• Coagulopathy
• Hyperviscosity syndromes
• Retinopathy of prematurity

MICROANEURYSMS

Microaneurysms are outpouchings of the retinal capillaries, appearing as red dots (similar to dot hemorrhages) and measuring 15–50 μm. Microaneurysms have increased permeability and may bleed or leak, resulting in localized retinal hemorrhage or edema. A microaneurysm ultimately thromboses and disappears within 3–6 months. Microaneurysms may occur in any condition that causes retinal microvasculopathy (Table 26-3).

HARD EXUDATES

Hard exudates are well-circumscribed, shiny, yellow deposits located within the retina. They arise at the margins of areas of retinal edema and indicate increased capillary permeability. Hard exudates contain lipoproteins and lipid-laden macrophages. They may clear spontaneously or following laser photocoagulation, often within 6 months. Hard exudates may occur in isolation or may be scattered throughout the fundus. They may occur in a circular (circinate) pattern centered around an area of leaking microaneurysms. A macular star consists of a radiating, star-shaped pattern of hard exudates that is characteristically seen in severe systemic hypertension and in neuroretinitis associated with cat-scratch disease. Conditions associated with hard exudates include those causing retinal microvasculopathy (Table 26-3), papilledema, neuroretinitis such as cat-scratch disease and Lyme disease, retinal vascular lesions (macroaneurysm, retinal capillary hemangioma, Coats' disease), intraocular tumors, and wet age-related macular degeneration. Drusen may be mistaken for hard exudates on ophthalmoscopy. Unlike hard exudates, drusen are nonrefractile subretinal deposits with blurred margins. They are usually seen in association with age-related macular degeneration.

COTTON-WOOL SPOTS

Cotton-wool spots are yellow/white superficial retinal lesions with indistinct feathery borders measuring 0.25–1 DD in size **(Fig. 26-5)**. They represent areas of edema within the retinal nerve fiber layer due to focal ischemia. Cotton-wool spots usually resolve spontaneously within 3 months. If the underlying ischemic condition persists, new lesions can develop in different locations. Cotton-wool spots often occur in conjunction with retinal hemorrhages and microaneurysms and represent retinal microvasculopathy caused by a number of systemic conditions (Table 26-3). They may

www.ketabpezeshki.com (021) 66485457 - 66485438

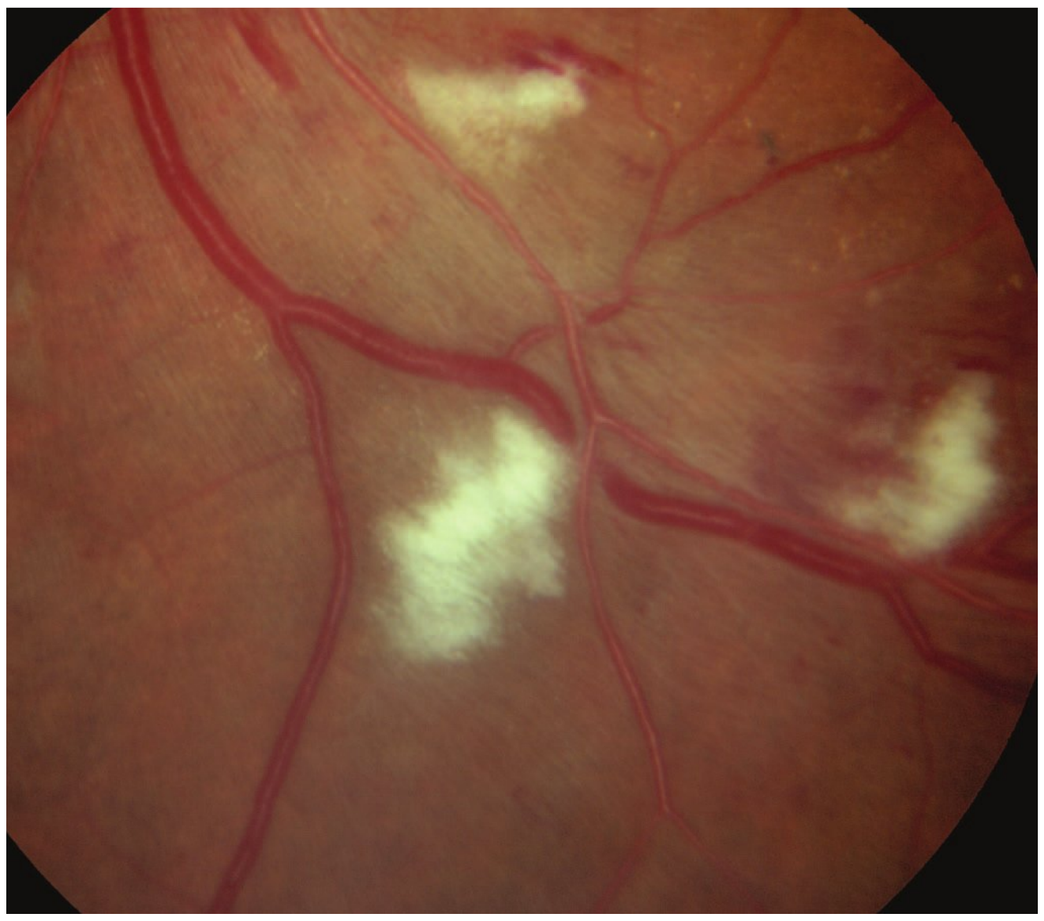


FIGURE 26-5
Cotton-wool spots, yellow-white superficial lesions with characteristic feathery borders, in a patient with hypertensive retinopathy. (From H Tabandeh, MF Goldberg: Retina in Systemic Disease: A Color Manual of Ophthalmoscopy. New York, Thieme, 2009.)

occur in isolation in HIV retinopathy, systemic lupus erythematosus, anemia, bodily trauma, other systemic conditions (Purtscher's/Purtscher's-like retinopathy), and interferon therapy.

RETINAL NEOVASCULARIZATION

Retinal neovascular complexes are irregular meshworks of fine blood vessels that grow in response to severe retinal ischemia or chronic inflammation **(Fig. 26-6)**. They

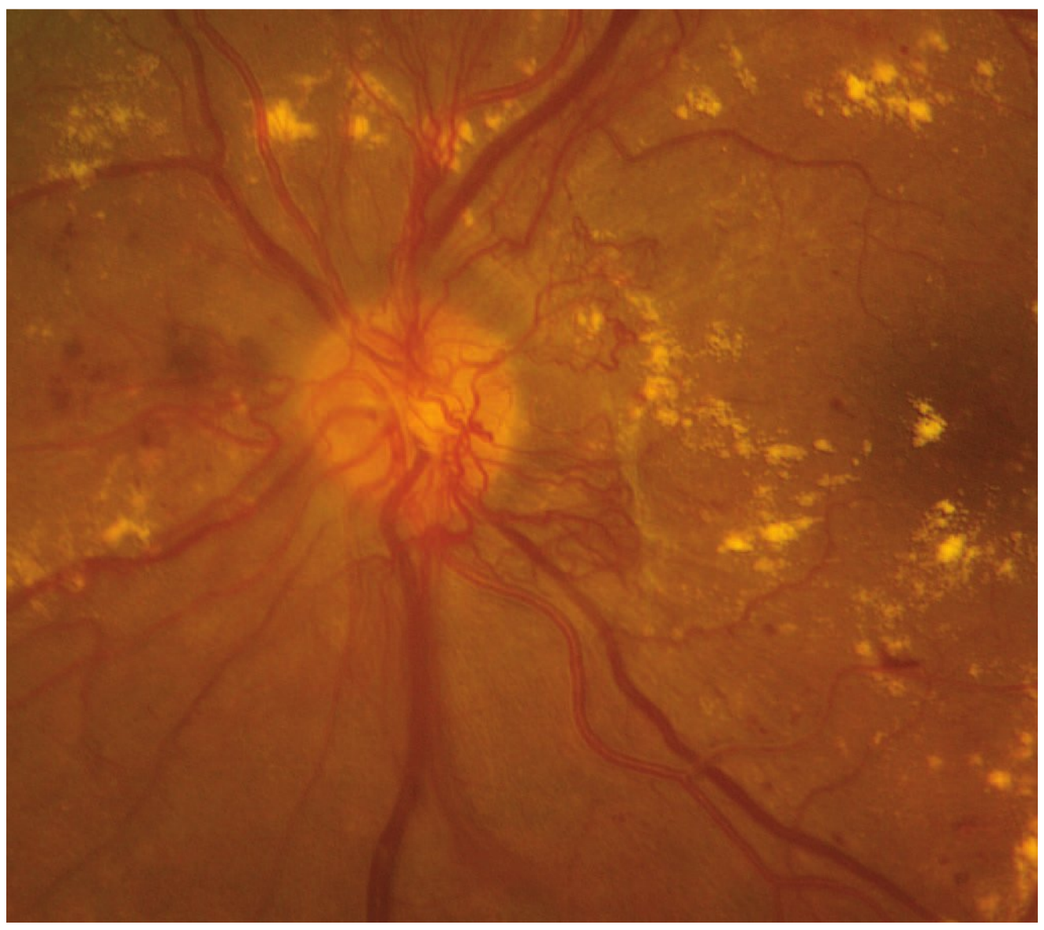


FIGURE 26-6
Optic disc neovascularization in a patient with severe proliferative diabetic retinopathy. Multiple hard exudates are also present.

may occur on or adjacent to the optic disc or elsewhere in the retina. Neovascular complexes are very fragile and have a high risk for hemorrhaging, often causing visual loss. Diseases associated with retinal neovascularization include conditions that cause severe retinal microvasculopathy, especially diabetic and sickle cell retinopathies (Table 26-3), intraocular tumors, intraocular inflammation (sarcoidosis, chronic uveitis), and chronic retinal detachment.

RETINAL EMBOLI

Common sources of retinal emboli include carotid artery atheromatous plaque, cardiac valve and septal abnormalities, cardiac arrhythmias, atrial myxoma, bacterial endocarditis, septicemia, fungemia, and intravenous drug abuse.

Platelet emboli are yellowish in appearance and conform to the shape of the blood vessel. They usually originate from an atheromatous plaque within the carotid artery and can cause transient loss of vision (amaurosis fugax). Cholesterol emboli, otherwise termed Hollenhorst plaques, are yellow crystalline deposits that are commonly found at the bifurcations of the retinal arteries and may be associated with amaurosis fugax. Calcific emboli have a pearly white appearance, are larger than the platelet and cholesterol emboli, and tend to lodge in the larger retinal arteries in or around the optic disc. Calcific emboli often result in retinal arteriolar occlusion. Septic emboli can cause white-centered retinal hemorrhages (Roth spots), retinal microabscesses, and endogenous endophthalmitis. Fat embolism and amniotic fluid embolism are characterized by multiple small vessel occlusions, typically causing cotton-wool spots and few hemorrhages (Purtscher's-like retinopathy). Talc embolism occurs with intravenous drug abuse and is characterized by multiple refractile deposits within the small retinal vessels. Any severe form of retinal artery embolism may result in retinal ischemia and its sequelae, including retinal neovascularization.

CHERRY RED SPOT AT THE MACULA

Cherry red spot at the macula is the term used to describe the dark red appearance of the central foveal area in comparison to the surrounding macular region **(Fig. 26-7)**. This appearance is most commonly due to a relative loss of transparency of the parafoveal retina resulting from ischemic cloudy swelling or storage of macromolecules within the ganglion cell layer. Diseases associated with a cherry red spot at the macula include central retinal artery occlusion, sphingolipidoses, and mucolipidoses.

www.ketabpezeshki.com (021) 66485457 - 66485438

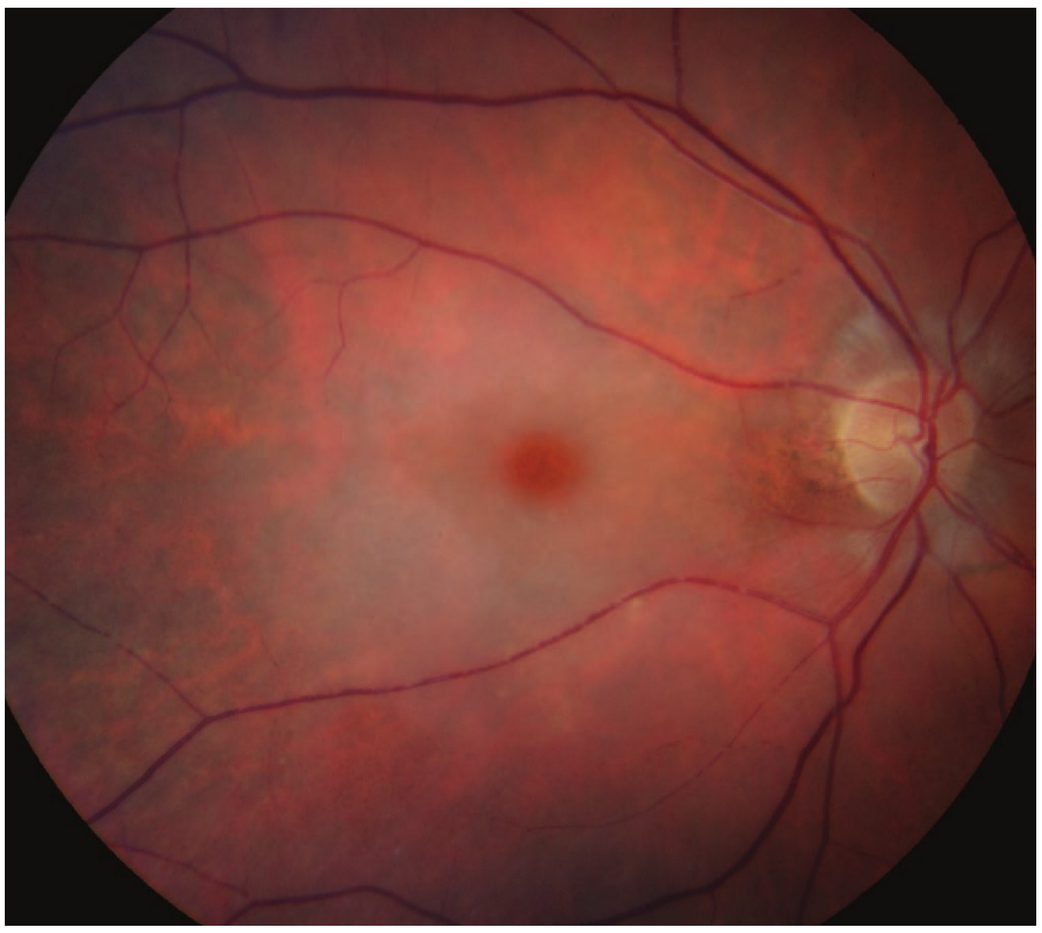


FIGURE 26-7
Cherry red spot at the macula and cloudy swelling of the macula in a patient with central retinal artery occlusion due to embolus originating from a carotid artery atheromatous plaque.

FIGURE 26-8
Vascular sheathing over the optic disc in a patient with neurosarcoidosis.

RETINAL CRYSTAL DEPOSITION

Retinal crystals appear as fine, refractile, yellow-white deposits. Associated conditions include infantile cystinosis, primary hyperoxaluria, secondary oxalosis, Sjögren-Larson syndrome, intravenous drug abuse (talc retinopathy), and drugs such as tamoxifen, canthaxanthin, nitrofurantoin, methoxyflurane, and ethylene glycol. Crystals may also be seen in primary retinal diseases such as juxtafoveal telangiectasia, gyrate atrophy, and Bietti's crystalline degeneration. Old microemboli may mimic retinal crystals.

RETINAL VASCULAR SHEATHING

Vascular sheathing appears as a yellow-white cuff surrounding a retinal artery or vein **(Fig. 26-8)**. Diseases associated with retinal vascular sheathing include sarcoidosis, tuberculosis, toxoplasmosis, syphilis, HIV, retinitis (cytomegalovirus, herpes zoster, and herpes simplex), Lyme disease, cat-scratch disease, multiple sclerosis, chronic leukemia, amyloidosis, Behçet's disease, retinal vasculitis, retinal vascular occlusion, and chronic uveitis.

RETINAL DETACHMENT

Retinal detachment is the separation of the retina from the underlying RPE. There are three main types: (1) serous/exudative, (2) tractional, and (3) rhegmatogenous retinal detachment.

In serous retinal detachment, the location of the subretinal fluid is position-dependent, characteristically gravitating to the lowermost part of the fundus (shifting fluid sign), and retinal breaks are absent. Diseases associated with serous/exudative retinal detachment include severe systemic hypertension, dural arteriovenous shunt, retinal vascular anomalies, hyperviscosity syndromes, papilledema, posterior uveitis, scleritis, orbital inflammation, and intraocular neoplasms such as choroidal melanoma, choroidal metastasis, lymphoma, and multiple myeloma.

Tractional retinal detachment is caused by internal traction on the retina in the absence of a retinal break. The retina in the area of detachment is immobile and concaved internally. Fibrovascular proliferation is a frequent associated finding. Conditions associated with tractional retinal detachment include vascular proliferative retinopathies such as severe proliferative diabetic retinopathy, branch retinal vein occlusion, sickle cell retinopathy, and retinopathy of prematurity. Ocular trauma, proliferative vitreoretinopathy, and intraocular inflammation are other causes of a tractional retinal detachment.

Rhegmatogenous retinal detachment is caused by the presence of a retinal break, allowing fluid from the vitreous cavity to gain access to the subretinal space. The surface of the retina is usually convex forward. Rhegmatogenous retinal detachment has a corrugated appearance, and undulates with eye movement. Causes of retinal breaks include posterior vitreous detachment,

www.ketabpezeshki.com (021) 66485457 - 66485438

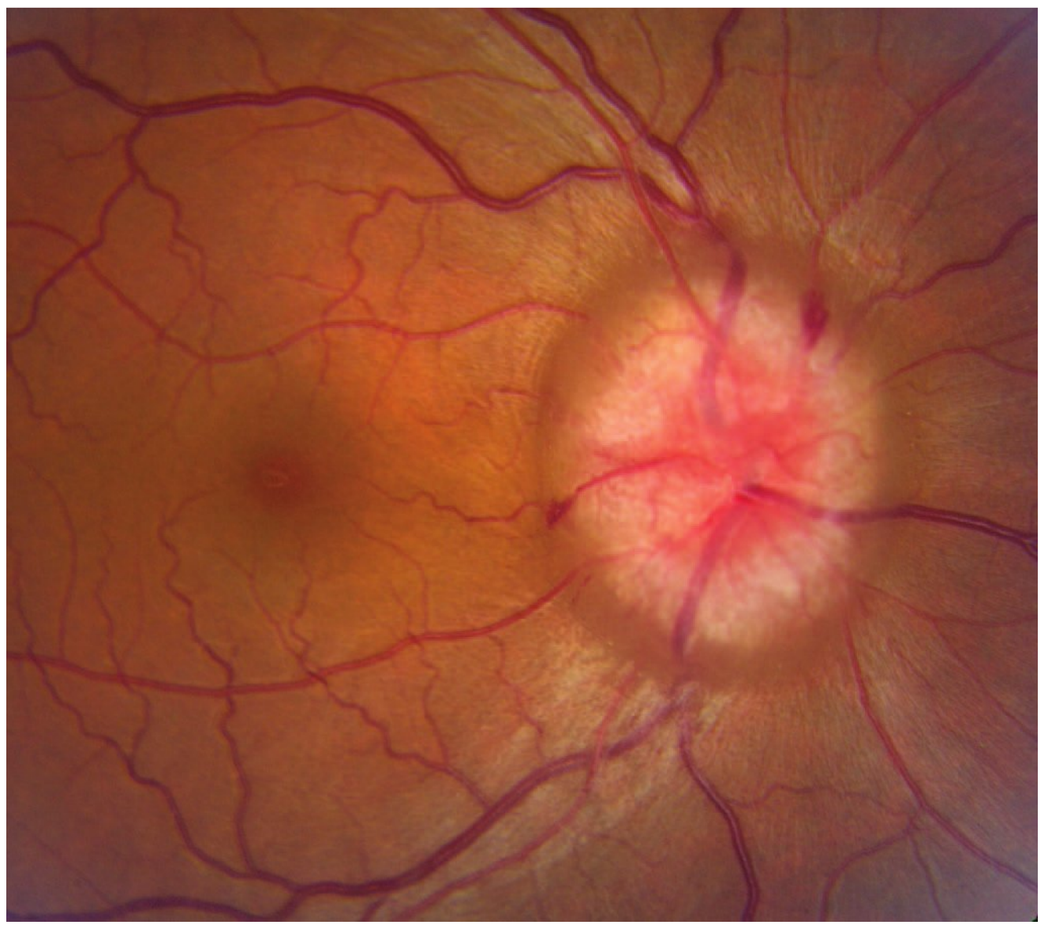


FIGURE 26-9
Optic disc swelling in a patient with papilledema due to idiopathic intracranial hypertension. The optic disc is hyperemic, with indistinct margins. Superf cial hemorrhages are present.

FIGURE 26-10
Optic disc edema and retinal hemorrhages in a patient with malignant hypertension.

severe vitreoretinal traction, trauma, intraocular surgery, retinitis, and atrophic holes.

OPTIC DISC SWELLING

Optic disc swelling is abnormal elevation of the optic disc with blurring of its margins **(Fig. 26-9)**. T e term "papilledema" is used to describe swelling of the optic disc secondary to elevation of intracranial pressure. In papilledema, the normal venous pulsation at the disc is characteristically absent. T e differential diagnosis of optic disc swelling includes papilledema, anterior optic neuritis (papillitis), central retinal vein occlusion, anterior ischemic optic neuropathy, toxic optic neuropathy, hereditary optic neuropathy, neuroretinitis, diabetic papillopathy, hypertension **(Fig. 26-10)**, respiratory failure, carotid-cavernous fistula, optic disc nerve infiltration (glioma, lymphoma, leukemia, sarcoidosis, and granulomatous infections), ocular hypotony, chronic intraocular inf ammation, optic disc drusen (pseudopapilledema), and high hypermetropia (pseudopapilledema).

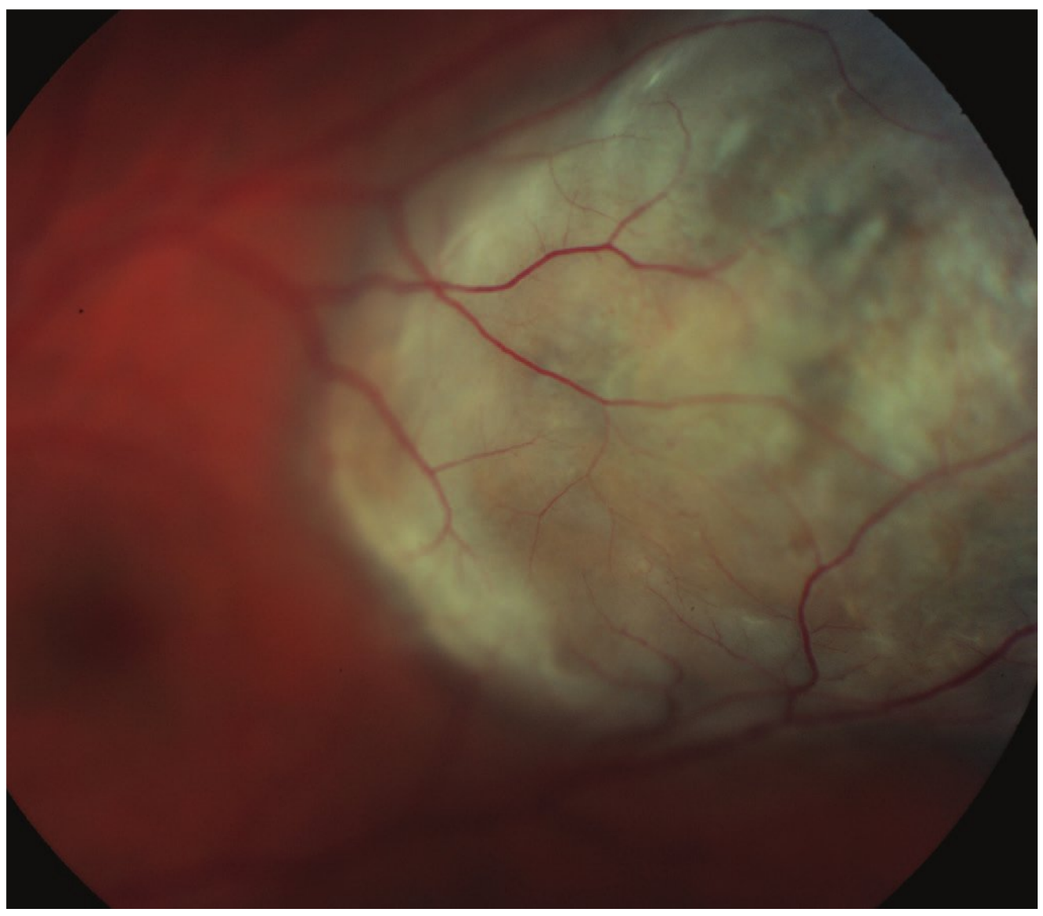


FIGURE 26-11
Choroidal malignant melanoma. The lesion is highly elevated and pigmented, and has subretinal orange pigment deposits characteristic for malignant melanoma.

CHORIORETINAL MASS LESIONS

Choroidal mass lesions appear thickened and may or may not be associated with increased pigmentation. Pigmented mass lesions include choroidal nevus (usually f at), choroidal malignant melanoma **(Fig. 26-11)**, and melanocytoma. Nonpigmented lesions include amelanotic choroidal melanoma, choroidal metastasis, retinoblastoma, capillary hemangioma, granuloma (e.g., Toxocara canis), choroidal detachment, choroidal hemorrhage, and wet age-related macular degeneration. Other rare tumors that may be visible on ophthalmoscopy include osteoma, astrocytoma (e.g., tuberous sclerosis), neurilemmoma, and leiomyoma.

www.ketabpezeshki.com (021) 66485457 - 66485438

PIGMENTED LESIONS

The differential diagnosis of flat pigmented lesions of the fundus is summarized in **Table 26-4**. The appearance of chorioretinal scarring from old Toxoplasma chorioretinitis is shown in **Fig. 26-12**.

TABLE 26-4

DIFFERENTIAL DIAGNOSIS OF FLAT PIGMENTED LESIONS OF THE FUNDUS

Bone spicule pigmentation
- Retinitis pigmentosa and its variants
- Pigmentary retinopathy in systemic diseases: Usher's syndrome, abetalipoproteinemia, Refsum's disease, Kearns-Sayre syndrome, Alström's syndrome, Cockayne's syndrome, Friedreich's ataxia, mucopolysaccharidoses, paraneoplastic syndrome
- Infections: congenital rubella (salt and pepper retinopathy), congenital syphilis
- Resolved choroidal/retinal detachment
- Age-related reticular pigmentary degeneration

Patchy pigmented lesions
- Chorioretinal scars
- Infections: Toxoplasma gondii, Toxocara canis, syphilis, cytomegalovirus, herpes zoster and herpes simplex viruses, west Nile virus, histoplasmosis, parasitic infection
- Choroiditis: sarcoidosis, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome
- Choroidal infarct: severe hypertension, sickle cell hemoglobinopathies
- Trauma, cryotherapy, laser photocoagulation scars
- Age-related macular degeneration
- Drugs: chloroquine/hydroxychloroquine, thioridazine, chlorpromazine, desferrioxamine
- Choroidal nevus
- Congenital hypertrophy of the retinal pigment epithelium

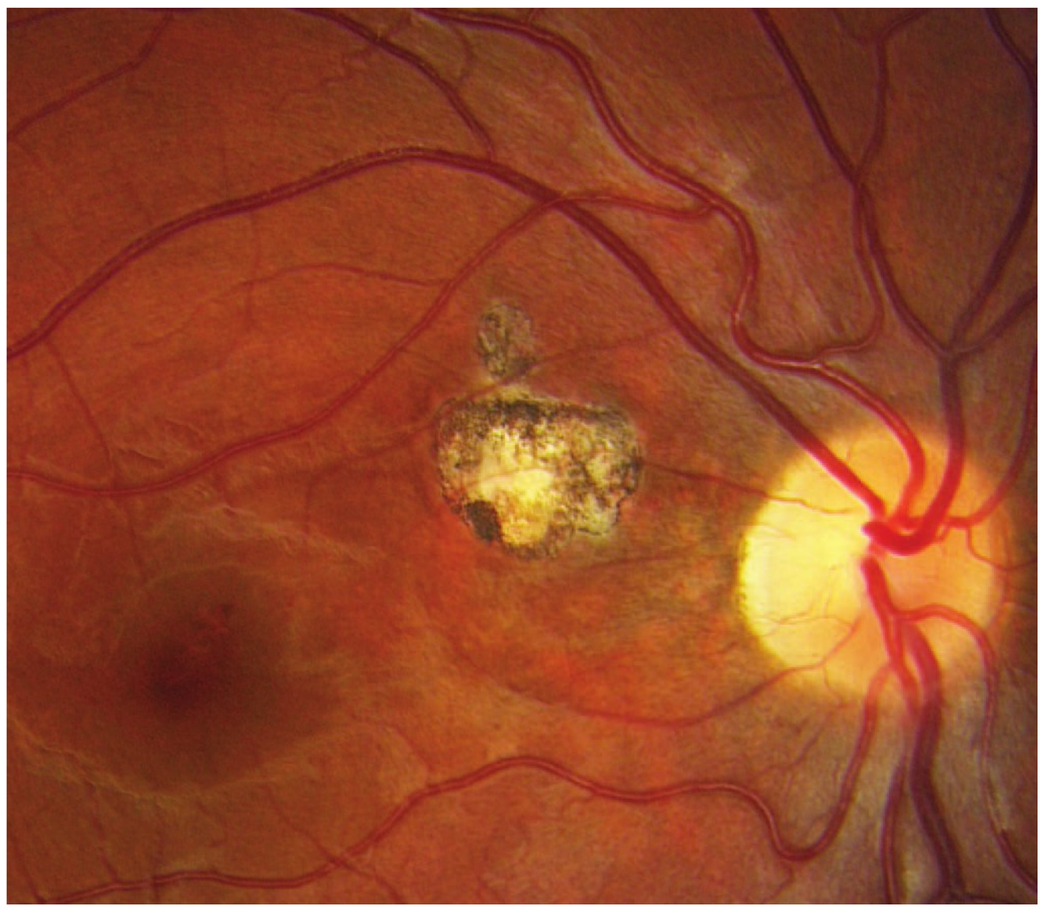


FIGURE 26-12
Chorioretinal scarring due to old Toxoplasma chorioretinitis. The lesion is flat and pigmented. Areas of hypopigmentation are also present.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 27

VIDEO LIBRARY OF NEURO-OPHTHALMOLOGY

Shirley H. Wray

The proper control of eye movements requires the coordinated activity of many different anatomic structures in the peripheral and central nervous system, and in turn, manifestations of a diverse array of neurologic and medical disorders are revealed as disorders of eye movement. In this remarkable video collection, an introduction to distinctive eye movement disorders encountered in the context of neuromuscular, paraneoplastic, demyelinating, neurovascular, and neurodegenerative disorders is presented.

Videos for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Cases with Multiple Sclerosis

Video 27–1. Fisher's one-and-a-half syndrome (ID164-2)

Video 27–2. A Case of ocular flutter (ID166-2)

Video 27–3. Downbeat nystagmus and periodic alternating nystagmus (ID168-6)

Video 27–4. Bilateral internuclear ophthalmoplegia (ID933-1)

Cases with Myasthenia Gravis or Mitochondrial Myopathy

Video 27–5. Unilateral ptosis: myasthenia gravis (thymic tumor) (ID163-1)

Video 27–6. Progressive external ophthalmoplegia (progressive external ophthalmoplegia: mitochondrial cytopathy) (ID906-2)

Cases with Paraneoplastic Disease

Video 27–7. Paraneoplastic upbeat nystagmus, cancer of the pancreas, positive anti-hu antibody (ID212-3)

Video 27–8. Paraneoplastic ocular flutter, small-cell adenocarcinoma of the lung, negative marker (ID936-7)

Video 27–9. Opsoclonus/flutter, bilateral sixth nerve palsy, adenocarcinoma of the breast, negative marker (ID939-8)

Cases with Fisher's Syndrome

Video 27–10. Bilateral ptosis: facial diplegia, total external ophthalmoplegia, positive anti-gQ_{1b} antibody (ID944-1)

Cases with Vascular Disease

Video 27–11. Retinal emboli (film or fundus) (ID16-1)

Video 27–12. Third nerve palsy (microinfarct) (ID939-2)

Case with Neurodegenerative Disease

Video 27–13. Apraxia of eyelid opening (progressive supranuclear palsy) (ID932-3)

Case of Thyroid-Associated Ophthalmopathy

Video 27–14. Restrictive orbitopathy of graves' disease, bilateral exophthalmos (ID925-4)

www.ketabpezeshki.com (021) 66485457 - 66485438

Case with Wernicke's Encephalopathy

Video 27–15. Bilateral sixth nerve palsies (ID 163-3)

Case with the Locked-in-Syndrome

Video 27–16. Ocular dipping (ID 4-1)

Case in a Comatose Patient

Video 27–17. Downbeat nystagmus (ID 166-11)

Case Two Years After a Pontine Hemorrhage

Video 27–18. Palatal tremor (ID 936-4)

The Video Library of Neuro-Ophthalmology shows a number of cases with eye movement disorders. All the clips are taken from Dr. Shirley Wray's collection on the NOVEL website.

To access go to:

- http://NOVEL.utah.edu/Wray
- http://Respitory.Countway.Harvard.edu/Wray
- and/or to her book
- Eye Movement Disorders in Clinical Practice
- Shirley H. Wray, MD, PhD, Oxford University Press, 2014.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 28

DISORDERS OF SMELL AND TASTE

Richard L. Doty ■ Steven M. Bromley

All environmental chemicals necessary for life enter the body by the nose and mouth. The senses of smell (olfaction) and taste (gustation) monitor such chemicals, determine the flavor and palatability of foods and beverages, and warn of dangerous environmental conditions, including fire, air pollution, leaking natural gas, and bacteria-laden foodstuffs. These senses contribute significantly to quality of life and, when dysfunctional, can have untoward physical and psychological consequences. A basic understanding of these senses in health and disease is critical for the physician, because thousands of patients present to doctors' offices each year with complaints of chemosensory dysfunction. Among the more important recent developments in neurology is the discovery that decreased smell function is among the first signs, if not the first sign, of such neurodegenerative diseases as Parkinson's disease (PD) and Alzheimer's disease (AD), signifying their "presymptomatic" phase.

ANATOMY AND PHYSIOLOGY

Olfactory system

Odorous chemicals enter the front of nose during inhalation and active sniffing, as well as the back of the nose (nasopharynx) during deglutition. After reaching the highest recesses of the nasal cavity, they dissolve in the olfactory mucus and diffuse or are actively transported by specialized proteins to receptors located on the cilia of olfactory receptor cells. The cilia, dendrites, cell bodies, and proximal axonal segments of these bipolar cells are located within a unique neuroepithelium covering the cribriform plate, the superior nasal septum, superior turbinate, and sectors of the middle turbinate **(Fig. 28-1)**. Each of the ~6 million bipolar receptor cells expresses only one of ~450 receptor protein types, most of which respond to more than a single chemical. When damaged, the receptor cells can be replaced by stem cells near the basement membrane. Unfortunately, such replacement is often incomplete.

After coalescing into bundles surrounded by glia-like ensheathing cells (termed fila), the receptor cell axons pass through the cribriform plate to the olfactory bulbs, where they synapse with dendrites of other cell types within the glomeruli **(Fig. 28-2)**. These spherical structures, which make up a distinct layer of the olfactory bulb, are a site of convergence of information, because many more fibers enter than leave them. Receptor cells that express the same type of receptor project to the same glomeruli, effectively making each glomerulus a functional unit. The major projection neurons of the olfactory system—the mitral and tufted cells—send primary dendrites into the glomeruli, connecting not only with the incoming receptor cell axons, but with dendrites of periglomerular cells. The activity of the mitral/tufted cells is modulated by the periglomerular cells, secondary dendrites from other mitral/tufted cells, and granule cells, the most numerous cells of the bulb. The latter cells, which are largely GABAergic, receive inputs from central brain structures and modulate the output of the mitral/tufted cells. Interestingly, like the olfactory receptor cells, some cells within the bulb undergo replacement. Thus, neuroblasts formed within the anterior subventricular zone of the brain migrate along the rostral migratory stream, ultimately becoming granule and periglomerular cells.

The axons of the mitral and tufted cells synapse within the primary olfactory cortex (POC) **(Fig. 28-3)**. The POC is defined as those cortical structures that receive direct projections from the olfactory bulb, most notably the piriform and entorhinal cortices. Although olfaction is unique in that its initial afferent projections bypass the thalamus, persons with damage to the thalamus can exhibit olfactory deficits, particularly ones of odor identification. Such deficits likely reflect

www.ketabpezeshki.com (021) 66485457 - 66485438

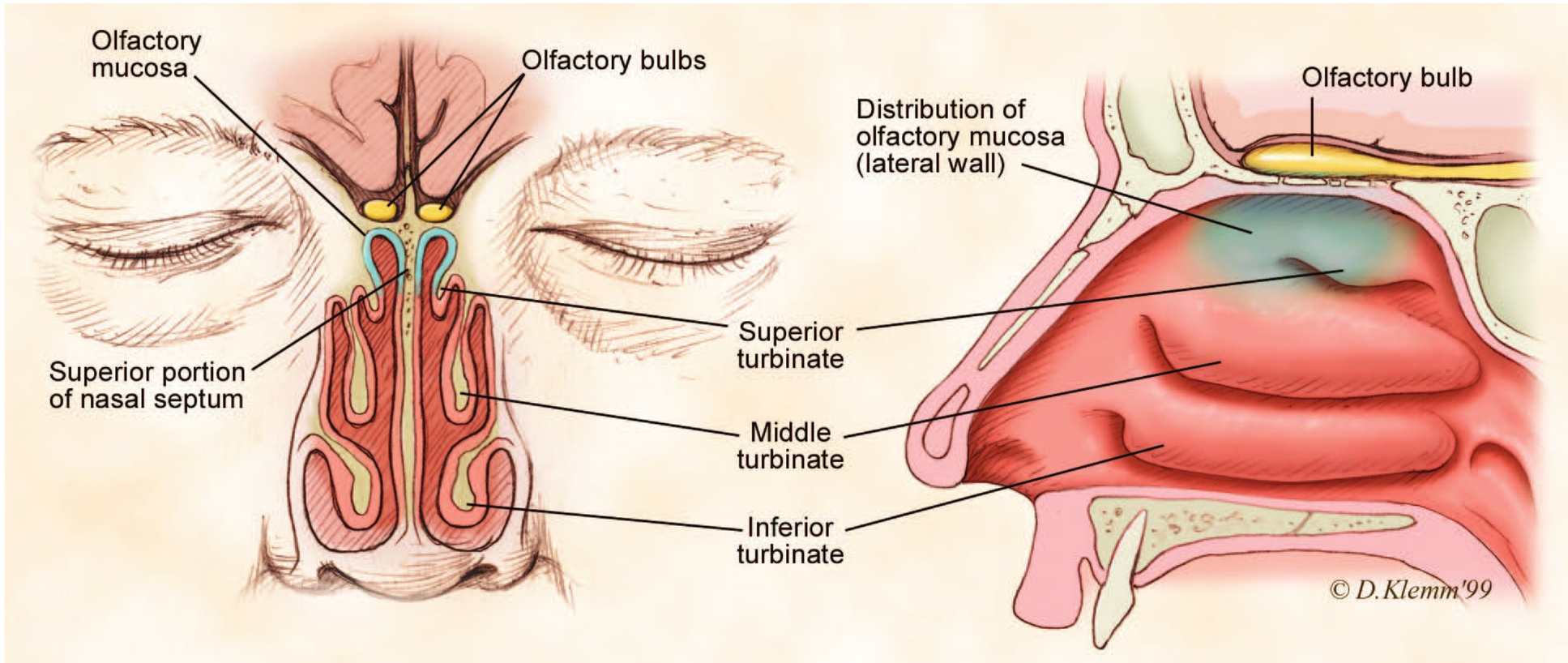


FIGURE 28-1
Anatomy of the olfactory neural pathways, showing the distribution of olfactory receptors in the roof of the nasal cavity. (Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center; used with permission.)

the involvement of thalamic connections between the primary olfactory cortex and the orbitofrontal cortex (OFC), where odor identification occurs. T e close anatomic ties between the olfactory system and the amygdala, hippocampus, and hypothalamus help to explain the intimate associations between odor perception and cognitive functions such as memory, motivation, arousal, autonomic activity, digestion, and sex.

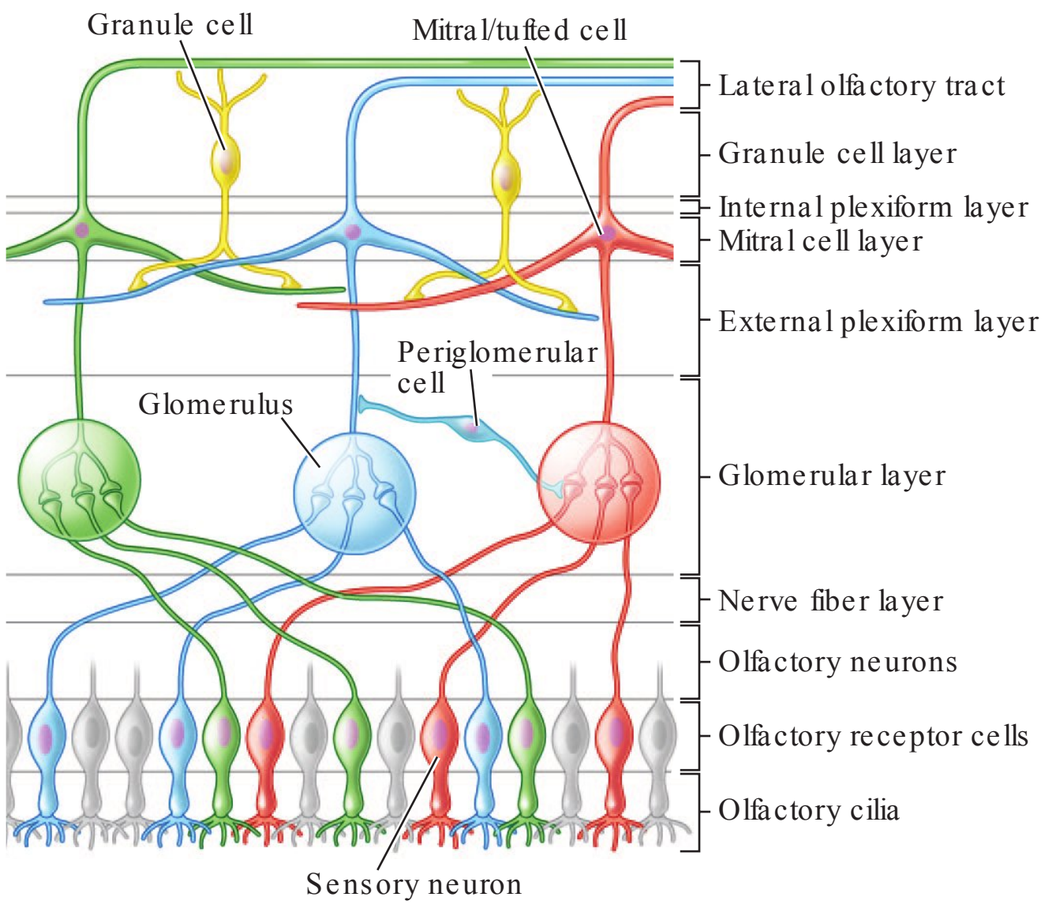


FIGURE 28-2
Schematic of the layers and wiring of the olfactory bulb. Each receptor type (red, green, blue) projects to a common glomerulus. The neural activity within each glomerulus is modulated by periglomerular cells. The activity of the primary projection cells, the mitral and tufted cells, is modulated by granule cells, periglomerular cells, and secondary dendrites from adjacent mitral and tufted cells. (From www.medicine.yale.edu/neurosurgery.)

Taste system

Tastants are sensed by specialized receptor cells present within taste buds—small grapefruit-like segmented structures located on the lateral margins and dorsum of the tongue, roof of the mouth, pharynx, larynx, and superior esophagus **(Fig. 28-4)**. Lingual taste buds are imbedded in well-defined protuberances, termed

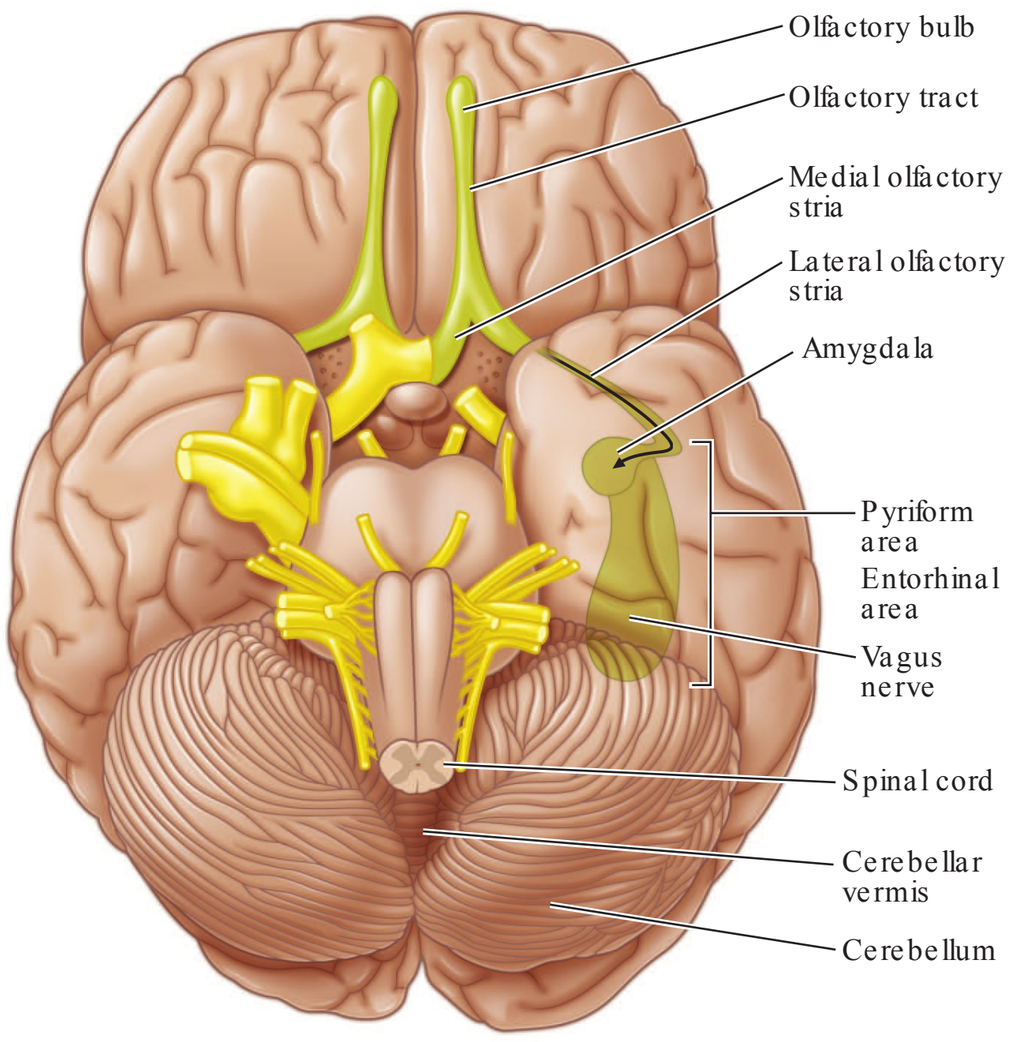


FIGURE 28-3
Anatomy of the base of the brain showing the primary olfactory cortex.

www.ketabpezeshki.com (021) 66485457 - 66485438

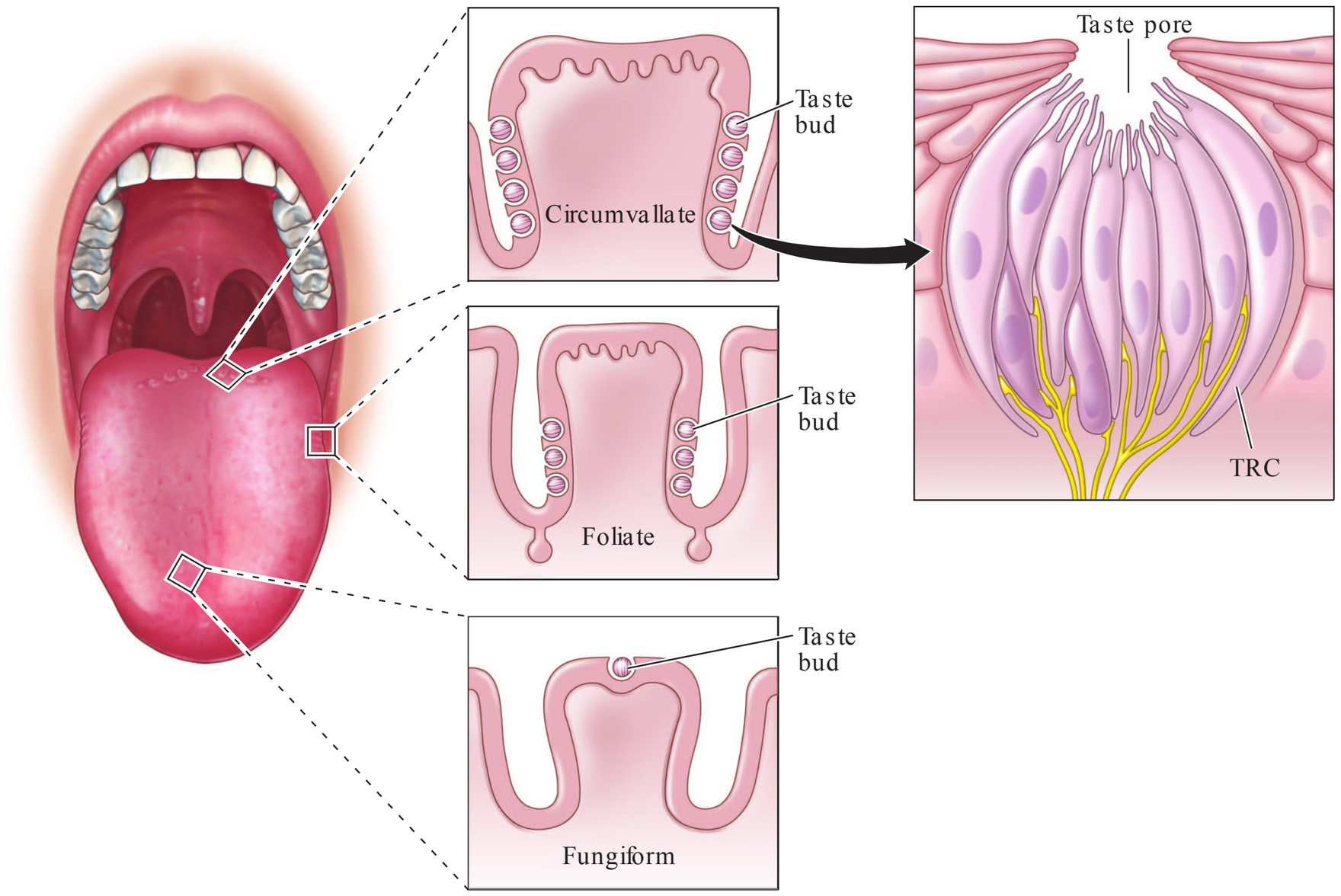


FIGURE 28-4
Schematic of the taste bud and its opening (pore), as well as the location of buds on the three major types of papillae: fungiform (anterior), foliate (lateral), and circumvallate (posterior).

fungiform, foliate, and circumvallate papillae. After dissolving in a liquid, tastants enter the opening of the taste bud—the taste pore—and bind to receptors on microvilli, small extensions of receptor cells within each taste bud. Such binding changes the electrical potential across the taste cell, resulting in neurotransmitter release onto the first-order taste neurons. Although humans have ~7500 taste buds, not all harbor taste-sensitive cells; some contain only one class of receptor (e.g., cells responsive only to sugars), whereas others contain cells sensitive to more than one class. The number of taste receptor cells per taste bud ranges from zero to well over 100. A small family of three G-protein-coupled receptors (GPCRs), namely T1R1, T1R2, and T1R3, mediate sweet and umami taste sensations. Bitter sensations, on the other hand, depend on T2R receptors, a family of ~30 GPCRs expressed on cells different from those that express the sweet and umami receptors. T2Rs sense a wide range of bitter substances but do not distinguish among them. Sour tastants are sensed by the PKD2L1 receptor, a member of the transient receptor potential protein (TRP) family. Perception of salty sensations, such as induced by sodium chloride, arises from the entry of Na^+ ions into the cells via specialized membrane channels, such as the amiloride-sensitive Na^+ channel.

Recent studies have found that both bitter and sweet taste-related receptors are also present elsewhere in the body, most notably in the alimentary and respiratory tracts. This important discovery generalizes the concept of taste-related chemoreception to areas of the body beyond the mouth and throat, with α-gustducin, the taste-specific G-protein α-subunit, expressed in so-called brush cells found specifically within the human trachea, lung, pancreas, and gallbladder. These brush cells are rich in nitric oxide (NO) synthase, known to defend against xenobiotic organisms, protect the mucosa from acid-induced lesions, and, in the case of the gastrointestinal tract, stimulate vagal and splanchnic afferent neurons. NO further acts on nearby cells, including enteroendocrine cells, absorptive or secretory epithelial cells, mucosal blood vessels, and cells of the immune system. Members of the T2R family of bitter receptors and the sweet receptors of the T1R family have been identified within the gastrointestinal tract and in enteroendocrine cell lines. In some cases, these receptors are important for metabolism, with the T1R3 receptors and gustducin playing decisive roles in the sensing and transport of dietary sugars from the intestinal lumen into absorptive enterocytes via a sodium-dependent glucose transporter and in regulation of hormone release from gut enteroendocrine cells. In other cases, these receptors may be important for airway protection, with a number of T2R bitter receptors in the motile cilia of the human airway that responded to bitter compounds by increasing their beat frequency. One specific T2R38 taste receptor is expressed

www.ketabpezeshki.com (021) 66485457 - 66485438

in human upper respiratory epithelia and responds to acyl-monoserine lactone quorum-sensing molecules secreted by Pseudomonas aeruginosa and other gram-negative bacteria. Differences in T2R38 functionality, as related to TAS2R38 genotype, correlate with susceptibility to upper respiratory infections in humans.

Taste information is sent to the brain via three cranial nerves (CNs): CN VII (the facial nerve, which involves the intermediate nerve with its branches, the greater petrosal and chorda tympani nerves), CN IX (the glossopharyngeal nerve), and CN X (the vagus nerve) **(Fig. 28-5)**. CN VII innervates the anterior tongue and all of the soft palate, CN IX innervates the posterior tongue, and CN X innervates the laryngeal surface of the epiglottis, larynx, and proximal portion of the esophagus. The mandibular branch of CN V (V_3) conveys somatosensory information (e.g., touch, burning, cooling, irritation) to the brain. Although not technically a gustatory nerve, CN V shares primary nerve routes with many of the gustatory nerve fibers and adds temperature, texture, pungency, and spiciness to the taste experience. The chorda tympani nerve is famous for taking a recurrent course through the facial canal in the petrosal portion of the temporal bone, passing through the middle ear, and then exiting the skull via the petrotympanic fissure, where it joins the lingual nerve (a division of CN V) near the tongue. This nerve also carries parasympathetic fibers to the submandibular and sublingual glands, whereas the greater petrosal nerve supplies the palatine glands, thereby influencing saliva production.

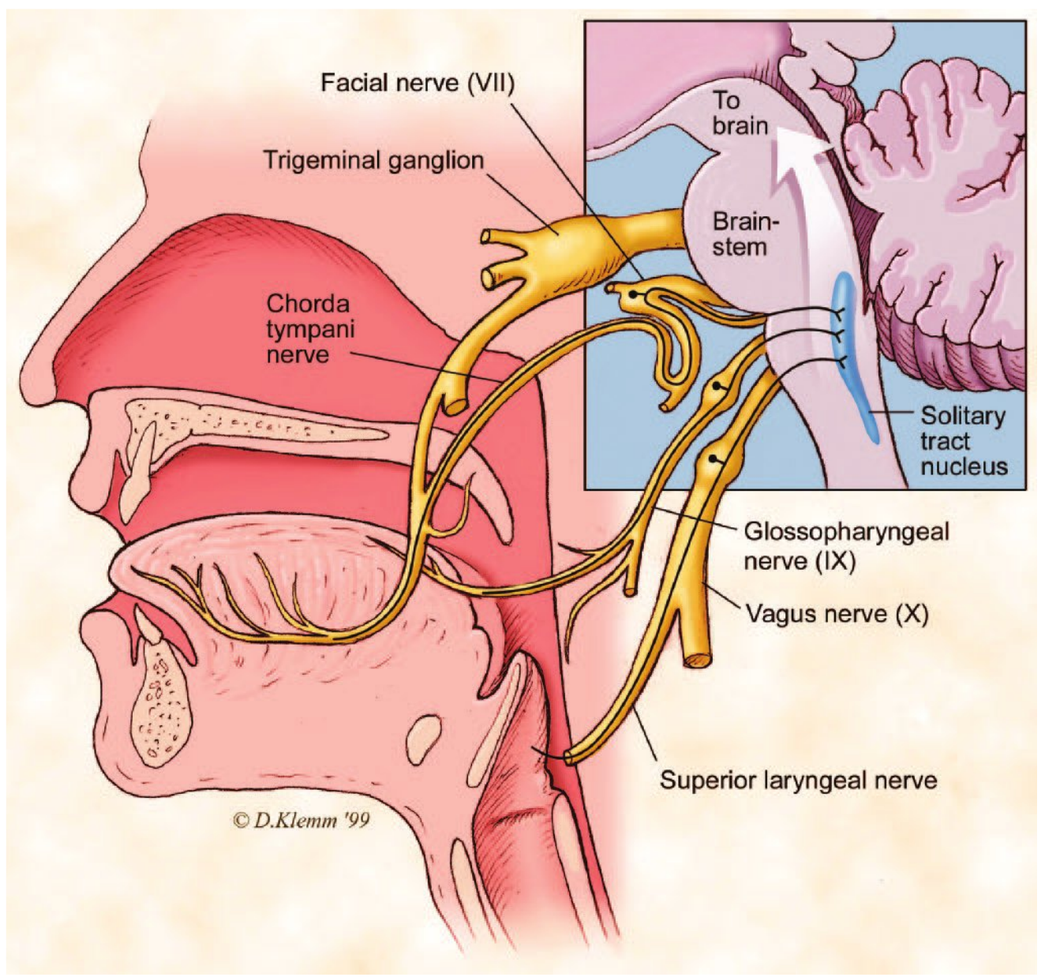


FIGURE 28-5
Schematic of the cranial nerves (CNs) that mediate taste function, including the chorda tympani nerve (CN VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X). (Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center; used with permission.)

The axons of the projection cells, which synapse with taste buds, enter the rostral portion of the nucleus of the solitary tract (NTS) within the medulla of the brainstem (Fig. 28-5). From the NTS, neurons then project to a division of the ventroposteromedial thalamic nucleus (VPM) via the medial lemniscus. From here, projections are made to the rostral part of the frontal operculum and adjoining insula, a brain region considered the primary taste cortex (PTC). Projections from the PTC then go to the secondary taste cortex, namely the caudolateral OFC. This brain region is involved in the conscious recognition of taste qualities. Moreover, because it contains cells that are activated by several sensory modalities, it is likely a center for establishing "flavor."

DISORDERS OF OLFACTION

The ability to smell is influenced, in everyday life, by such factors as age, gender, general health, nutrition, smoking, and reproductive state. Women typically outperform men on tests of olfactory function and retain normal smell function to a later age than do men. Significant decrements in the ability to smell are present in over 50% of the population between 65 and 80 years of age and in 75% of those 80 years of age and older **(Fig. 28-6)**. Such presbyosmia helps to explain why many elderly report that food has little flavor, a problem that can result in nutritional disturbances. This is also helps to explain why a disproportionate number of elderly die in accidental gas poisonings. A relatively complete listing of conditions and disorders that have been associated with olfactory dysfunction is presented in **Table 28-1**.

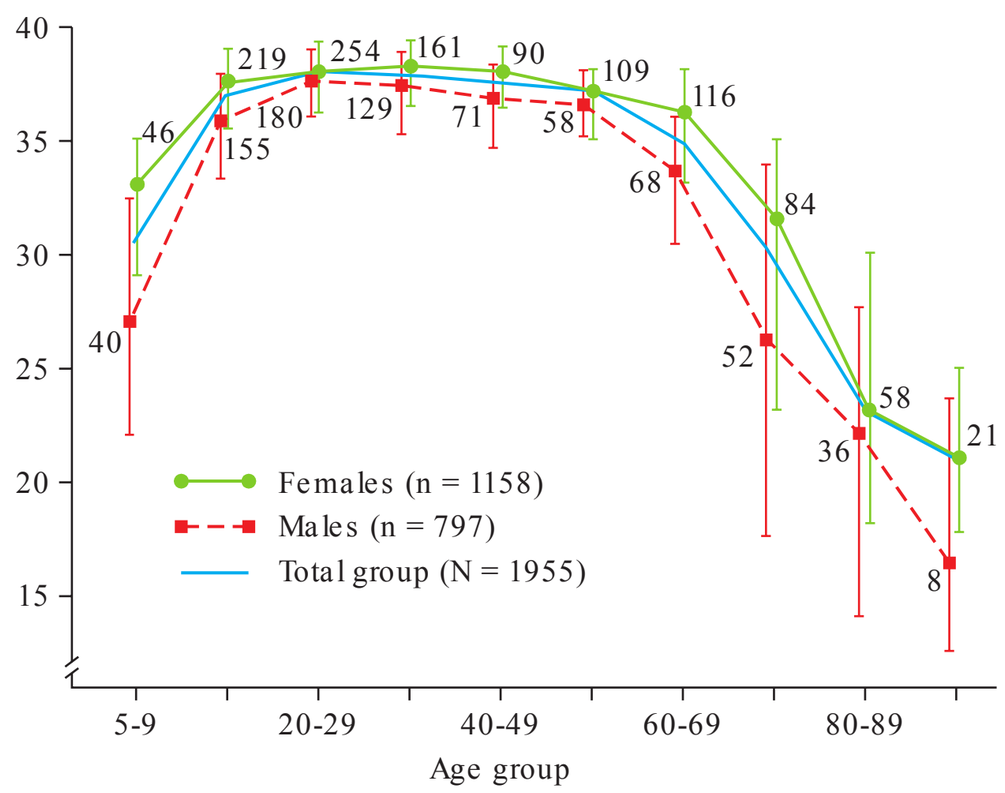


FIGURE 28-6
Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of subject age and sex. Numbers by each data point indicate sample sizes. Note that women identify odorants better than men at all ages. (From RL Doty et al: Science 226:1421, 1984. Copyright © 1984 American Association for the Advancement of Science.)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 28-1

DISORDERS AND CONDITIONS ASSOCIATED WITH COMPROMISED OLFACTORY FUNCTION, AS MEASURED BY OLFACTORY TESTING

22q11 deletion syndrome
AIDS/HIV infection
Adenoid hypertrophy
Adrenal cortical insufficiency
Age
Alcoholism
Allergies
Alzheimer's disease
Amyotrophic lateral sclerosis (ALS)
Anorexia nervosa
Asperger's syndrome
Ataxias
Attention deficit/hyperactivity disorder
Bardet-Biedl syndrome
Chagas' disease
Chemical exposure
Chronic obstructive pulmonary disease
Congenital
Cushing's syndrome
Cystic fibrosis
Degenerative ataxias
Diabetes
Down's syndrome
Epilepsy
Facial paralysis
Frontotemporal lobe degeneration
Gonadal dysgenesis (Turner's syndrome)
Guamanian ALS/PD/dementia syndrome
Head trauma
Herpes simplex encephalitis
Hypothyroidism
Huntington's disease
Iatrogenesis
Kallmann's syndrome
Korsakof 's psychosis
Leprosy
Liver disease
Lubag disease
Medications
Migraine
Multiple sclerosis
Multi-infarct dementia
Myasthenia gravis
Narcolepsy with cataplexy
Neoplasms, cranial/nasal
Nutritional deficiencies
Obstructive pulmonary disease
Obesity
Obsessive compulsive disorder
Orthostatic tremor
Panic disorder
Parkinson's disease (PD)
Pick's disease
Posttraumatic stress disorder
Pregnancy
Pseudohypoparathyroidism
Psychopathy
Radiation (therapeutic, cranial)
REM behavior disorder
Refsum's disease
Renal failure/end-stage kidney disease
Restless leg syndrome
Rhinosinusitis/polyposis
Schizophrenia
Seasonal af ective disorder
Sjögren's syndrome
Stroke
Tobacco smoking
Toxic chemical exposure
Upper respiratory infections
Usher syndrome
Vitamin B_{12} deficiency

Aside from aging, the three most common identifiable causes of long-lasting or permanent smell loss seen in the clinic are, in order of frequency, severe upper respiratory infections, head trauma, and chronic rhinosinusitis. T e physiologic basis for most head trauma–related losses is the shearing and subsequent scarring of the olfactory fila as they pass from the nasal cavity into the brain cavity. T e cribriform plate does not have to be fractured or show pathology for smell loss to be present. Severity of trauma, as indexed by a poor Glasgow Coma Scale score on presentation and the length of posttraumatic amnesia, is associated with higher risk of olfactory impairment. Less than 10% of posttraumatic anosmic patients will recover age-related normal function over time. T is increases to nearly 25% of those with less-than-total loss. Upper respiratory infections, such as those associated with the common cold, influenza, pneumonia, or HIV, can directly and permanently harm the olfactory epithelium by decreasing receptor cell number, damaging cilia on remaining receptor cells, and inducing the replacement of sensory epithelium with respiratory epithelium. T e smell loss associated with chronic rhinosinusitis is related to disease severity, with most loss occurring in cases where rhinosinusitis and polyposis are both present. Although systemic glucocorticoid therapy can usually induce short-term functional improvement, it does not, on average, return smell test scores to normal, implying that chronic permanent neural loss is present and/or that short-term administration of systemic glucocorticoids does not completely mitigate the inflammation. It is well established that microinflammation in an otherwise seemingly normal epithelium can influence smell function.

A number of neurodegenerative diseases are accompanied by olfactory impairment, including PD, AD, Huntington's disease, Down's syndrome, parkinsonism-dementia complex of Guam, dementia with Lewy bodies (DLB), multiple system atrophy, corticobasal degeneration, and frontotemporal dementia; smell loss can also occur in multiple sclerosis (MS) and idiopathic rapid eye movement (REM) behavioral sleep disorder (iRBD). Olfactory impairment in PD of en predates the clinical diagnosis by at least 4 years. In staged cases, studies of the sequence of formation of abnormal α-synuclein aggregates and Lewy bodies suggest that the olfactory bulbs may be, along with the dorsomotor nucleus of the vagus, the first site of neural damage in PD. In postmortem studies of patients with very mild "presymptomatic" signs of AD, poorer smell function has been associated with higher levels of AD-related pathology. Smell loss is more marked in patients with early clinical manifestations of DLB than in those with mild AD. Interestingly, smell loss is minimal or nonexistent in progressive supranuclear palsy and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. In MS, the olfactory disturbance varies as a function of the plaque activity within the frontal and temporal lobes.

T e smell loss seen in iRBD is of the same magnitude as that found in PD. T is is of particular interest because patients with iRBD frequently develop PD and hyposmia. T ere is some evidence that iRBD may actually represent an early associated condition of PD. REM behavior disorder is not only seen in its idiopathic form, but can also be associated with narcolepsy. T is

www.ketabpezeshki.com (021) 66485457 - 66485438

led to a recent study of narcoleptic patients with and without REM behavior disorder, which demonstrated that narcolepsy, independent of REM behavior disorder, was associated with impairments in olfactory function. Orexin A, also known as hypocretin-1, is dramatically diminished or undetectable in the cerebrospinal fluid of patients with narcolepsy and cataplexy **(Chap. 24)**. T e orexin-containing neurons in the hypothalamus project throughout the entire olfactory system (from the olfactory epithelium to the olfactory cortex), and damage to these orexin-containing projections may be one underlying mechanism for impaired olfactory performance in narcoleptic patients. T e administration of intranasal orexin A (hypocretin-1) appears to result in improved olfactory function, supporting the notion that mild olfactory impairment is not only a primary feature of narcolepsy with cataplexy, but that central nervous system orexin deficiency may be a fundamental part of the mechanism for this loss.

DISORDERS OF TASTE

T e majority of patients who present with taste dysfunction exhibit olfactory, not taste, loss. T is is because most flavors attributed to taste actually depend on retronasal stimulation of the olfactory receptors during deglutition. As noted earlier, taste buds only mediate basic tastes such as sweet, sour, bitter, salty, and umami. Significant impairment of whole-mouth gustatory function is rare outside of generalized metabolic disturbances or systemic use of some medications, because taste bud regeneration occurs and peripheral damage alone would require the involvement of multiple cranial nerve pathways. Nonetheless, taste can be influenced by (1) the release of foul-tasting materials from the oral cavity from oral medical conditions or appliances (e.g., gingivitis, purulent sialadenitis), (2) transport problems of tastants to the taste buds (e.g., drying of the orolingual mucosa, infections, inflammatory conditions), (3) damage to the taste buds themselves (e.g., local trauma, invasive carcinomas), (4) damage to the neural pathways innervating the taste buds (e.g., middle ear infections), (5) damage to central structures (e.g., multiple sclerosis, tumor, epilepsy, stroke), and (6) systemic disturbances of metabolism (e.g., diabetes, thyroid disease, medications). Unlike CN VII, CN IX is relatively protected along its path, although iatrogenic interventions such as tonsillectomy, bronchoscopy, laryngoscopy, endotracheal intubation, and radiation therapy can result in selective injury. CN VII damage commonly results from mastoidectomy, tympanoplasty, and stapedectomy, in some cases inducing persistent metallic sensations. Bell's palsy **(Chap. 42)** is one of the most common causes of CN VII injury that results in taste disturbance. On rare occasions, migraines **(Chap. 34)** are associated with a gustatory prodrome or aura, and in some cases, tastants can trigger a migraine attack. Interestingly, dysgeusia occurs in some cases of burning mouth syndrome (BMS; also termed glossodynia or glossalgia), as do dry mouth and thirst. BMS is likely associated with dysfunction of the trigeminal nerve (CN V). Some of the etiologies suggested for this poorly understood syndrome are amenable to treatment, including (1) nutritional deficiencies (e.g., iron, folic acid, B vitamins, zinc), (2) diabetes mellitus (possibly predisposing to oral candidiasis), (3) denture allergy, (4) mechanical irritation from dentures or oral devices, (5) repetitive movements of the mouth (e.g., tongue thrusting, teeth grinding, jaw clenching), (6) tongue ischemia as a result of temporal arteritis, (7) periodontal disease, (8) reflux esophagitis, and (9) geographic tongue.

Although both taste and smell can be adversely influenced by pharmacologic agents, drug-related taste alterations are more common. Indeed, over 250 medications have been reported to alter the ability to taste. Major offenders include antineoplastic agents, antirheumatic drugs, antibiotics, and blood pressure medications. Terbinafine, a commonly used antifungal, has been linked to taste disturbance lasting up to 3 years. In a recent controlled trial, nearly two-thirds of individuals taking eszopiclone (Lunesta) experienced a bitter dysgeusia that was stronger in women, systematically related to the time since drug administration, and positively correlated with both blood and saliva levels of the drug. Intranasal use of nasal gels and sprays containing zinc, which are common over-the-counter prophylactics for upper respiratory viral infections, has been implicated in loss of smell function. Whether their efficacy in preventing such infections, which are the most common cause of anosmia and hyposmia, outweighs their potential detriment to smell function requires study. Dysgeusia occurs commonly in the context of drugs used to treat or minimize symptoms of cancer, with a weighted prevalence from 56–76% depending on the type of cancer treatment. Attempts to prevent taste problems from such drugs using prophylactic zinc sulfate or amifostine have proven to be minimally beneficial. Although antiepileptic medications are occasionally used to treat smell or taste disturbances, the use of topiramate has been reported to result in a reversible loss of an ability to detect and recognize tastes and odors during treatment.

As with olfaction, a number of systemic disorders can affect taste. T ese include chronic renal failure, end-stage liver disease, vitamin and mineral deficiencies, diabetes mellitus, and hypothyroidism (to name a few). In diabetes, there appears to be a progressive loss of taste beginning with glucose and then extending to other sweeteners, salty stimuli, and then all

www.ketabpezeshki.com (021) 66485457 - 66485438

stimuli. Psychiatric conditions can be associated with chemosensory alterations (e.g., depression, schizophrenia, bulimia). A recent review of tactile, gustatory, and olfactory hallucinations demonstrated that no one type of hallucinatory experience is pathognomonic to any given diagnosis.

Pregnancy proves to be a unique condition with regard to taste function. T ere appears to be an increase in dislike and intensity of bitter tastes during the first trimester that may help to ensure that pregnant women avoid poisons during a critical phase of fetal development. Similarly, a relative increase in the preference for salt and bitter in the second and third trimesters may support the ingestion of much needed electrolytes to expand fluid volume and support a varied diet.

CLINICAL EVALUATION

In most cases, a careful clinical history will establish the probable etiology of a chemosensory problem, including questions about its nature, onset, duration, and pattern of fluctuations. Sudden loss suggests the possibility of head trauma, ischemia, infection, or a psychiatric condition. Gradual loss can reflect the development of a progressive obstructive lesion. Intermittent loss suggests the likelihood of an inflammatory process. T e patient should be asked about potential precipitating events, such as cold or flu infections prior to symptom onset, because these of en go underappreciated. Information regarding head trauma, smoking habits, drug and alcohol abuse (e.g., intranasal cocaine, chronic alcoholism in the context of Wernicke's and Korsakoff's syndromes), exposures to pesticides and other toxic agents, and medical interventions is also informative. A determination of all the medications that the patient was taking before and at the time of symptom onset is important, because many can cause chemosensory disturbances. Comorbid medical conditions associated with smell impairment, such as renal failure, liver disease, hypothyroidism, diabetes, or dementia, should be assessed. Delayed puberty in association with anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann's syndrome. Recollection of epistaxis, discharge (clear, purulent, or bloody), nasal obstruction, allergies, and somatic symptoms, including headache or irritation, may have localizing value. Questions related to memory, parkinsonian signs, and seizure activity (e.g., automatisms, blackouts, auras, déjà vu) should be posed. Pending litigation and the possibility of malingering should be considered. Modern forced-choice olfactory tests can detect malingering from improbable responses.

Neurologic and otorhinolaryngologic (ORL) examinations, along with appropriate brain and nasosinus imaging, aid in the evaluation of patients with olfactory or gustatory complaints. T e neural evaluation should focus on cranial nerve function, with particular attention to possible skull base and intracranial lesions. Visual acuity, field, and optic disc examinations aid in the detection of intracranial mass lesions that induce intracranial pressure (papilledema) and optic atrophy, especially when considering Foster Kennedy syndrome. T e ORL examination should thoroughly assess the intranasal architecture and mucosal surfaces. Polyps, masses, and adhesions of the turbinates to the septum may compromise the flow of air to the olfactory receptors, because less than a fif h of the inspired air traverses the olfactory clef in the unobstructed state. Blood tests may be helpful to identify such conditions as diabetes, infection, heavy metal exposure, nutritional deficiency (e.g., vitamin B_6 or B_{12}), allergy, and thyroid, liver, and kidney disease.

As with other sensory disorders, quantitative sensory testing is advised. Self-reports of patients can be misleading, and a number of patients who complain of chemosensory dysfunction have normal function for their age and gender. Quantitative smell and taste testing provides valid information for worker's compensation and other legal claims, as well as a way to accurately assess treatment interventions. A number of standardized olfactory and taste tests are commercially available. Most evaluate the ability of patients to detect and identify odors or tastes. For example, the most widely used of these tests, the 40-item University of Pennsylvania Smell Identification Test (UPSIT), uses norms based on nearly 4000 normal subjects. A determination is made of both absolute dysfunction (i.e., mild loss, moderate loss, severe loss, total loss, probable malingering) and relative dysfunction (percentile rank for age and gender). Although electrophysiologic testing is available at some smell and taste centers (e.g., odor event-related potentials), they require complex stimulus presentation and recording equipment and rarely provide additional diagnostic information. With the exception of electrogustometers, commercially available taste tests have only recently become available. Most use filter paper strips impregnated with tastants, so no stimulus preparation is required.

TREATMENT AND MANAGEMENT

Given the various mechanisms by which olfactory and gustatory disturbance can occur, management of patients tends to be condition specific. For example, patients with hypothyroidism, diabetes, or infections of en benefit from specific treatments to correct the underlying disease process that is adversely influencing chemoreception. For most patients who present primarily with obstructive/transport loss affecting the

www.ketabpezeshki.com (021) 66485457 - 66485438

nasal and paranasal regions (e.g., allergic rhinitis, polyposis, intranasal neoplasms, nasal deviations), medical and/or surgical intervention is often beneficial. Antifungal and antibiotic treatments may reverse taste problems secondary to candidiasis or other oral infections. Chlorhexidine mouthwash mitigates some salty or bitter dysgeusias, conceivably as a result of its strong positive charge. Excessive dryness of the oral mucosa is a problem with many medications and conditions, and artificial saliva (e.g., Xerolube) or oral pilocarpine treatments may prove beneficial. Other methods to improve salivary flow include the use of mints, lozenges, or sugarless gum. Flavor enhancers may make food more palatable (e.g., monosodium glutamate), but caution is advised to avoid overusing ingredients containing sodium or sugar, particularly in circumstances when a patient also has underlying hypertension or diabetes. Medications that induce distortions of taste can often be discontinued and replaced with other types of medications or modes of therapy. As mentioned earlier, pharmacologic agents result in taste disturbances much more frequently than smell disturbances, and over 250 medications have been reported to alter the sense of taste. It is important to note, however, that many drug-related effects are long lasting and not reversed by short-term drug discontinuance.

A recent study of endoscopic sinus surgery in patients with chronic rhinosinusitis and hyposmia revealed that patients with severe olfactory dysfunction prior to the surgery had a more dramatic and sustained improvement over time compared to patients with more mild olfactory dysfunction prior to intervention. In the case of intranasal and sinus-related inflammatory conditions, such as seen with allergy, viruses, and traumas, the use of intranasal or systemic glucocorticoids may also be helpful. One common approach is to use a tapering course of oral prednisone. The utility of restoring olfaction with either topical or systemic glucocorticoids has been studied. Topical intranasal administration was found to be less effective in general than systemic administration; however, the effects of different nasal administration techniques were not analyzed; for example, intranasal glucocorticoids are more effective if administered in the Moffett's position (head in the inverted position such as over the edge of the bed with the bridge of the nose perpendicular to the floor). After head trauma, an initial trial of glucocorticoids may help to reduce local edema and the potential deleterious deposition of scar tissue around olfactory fila at the level of the cribriform plate.

Treatments are limited for patients with chemosensory loss or primary injury to neural pathways. Nonetheless, spontaneous recovery can occur. In a follow-up study of 542 patients presenting to our center with smell loss from a variety of causes, modest improvement occurred over an average time period of 4 years in about half of the participants. However, only 11% of the anosmic and 23% of the hyposmic patients regained normal age-related function. Interestingly, the amount of dysfunction present at the time of presentation, not etiology, was the best predictor of prognosis. Other predictors were age and the duration of dysfunction prior to initial testing.

A nonblinded study has reported that patients with hyposmia may benefit from smelling strong odors (e.g., eucalyptol, citronella, eugenol, and phyenyl ethyl alcohol) before going to bed and immediately upon awakening each day over the course of several months. The rationale for such an approach comes from animal studies demonstrating that prolonged exposure to odorants can induce increased neural activity within the olfactory bulb. In an uncontrolled study, α-lipoic acid (400 mg/d), an essential cofactor for many enzyme complexes with possible antioxidant effects, was reported to be beneficial in mitigating smell loss following viral infection of the upper respiratory tract; controlled studies are needed to confirm this observation. This agent has also been suggested to be useful in some cases of hypogeusia and BMS.

The use of zinc and vitamin A in treating olfactory disturbances is controversial, and there does not appear to be much benefit beyond replenishing established deficiencies. However, zinc has been shown to improve taste function secondary to hepatic deficiencies, and retinoids (bioactive vitamin A derivatives) are known to play an essential role in the survival of olfactory neurons. One protocol in which zinc was infused with chemotherapy treatments suggested a possible protective effect against developing taste impairment. Diseases of the alimentary tract can not only influence chemoreceptive function, but also occasionally influence vitamin B_{12} absorption. This can result in a relative deficiency of vitamin B_{12}, theoretically contributing to olfactory nerve disturbance. Vitamin B_2 (riboflavin) and magnesium supplements are reported in the alternative literature to aid in the management of migraine that, in turn, may be associated with smell dysfunction. Because vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia, adding vitamin D_3, 1000–2000 units per day, may benefit some patients with smell and taste complaints during or following chemotherapy.

A number of medications have reportedly been used with success in ameliorating olfactory symptoms, although strong scientific evidence for efficacy is generally lacking. A report that theophylline improved smell function was uncontrolled and failed to account for the fact that some meaningful improvement occurs without treatment; indeed, the percentage of responders was about the same (~50%) as that noted by others to

www.ketabpezeshki.com (021) 66485457 - 66485438

show spontaneous improvement over a similar time period. Antiepileptics and some antidepressants (e.g., amitriptyline) have been used to treat dysosmias and smell distortions, particularly following head trauma. Ironically, amitriptyline is also frequently on the list of medications that can ultimately distort smell and taste function, possibly from its anticholinergic effects. A recent study suggests that the use of the centrally acting acetylcholinesterase inhibitor donepezil in AD resulted in improvements on smell identification measures that correlated with overall clinician-based impressions of change in dementia severity scores.

Alternative therapies, such as acupuncture, meditation, cognitive-behavioral therapy, and yoga, can help patients manage uncomfortable experiences associated with chemosensory disturbance and oral pain syndromes and to cope with the psychosocial stressors surrounding the impairment. Additionally, modification of diet and eating habits is also important. By accentuating the other sensory experiences of a meal, such as food texture, aroma, temperature, and color, one can optimize the overall eating experience for a patient. In some cases, a flavor enhancer like monosodium glutamate (MSG) can be added to foods to increase palatability and encourage intake.

Proper oral and nasal hygiene and routine dental care are extremely important ways for patients to protect themselves from disorders of the mouth and nose that can ultimately result in chemosensory disturbance. Patients should be warned not to overcompensate for their taste loss by adding excessive amounts of sugar or salt. Smoking cessation and the discontinuance of oral tobacco use are essential in the management of any patient with smell and/or taste disturbance and should be repeatedly emphasized.

A major and of en overlooked element of therapy comes from chemosensory testing itself. Confirmation or lack of conformation of loss is beneficial to patients who come to believe, in light of unsupportive family members and medical providers, that they may be "crazy." In cases where the loss is minor, patients can be informed of the likelihood of a more positive prognosis. Importantly, quantitative testing places the patient's problem into overall perspective. T us, it is of en therapeutic for an older person to know that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group. Without testing, many such patients are simply told they are getting old and nothing can be done for them, leading in some cases to depression and decreased self-esteem.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 29

DISORDERS OF HEARING

Anil K. Lalwani

Hearing loss is one of the most common sensory disorders in humans and can present at any age. Nearly 10% of the adult population has some hearing loss, and one-third of individuals age >65 years have a hearing loss of sufficient magnitude to require a hearing aid.

PHYSIOLOGY OF HEARING

T e function of the external and middle ear is to amplify sound to facilitate conversion of the mechanical energy of the sound wave into an electrical signal by the inner ear hair cells, a process called mechanotransduction **(Fig. 29-1)**. Sound waves enter the external auditory canal and set the tympanic membrane (eardrum) in motion, which in turn moves the malleus, incus, and stapes of the middle ear. Movement of the footplate of the stapes causes pressure changes in the fluid-filled inner ear, eliciting a traveling wave in the basilar membrane of the cochlea. T e tympanic membrane and the ossicular chain in the middle ear serve as an impedance-matching mechanism, improving the efficiency of energy transfer from air to the fluid-filled inner ear.

Stereocilia of the hair cells of the organ of Corti, which rests on the basilar membrane, are in contact with the tectorial membrane and are deformed by the traveling wave. A point of maximal displacement of the basilar membrane is determined by the frequency of the stimulating tone. High-frequency tones cause maximal displacement of the basilar membrane near the base of the cochlea, whereas for low-frequency sounds, the point of maximal displacement is toward the apex of the cochlea.

T e inner and outer hair cells of the organ of Corti have different innervation patterns, but both are mechanoreceptors. T e afferent innervation relates principally to the inner hair cells, and the efferent innervation relates principally to outer hair cells. T e motility of the outer hair cells alters the micromechanics of the inner hair cells, creating a cochlear amplifier, which explains the exquisite sensitivity and frequency selectivity of the cochlea.

Beginning in the cochlea, the frequency specificity is maintained at each point of the central auditory pathway: dorsal and ventral cochlear nuclei, trapezoid body, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body, and auditory cortex. At low frequencies, individual auditory nerve fibers can respond more or less synchronously with the stimulating tone. At higher frequencies, phase-locking occurs so that neurons alternate in response to particular phases of the cycle of the sound wave. Intensity is encoded by the amount of neural activity in individual neurons, the number of neurons that are active, and the specific neurons that are activated.

T ere is evidence that the right and left ears as well as the central nervous system may process speech asymmetrically. Generally, a sound is processed symmetrically from the peripheral to the central auditory system. However, a “right ear advantage” exists for dichotic listening tasks, in which subjects are asked to report on competing sounds presented to each ear. In most individuals, a perceptual right ear advantage for consonant-vowel syllables, stop consonants, and words also exists. Similarly, whereas central auditory processing for sounds is symmetric with minimal lateral specialization for the most part, speech processing is lateralized. T ere is specialization of the left auditory cortex for speech recognition and production, and of the right hemisphere for emotional and tonal aspects of speech. Left hemisphere dominance for speech is found in 95–98% of right-handed persons and 70–80% of left-handed persons.

DISORDERS OF THE SENSE OF HEARING

Hearing loss can result from disorders of the auricle, external auditory canal, middle ear, inner ear, or central auditory pathways **(Fig. 29-2)**. In general, lesions in

www.ketabpezeshki.com (021) 66485457 - 66485438

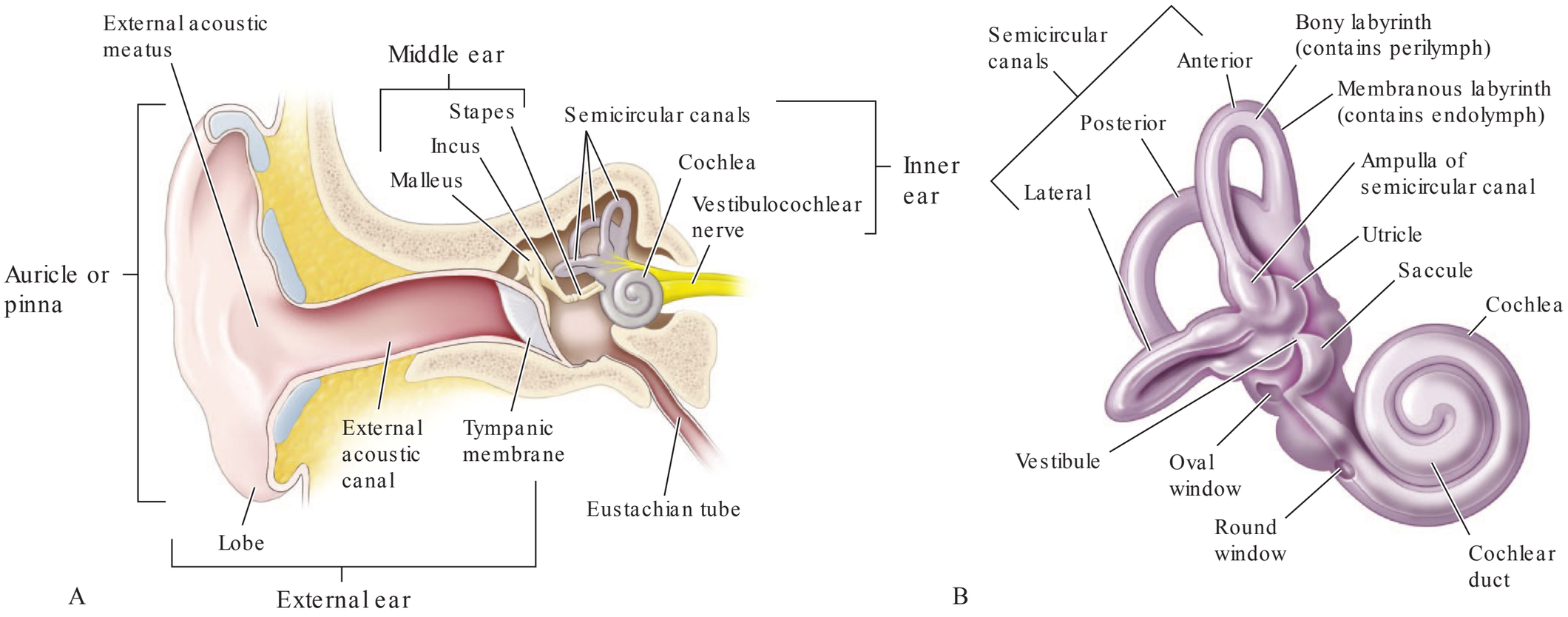


FIGURE 29-1

Ear anatomy. A. Drawing of modified coronal section through external ear and temporal bone, with structures of the middle and inner ear demonstrated. B. High-resolution view of inner ear.

the auricle, external auditory canal, or middle ear that impede the transmission *of* sound *from* the external environment to the inner ear cause conductive hearing loss, whereas lesions that impair mechanotransduction in the inner ear or transmission *of* the electrical signal along the eighth nerve to the brain cause sensorineural hearing loss.

Conductive hearing loss

T e external ear, the external auditory canal, and the middle ear apparatus is designed to collect and amplify sound and efficiently transfer the mechanical energy of the sound wave to the fluid-filled cochlea. Factors that obstruct the transmission of sound or serve to dampen the acoustical energy result in conductive hearing loss. Conductive hearing loss can occur from obstruction of the external auditory canal by cerumen, debris, and foreign bodies; swelling of the lining of the canal; atresia or neoplasms of the canal; perforations of the tympanic membrane; disruption of the ossicular chain, as occurs with necrosis of the long process of the incus in trauma or infection; otosclerosis; or fluid, scarring, or neoplasms in the middle ear. Rarely, inner ear malformations or pathologies, such as superior semicircular canal dehiscence, lateral semicircular canal dysplasia, incomplete partition of the inner ear, and large vestibular aqueduct, may also be associated with conductive hearing loss.

Eustachian tube dysfunction is extremely common in adults and may predispose to acute otitis media (AOM) or serous otitis media (SOM). Trauma, AOM, and chronic otitis media are the usual factors responsible for tympanic membrane perforation. While small perforations often heal spontaneously, larger defects usually require surgical intervention. Tympanoplasty is highly effective (>90%) in the repair of tympanic membrane perforations. Otoscopy is usually sufficient to diagnose AOM, SOM, chronic otitis media, cerumen impaction, tympanic membrane perforation, and eustachian tube dysfunction; tympanometry can be useful to confirm the clinical suspicion of these conditions.

Cholesteatoma, a benign tumor composed of stratified squamous epithelium in the middle ear or mastoid, occurs frequently in adults. T is is a slowly growing lesion that destroys bone and normal ear tissue. T eories of pathogenesis include traumatic immigration and invasion of squamous epithelium through a retraction pocket, implantation of squamous epithelia in the middle ear through a perforation or surgery, and metaplasia following chronic infection and irritation. On examination, there is often a perforation of the tympanic membrane filled with cheesy white squamous debris. T e presence of an aural polyp obscuring the tympanic membrane is highly suggestive of an underlying cholesteatoma. A chronically draining ear that fails to respond to appropriate antibiotic therapy should raise suspicion of a cholesteatoma. Conductive hearing loss secondary to ossicular erosion is common. Surgery is required to remove this destructive process.

Conductive hearing loss with a normal ear canal and intact tympanic membrane suggests either ossicular pathology or the presence of "third window" in the inner ear (see below). Fixation of the stapes from otosclerosis is a common cause of low-frequency conductive hearing loss. It occurs equally in men and women and is inherited as an autosomal dominant trait with incomplete penetrance; in some cases, it may be a manifestation of osteogenesis imperfecta. Hearing impairment usually presents between the late teens and the forties. In women, the otosclerotic process is accelerated

www.ketabpezeshki.com (021) 66485457 - 66485438

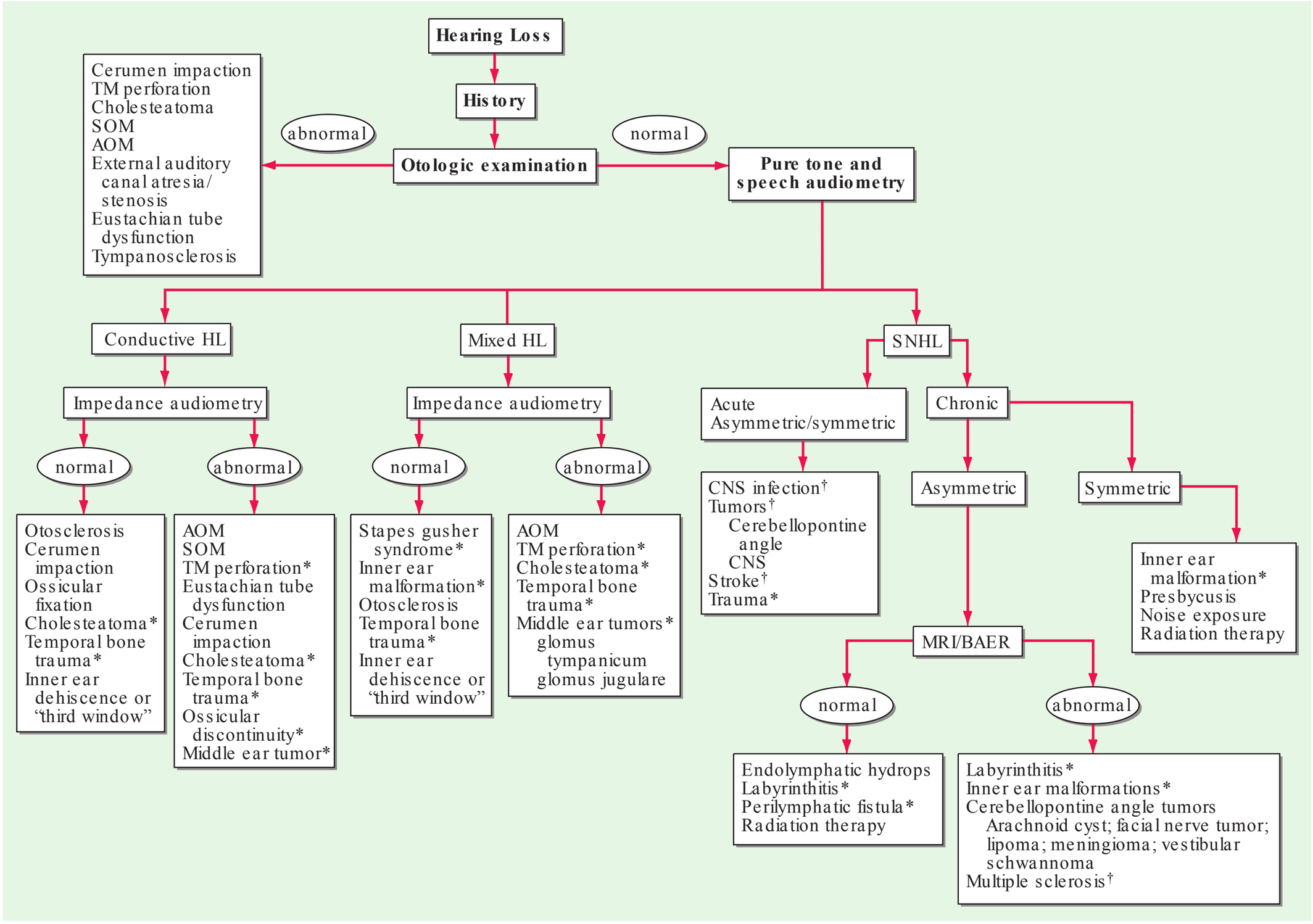


FIGURE 29-2

An algorithm for the approach to hearing loss. AOM, acute otitis media; BAER, brainstem auditory evoked response; CNS, central nervous system; HL, hearing loss; SNHL, sensorineural hearing loss; SOM, serous otitis media; TM, tympanic membrane. *Computed tomography scan of temporal bone. †Magnetic resonance imaging (MRI) scan.

during pregnancy, and the hearing loss is often first noticeable at this time. A hearing aid or a simple outpatient surgical procedure (stapedectomy) can provide adequate auditory rehabilitation. Extension of otosclerosis beyond the stapes footplate to involve the cochlea (cochlear otosclerosis) can lead to mixed or sensorineural hearing loss. Fluoride therapy to prevent hearing loss from cochlear otosclerosis is of uncertain value.

Disorders that lead to the formation of a pathologic "third window" in the inner ear can be associated with conductive hearing loss. T ere are normally two major openings, or windows, that connect the inner ear with the middle ear and serve as conduits for transmission of sound; these are, respectively, the oval and round windows. A third window is formed where the normally hard otic bone surrounding the inner ear is eroded; dissipation of the acoustic energy at the third window is responsible for the "inner ear conductive hearing loss." T e superior semicircular canal dehiscence syndrome resulting from erosion of the otic bone over the superior circular canal can present with conductive hearing loss that mimics otosclerosis. A common symptom is vertigo evoked by loud sounds (Tullio phenomenon), by Valsalva maneuvers that change middle ear pressure, or by applying positive pressure on the tragus (the cartilage anterior to the external opening of the ear canal). Patients with this syndrome also complain of being able to hear the movement of their eyes and neck. A large jugular bulb or jugular bulb diverticulum can create a "third window" by eroding into the vestibular aqueduct or posterior semicircular canal; the symptoms are similar to those of the superior semicircular canal dehiscence syndrome.

Sensorineural hearing loss

Sensorineural hearing loss results from either damage to the mechanotransduction apparatus of the cochlea or disruption of the electrical conduction pathway from the inner ear to the brain. T us, injury to hair

www.ketabpezeshki.com (021) 66485457 - 66485438

cells, supporting cells, auditory neurons, or the central auditory pathway can cause sensorineural hearing loss. Damage to the hair cells of the organ of Corti may be caused by intense noise, viral infections, ototoxic drugs (e.g., salicylates, quinine and its synthetic analogues, aminoglycoside antibiotics, loop diuretics such as furosemide and ethacrynic acid, and cancer chemotherapeutic agents such as cisplatin), fractures of the temporal bone, meningitis, cochlear otosclerosis (see above), Ménière's disease, and aging. Congenital malformations of the inner ear may be the cause of hearing loss in some adults. Genetic predisposition alone or in concert with environmental exposures may also be responsible (see below).

Presbycusis (age-associated hearing loss) is the most common cause of sensorineural hearing loss in adults. In the early stages, it is characterized by symmetric, gentle to sharply sloping high-frequency hearing loss **(Fig. 29-3)**. With progression, the hearing loss involves all frequencies. More importantly, the hearing impairment is associated with significant loss in clarity. There is a loss of discrimination for phonemes, recruitment (abnormal growth of loudness), and particular difficulty in understanding speech in noisy environments such as at restaurants and social events. Hearing aids are helpful in enhancing the signal-to-noise ratio by amplifying sounds that are close to the listener. Although hearing aids are able to amplify sounds, they cannot restore the clarity *of* hearing. Thus, amplification with hearing aids may provide only limited rehabilitation once the word recognition score deteriorates below 50%. Cochlear implants are the treatment of choice when hearing aids prove inadequate, even when hearing loss is incomplete (see below).

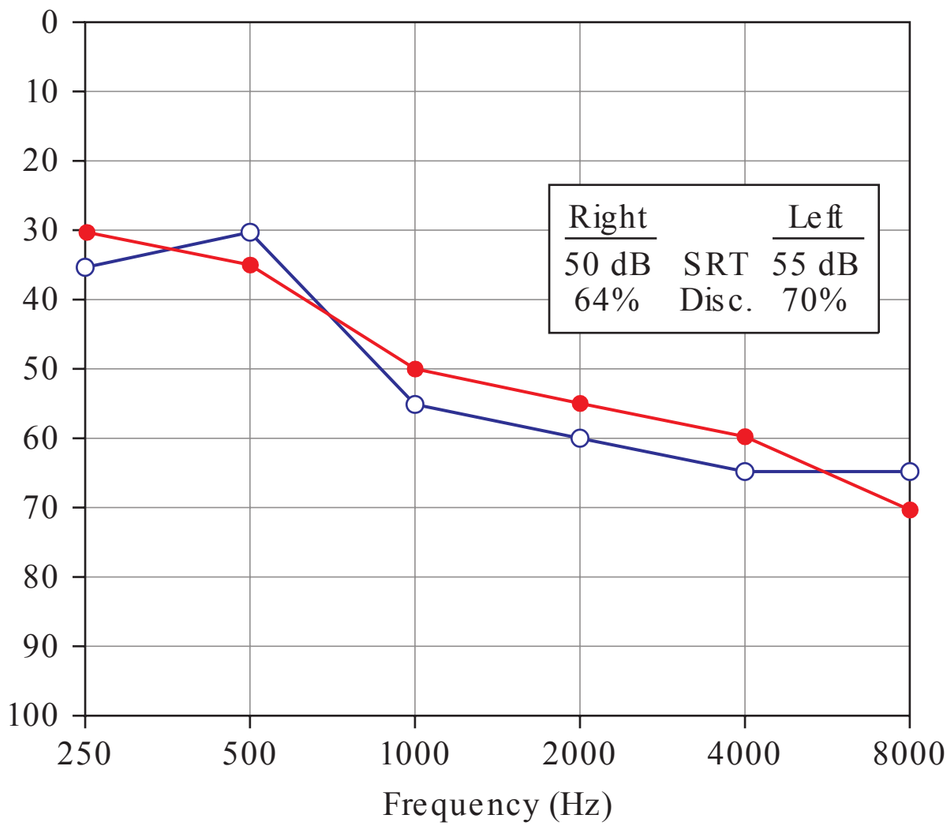


FIGURE 29-3

Presbyacusis or age-related hearing loss. The audiogram shows a moderate to severe downsloping sensorineural hearing loss typical of presbyacusis. The loss of high-frequency hearing is associated with a decreased speech discrimination score; consequently, patients complain of lack of clarity of hearing, especially in a noisy background. HL, hearing threshold level; SRT, speech reception threshold.

Ménière's disease is characterized by episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. Tinnitus and/or deafness may be absent during the initial attacks of vertigo, but it invariably appears as the disease progresses and increases in severity during acute attacks. The annual incidence of Ménière's disease is 0.5–7.5 per 1000; onset is most frequently in the fifth decade of life but may also occur in young adults or the elderly. Histologically, there is distention of the endolymphatic system (endolymphatic hydrops) leading to degeneration of vestibular and cochlear hair cells. This may result from endolymphatic sac dysfunction secondary to infection, trauma, autoimmune disease, inflammatory causes, or tumor; an idiopathic etiology constitutes the largest category and is most accurately referred to as Ménière's disease. Although any pattern of hearing loss can be observed, typically, low-frequency, unilateral sensorineural hearing impairment is present. Magnetic resonance imaging (MRI) should be obtained to exclude retrocochlear pathology such as a cerebellopontine angle tumor or demyelinating disorder. Therapy is directed toward the control of vertigo. A 2-g/d low-salt diet is the mainstay of treatment for control of rotatory vertigo. Diuretics, a short course of glucocorticoids, and intratympanic gentamicin may also be useful adjuncts in recalcitrant cases. Surgical therapy of vertigo is reserved for unresponsive cases and includes endolymphatic sac decompression, labyrinthectomy, and vestibular nerve section. Both labyrinthectomy and vestibular nerve section abolish rotatory vertigo in >90% of cases. Unfortunately, there is no effective therapy for hearing loss, tinnitus, or aural fullness from Ménière's disease.

Sensorineural hearing loss may also result from any neoplastic, vascular, demyelinating, infectious, or degenerative disease or trauma affecting the central auditory pathways. HIV leads to both peripheral and central auditory system pathology and is associated with sensorineural hearing impairment.

Primary diseases of the central nervous system can also present with hearing impairment. Characteristically, a reduction in clarity of hearing and speech comprehension is much greater than the loss of the ability to hear pure tone. Auditory testing is consistent with an auditory neuropathy; normal otoacoustic emissions (OAE) and an abnormal auditory brainstem response (ABR) is typical (see below). Hearing loss can accompany hereditary sensorimotor neuropathies and inherited disorders of myelin. Tumors of the cerebellopontine angle such as vestibular schwannoma and meningioma usually present with asymmetric sensorineural hearing loss with greater deterioration of speech understanding

www.ketabpezeshki.com (021) 66485457 - 66485438

than pure tone hearing. Multiple sclerosis may present with acute unilateral or bilateral hearing loss; typically, pure tone testing remains relatively stable while speech understanding fluctuates. Isolated labyrinthine infarction can present with acute hearing loss and vertigo due to a cerebrovascular accident involving the posterior circulation, usually the anterior inferior cerebellar artery; it may also be the heralding sign of impending catastrophic basilar artery infarction **(Chap. 32)**.

A finding of conductive and sensory hearing loss in combination is termed mixed hearing loss. Mixed hearing losses are due to pathology of both the middle and inner ear, as can occur in otosclerosis involving the ossicles and the cochlea, head trauma, chronic otitis media, cholesteatoma, middle ear tumors, and some inner ear malformations.

Trauma resulting in temporal bone fractures may be associated with conductive, sensorineural, or mixed hearing loss. If the fracture spares the inner ear, there may simply be conductive hearing loss due to rupture of the tympanic membrane or disruption of the ossicular chain. T ese abnormalities can be surgically corrected. Profound hearing loss and severe vertigo are associated with temporal bone fractures involving the inner ear. A perilymphatic fistula associated with leakage of inner ear fluid into the middle ear can occur and may require surgical repair. An associated facial nerve injury is not uncommon. Computed tomography (CT) is best suited to assess fracture of the traumatized temporal bone, evaluate the ear canal, and determine the integrity of the ossicular chain and the involvement of the inner ear. Cerebrospinal fluid leaks that accompany temporal bone fractures are usually self-limited; the value of prophylactic antibiotics is uncertain.

Tinnitus is defined as the perception of a sound when there is no sound in the environment. It may have a buzzing, roaring, or ringing quality and may be pulsatile (synchronous with the heartbeat). Tinnitus is often associated with either a conductive or sensorineural hearing loss. T e pathophysiology of tinnitus is not well understood. T e cause of the tinnitus can usually be determined by finding the cause of the associated hearing loss. Tinnitus may be the first symptom of a serious condition such as a vestibular schwannoma. Pulsatile tinnitus requires evaluation of the vascular system of the head to exclude vascular tumors such as glomus jugulare tumors, aneurysms, dural arteriovenous fistulas, and stenotic arterial lesions; it may also occur with SOM. It is most commonly associated with some abnormality of the jugular bulb such as a large jugular bulb or jugular bulb diverticulum.

GENETIC CAUSES OF HEARING LOSS

More than half of childhood hearing impairment is thought to be hereditary; hereditary hearing impairment (HHI) can also manifest later in life. HHI may be classified as either nonsyndromic, when hearing loss is the only clinical abnormality, or syndromic, when hearing loss is associated with anomalies in other organ systems. Nearly two-thirds of HHIs are nonsyndromic, and the remaining one-third are syndromic. Between 70 and 80% of nonsyndromic HHI is inherited in an autosomal recessive manner and designated DFNB; another 15–20% is autosomal dominant (DFNA). Less than 5% is X-linked (DFNX) or maternally inherited via the mitochondria.

More than 150 loci harboring genes for nonsyndromic HHI have been mapped, with recessive loci outnumbering dominant; numerous genes have now been identified **(Table 29-1)**. T e hearing genes fall into the categories of structural proteins (MYH9, MYO7A, MYO15, TECTA, DIAPH1), transcription factors (POU3F4, POU4F3), ion channels (KCNQ4, SLC26A4), and gap junction proteins (GJB2, GJB3, GJB6). Several of these genes, including GJB2, TECTA, and TMC1, cause both autosomal dominant and recessive forms of nonsyndromic HHI. In general, the hearing loss associated with dominant genes has its onset in adolescence or adulthood, varies in severity, and progresses with age, whereas the hearing loss associated with recessive inheritance is congenital and profound. Connexin 26, product of the GJB2 gene, is particularly important because it is responsible for nearly 20% of all cases of childhood deafness; half of genetic deafness in children is GJB2-related. Two frameshift mutations, 35delG and 167delT, account for >50% of the cases; however, screening for these two mutations alone is insufficient, and sequencing of the entire gene is required to diagnose GJB2-related recessive deafness. T e 167delT mutation is highly prevalent in Ashkenazi Jews; ~1 in 1765 individuals in this population are homozygous and affected. T e hearing loss can also vary among the members of the same family, suggesting that other genes or factors influence the auditory phenotype.

In addition to GJB2, several other nonsyndromic genes are associated with hearing loss that progresses with age. T e contribution of genetics to presbycusis is also becoming better understood. Sensitivity to aminoglycoside ototoxicity can be maternally transmitted through a mitochondrial mutation. Susceptibility to noise-induced hearing loss may also be genetically determined.

T ere are >400 syndromic forms of hearing loss. T ese include Usher's syndrome (retinitis pigmentosa and hearing loss), Waardenburg's syndrome (pigmentary abnormality and hearing loss), Pendred's syndrome (thyroid organification defect and hearing loss), Alport's syndrome (renal disease and hearing loss), Jervell and Lange-Nielsen syndrome (prolonged QT interval and hearing loss), neurofibromatosis type 2 (bilateral acoustic schwannoma), and mitochondrial disorders

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 29-1

HEREDITARY HEARING IMPAIRMENT GENES

DESIGNATION	GENE	FUNCTION
Autosomal Dominant		
	CRYM	Thyroid hormone–binding protein
DFNA1	DIAPH1	Cytoskeletal protein
DFNA2A	KCNQ4	Potassium channel
DFNA2B	GJB3 (Cx31)	Gap junction
DFNA3A	GJB2 (Cx26)	Gap junction
DFNA3B	GJB6 (Cx30)	Gap junction
DFNA4	MYH14 CEACAM16	Class II nonmuscle myosin Cell adhesion molecule
DFNA5	DFNA5	Unknown
DFNA6/14/38	WFS1	Transmembrane protein
DFNA8/12	TECTA	Tectorial membrane protein
DFNA9	COCH	Unknown
DFNA10	EYA4	Developmental gene
DFNA11	MYO7A	Cytoskeletal protein
DFNA13	COL11A2	Cytoskeletal protein
DFNA15	POU4F3	Transcription factor
DFNA17	MYH9	Cytoskeletal protein
DFNA20/26	ACTG1	Cytoskeletal protein
DFNA22	MYO6	Unconventional myosin
DFNA23	SIX1	Developmental gene
DFNA25	SLC17AB	Vesicular glutamate transporter
DFNA28	TFCP2L3	Transcription factor
DFNA36	TMC1	Transmembrane protein
DFNA41	P2RX2	Purinergic receptor
DFNA44	CCDC50	Effector of epidermal growth factor–mediated signaling
DFNA48	MYO1A	Unconventional myosin
DFNA50	MIRN96	MicroRNA
DFNA51	TJP2	Tight junction protein
DFNA56	TNC	Extracellular matrix protein
DFNA64	SMAC/DIABLO	Mitochondrial proapoptotic protein
Autosomal Recessive		
DFNB1A	GJB2 (CX26)	Gap junction
DFNB1B	GJB6 (CX30)	Gap junction
DFNB2	MYO7A	Cytoskeletal protein
DFNB3	MYO15	Cytoskeletal protein
DFNB4	PDS (SLC26A4)	Chloride/iodide transporter
DFNB6	TMIE	Transmembrane protein
DFNB7/B11	TMC1	Transmembrane protein
DFNB9	OTOF	Traf cking of membrane vesicles
DFNB8/10	TMPRSS3	Transmembrane serine protease
DFNB12	CDH23	Intercellular adherence protein
DFNB15/72/95	GIPC3	PDZ domain containing protein
DFNB16	STRC	Stereocilia protein
DFNB18	USH1C	Unknown
DFNB21	TECTA	Tectorial membrane protein
DFNB22	OTOA	Gel attachment to nonsensory cell
DFNB23	PCDH15	Morphogenesis and cohesion
DFNB24	RDX	Cytoskeletal protein
DFNB25	GRXCR1	Reversible S-glutathionylation of proteins
DFNB28	TRIOBP	Cytoskeletal-organizing protein
DFNB29	CLDN14	Tight junctions
DFNB30	MYO3A	Hybrid motor-signaling myosin
DFNB31	WHRN	PDZ domain–containing protein
DFNB35	ESRRB	Estrogen-related receptor beta protein
DFNB36	ESPN	Ca-insensitive actin-bundling protein
DFNB37	MYO6	Unconventional myosin
DFNB39	HFG	Hepatocyte growth factor
DFNB42	ILDR1	Ig-like domain-containing receptor
DFNB48	CIB2	Calcium and integrin binding protein
DFNB49	MARVELD2	Tight junction protein
DFNB53	COL11A2	Collagen protein
DFNB59	PJVK	Zn-binding protein
DFNB61	SLC26A5	Motor protein
DFNB63	LRTOMT/COMT2	Putative methyltransferase
DFNB66/67	LHFPL5	Tetraspan protein
DFNB70	PNPT1	Mitochondrial-RNA-import protein
DFNB74	MSRB3	Methionine sulfoxide reductase
DFNB77	LOXHD1	Stereociliary protein
DFNB79	TPRN	Unknown
DFNB82	GPSM2	G protein signaling modulator
DFNB84	PTPRQ	Type III receptor-like protein-tyrosine phosphatase family
DFNB86	TBC1D24	GTPase-activating protein
DFNB88	ELMOD3	GTPase-activating protein
DFNB89	KARS	Lysyl-tRNA synthetase
DFNB91	GJB3	Gap junction
DFNB93	CABP2	Calcium binding protein
DFNB98	TSPEAR	Epilepsy-associated repeats containing protein
	SERPINB6	Protease inhibitor

www.ketabpezeshki.com (021) 66485457 - 66485438

(mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy and ragged red fibers [MERRF]; progressive external ophthalmoplegia [PEO]) **(Table 29-2)**.

TABLE 29-2

SYNDROMIC HEREDITARY HEARING IMPAIRMENT GENES

SYNDROME	GENE	FUNCTION
Alport's syndrome	COL4A3-5	Cytoskeletal protein
BOR syndrome	EYA1	Developmental gene
	SIX5	Developmental gene
	SIX1	Developmental gene
Jervell and Lange-Nielsen syndrome	KCNQ1	Delayed rectifier K^+ channel
	KCNE1	Delayed rectifier K^+ channel
Norrie's disease	NDP	Cell-cell interactions
Pendred's syndrome	SLC26A4	Chloride/iodide transporter
	FOXI1	Transcriptional activator of SLC26A4
	KCNJ10	Inwardly rectifying K^+ channel
Treacher Collins syndrome	TCOF1	Nucleolar-cytoplasmic transport
	POLR1D	Subunit of RNA polymerases I and III
	POLR1C	Subunit of RNA polymerases I and III
Usher's syndrome	MYO7A	Cytoskeletal protein
	USH1C	Unknown
	CDH23	Intercellular adherence protein
	PCDH15	Cell adhesion molecule
	SANS	Harmonin-associated protein
	CIB2	Calcium and integrin binding protein
	USH2A	Cell adhesion molecule
	VLGR1	G protein–coupled receptor
	WHRN	PDZ domain–containing protein
	CLRN1	Cellular synapse protein?
	PDZD7	PDZ domain containing protein
WS type I, III	PAX3	Transcription factor
WS type II	MITF	Transcription factor
	SNAI2	Transcription factor
WS type IV	EDNRB	Endothelin B receptor
	EDN3	Endothelin B receptor ligand
	SOX10	Transcription factor

Abbreviations: BOR, branchio-oto-renal syndrome; WS, Waardenburg's syndrome.

APPROACH TO THE PATIENT: Disorders of the Sense of Hearing

The goal in the evaluation of a patient with auditory complaints is to determine (1) the nature of the hearing impairment (conductive vs sensorineural vs mixed), (2) the severity of the impairment (mild, moderate, severe, or profound), (3) the anatomy of the impairment (external ear, middle ear, inner ear, or central auditory pathway), and (4) the etiology. The history should elicit characteristics of the hearing loss, including the duration of deafness, unilateral versus bilateral involvement, nature of onset (sudden vs insidious), and rate of progression (rapid vs slow). Symptoms of tinnitus, vertigo, imbalance, aural fullness, otorrhea, headache, facial nerve dysfunction, and head and neck paresthesias should be noted. Information regarding head trauma, exposure to ototoxins, occupational or recreational noise exposure, and family history of hearing impairment may also be important. A sudden onset of unilateral hearing loss, with or without tinnitus, may represent a viral infection of the inner ear, vestibular schwannoma, or a stroke. Patients with unilateral hearing loss (sensory or conductive) usually complain of reduced hearing, poor sound localization, and difficulty hearing clearly with background noise. Gradual progression of a hearing deficit is common with otosclerosis, noise-induced hearing loss, vestibular schwannoma, or Ménière's disease. Small vestibular schwannomas typically present with asymmetric hearing impairment, tinnitus, and imbalance (rarely vertigo); cranial neuropathy, in particular of the trigeminal or facial nerve, may accompany larger tumors. In addition to hearing loss, Ménière's disease may be associated with episodic vertigo, tinnitus, and aural fullness. Hearing loss with otorrhea is most likely due to chronic otitis media or cholesteatoma.

Examination should include the auricle, external ear canal, and tympanic membrane. The external ear canal of the elderly is often dry and fragile; it is preferable to clean cerumen with wall-mounted suction or cerumen loops and to avoid irrigation. In examining the eardrum, the topography of the tympanic membrane is more important than the presence or absence of the light reflex. In addition to the pars tensa (the lower two-thirds of the tympanic membrane), the pars flaccida (upper one-third of the tympanic membrane) above the short process of the malleus should also be examined for retraction pockets that may be evidence of chronic eustachian tube dysfunction or cholesteatoma. Insufflation of the ear canal is necessary to assess tympanic membrane mobility and compliance. Careful inspection of the nose, nasopharynx, and upper respiratory tract is indicated. Unilateral serous effusion should prompt a fiberoptic examination of the nasopharynx to exclude neoplasms. Cranial nerves should be evaluated with special attention to facial and trigeminal

www.ketabpezeshki.com (021) 66485457 - 66485438

nerves, which are commonly affected with tumors involving the cerebellopontine angle.

T e Rinne and Weber tuning fork tests, with a 512-Hz tuning fork, are used to screen for hearing loss, differentiate conductive from sensorineural hearing losses, and confirm the findings of audiologic evaluation. T e Rinne test compares the ability to hear by air conduction with the ability to hear by bone conduction. T e tines of a vibrating tuning fork are held near the opening of the external auditory canal, and then the stem is placed on the mastoid process; for direct contact, it may be placed on teeth or dentures. T e patient is asked to indicate whether the tone is louder by air conduction or bone conduction. Normally, and in the presence of sensorineural hearing loss, a tone is heard louder by air conduction than by bone conduction; however, with conductive hearing loss of ≥30 dB (see "Audiologic Assessment," below), the bone-conduction stimulus is perceived as louder than the air-conduction stimulus. For the Weber test, the stem of a vibrating tuning fork is placed on the head in the midline and the patient is asked whether the tone is heard in both ears or better in one ear than in the other. With a unilateral conductive hearing loss, the tone is perceived in the affected ear. With a unilateral sensorineural hearing loss, the tone is perceived in the unaffected ear. A 5-dB difference in hearing between the two ears is required for lateralization.

LABORATORY ASSESSMENT OF HEARING

Audiologic assessment

T e minimum audiologic assessment for hearing loss should include the measurement of pure tone air-conduction and bone-conduction thresholds, speech reception threshold, word recognition score, tympanometry, acoustic reflexes, and acoustic-reflex decay. T is test battery provides a screening evaluation of the entire auditory system and allows one to determine whether further differentiation of a sensory (cochlear) from a neural (retrocochlear) hearing loss is indicated.

Pure tone audiometry assesses hearing acuity for pure tones. T e test is administered by an audiologist and is performed in a sound-attenuated chamber. T e pure tone stimulus is delivered with an audiometer, an electronic device that allows the presentation of specific frequencies (generally between 250 and 8000 Hz) at specific intensities. Air- and bone-conduction thresholds are established for each ear. Air-conduction thresholds are determined by presenting the stimulus in air with the use of headphones. Bone-conduction thresholds are determined by placing the stem of a vibrating tuning fork or an oscillator of an audiometer in contact with the head. In the presence of a hearing loss, broad-spectrum noise is presented to the nontest ear for masking purposes so that responses are based on perception from the ear under test.

T e responses are measured in decibels. An audiogram is a plot of intensity in decibels of hearing threshold versus frequency. A decibel (dB) is equal to 20 times the logarithm of the ratio of the sound pressure required to achieve threshold in the patient to the sound pressure required to achieve threshold in a normal-hearing person. T erefore, a change of 6 dB represents doubling of sound pressure, and a change of 20 dB represents a tenfold change in sound pressure. Loudness, which depends on the frequency, intensity, and duration of a sound, doubles with approximately each 10-dB increase in sound pressure level. Pitch, on the other hand, does not directly correlate with frequency. T e perception of pitch changes slowly in the low and high frequencies. In the middle tones, which are important for human speech, pitch varies more rapidly with changes in frequency.

Pure tone audiometry establishes the presence and severity of hearing impairment, unilateral versus bilateral involvement, and the type of hearing loss. Conductive hearing losses with a large mass component, as is often seen in middle ear effusions, produce elevation of thresholds that predominate in the higher frequencies. Conductive hearing losses with a large stiffness component, as in fixation of the footplate of the stapes in early otosclerosis, produce threshold elevations in the lower frequencies. Often, the conductive hearing loss involves all frequencies, suggesting involvement of both stiffness and mass. In general, sensorineural hearing losses such as presbycusis affect higher frequencies more than lower frequencies (Fig. 29-3). An exception is Ménière's disease, which is characteristically associated with low-frequency sensorineural hearing loss. Noise-induced hearing loss has an unusual pattern of hearing impairment in which the loss at 4000 Hz is greater than at higher frequencies. Vestibular schwannomas characteristically affect the higher frequencies, but any pattern of hearing loss can be observed.

Speech recognition requires greater synchronous neural firing than is necessary for appreciation of pure tones. Speech audiometry tests the clarity with which one hears. T e speech reception threshold (SRT) is defined as the intensity at which speech is recognized as a meaningful symbol and is obtained by presenting two-syllable words with an equal accent on each syllable. T e intensity at which the patient can repeat 50% of the words correctly is the SRT. Once the SRT is determined, discrimination or word recognition ability is tested by presenting one-syllable words at 25–40 dB above the SRT. T e words are phonetically balanced in that the phonemes (speech sounds) occur in the list of words at the same frequency that they occur

www.ketabpezeshki.com (021) 66485457 - 66485438

in ordinary conversational English. An individual with normal hearing or conductive hearing loss can repeat 88–100% of the phonetically balanced words correctly. Patients with a sensorineural hearing loss have variable loss of discrimination. As a general rule, neural lesions produce greater deficits in discrimination than do cochlear lesions. For example, in a patient with mild asymmetric sensorineural hearing loss, a clue to the diagnosis of vestibular schwannoma is the presence of greater than expected deterioration in discrimination ability. Deterioration in discrimination ability at higher intensities above the SRT also suggests a lesion in the eighth nerve or central auditory pathways.

Tympanometry measures the impedance of the middle ear to sound and is useful in diagnosis of middle ear effusions. A tympanogram is the graphic representation of change in impedance or compliance as the pressure in the ear canal is changed. Normally, the middle ear is most compliant at atmospheric pressure, and the compliance decreases as the pressure is increased or decreased (type A); this pattern is seen with normal hearing or in the presence of sensorineural hearing loss. Compliance that does not change with change in pressure suggests middle ear effusion (type B). With a negative pressure in the middle ear, as with eustachian tube obstruction, the point of maximal compliance occurs with negative pressure in the ear canal (type C). A tympanogram in which no point of maximal compliance can be obtained is most commonly seen with discontinuity of the ossicular chain (type A_d). A reduction in the maximal compliance peak can be seen in otosclerosis (type A_s).

During tympanometry, an intense tone elicits contraction of the stapedius muscle. T e change in compliance of the middle ear with contraction of the stapedius muscle can be detected. T e presence or absence of this acoustic ref ex is important in determining the etiology of hearing loss as well as in the anatomic localization of facial nerve paralysis. T e acoustic reflex can help differentiate between conductive hearing loss due to otosclerosis and that caused by an inner ear "third window": it is absent in otosclerosis and present in inner ear conductive hearing loss. Normal or elevated acoustic reflex thresholds in an individual with sensorineural hearing impairment suggest a cochlear hearing loss. An absent acoustic reflex in the setting of sensorineural hearing loss is not helpful in localizing the site of lesion. Assessment of acoustic ref ex decay helps differentiate sensory from neural hearing losses. In neural hearing loss, such as with vestibular schwannoma, the reflex adapts or decays with time.

OAEs generated by outer hair cells only can be measured with microphones inserted into the external auditory canal. T e emissions may be spontaneous or evoked with sound stimulation. T e presence of OAEs indicates that the outer hair cells of the organ of Corti are intact and can be used to assess auditory thresholds and to distinguish sensory from neural hearing losses.

Evoked responses

Electrocochleography measures the earliest evoked potentials generated in the cochlea and the auditory nerve. Receptor potentials recorded include the cochlear microphonic, generated by the outer hair cells of the organ of Corti, and the summating potential, generated by the inner hair cells in response to sound. T e whole nerve action potential representing the composite firing of the first-order neurons can also be recorded during electrocochleography. Clinically, the test is useful in the diagnosis of Ménière's disease, where an elevation of the ratio of summating potential to action potential is seen.

Brainstem auditory evoked responses (BAERs), also known as auditory brainstem responses (ABRs), are useful in differentiating the site of sensorineural hearing loss. In response to sound, five distinct electrical potentials arising from different stations along the peripheral and central auditory pathway can be identified using computer averaging from scalp surface electrodes. BAERs are valuable in situations in which patients cannot or will not give reliable voluntary thresholds. T ey are also used to assess the integrity of the auditory nerve and brainstem in various clinical situations, including intraoperative monitoring, and in determination of brain death.

T e vestibular-evoked myogenic potential (VEMP) test elicits a vestibulocolic reflex whose afferent limb arises from acoustically sensitive cells in the saccule, with signals conducted via the inferior vestibular nerve. VEMP is a biphasic, short-latency response recorded from the tonically contracted sternocleidomastoid muscle in response to loud auditory clicks or tones. VEMPs may be diminished or absent in patients with early and late Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo, and vestibular schwannoma. On the other hand, the threshold for VEMPs may be lower in cases of superior canal dehiscence, other inner ear dehiscence, and perilymphatic fistula.

Imaging studies

T e choice of radiologic tests is largely determined by whether the goal is to evaluate the bony anatomy of the external, middle, and inner ear or to image the auditory nerve and brain. Axial and coronal CT of the temporal bone with fine 0.3- to 0.6-mm cuts is ideal for determining the caliber of the external auditory canal, integrity of the ossicular chain, and presence of middle ear or mastoid disease; it can also detect inner

www.ketabpezeshki.com (021) 66485457 - 66485438

ear malformations. CT is also ideal for the detection of bone erosion with chronic otitis media and cholesteatoma. Pöschl reformatting in the plane of the superior semicircular canal is required for the identification of dehiscence or absence of bone over the superior semicircular canal. MRI is superior to CT for imaging of retrocochlear pathology such as vestibular schwannoma, meningioma, other lesions of the cerebellopontine angle, demyelinating lesions of the brainstem, and brain tumors. Both CT and MRI are equally capable of identifying inner ear malformations and assessing cochlear patency for preoperative evaluation of patients for cochlear implantation.

TREATMENT Disorders of the Sense of Hearing

In general, conductive hearing losses are amenable to surgical correction, whereas sensorineural hearing losses are usually managed medically. Atresia of the ear canal can be surgically repaired, often with significant improvement in hearing. Tympanic membrane perforations due to chronic otitis media or trauma can be repaired with an outpatient tympanoplasty. Likewise, conductive hearing loss associated with otosclerosis can be treated by stapedectomy, which is successful in >95% of cases. Tympanostomy tubes allow the prompt return of normal hearing in individuals with middle ear effusions. Hearing aids are effective and well tolerated in patients with conductive hearing losses.

Patients with mild, moderate, and severe sensorineural hearing losses are regularly rehabilitated with hearing aids of varying configuration and strength. Hearing aids have been improved to provide greater fidelity and have been miniaturized. T e current generation of hearing aids can be placed entirely within the ear canal, thus reducing any stigma associated with their use. In general, the more severe the hearing impairment, the larger the hearing aid required for auditory rehabilitation. Digital hearing aids lend themselves to individual programming, and multiple and directional microphones at the ear level may be helpful in noisy surroundings. Because all hearing aids amplify noise as well as speech, the only absolute solution to the problem of noise is to place the microphone closer to the speaker than the noise source. T is arrangement is not possible with a self-contained, cosmetically acceptable device. A significant limitation of rehabilitation with a hearing aid is that although it is able to enhance detection of sound with amplification, it cannot restore clarity of hearing that is lost with presbycusis.

Patients with unilateral deafness have difficulty with sound localization and reduced clarity of hearing in background noise. T ey may benefit from a CROS (contralateral routing of signal) hearing aid in which a microphone is placed on the hearing-impaired side and the sound is transmitted to the receiver placed on the contralateral ear. T e same result may be obtained with a bone-anchored hearing aid (BAHA), in which a hearing aid clamps to a screw integrated into the skull on the hearing-impaired side. Like the CROS hearing aid, the BAHA transfers the acoustic signal to the contralateral hearing ear, but it does so by vibrating the skull. Patients with profound deafness on one side and some hearing loss in the better ear are candidates for a BICROS hearing aid; it differs from the CROS hearing aid in that the patient wears a hearing aid, and not simply a receiver, in the better ear. Unfortunately, while CROS and BAHA devices provide benefit, they do not restore hearing in the deaf ear. Only cochlear implants can restore hearing (see below). Increasingly, cochlear implants are being investigated for the treatment of patients with single-sided deafness; early reports show great promise in not only restoring hearing but also improving sound localization and performance in background noise.

In many situations, including lectures and the theater, hearing-impaired persons benefit from assistive devices that are based on the principle of having the speaker closer to the microphone than any source of noise. Assistive devices include infrared and frequency-modulated (FM) transmission as well as an electromagnetic loop around the room for transmission to the individual's hearing aid. Hearing aids with telecoils can also be used with properly equipped telephones in the same way.

In the event that the hearing aid provides inadequate rehabilitation, cochlear implants may be appropriate **(Fig. 29-4)**. Criteria for implantation include severe to profound hearing loss with open-set sentence cognition of ≤40% under best aided conditions. Worldwide, more than 300,000 hearing-impaired individuals have received cochlear implants. Cochlear implants are neural prostheses that convert sound energy to electrical energy and can be used to stimulate the auditory division of the eighth nerve directly. In most cases of profound hearing impairment, the auditory hair cells are lost but the ganglionic cells of the auditory division of the eighth nerve are preserved. Cochlear implants consist of electrodes that are inserted into the cochlea through the round window, speech processors that extract acoustical elements of speech for conversion to electrical currents, and a means of transmitting the electrical energy through the skin. Patients with implants experience sound that helps with speech reading, allows open-set word recognition, and helps in modulating the person's own voice. Usually, within the first 3–6 months after implantation, adult patients can understand speech without visual cues. With the current generation of multichannel cochlear implants, nearly 75% of patients are able to converse on the telephone.

T e U.S. Food and Drug Administration recently approved the first hybrid cochlear implant for the treatment of high-frequency hearing loss. Patients with presbyacusis typically have normal low-frequency hearing, while suffering from high-frequency hearing loss associated with loss of clarity that cannot always be adequately rehabilitated with a hearing aid. However, these patients are not candidates for

www.ketabpezeshki.com (021) 66485457 - 66485438

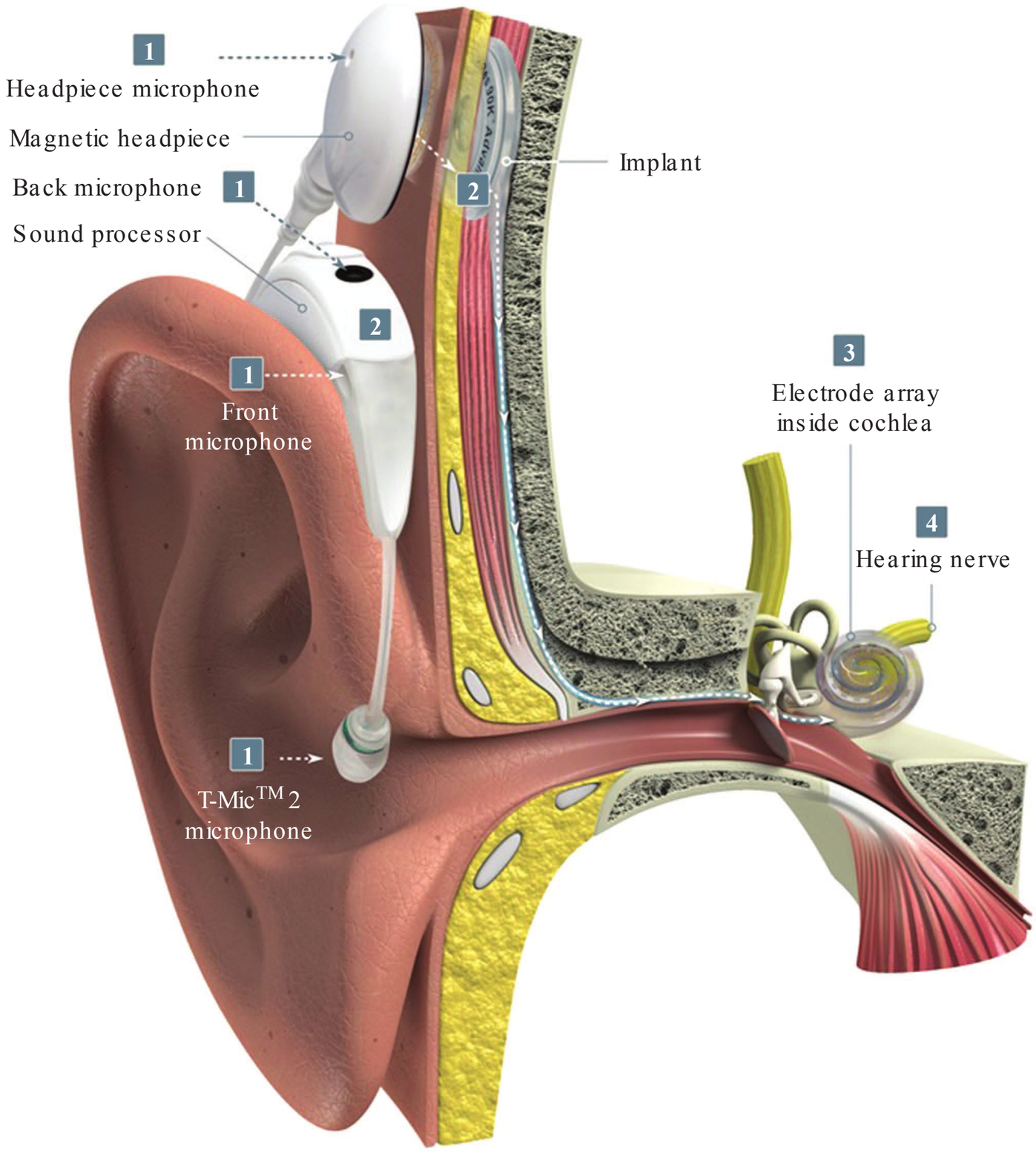


FIGURE 29-4
A cochlear implant is composed of an external microphone and speech processor worn on the ear and a receiver implanted underneath the temporalis muscle. The internal receiver is attached to an electrode that is placed surgically in the cochlea.

conventional cochlear implants because they have too much residual hearing. T e hybrid implant has been specifically designed for this patient population; it has a shorter electrode than a conventional cochlear implant and can be introduced into the cochlea atraumatically, thus preserving low-frequency hearing. Individuals with a hybrid implant use their own natural low-frequency "acoustic" hearing and rely on the implant for providing "electrical" high-frequency hearing. Patients who have received the hybrid implant perform better on speech testing in both quiet and noisy backgrounds.

For individuals who have had both eighth nerves destroyed by trauma or bilateral vestibular schwannomas (e.g., neurofibromatosis type 2), brainstem auditory implants placed near the cochlear nucleus may provide auditory rehabilitation.

Tinnitus often accompanies hearing loss. As for background noise, tinnitus can degrade speech comprehension in individuals with hearing impairment. T erapy for tinnitus is usually directed toward minimizing the appreciation of tinnitus. Relief of the tinnitus may be obtained by masking it with background music. Hearing aids are also helpful in tinnitus suppression, as are tinnitus maskers, devices that present a sound to the affected ear that is more pleasant to listen to than the tinnitus. T e use of a tinnitus masker is often followed by several hours of inhibition of the tinnitus. Antidepressants have been shown to be beneficial in helping patients cope with tinnitus.

Hard-of-hearing individuals often benefit from a reduction in unnecessary noise in the environment (e.g., radio or television) to enhance the signal-to-noise ratio. Speech comprehension is aided by lip reading; therefore, the impaired listener should be seated so that the face of the speaker is well illuminated and easily seen. Although speech should be in a loud, clear voice, one should be aware that in sensorineural hearing losses in general and in hard-of-hearing elderly in particular, recruitment (abnormal perception of loud sounds) may be troublesome. Above all, optimal communication cannot take place without both parties giving it their full and undivided attention.

www.ketabpezeshki.com (021) 66485457 - 66485438

PREVENTION

Conductive hearing losses may be prevented by prompt antibiotic therapy of adequate duration for AOM and by ventilation of the middle ear with tympanostomy tubes in middle ear effusions lasting ≥12 weeks. Loss of vestibular function and deafness due to aminoglycoside antibiotics can largely be prevented by careful monitoring of serum peak and trough levels.

Some 10 million Americans have noise-induced hearing loss, and 20 million are exposed to hazardous noise in their employment. Noise-induced hearing loss can be prevented by avoidance of exposure to loud noise or by regular use of ear plugs or fluid-filled ear muffs to attenuate intense sound. **Table 29-3** lists loudness levels for a variety of environmental sounds. High-risk activities for noise-induced hearing loss include use of electrical equipment for wood and metal working and target practice or hunting with small firearms. All internal-combustion and electric engines, including snow and leaf blowers, snowmobiles, outboard motors, and chainsaws, require protection of the user with hearing protectors. Virtually all noise-induced hearing loss is preventable through education, which should begin before the teenage years. Programs for conservation of hearing in the workplace are required by the Occupational Safety and Health Administration (OSHA) whenever the exposure over an 8-h period averages 85 dB. OSHA mandates that workers in such noisy environments have hearing monitoring and protection programs that include a preemployment screen, an annual audiologic assessment, and the mandatory use of hearing protectors. Exposure to loud sounds above 85 dB in the work environment is restricted by OSHA, with halving of allowed exposure time for each increment of 5 dB above this threshold; for example, exposure to 90 dB is permitted for 8 h; 95 dB for 4 h, and 100 dB for 2 h **(Table 29-4)**.

TABLE 29-3

DECIBEL (LOUDNESS) LEVEL OF COMMON ENVIRONMENTAL NOISE

SOURCE	DECIBEL (DB)
Weakest sound heard	0
Whisper	30
Normal conversation	55–65
City traf c inside car	85
OSHA monitoring requirement begins	**90**
Jackhammer	95
Subway train at 200 ft	95
Power mower	107
Power saw	110
Painful sound	**125**
Jet engine at 100 feet	140
12-gauge shotgun blast	165
Loudest sound that can occur	194

Abbreviation: OSHA, Occupational Safety and Health Administration.

TABLE 29-4

OSHA DAILY PERMISSIBLE NOISE LEVEL EXPOSURE

SOUND LEVEL (DB)	DURATION PER DAY (H)
90	8
92	6
95	4
97	3
100	2
102	1.5
105	1
110	0.5
115	≤0.25

Note: Exposure to impulsive or impact noise should not exceed 140-dB peak sound pressure level.

Source: From https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9735.

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION III

DISEASES OF THE NERVOUS SYSTEM

CHAPTER 30

BIOLOGY OF NEUROLOGIC DISEASES

Stephen L. Hauser ■ Stanley B. Prusiner ■ M. Flint Beal

The human nervous system is the organ of consciousness, cognition, ethics, and behavior; as such, it is the most intricate structure known to exist. More than one-third of the 23,000 genes encoded in the human genome are expressed in the nervous system. Each mature brain is composed of 100 billion neurons, several million miles of axons and dendrites, and $>10^{15}$ synapses. Neurons exist within a dense parenchyma of multifunctional glial cells that synthesize myelin, preserve homeostasis, and regulate immune responses. Measured against this background of complexity, the achievements of molecular neuroscience have been extraordinary. This chapter reviews selected themes in neuroscience that provide a context for understanding fundamental mechanisms underlying neurologic disorders.

NEUROGENETICS

The landscape of neurology has been transformed by modern molecular genetics. Several hundred neurologic and psychiatric disorders can now be diagnosed through genetic testing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests). The vast majority of these represent highly penetrant mutations that cause rare neurologic disorders; alternatively, they represent rare monogenic causes of common phenotypes. Examples of the latter include mutations of the amyloid precursor protein in familial Alzheimer's disease, the microtubule-associated protein tau (MAPT) in frontotemporal dementia, and α-synuclein in Parkinson's disease. These discoveries have been profoundly important because the mutated gene in the familial disorder often encodes a protein that is also pathogenetically involved (although not mutated) in the typical, sporadic form. The common mechanism involves disordered processing and, ultimately, aggregation of the protein leading to cell death (see "Protein Aggregation and Neurodegeneration," below).

There is optimism that complex genetic disorders, caused by combinations of both genetic and environmental factors, have now become tractable problems. Genome-wide association studies (GWAS) have been carried out in many complex neurologic disorders, with many hundreds of variants identified, nearly all of which confer only a small increment in disease risk (1.15- to 1.5-fold). GWAS studies are rooted in the "common disease, common variant" hypothesis, as they examine potential risk alleles that are relatively frequent (e.g. >5%) in the general population. More than 1500 GWAS studies have been carried out, with notable successes such as the identification of 110 risk alleles for multiple sclerosis **(Chap. 45)**. Furthermore, using bioinformatics tools, risk variants can be aligned in functional biologic pathways to identify novel pathogenic mechanisms as well as to reveal heterogeneity (e.g., different pathways in different individuals). Despite these successes, many experienced geneticists question the real value of common disease-associated variants, particularly whether they are actually causative or merely mark the approximate locations of more important—truly causative—rare mutations.

This debate has set the stage for the next revolution in human genetics, made possible by the development of increasingly efficient and cost-effective high-throughput sequencing methodologies. It is already possible to sequence an entire human genome in approximately an hour, at a cost of only $1300 for the entire coding sequence ("whole-exome") or $3000 for the entire genome; it is certain that these costs will continue to decline. This makes it feasible to look for disease-causing sequence variations in individual patients with the possibility of identifying rare variants that cause disease. The utility of this approach was demonstrated by whole-genome sequencing in a patient with

www.ketabpezeshki.com (021) 66485457 - 66485438

Charcot-Marie-Tooth (CMT) neuropathy, in which compound heterozygous mutations were identified in the SH3TC2 gene, which then were shown to co-segregate with the disease in other members of the family.

It is increasingly recognized that not all genetic diseases or predispositions are caused by simple changes in the linear nucleotide sequence of genes. Disease-causative mutations also occur commonly in noncoding sequences of DNA. For example, large intronic GGGGCC repeat expansions in a gene of unknown function C9orf 72 (chromosome 9 open reading frame 72) were recently identified as a common cause of both frontotemporal dementia and amyotrophic lateral sclerosis (ALS). T is mutation is the most common cause of both familial and sporadic ALS identified thus far. It was shown to be associated with TDP-43 (tar DNA binding protein-43) inclusions in both hippocampal and cerebral neurons. Interestingly, despite the absence of a start codon, the three alternate dipeptide sequences consisting of two amino acids are translated and found in postmortem brain tissue of affected patients. T ree potential pathogenic mechanisms have been proposed, including (1) haploinsufficiency, (2) repeat RNA-mediated toxicity, and (3) dipeptide protein toxicity. T e possibility of RNA toxicity is supported by the finding of intranuclear RNA foci containing C9orf 72 hexanucleotide repeats and specific RNA-binding proteins. T e C9orf 72 mRNA forms quadruplexes of DNA and RNA, which then can halt transcription and also bind transcription factors. Mutations in both TARDP (transactive region DNA binding protein) and FUS (fused in sarcoma) also encode DNA/RNA-processing polypeptides and are a cause of familial and sporadic ALS.

As the complex architecture of the human genome becomes better defined, many disorders that result from alterations in copy numbers of genes ("gene-dosage" effects) resulting from unequal crossing-over are also likely to be identified. As much as 5–10% of the human genome consists of nonhomologous duplications and deletions, and these appear to occur with a much higher mutational rate than is the case for single base pair mutations. T e first copy-number disorders to be recognized were Charcot-Marie-Tooth disease type 1A (CMT1A), caused by a duplication in the gene encoding the myelin protein PMP22, and the reciprocal deletion of the gene causing hereditary liability to pressure palsies **(Chap. 53)**. Gene-dosage effects are causative in some cases of Parkinson's disease (α-synuclein), Alzheimer's disease (amyloid precursor protein), spinal muscular atrophy (survival motor neuron 2), the dysmyelinating disorder Pelizaeus-Merzbacher syndrome (proteolipid protein 1), late-onset leukodystrophy (lamin B1), and a variety of developmental neurologic disorders. It is likely that copy-number variations contribute substantially to normal human genomic variation for numerous genes involved in neurologic function, regulation of cell growth, and regulation of metabolism. It is also already clear that gene-dosage effects will influence many behavioral phenotypes, learning disorders, and autism spectrum disorders. Deletions at ch30q and ch15q have been associated with schizophrenia, and deletions at 15q and 16p with autism. Interestingly, the 16p deletion is also associated with epilepsy. Duplications of the X-linked MeCP2 gene cause autism in males and psychiatric disorders with anxiety in females, whereas point mutations in this gene produce the neurodevelopmental disorder Rett's syndrome. T e understanding of the role of copy number variation in human disease is still in its infancy.

T e role of splicing variation as a contributor to neurologic disease is another area of active investigation. Alternative splicing refers to the inclusion of different combinations of exons in mature mRNA, resulting in the potential for many different protein products encoded by a single gene. Alternative splicing represents a powerful mechanism for generation of complexity and variation, and this mechanism appears to be highly prevalent in the nervous system, affecting key processes such as neurotransmitter receptors and ion channels. Numerous diseases are already known to result from abnormalities in alternative splicing. Increased inclusion of exon 10–containing transcripts of MAPT can cause frontotemporal dementia. Aberrant splicing also contributes to the pathogenesis of Duchenne's, myotonic, and facioscapulohumeral muscular dystrophies; ataxia telangiectasia; neurofibromatosis; some inherited ataxias; and fragile X syndrome, among other disorders. It is also likely that subtle variations of splicing will influence many genetically complex disorders. A splicing variant of the interleukin 7 receptor α chain, resulting in production of more soluble and less membrane-bound receptor, is associated with susceptibility to multiple sclerosis (MS) in multiple different populations.

Epigenetics refers to the mechanisms by which levels of gene expression can be exquisitely modulated, not by variations in the primary genetic sequence of DNA but rather by postgenomic alterations in DNA and chromatin structure, which influence how, when, and where genes are expressed. DNA methylation and methylation and acetylation of histone proteins that interact with nuclear DNA to form chromatin are key mediators of these events. Epigenetic processes appear to be dynamically active even in postmitotic neurons. Imprinting refers to an epigenetic feature, present for a subset of genes, in which the predominant expression of one allele is determined by its parent of origin. T e distinctive neurodevelopmental disorders Prader-Willi syndrome (mild mental retardation and endocrine abnormalities) and Angelman's syndrome

www.ketabpezeshki.com (021) 66485457 - 66485438

(cortical atrophy, cerebellar dysmyelination, Purkinje cell loss) are classic examples of imprinting disorders whose distinctive features are determined by whether the paternal or maternal copy of the chromosome of the critical genetic region 15q11-13 is responsible. In a study of discordant monozygotic twins for MS in which the entire DNA sequence, transcriptome (e.g., mRNA levels), and methylome were assessed genome-wide, tantalizing allelic differences in the use of the paternal, compared to maternal, copy for a group of genes were identified. Preferential allelic expression, whether due to imprinting, resistance to X-inactivation, or other mechanisms, is likely to play a major role in determining complex behaviors and susceptibility to many neurologic and psychiatric disorders.

Another advance is the development of transgenic mouse models of neurologic diseases, which has been particularly fruitful in producing models relevant to Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS. T ese models are useful in both studying disease pathogenesis and developing and testing new therapies. New transgenic mouse models with conditional expression have fostered investigations in which late gene expression avoids developmental compensation or in which the reversibility of a disease phenotype can be examined by turning a gene off after the disease phenotype has manifested. One can also examine the effects of gene expression in specific subsets of neurons, such as entorhinal cortex, or selectively in neurons, astrocytes, or microglia. Models in both Caenorhabditis elegans and Drosophila have also been extremely useful, particularly in studying genetic modifiers and therapeutic interventions.

ION CHANNELS AND CHANNELOPATHIES

T e resting potential of neurons and the action potentials responsible for impulse conduction are generated by ion currents and ion channels. Most ion channels are gated, meaning that they can transition between conformations that are open or closed to ion conductance. Individual ion channels are distinguished by the specific ions they conduct; by their kinetics; and by whether they directly sense voltage, are linked to receptors for neurotransmitters or other ligands such as neurotrophins, or are activated by second messengers. T e diverse characteristics of different ion channels provide a means by which neuronal excitability can be exquisitely modulated at both the cellular and the subcellular levels. Disorders of ion channels—channelopathies—are responsible for a growing list of human neurologic diseases **(Table 30-1)**. Most are caused by mutations

TABLE 30-1

EXAMPLES OF NEUROLOGIC CHANNELOPATHIES

CATEGORY	DISORDER	CHANNEL TYPE	MUTATED GENE	CHAP. REF.
Genetic				
Ataxias	Episodic ataxia-1	K	KCNA1	37
	Episodic ataxia-2	Ca	CACNL1A	
	Spinocerebellar ataxia-6	Ca	CACNL1A	
Migraine	Familial hemiplegic migraine 1	Ca	CACNL1A	34
	Familial hemiplegic migraine 2	Na	SCN1A	
Epilepsy	Benign neonatal familial convulsions	K	KCNQ2, KCNQ3	31
	Generalized epilepsy with febrile convulsions plus	Na	SCN1B	
Periodic paralysis	Hyperkalemic periodic paralysis	Na	SCN4A	56
	Hypokalemic periodic paralysis	Ca	CACNL1A3	
Myotonia	Myotonia congenita	Cl	CLCN1	56
	Paramyotonia congenita	Na	SCN4A	
Deafness	Jervell and Lange-Nielsen syndrome (deafness, prolonged QT interval, and arrhythmia)	K	KCNQ1, KCNE1	29
	Autosomal dominant progressive deafness	K	KCNQ4	
Autoimmune				
Paraneoplastic	Limbic encephalitis	Kv1	—	50
	Acquired neuromyotonia	Kv1	—	
	Cerebellar ataxia	Ca (P/Q type)	—	
	Lambert-Eaton syndrome	Ca (P/Q type)	—	

www.ketabpezeshki.com (021) 66485457 - 66485438

in ion channel genes or by autoantibodies against ion channel proteins. One example is epilepsy, a syndrome of diverse causes characterized by repetitive, synchronous firing of neuronal action potentials. Action potentials are normally generated by the opening of sodium channels and the inward movement of sodium ions down the intracellular concentration gradient. Depolarization of the neuronal membrane opens potassium channels, resulting in outward movement of potassium ions, repolarization, closure of the sodium channel, and hyperpolarization. Sodium or potassium channel subunit genes have long been considered candidate disease genes in inherited epilepsy syndromes, and recently such mutations have been identified. T ese mutations appear to alter the normal gating function of these channels, increasing the inherent excitability of neuronal membranes in regions where the abnormal channels are expressed.

Whereas the specific clinical manifestations of channelopathies are quite variable, one common feature is that manifestations tend to be intermittent or paroxysmal, such as occurs in epilepsy, migraine, ataxia, myotonia, or periodic paralysis. Exceptions are clinically progressive channel disorders such as autosomal dominant hearing impairment. T e genetic channelopathies identified to date are all uncommon disorders caused by obvious mutations in channel genes. As the full repertoire of human ion channels and related proteins is identified, it is likely that additional channelopathies will be discovered. In addition to rare disorders that result from obvious mutations, it is also likely that less penetrant allelic variations in channel genes or in their pattern of expression might underlie susceptibility to some apparently sporadic forms of epilepsy, migraine, or other disorders. For example, mutations in the potassium channel gene Kir2.6 have been found in many individuals with thyrotoxic hypokalemic periodic paralysis, a disorder similar to hypokalemic periodic paralysis but precipitated by stress from thyrotoxicosis or carbohydrate loading.

NEUROTRANSMITTERS AND NEUROTRANSMITTER RECEPTORS

Synaptic neurotransmission is the predominant means by which neurons communicate with each other. Classic neurotransmitters are synthesized in the presynaptic region of the nerve terminal; stored in vesicles; and released into the synaptic cleft, where they bind to receptors on the postsynaptic cell. Secreted neurotransmitters are eliminated by reuptake into the presynaptic neuron (or glia), by diffusion away from the synaptic cleft, and/or by specific inactivation. In addition to the classic neurotransmitters, many neuropeptides have been identified as definite or probable neurotransmitters; these include substance P, neurotensin, enkephalins, b-endorphin, histamine, vasoactive intestinal polypeptide, cholecystokinin, neuropeptide Y, and somatostatin. Peptide neurotransmitters are synthesized in the cell body rather than the nerve terminal and may colocalize with classic neurotransmitters in single neurons. A number of neuropeptides are important in pain modulation including substance P and calcitonin gene-related peptide (CGRP), which causes migraine-like headaches in patients. As a consequence, CGRP receptor antagonists have been developed and shown to be effective in treating migraine headaches. Nitric oxide and carbon monoxide are gases that appear also to function as neurotransmitters, in part by signaling in a retrograde fashion from the postsynaptic to the presynaptic cell.

Neurotransmitters modulate the function of postsynaptic cells by binding to specific neurotransmitter receptors, of which there are two major types. Ionotropic receptors are direct ion channels that open after engagement by the neurotransmitter. Metabotropic receptors interact with G proteins, stimulating production of second messengers and activating protein kinases, which modulate a variety of cellular events. Ionotropic receptors are multiple subunit structures, whereas metabotropic receptors are composed of single subunits only. One important difference between ionotropic and metabotropic receptors is that the kinetics of ionotropic receptor effects are fast (generally <1 ms) because neurotransmitter binding directly alters the electrical properties of the postsynaptic cell, whereas metabotropic receptors function over longer time periods. T ese different properties contribute to the potential for selective and finely modulated signaling by neurotransmitters.

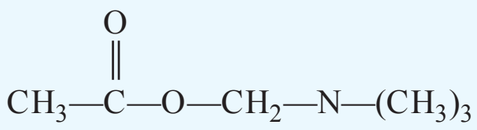
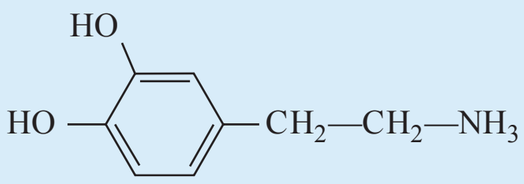
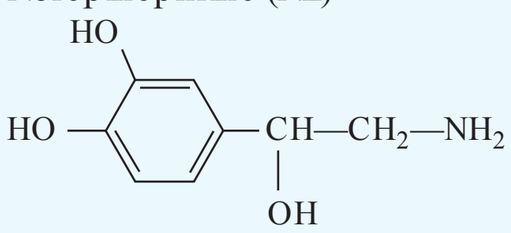
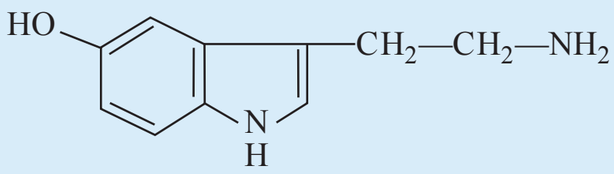
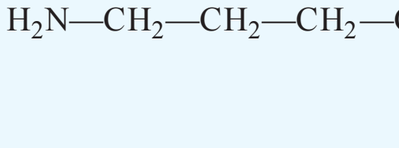
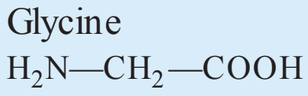
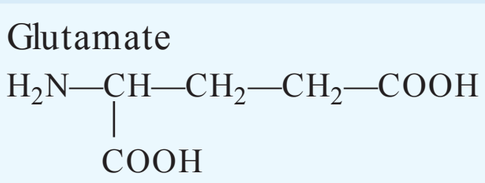
Neurotransmitter systems are perturbed in a large number of clinical disorders, several of which are highlighted in **Table 30-2**. One example is the involvement of dopaminergic neurons originating in the substantia nigra of the midbrain and projecting to the striatum (nigrostriatal pathway) in Parkinson's disease and in heroin addicts after the ingestion of the toxin MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine).

A second important dopaminergic system arising in the midbrain is the mediocorticolimbic pathway, which is implicated in the pathogenesis of addictive behaviors including drug reward. Its key components include the midbrain ventral tegmental area (VTA), median forebrain bundle, and nucleus accumbens **(see Fig. 60-2)**. T e cholinergic pathway originating in the nucleus basalis of Meynert plays a role in memory function in Alzheimer's disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 30-2

PRINCIPAL CLASSIC NEUROTRANSMITTERS

NEUROTRANSMITTER	ANATOMY	CLINICAL ASPECTS
Acetylcholine (ACh) 	Motor neurons in spinal cord → neuromuscular junction	Acetylcholinesterases (nerve gases) Myasthenia gravis (antibodies to ACh receptor) Congenital myasthenic syndromes (mutations in ACh receptor subunits) Lambert-Eaton syndrome (antibodies to Ca channels impair ACh release) Botulism (toxin disrupts ACh release by exocytosis)
	Basal forebrain → widespread cortex	Alzheimer disease (selective cell death) Autosomal dominant frontal lobe epilepsy (mutations in CNS ACh receptor)
	Interneurons in striatum	Parkinson's disease (tremor)
	Autonomic nervous system (preganglionic and postganglionic parasympathetic; preganglionic sympathetic)	
Dopamine 	Substantia nigra → striatum (nigrostriatal pathway) Substantia nigra → limbic system and widespread cortex Arcuate nucleus of hypothalamus → anterior pituitary (via portal veins)	Parkinson's disease (selective cell death) MPTP parkinsonism (toxin transported into neurons) Addiction, behavioral disorders Inhibits prolactin secretion
Norepinephrine (NE) 	Locus coeruleus (pons) → limbic system, hypothalamus, cortex Medulla → locus coeruleus, spinal cord Postganglionic neurons of sympathetic nervous system	Mood disorders (MAOA inhibitors and tricyclics increase NE and improve depression) Anxiety Orthostatic tachycardia syndrome (mutations in NE transporter)
Serotonin 	Pontine raphe nuclei → widespread projections Medulla/pons → dorsal horn of spinal cord	Mood disorders (SSRIs improve depression) Migraine pain pathway Pain pathway
γ-Aminobutyric acid (GABA) 	Major inhibitory neurotransmitter in brain; widespread cortical interneurons and long projection pathways	Stiff person syndrome (antibodies to glutamic acid decarboxylase, the biosynthetic enzyme for GABA) Epilepsy (gabapentin and valproic acid increase GABA)
Glycine 	Major inhibitory neurotransmitter in spinal cord	Spasticity Hyperekplexia (myoclonic startle syndrome) due to mutations in glycine receptor
Glutamate 	Major excitatory neurotransmitter; located throughout CNS, including cortical pyramidal cells	Seizures due to ingestion of domoic acid (a glutamate analogue) Rasmussen's encephalitis (antibody against glutamate receptor 3) Excitotoxic cell death

Abbreviations: CNS, central nervous system; MAOA, monoamine oxidase A; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SSRI, selective serotonin reuptake inhibitor.

www.ketabpezeshki.com (021) 66485457 - 66485438

Addictive drugs share the property of increasing dopamine release in the nucleus accumbens **(Chap. 60)**. Amphetamine increases intracellular release of dopamine from vesicles and reverses transport of dopamine through the dopamine transporters. Patients prone to addiction show increased activation of the nucleus accumbens following administration of amphetamine. Cocaine binds to dopamine transporters and inhibits dopamine reuptake. Ethanol inhibits inhibitory neurons in the VTA, leading to increased dopamine release in the nucleus accumbens. Opioids also disinhibit these dopaminergic neurons by binding to μ receptors expressed by γ-aminobutyric acid (GABA)–containing interneurons in the VTA. Nicotine increases dopamine release by activating nicotinic acetylcholine receptors on cell bodies and nerve terminals of dopaminergic VTA neurons. Tetrahydrocannabinol, the active ingredient of cannabis, also increases dopamine levels in the nucleus accumbens. Blockade of dopamine in the nucleus accumbens can terminate the rewarding effects of addictive drugs.

Not all cell-to-cell communication in the nervous system occurs via neurotransmission. Gap junctions provide for direct neuron-neuron electrical conduction and also create openings for the diffusion of ions and metabolites between cells. In addition to neurons, gap junctions are also widespread in glia, creating a syncytium that protects neurons by removing glutamate and potassium from the extracellular environment. Gap junctions consist of membrane-spanning proteins, termed connexins, that pair across adjacent cells. Mechanisms that involve gap junctions have been related to a variety of neurologic disorders. Mutations in connexin 32, a gap junction protein expressed by Schwann cells, are responsible for the X-linked form of CMT disease **(Chap. 53)**. Mutations in either of two gap junction proteins expressed in the inner ear—connexin 26 and connexin 31—result in autosomal dominant progressive hearing loss **(Chap. 29)**. Glial calcium waves mediated through gap junctions also appear to explain the phenomenon of spreading depression associated with migraine auras and the march of epileptic discharges. Spreading depression is a neural response that follows a variety of different stimuli and is characterized by a circumferentially expanding negative potential that propagates at a characteristic speed of 20 m/s and is associated with an increase in extracellular potassium.

SIGNALING PATHWAYS AND GENE TRANSCRIPTION

T e fundamental issue of how memory, learning, and thinking are encoded in the nervous system is likely to be clarified by identifying the signaling pathways involved in neuronal differentiation, axon guidance, and synapse formation, and by understanding how these pathways are modulated by experience. Many families of transcription factors, each comprising multiple individual components, are expressed in the nervous system. Elucidation of these signaling pathways has already begun to provide insights into the cause of a variety of neurologic disorders, including inherited disorders of cognition such as X-linked mental retardation. T is problem affects ~1 in 500 males, and linkage studies in different families suggest that as many as 60 different X-chromosome-encoded genes may be responsible. T e formation of RNA-DNA duplexes that block transcription has also been observed with the CGG repeat expansions that occur in fragile X gene-associated mental retardation. Rett's syndrome, a common cause of (dominant) X-linked progressive mental retardation in females, is due to a mutation in a gene (MECP2) encoding a DNA-binding protein involved in transcriptional repression. Because the X chromosome comprises only ~3% of germline DNA, then by extrapolation, the number of genes that potentially contribute to clinical disorders affecting intelligence in humans must be potentially very large. As discussed below, there is increasing evidence that abnormal gene transcription may play a role in neurodegenerative diseases, such as Huntington's disease, in which proteins with polyglutamine expansions bind to and sequester transcription factors. A critical transcription factor for neuronal survival is CREB (cyclic adenosine monophosphate responsive element-binding) protein, which also plays an important role in memory in the hippocampus. T e regulatory gene repressor element 1-silencing transcription factor (REST) coordinates the expression of neuroprotective stress genes during normal aging. It turns off genes involved in cell death and pathology and boosts protective factors. High levels of REST are associated with normal cognition even in the presence of both amyloid plaques and neurofibrillary tangles. Although REST increases with normal aging, it fails to increase in the nucleus in patients with Alzheimer's disease and is found clumped with amyloid in autophagosomes.

MYELIN AND NEUROINFLAMMATION

Myelin is the multilayered insulating substance that surrounds axons and speeds impulse conduction by permitting action potentials to jump between naked regions of axons (nodes of Ranvier) and across myelinated segments. Molecular interactions between the myelin membrane and axon are required to maintain the stability, function, and normal life span of both structures. A single oligodendrocyte usually ensheaths multiple axons in the central nervous system (CNS),

www.ketabpezeshki.com (021) 66485457 - 66485438

whereas in the peripheral nervous system (PNS), each Schwann cell typically myelinates a single axon. Myelin is a lipid-rich material formed by a spiraling process of the membrane of the myelinating cell around the axon, creating multiple membrane bilayers that are tightly apposed (compact myelin) by charged protein interactions. Several inhibitors of axon growth are expressed on the innermost (periaxonal) lamellae of the myelin membrane (see "Stem Cells and Transplantation," below). A number of clinically important neurologic disorders are caused by inherited mutations in myelin proteins of the CNS or PNS **(Fig. 30-1)**. Constituents of myelin also have a propensity to be targeted as autoantigens in autoimmune demyelinating disorders **(Fig. 30-2)**.

Specification to oligodendrocyte precursor cells (OPCs) is transcriptionally regulated by the Olig 2 and Yin Yang 1 genes, whereas myelination mediated by postmitotic oligodendrocytes depends on a different transcription factor, myelin gene regulatory factor (MRF). It is noteworthy that in the normal adult brain, large numbers of OPCs (expressing PDGFR-α and NG2) are widely distributed but do not myelinate axons, even in demyelinating environments such as in lesions of MS. Several families of molecules have now been identified that regulate oligodendrocyte differentiation and myelination, including LINGO-1, PSA-NCAM, hyaluronan, Nogo-A, the Wnt pathway, notch signaling (and its receptor Jagged), and the retinoic acid receptor RXRγ; all are inhibitory, with the exception of RXRγ, which is excitatory. All are also potential targets for myelin repair therapies, and a monoclonal antibody against LINGO-1 is in clinical testing for remyelination in MS. Very recently, a series of observations has called into question the traditional concept that axon-derived cues are always required for myelination to occur. Fixed (i.e., dead) axons could be efficiently myelinated by oligodendrocytes in vitro, as could artificial polystyrene nanowires of a similar diameter. T is led to development of new high-throughput screening assays based on myelination of polystyrene nanowires to identify compounds that could promote myelination.

Macrophages and microglia represent the major cell types in the nervous system responsible for antigen presentation and innate immunity. Brain macrophages are derived from either hematopoietic stem cell–derived bone marrow monocytes or from brain microglia that migrate from the yolk sac early in embryogenesis before the blood-brain barrier is formed. In a murine model of autoimmune

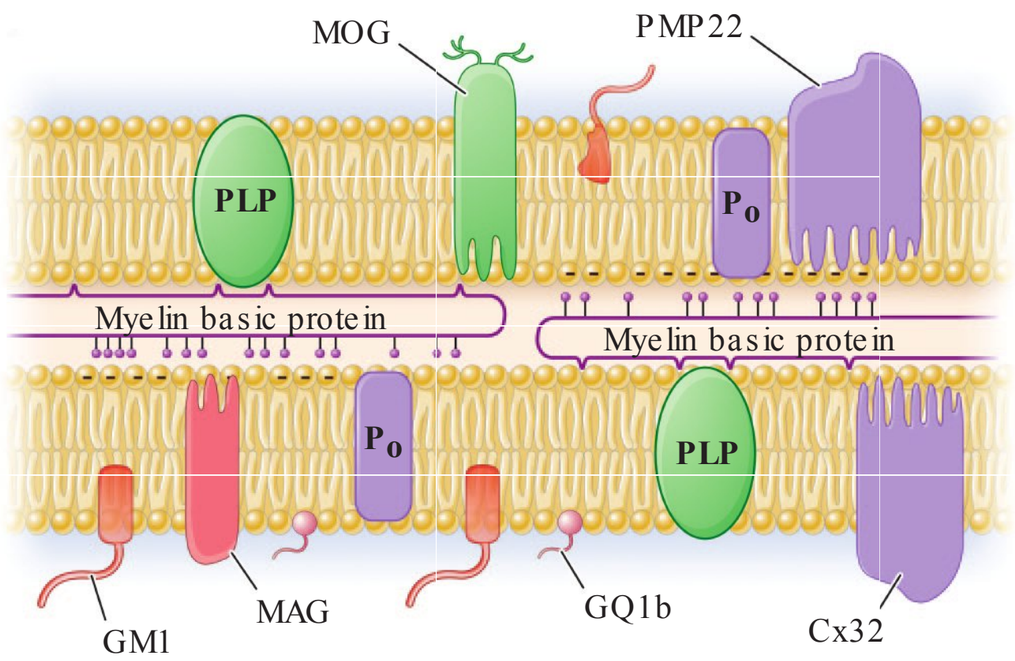


FIGURE 30-1

The molecular architecture of the myelin sheath illustrating the most important disease-related proteins. The illustration represents a composite of central nervous system (CNS) and peripheral nervous system (PNS) myelin. Proteins restricted to CNS myelin are shown in green, proteins of PNS myelin are lavender, and proteins present in both CNS and PNS are red. In the CNS, the X-linked allelic disorders, Pelizaeus-Merzbacher disease and one variant of familial spastic paraplegia, are caused by mutations in the gene for proteolipid protein (PLP) that normally promotes extracellular compaction between adjacent myelin lamellae. The homologue of PLP in the PNS is the P_0 protein, mutations in which cause the neuropathy CMT disease type 1B. The most common form of CMT is the 1A subtype caused by a duplication of the PMP22 gene; deletions in PMP22 are responsible for another inherited neuropathy termed hereditary liability to pressure palsies (Chap. 53).

In multiple sclerosis (MS), myelin basic protein (MBP) and the quantitatively minor CNS protein, myelin oligodendrocyte glycoprotein (MOG), are likely T cell and B cell antigens, respectively (Chap. 45). The location of MOG at the outermost lamella of the CNS myelin membrane may facilitate its targeting by autoantibodies. In the PNS, autoantibodies against myelin gangliosides are implicated in a variety of disorders, including GQ1b in the Fisher variant of Guillain-Barré syndrome, GM1 in multifocal motor neuropathy, and sulfatide constituents of myelin-associated glycoprotein (MAG) in peripheral neuropathies associated with monoclonal gammopathies (Chap. 54).

www.ketabpezeshki.com (021) 66485457 - 66485438

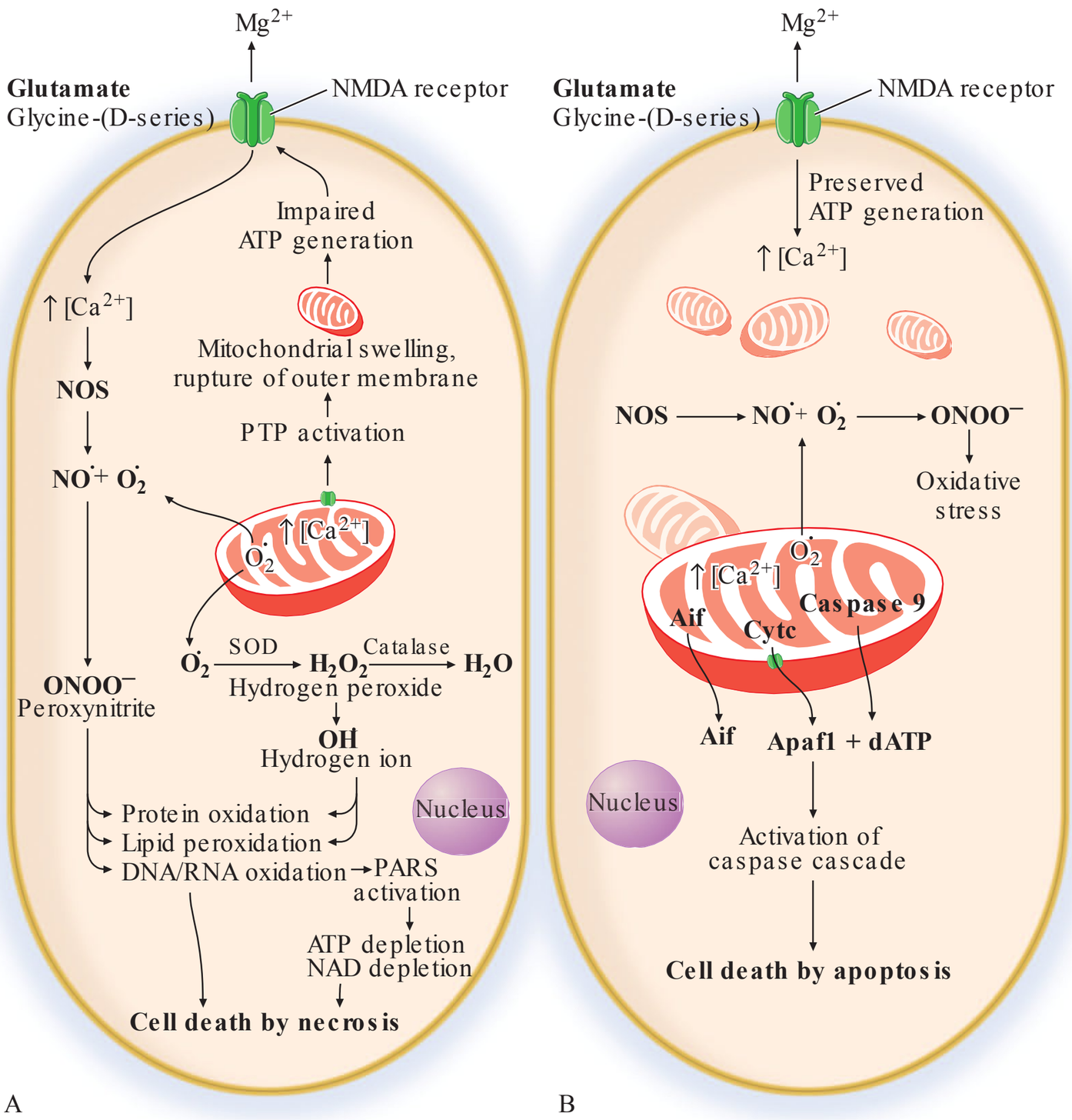


FIGURE 30-2

Involvement of mitochondria in cell death. A severe excitotoxic insult (A) results in cell death by necrosis, whereas a mild excitotoxic insult (B) results in apoptosis. After a severe insult (such as ischemia), there is a large increase in glutamate activation of N-methyl-d-aspartate (NMDA) receptors, an increase in intracellular Ca^{2+} concentrations, activation of nitric oxide synthase (NOS), and increased mitochondrial Ca^{2+} and superoxide generation followed by the formation of $ONOO^-$. This sequence results in damage to cellular macromolecules including DNA, leading to activation of poly-ADP-ribose polymerase (PARS). Both mitochondrial accumulation of Ca^{2+} and oxidative damage lead to activation of the permeability transition pore (PTP) that is linked to excitotoxic cell death. A mild excitotoxic insult can occur due either to an abnormality in an excitotoxicity amino acid receptor, allowing more Ca^{2+} flux, or to impaired functioning of other ionic channels or of energy production, which may allow the voltage-dependent NMDA receptor to be activated by ambient concentrations of glutamate. This event can then lead to increased mitochondrial Ca^{2+} and free radical production, yet relatively preserved ATP generation. The mitochondria may then release cytochrome c (Cytc), caspase 9, apoptosis-inducing factor (Aif), and perhaps other mediators that lead to apoptosis. The precise role of the PTP in this mode of cell death is still being clarified, but there does appear to be involvement of the adenine nucleotide transporter that is a key component of the PTP.

demyelination, experimental allergic encephalomyelitis (EAE) **(Fig. 30-3)**, macrophages derived from bone marrow monocytes, but not microglia, were found to represent the critical population that initiated inflammatory demyelination at paraxonal regions near nodes of Ranvier. An additional, unexpected role for brain microglia was also identified in the regulation of neural circuits through pruning of excitatory synapses and control of dendritic spine densities; mice depleted of microglia during development exhibited a variety of cognitive learning and behavioral deficits, including abnormal social behaviors. Remarkably, depletion of microglia in adult mice by administration of a selective inhibitor of colony-stimulating factor receptor 1 (CSFR1) was followed by their rapid repopulation, suggesting that a pool of resident microglial precursor cells may exist throughout the CNS.

www.ketabpezeshki.com (021) 66485457 - 66485438

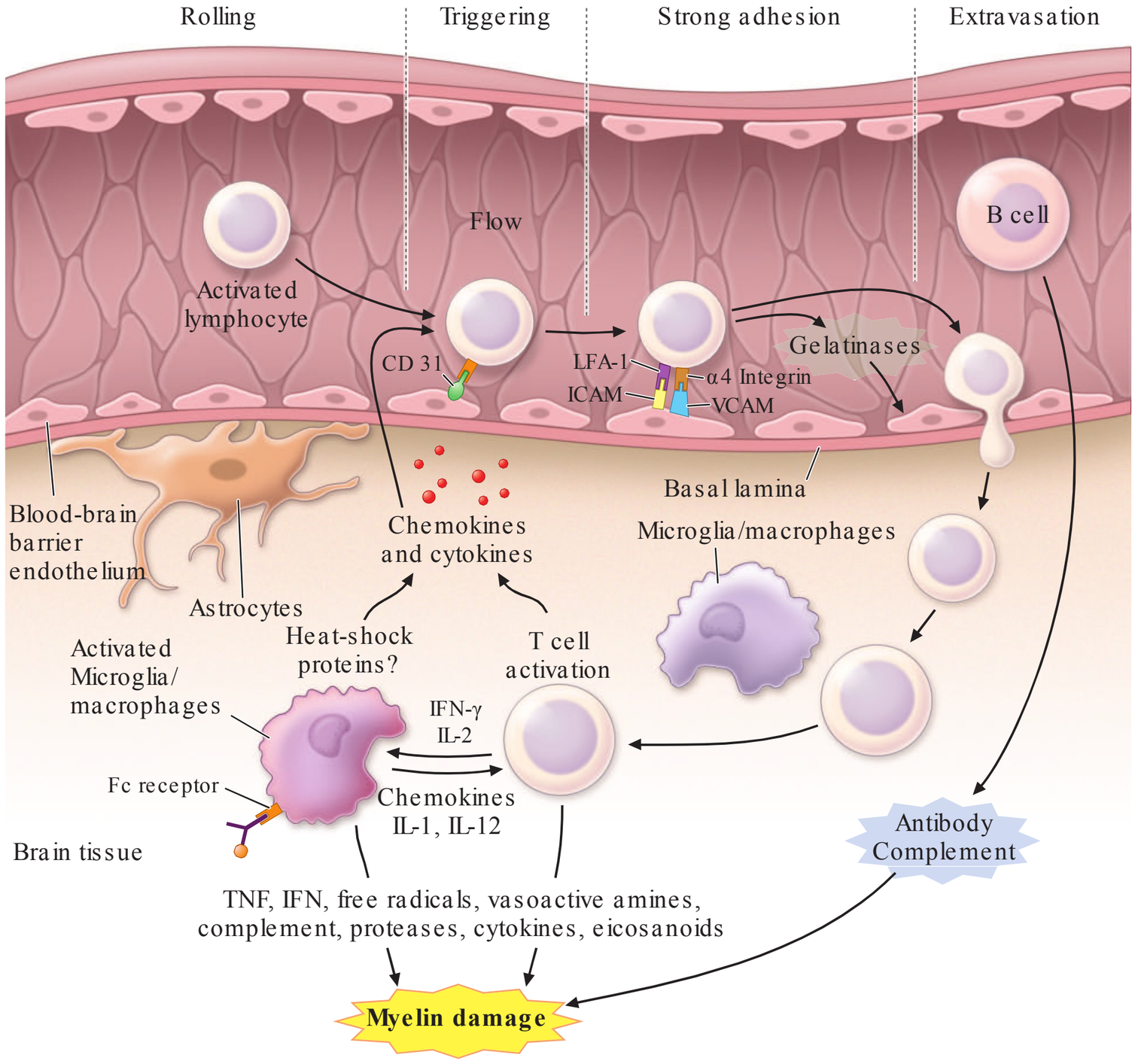


FIGURE 30-3

A model for experimental allergic encephalomyelitis (EAE). Crucial steps for disease initiation and progression include peripheral activation of preexisting autoreactive T cells; homing to the central nervous system (CNS) and extravasation across the blood-brain barrier; reactivation of T cells by exposed autoantigens; secretion of cytokines; activation of microglia and astrocytes and recruitment of a secondary inflammatory wave; and immune-mediated myelin destruction. ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LFA-1, leukocyte function-associated antigen-1; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

MICROBIOTA AND NEUROLOGIC DISEASE

T e human microbiome represents the collective set of genes from the 10^{14} organisms living in our gut, skin, mucosa, and other sites. Different microbial communities are associated with different ethnicities, diets, and environments. In any individual, the predominant gut microbiota can be remarkably stable over decades, but also can be altered by exposure to certain microbial species, for example by ingestion of probiotics.

T ere is compelling evidence that gut microbes can shape immune responses through the interaction of their metabolism with that of humans. T ese gut-brain interactions are likely to be important in understanding the pathogenesis of many autoimmune neurologic diseases. For example, mice treated with broad-spectrum antibiotics are resistant to EAE, an effect associated with decreases in production of proinflammatory cytokines, and conversely more production of the immunosuppressive cytokines interleukin (IL) 10 and IL-13 and an increase in regulatory T and B lymphocytes. Oral administration of polysaccharide A (PSA) from Bacillus fragilis also protects mice from EAE, via increases in IL-10.

In addition to nonspecific effects on immune homeostasis mediated by cytokines and regulatory cells, some microbial proteins can trigger, in susceptible individuals, a cross-reactive immune response against a homologous protein in the nervous system, a mechanism termed molecular mimicry. Examples include cross-reactivity between the astrocyte water channel aquaporin-4 and an ABC transporter permease from Clostridia perfringens in neuromyelitis optica **(Chap. 45)**; the neural ganglioside Gm1 and similar sialic acid–containing structures from Campylobacter jejuni in Guillain-Barré syndrome **(Chap. 54)**; and the sleep-promoting protein hypocretin and hemagglutinin from H1N1 influenza virus in narcolepsy **(Chap. 24)**, among others.

www.ketabpezeshki.com (021) 66485457 - 66485438

Recently, a number of tantalizing observations have incriminated the microbial environment in the pathogenesis of a much wider spectrum of neurologic conditions and behaviors, extending well beyond the traditional boundaries of immune-mediated pathologies. T is is perhaps not surprising, as it has long been known in neurology that gut bacteria can influence brain function, based mostly on classic studies demonstrating that products of gut microbes can worsen hepatic encephalopathy, forming the basis of treatment with antibiotics for this condition.

Mice that developed in a completely germ-free environment displayed less anxiety, lower responses to stressful situations, more exploratory locomotive behaviors, and impaired memory formation compared with non-germ-free counterparts. T ese behaviors were related to changes in gene expression in pathways related to neural signaling, synaptic function, and modulation of neurotransmitters. Moreover, this behavior could be reversed when the germ-free mice were co-housed with non-germ-free mice.

T e enteric autonomic nervous system in humans provides a bidirectional neural connection between the brain and gut. T e vagus nerve, which innervates the upper gut and proximal colon, has been implicated in anxiety- and depression-like behaviors in mice. Ingestion of Lactobacillus rhamnosus induced changes in expression of the inhibitory neurotransmitter GABA1b in neurons of the limbic cortex, hippocampus, and amygdala, associated with reduced levels of corticosteroids and reduced anxiety- and depression-like behaviors. Remarkably, these changes could be blocked by vagotomy.

Another area of emerging interest is in a possible contribution of the gut microbiome to autism and related disorders. Children with autistic spectrum disorders have long been known to have gastrointestinal disturbances, and it has been claimed that the severity of dysbiosis correlates with the severity of autism. A murine model of autism was recently induced in offspring after injecting the pregnant mother with the viral RNA mimic polyinosinic:polycytidylic acid (poly I:C). Remarkably, oral treatment of offspring with B. fragilis corrected a range of autistic behaviors in these mice and also improved gut permeability.

NEUROTROPHIC FACTORS

Neurotrophic factors **(Table 30-3)** are secreted proteins that modulate neuronal growth, differentiation, repair, and survival; some have additional functions, including roles in neurotransmission and in the synaptic reorganization involved in learning and memory. T e neurotrophin (NT) family contains nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT3, and NT4/5. T e neurotrophins act at TrK and p75 receptors to promote survival of neurons. BDNF is linked to synaptogenesis. Certain polymorphisms are linked to increased risk for Alzheimer's disease (AD), and BDNF is depleted in Huntington's disease. Because of their survival-promoting and antiapoptotic effects, neurotrophic factors are in theory outstanding candidates for therapy of disorders characterized by premature death of neurons such as occurs in ALS and other degenerative motor neuron disorders. Knockout mice lacking receptors for ciliary neurotrophic factor (CNTF) or BDNF show loss of motor neurons, and experimental motor neuron death can be rescued by treatment with various neurotrophic factors including CNTF, BDNF, and vascular endothelial growth factor (VEGF). However, in phase 3 clinical trials, growth factors were ineffective in human ALS. T e growth factor glial-derived neurotrophic factor (GDNF) is important for survival of dopaminergic neurons. Direct infusions of GDNF showed initial promise in Parkinson's disease, but the benefits were not replicated in a larger clinical trial.

TABLE 30-3

NEUROTROPHIC FACTORS	
Neurotrophin family	Transforming growth factor β family
Nerve growth factor	Glial-derived neurotrophic family
Brain-derived neurotrophic factor	Neurturin
Neurotrophin-3	Persephin
Neurotrophin-4	Fibroblast growth factor family
Neurotrophin-6	Hepatocyte growth factor
Cytokine family	Insulin-like growth factor (IGF) family
Ciliary neurotrophic factor	IGF-1
Leukemia inhibitory factor	IGF-2
Interleukin 6	
Cardiotrophin-1	

STEM CELLS AND TRANSPLANTATION

T e nervous system is traditionally considered to be a nonmitotic organ, in particular with respect to neurons. T ese concepts have been challenged by the finding that neural progenitor or stem cells exist in the adult CNS that are capable of differentiation, migration over long distances, and extensive axonal arborization and synapse formation with appropriate targets. T ese capabilities also indicate that the repertoire of factors required for growth, survival, differentiation, and migration of these cells exists in the mature nervous system. In rodents, neural stem cells, defined as progenitor cells capable of differentiating into mature cells of neural or

www.ketabpezeshki.com (021) 66485457 - 66485438

glial lineage, have been experimentally propagated from fetal CNS and neuroectodermal tissues and also from adult germinal matrix and ependyma regions. Human fetal CNS tissue is also capable of differentiation into cells with neuronal, astrocyte, and oligodendrocyte morphology when cultured in the presence of growth factors.

Once the repertoire of signals required for cell type specification is better understood, differentiation into specific neural or glial subpopulations can be directed in vitro; such cells could also be engineered to express therapeutic molecules. Another promising approach is to use growth factors, such as BDNF, to stimulate endogenous stem cells to proliferate and migrate to areas of neuronal damage.

A major advance has been the development of induced pluripotent stem cells. Using this technique, adult somatic cells such as skin fibroblasts are treated with four pluripotency factors (SOX2, KLF4, cMYC, and Oct4), and this generates induced pluripotent stem cells (iPSCs). T ese adult-derived stem cells sidestep the ethical issues of using stem cells derived from human embryos. T e development of these cells has tremendous promise for both studying disease mechanisms and testing therapeutics. As yet there is no consensus on the best way to generate and differentiate the iPSCs; however, techniques to avoid using viral vectors and use of Cre-lox systems to remove reprogramming factors result in a better match of gene expression profiles with those of embryonic stem cells. Over the years, the field of directed differentiation has used three main strategies to specify neural lineages from human pluripotent stem cells. T ese strategies are embryoid body formation, coculture on neural-inducing feeders, and direct neural induction. T us far, iPSCs have been made from patients with all of the major human neurodegenerative diseases, and studies using them are under way.

Although stem cells hold tremendous promise for the treatment of debilitating neurologic diseases, such as Parkinson's disease and spinal cord injury, it should be emphasized that medical application is in its infancy. Major obstacles are the generation of position- and neurotransmitter-defined subtypes of neurons and their isolation as pure populations of the desired cells. T is is crucial to avoid persistence of undifferentiated embryonic stem (ES) cells, which can generate tumors. T e establishment of appropriate neural connections and afferent control is also critical. For instance, human ES motor neurons will need to be introduced at multiple segments in the neuraxis, and then their axons will need to regenerate from the spinal cord to distal musculature.

Experimental transplantation of human fetal dopaminergic neurons in patients with Parkinson's disease has shown that these transplanted cells can survive within the host striatum; however, some patients developed disabling dyskinesias, and this approach is no longer in clinical development. T e possibility that iPSCs will be used in Parkinson's disease was strengthened by studies showing that they can be differentiated into dopaminergic neurons. T e dopaminergic neurons were then shown to rescue the parkinsonian phenotype in a MPTP-induced primate model with excellent dopaminergic neuron survival function and lack of neural overgrowth. T e correction of tau mutations in iPSC-derived neurons has been shown to reverse the toxic phenotype in dendrite retraction and cell death.

Another new use for iPSCs is to screen drugs as potential treatments for neurodegenerative and other diseases. T e feasibility of this has been shown using iPSC-induced macrophages from patients with Gaucher's disease, and verifying the efficacy of protein chaperones in these cells as a means of stabilizing the mutant glucocerebrosidase and increasing its activity and the duration of its effects. Other approaches are to attempt to reduce expression of proteins, such as amyloid, tau, and α-synuclein, implicated in the pathogenesis of neurodegenerative diseases. One difficulty has been that reprogramming cells to iPSCs resets their identity back to an embryonic age, which is a hurdle in modeling of late-onset diseases. One approach to this has been to express a fragment of the mutated gene, such as a portion of lamin A, which causes premature aging in progeria. T is approach showed that dendrite degeneration and progressive loss of tyrosine hydroxylase expression, as well as enlarged mitochondria and Lewy body precursor inclusions, were induced in iPSC-derived dopaminergic neurons with progerin-induced aging.

Studies of transplantation for patients with Huntington's disease have also reported encouraging, although very preliminary, results. OPCs transplanted into mice with a dysmyelinating disorder effectively migrated in the new environment, interacted with axons, and mediated myelination; such experiments raise hope that similar transplantation strategies may be feasible in human disorders of myelin such as MS. T e promise of stem cells for treatment of both neurodegenerative diseases and neural injury is great, but development has been slowed by unresolved concerns over safety (including the theoretical risk of malignant transformation of transplanted cells), ethics (particularly with respect to use of fetal tissue), and efficacy.

In developing brain, the extracellular matrix provides stimulatory and inhibitory signals that promote neuronal migration, neurite outgrowth, and axonal extension. After neuronal damage, reexpression of inhibitory molecules such as chondroitin sulfate proteoglycans may prevent tissue regeneration. Chondroitinase degraded these inhibitory molecules and enhanced axonal regeneration and motor recovery in a rat model of spinal cord injury. Several myelin proteins, specifically Nogo,

www.ketabpezeshki.com (021) 66485457 - 66485438

oligodendrocyte myelin glycoprotein (OMGP), and myelin-associated glycoprotein (MAG), may also interfere with axon regeneration. Sialidase, which cleaves one class of receptors for MAG, enhances axonal outgrowth. Antibodies against Nogo promote regeneration after experimental focal ischemia or spinal cord injury. Nogo, OMGP, and MAG all bind to the same neural receptor, the Nogo receptor, which mediates its inhibitory function via the p75 neurotrophin receptor signaling.

CELL DEATH: EXCITOTOXICITY AND APOPTOSIS

Excitotoxicity refers to neuronal cell death caused by activation of excitatory amino acid receptors **(Fig. 30-4)**. Compelling evidence for a role of excitotoxicity, especially in ischemic neuronal injury, is derived from experiments in animal models. Experimental models of stroke are associated with increased extracellular concentrations of the excitatory amino acid neurotransmitter glutamate, and neuronal damage is attenuated by denervation of glutamate-containing neurons or the administration of glutamate receptor antagonists. T e distribution of cells sensitive to ischemia corresponds closely with that of N-methyl-d-aspartate (NMDA) receptors (except for cerebellar Purkinje cells, which are vulnerable to hypoxia-ischemia but lack NMDA receptors); and competitive and noncompetitive NMDA antagonists are effective in preventing focal ischemia. In global cerebral ischemia, non-NMDA receptors (kainic acid and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate [AMPA]) are activated, and antagonists to these receptors are protective. Experimental brain damage induced by hypoglycemia is also attenuated by NMDA antagonists.

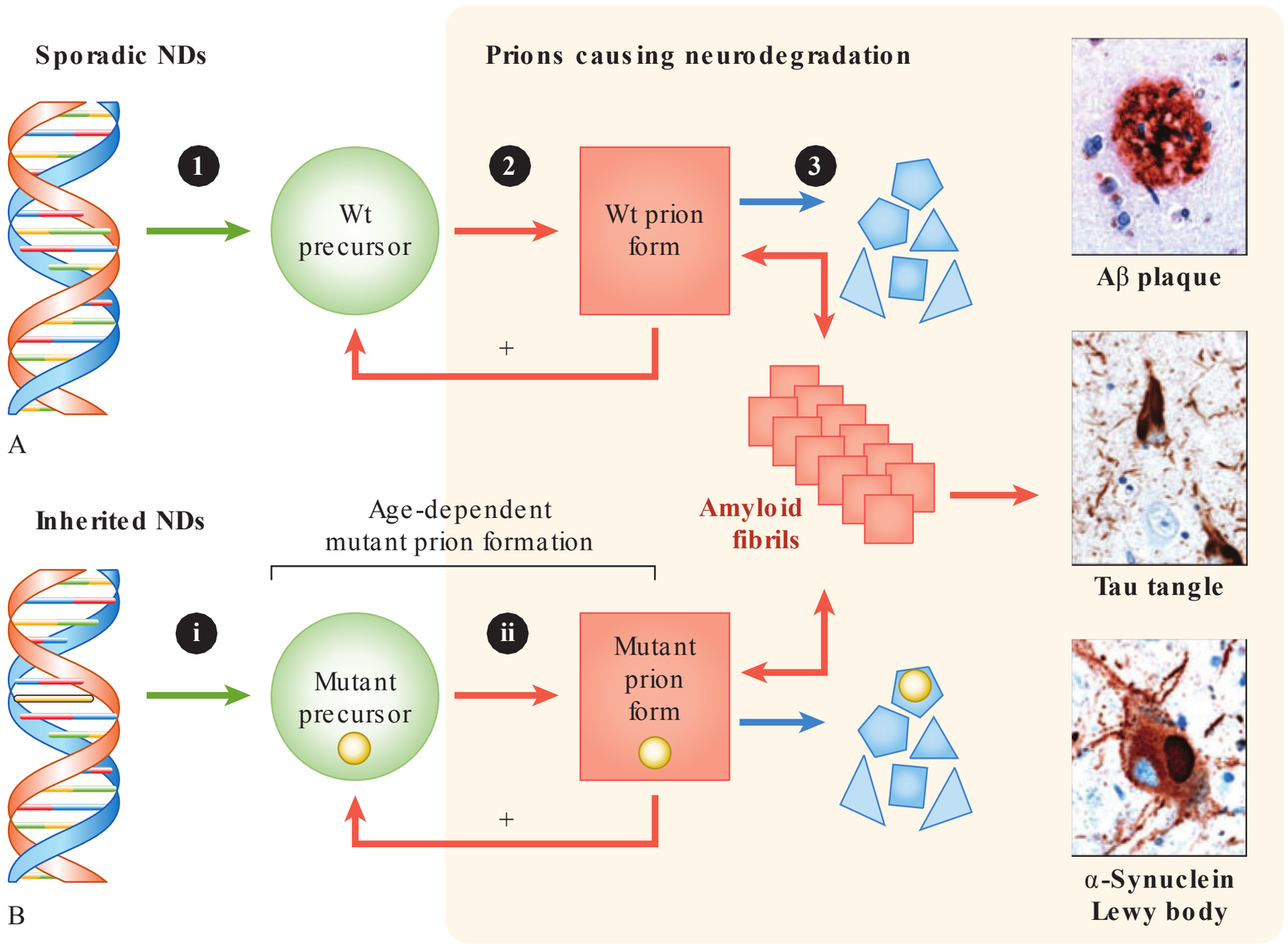


FIGURE 30-4

Neurodegeneration caused by prions. A. In sporadic neurodegenerative diseases (NDs), wild-type (Wt) prions multiply through self-propagating cycles of posttranslational modif cation, during which the precursor protein (green circle) is converted into the prion form (red square), which generally is high in β-sheet content. Pathogenic prions are most toxic as oligomers and less toxic after polymerization into amyloid f brils. The small polygons (blue) represent proteolytic cleavage products of the prion. Depending on the protein, the f brils coalesce into Aβ amyloid plaques in Alzheimer's disease (AD), neurof brillary tangles in AD and Pick's disease, or Lewy bodies in Parkinson's disease and Lewy body dementia. Drug targets for the development of therapeutics include: (1) lowering the precursor protein, (2) inhibiting prion formation, and (3) enhancing prion clearance. B. Late-onset heritable neurodegeneration argues for two discrete events: The (i) f rst event is the synthesis of mutant precursor protein (green circle), and the (ii) second event is the age-dependent formation of mutant prions (red square). The highlighted yellow bar in the DNA structure represents mutation of a base pair within an exon, and the small yellow circles signify the corresponding mutant amino acid substitution. Green arrows represent a normal process; red arrows, a pathogenic process; and blue arrows, a process that is known to occur but unknown whether it is normal or pathogenic. (Micrographs prepared by Stephen J. DeArmond. Reprinted with permission from SB Prusiner: Biology and genetics of prions causing neurodegeneration. Annu Rev Genet 47:601, 2013.)

www.ketabpezeshki.com (021) 66485457 - 66485438

Excitotoxicity is not a single event but rather a cascade of cell injury. Excitotoxicity causes influx of calcium into cells, and much of the calcium is sequestered in mitochondria rather than in the cytoplasm. Increased cytoplasmic calcium causes metabolic dysfunction and free radical generation; activates protein kinases, phospholipases, nitric oxide synthase, proteases, and endonucleases; and inhibits protein synthesis. Activation of nitric oxide synthase generates nitric oxide (NO•), which can react with superoxide ($O•_2$) to generate peroxynitrite ($ONOO^-$), which may play a direct role in neuronal injury. Another critical pathway is activation of poly-ADP-ribose polymerase, which occurs in response to free radical–mediated DNA damage. Experimentally, mice with knockout mutations of neuronal nitric oxide synthase or poly-ADP-ribose polymerase, or those that overexpress superoxide dismutase, are resistant to focal ischemia.

Another aspect of excitotoxicity is that it has been demonstrated that stimulation of extrasynaptic NMDA receptors mediates cell death, where as stimulation of synaptic receptors is protective. T is has been shown to play a role in excitotoxicity in transgenic mouse models of Huntington's disease, in which using low-dose memantine to selectively block the extrasynaptic receptors is beneficial.

Although excitotoxicity is clearly implicated in the pathogenesis of cell death in stroke, to date treatment with NMDA antagonists has not proven to be clinically useful. One approach has been to use an inhibitor of the postsynaptic density-95 protein that uncouples NMDA receptors from neurotoxic pathways, including the generation of nitric oxide. T is approach was effective in a primate stroke model and in a phase 2 clinical trial of stroke associated with endovascular repair of cerebral aneurysms. Transient receptor potentials (TRPs) are calcium channels that are activated by oxidative stress in parallel with excitotoxic signal pathways. In addition, glutamate-independent pathways of calcium influx via acid-sensing ion channels have been identified. T ese channels transport calcium in the setting of acidosis and substrate depletion, and pharmacologic blockade of these channels markedly attenuates stroke injury. T ese channels offer a potential new therapeutic target for stroke.

Apoptosis, or programmed cell death, plays an important role in both physiologic and pathologic conditions. During embryogenesis, apoptotic pathways operate to destroy neurons that fail to differentiate appropriately or reach their intended targets. T ere is mounting evidence for an increased rate of apoptotic cell death in a variety of acute and chronic neurologic diseases. Apoptosis is characterized by neuronal shrinkage, chromatin condensation, and DNA fragmentation, whereas necrotic cell death is associated with cytoplasmic and mitochondrial swelling followed by dissolution of the cell membrane. Apoptotic and necrotic cell death can coexist or be sequential events, depending on the severity of the initiating insult. Cellular energy reserves appear to have an important role in these two forms of cell death, with apoptosis favored under conditions in which ATP levels are preserved. Evidence of DNA fragmentation has been found in a number of degenerative neurologic disorders, including AD, Huntington's disease, and ALS. T e best characterized genetic neurologic disorder related to apoptosis is infantile spinal muscular atrophy (Werdnig-Hoffmann disease), in which two genes thought to be involved in the apoptosis pathways are causative.

Mitochondria are essential in controlling specific apoptosis pathways. T e redistribution of cytochrome c, as well as apoptosis-inducing factor (AIF), from mitochondria during apoptosis leads to the activation of a cascade of intracellular proteases known as caspases. Caspase-independent apoptosis occurs after DNA damage, activation of poly-ADP-ribose polymerase, and translocation of AIF into the nucleus. Redistribution of cytochrome c is prevented by overproduction of the apoptotic protein BCL2 and is promoted by the proapoptotic protein BAX. T ese pathways may be triggered by activation of a large pore in the mitochondrial inner membrane known as the permeability transition pore, although in other circumstances, they occur independently. T e permeability transition pore is made up of dimers of ATP synthase and is activated by cyclophilin D, leading to large calcium fluxes across the inner mitochondrial membrane. Certain forms of congenital muscular dystrophies are caused by mutations in collagen VI, which leads to increased activation of the permeability transition pore. Recent studies suggest that blocking the mitochondrial pore reduces both hypoglycemic and ischemic cell death. Mice deficient in cyclophilin D, a key protein involved in opening the permeability transition pore, are resistant to necrosis produced by focal cerebral ischemia.

PROTEIN AGGREGATION AND NEURODEGENERATION

T e possibility that protein aggregation plays a role in the pathogenesis of neurodegenerative diseases is a major focus of current research. Protein aggregation is a major histopathologic hallmark of neurodegenerative diseases. Deposition of b-amyloid is strongly implicated in the pathogenesis of AD. Genetic mutations in familial AD cause increased production of b-amyloid with 42 amino acids, which has an increased propensity to aggregate, as compared to b-amyloid with 40 amino acids. Furthermore, mutations in the amyloid

www.ketabpezeshki.com (021) 66485457 - 66485438

precursor protein (APP), which reduce the production of b-amyloid, protect against the development of AD and are associated with preserved cognition in the elderly. Mutations in genes encoding the MAPT lead to altered splicing of tau and the production of neurofibrillary tangles in frontotemporal dementia and progressive supranuclear palsy. Familial Parkinson's disease is associated with mutations in leucine-rich repeat kinase 2 (LRRK2), α-synuclein, parkin, PINK1, and DJ-1. PINK1 is a mitochondrial kinase (see below), and DJ-1 is a protein involved in protection from oxidative stress. Parkin, which causes autosomal recessive early-onset Parkinson's disease, is a ubiquitin ligase. T e characteristic histopathologic feature of Parkinson's disease is the Lewy body, an eosinophilic cytoplasmic inclusion that contains both neurofilaments and α-synuclein. Huntington's disease and cerebellar degenerations are associated with expansions of polyglutamine repeats in proteins, which aggregate to produce neuronal intranuclear inclusions. Familial ALS is associated with superoxide dismutase mutations and cytoplasmic inclusions containing superoxide dismutase. An important finding was the discovery that ubiquinated inclusions observed in most cases of ALS and the most common form of frontotemporal dementia are composed of TAR DNA binding protein 43 (TDP-43). Subsequently, mutations in the TDP-43 gene, and in the fused in sarcoma gene (FUS), were found in familial ALS. Both of these proteins are involved in transcription regulation as well as RNA metabolism. In autosomal dominant neurohypophyseal diabetes insipidus, mutations in vasopressin result in abnormal protein processing, accumulation in the endoplasmic reticulum, and cell death.

Another key mechanism linked to cell death is mitochondrial dynamics, which refers to the processes involved in movement of mitochondria, as well as in mitochondrial fission and fusion, which play a critical role mitochondrial turnover and in replenishment of damaged mitochondria. Mitochondrial dysfunction is strongly linked to the pathogenesis of a number of neurodegenerative diseases such as Friedreich's ataxia, which is caused by mutations in an iron-binding protein that plays an important role in transferring iron to iron-sulfur clusters in aconitase and complex I and II of the electron transport chain. Mitochondrial fission is dependent on the dynamin-related proteins (Drp1), which bind to its receptor Fis, whereas mitofuscins 1 and 2 (MF 1/2) and optic atrophy protein 1 (OPA1) are responsible for fusion of the outer and inner mitochondrial membrane, respectively. Mutations in MFN2 cause Charcot-Marie-Tooth neuropathy type 2A, and mutations in OPA1 cause autosomal dominant optic atrophy. Both b-amyloid and mutant huntingtin protein induce mitochondrial fragmentation and neuronal cell death associated with increased activity of Drp1. In addition, mutations in genes causing autosomal recessive Parkinson's disease, parkin and PINK1, cause abnormal mitochondrial morphology and result in impairment of the ability of the cell to remove damaged mitochondria by autophagy.

One major scientific question is whether protein aggregates directly contribute to neuronal death or whether they are merely secondary bystanders. A current focus in all the neurodegenerative diseases is on small protein aggregates termed oligomers. T ese may be the toxic species of b-amyloid, α-synuclein, and proteins with expanded polyglutamines such as are associated with Huntington's disease. Protein aggregates are usually ubiquinated, which targets them for degradation by the 26S component of the proteasome. An inability to degrade protein aggregates could lead to cellular dysfunction, impaired axonal transport, and cell death by apoptotic mechanisms.

Autophagy is the degradation of cystolic components in lysosomes. T ere is increasing evidence that autophagy plays an important role in degradation of protein aggregates in the neurodegenerative diseases, and it is impaired in AD, Parkinson's disease, and Huntington's disease. Autophagy is particularly important to the health of neurons, and failure of autophagy contributes to cell death. In Huntington's disease, a failure of cargo recognition occurs, contributing to protein aggregates and cell death. Rapamycin, which induces autophagy, exerts beneficial therapeutic effects in transgenic mouse models of AD, Parkinson's disease, and Huntington's disease.

T ere is other evidence for lysosomal dysfunction and impaired autophagy in Parkinson's disease. Mutations in glucocerebrosidase are associated with 5% of all Parkinson's disease cases as well as 8–9% of patients with dementia with Lewy bodies. T erefore, this is the most important genetic cause of both disorders thus far identified. T ere appear to be reciprocal interactions between glucocerebrosidase and α-synuclein. It has been shown that glucocerebrosidase concentrations and enzymatic activity are reduced in the substantia nigra of sporadic Parkinson's disease patients. Furthermore, α-synuclein is degraded by chaperone-mediated and macro autophagy. T e degradation of α-synuclein has been shown to be impaired in transgenic mice deficient in glucocerebrosidase as well as in mice in which the enzyme has been inhibited. Furthermore, it is known that α-synuclein inhibits the activity of glucocerebrosidase. T erefore, there is bidirectional feedback between α-synuclein and glucocerebrosidase. An attractive therapeutic intervention could be to use protein chaperones to increase the activity and duration of action of glucocerebrosidase. T is would also reduce α-synuclein levels and block the degeneration of dopaminergic neurons.

T e retromer complex is a conserved membrane-associated protein complex that functions in the

www.ketabpezeshki.com (021) 66485457 - 66485438

endosome-to-Golgi complex. T e retromer complex contains a cargo selective complex consisting of VPS35, VPS26, and VPS29, along with a sorting nexin dimer. Recently, mutations in VPS35 were shown to be a cause of late-onset autosomal dominant Parkinson's disease. T e retromer also traffics APP away from endosomes, where it is cleaved to generate b-amyloid. Deficiencies of VPS35 and VPS26 were also identified in hippocampal brain tissue from AD. A new therapeutic approach to these diseases might therefore be to use chaperones to stabilize the retromer and reduce the generation of b-amyloid and α-synuclein.

T e LRRK2 mutations were shown to have effects on clearance of Golgi-derived vesicles through the autophagy-lysosome system both in vitro and in vivo. LRRK2 mutations also are linked to elevated protein synthesis mediated by ribosomal protein s15 phosphorylation. Blocking this phosphorylation reduces LRRK2-mediated neurite loss and cell death in human dopamine and cortical neurons.

Interestingly, in experimental models of Huntington's disease and cerebellar degeneration, protein aggregates are not well correlated with neuronal death and may be protective. A substantial body of evidence suggests that the mutant proteins with polyglutamine expansions in these diseases bind to transcription factors and that this contributes to disease pathogenesis. In Huntington's disease, there is dysfunction of the transcriptional co-regulator, PGC-1α, a key regulator of mitochondrial biogenesis. T ere is evidence that impaired function of PGC-1α is also important in both Parkinson's disease and AD, making it an attractive target for treatments. Agents that upregulate gene transcription are neuroprotective in animal models of these diseases. A number of compounds have been developed to block b-amyloid production and/or aggregation, and these agents are being studied in early clinical trials in humans. Another approach under investigation is immunotherapy with antibodies that bind b-amyloid, tau, or α-synuclein. T ese studies have shown efficacy in preventing the spread of amyloid, tau, and α-synuclein in animal studies, raising hopes that this could lead to effective therapies by blocking neuron-to-neuron propagation. Two large clinical trials of b-amyloid immunotherapy, however, did not show efficacy, although this therapeutic strategy is still being studied.

PRIONS AND NEURODEGENERATIVE DISEASES

As we have learned more about the etiology and pathogenesis of the neurodegenerative diseases, it has become clear that the histologic abnormalities that were once curiosities, in fact, are likely to reflect the etiologies. For example, the amyloid plaques in kuru and Creutzfeldt-Jakob disease (CJD) are filled with the PrP^{Sc} prions that have assembled into fibrils. T e past three decades have witnessed an explosion of new knowledge about prions. For many years, kuru, CJD, and scrapie of sheep were thought to be caused by slow-acting viruses, but a large body of experimental evidence argues that the infectious pathogens causing these diseases are devoid of nucleic acid. Such pathogens are called prions, which are composed of host-encoded proteins that adopt alternative conformations **(Chap. 40)**. Prions are self-propagating by imposing their conformations on the normal, precursor protein; most prions are enriched for b-sheet and can assemble into amyloid fibrils.

Similar to the plaques in kuru and CJD that are composed of PrP prions, the amyloid plaques in AD are filled with Ab prions that have polymerized into fibrils. T is relationship between the neuropathologic findings and the etiologic prion was strengthened by the genetic linkage between familial CJD and mutations in the PrP gene, as well as (as noted above) between familial AD and mutations in the APP gene. Moreover, a mutation in the APP gene that prevents Ab peptide formation was correlated with a decreased incidence of AD in Iceland.

T e heritable neurodegenerative diseases offer an important insight into the pathogenesis of the more common, sporadic ones. Although the mutant proteins that cause these disorders are expressed in the brains of people early in life, the diseases do not occur for many decades. Many explanations for the late onset of familial neurodegenerative diseases have been offered, but none are supported by substantial experimental evidence. T e late onset might be due to a second event in which a mutant protein, after its conversion into a prion, begins to accumulate at some rather advanced age **(Fig. 30-5)**.Such a formulation is also consistent with data showing that the protein quality-control mechanisms diminish in efficiency with age. T us, the prion forms of both wild-type and mutant proteins are likely to be efficiently degraded in younger people but are less well handled in older individuals. T is explanation is consistent with the view that neurodegenerative diseases are disorders of the aging nervous system.

A new classification for neurodegenerative diseases can be proposed based on not only the traditional phenotypic presentation and neuropathology, but also the prion etiology **(Table 30-4)**. Over the past decade, an expanding body of experimental data has accumulated implicating prions in each of these illnesses. In addition to kuru and CJD, Gerstmann-Sträussler-Scheinker disease (GSS) and fatal insomnia in humans are caused by PrP^{Sc} prions. In animals, PrP^{Sc} prions cause scrapie of sheep and goats, bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD) of deer and elk, feline spongiform encephalopathy, and transmissible

www.ketabpezeshki.com (021) 66485457 - 66485438

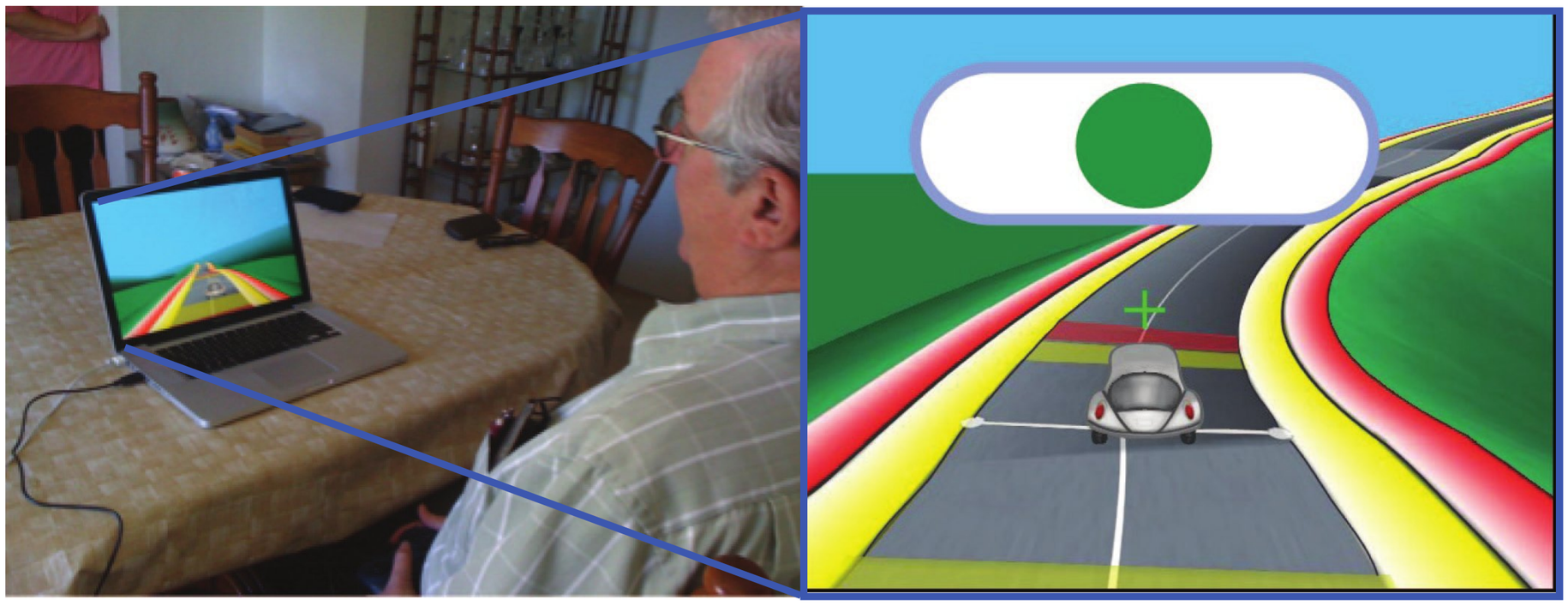


FIGURE 30-5

Video game training can enhance cognitive performance. A. An older participant engaging in NeuroRacer training (driving while responding to target signs), with (B) a screen shot of the experimental training session. C. NeuroRacer multitasking costs for target discrimination increased (i.e., a larger percentage decrease from single task performance when multitasking) in (i) a linear fashion across the lifespan and with (ii) costs before training 1 month after training and 6 months after training, showing a differential benefit of multitasking training compared to a no-contact control group and a single-task training group. D. Midline frontal theta activity obtained with electroencephalogram showed significantly enhanced activity only following multitasking training, mimicking the pattern of change in the behavioral data as well as performance improvements on untrained tests of working memory and sustained attention (not presented). For details, see JA Anguera et al: Nature 501:97, 2013.

mink encephalopathy (TME). Similar to PrP, Ab, tau, α-synuclein, superoxide dismutase 1 (SOD1), and possibly huntingtin all adopt alternative conformations that become self-propagating, and thus, each protein can become a prion and be transferred to synaptically connected neurons. Moreover, each of these prions causes a distinct constellation of neurodegenerative diseases.

Evidence for a prion etiology of AD comes from a series of transmission experiments initially performed in marmosets and more recently in transgenic (Tg) mice inoculated with a synthetic Ab peptide folded into a prion. Studies with the tau protein have shown that it not only features in the pathogenesis of AD, but also causes such illnesses as the frontotemporal dementias

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 30-4

A PRION-BASED CLASSIFICATION OF NEURODEGENERATIVE DISEASES

NEURODEGENERATIVE DISEASES	CAUSATIVE PRION PROTEINS
Creutzfeldt-Jakob disease (CJD) Kuru Gerstmann-Sträussler-Scheinker (GSS) Fatal insomnia Bovine spongiform encephalopathy (BSE) Scrapie Chronic wasting disease (CWD) Feline spongiform encephalopathy Transmissible mink encephalopathy	PrP^{Sc}
Alzheimer's disease (AD)	Aβ → tau
Parkinson's disease	α-Synuclein
Frontotemporal dementias (FTDs) Posttraumatic FTD, called chronic traumatic encephalopathy	Tau, TDP43, FUS (C9orf72, progranulin)
Amyotrophic lateral sclerosis	SOD1, TDP43, FUS (C9orf72)
Huntington's disease	Huntingtin

including chronic traumatic encephalopathy, which has been reported in both contact sport athletes and military personnel who have suffered traumatic brain injuries. A series of incisive studies using cultured cells and Tg mice has demonstrated that tau can become a prion and multiply in the brain. In contrast to the Ab and tau prions, a strain of α-synuclein prions found in the brains of patients who died of multiple system atrophy (MSA) killed the Tg mouse host ~90 days after intracerebral inoculation, whereas α-synuclein prions formed spontaneously in Tg mouse brains killed recipient mice in ~200 days.

For many years, the most frequently cited argument against prions was the existence of strains that produced distinct clinical presentations and different patterns of neuropathologic lesions. Some investigators argued that the biologic information carried in different prion strains could only be encoded within a nucleic acid. Subsequently, many studies demonstrated that strain-specified variation is enciphered in the conformation of PrP^{Sc}, but the molecular mechanisms responsible for the storage of biologic information remains enigmatic. T e neuroanatomical patterns of prion deposition have been shown to be dependent on the particular strain of prion. Convincing evidence in support of this proposition has been accumulated for PrP, Ab, tau, and α-synuclein prions.

Although the number of prions identified in mammals and in fungi continues to expand, the existence of prions in other phylogeny remains undetermined. Some mammalian prions perform vital functions and do not cause disease; such nonpathogenic prions include the cytoplasmic polyadenylation element binding (CPEB) protein, the mitochondrial antiviral-signaling (MAVS) protein, and T cell–restricted intracellular antigen 1 (TIA-1).

All mammalian prion proteins adopt a b-sheet-rich conformation and appear to readily oligomerize as this process becomes self-propagating. Control of the self-propagating state of benign mammalian prions is not well understood but is critical for the well-being of the host. In contrast, pathogenic mammalian prions appear to multiply exponentially, but the mechanisms by which they cause disease are poorly defined. We do not know if prions multiply as monomers or as oligomers; notably, the ionizing radiation target size of PrP^{Sc} prions seems to suggest it is a trimer. T e oligomeric states of pathogenic mammalian prions are thought to be the toxic forms, and assembly into larger polymers, such as amyloid fibrils, seems to be a mechanism for minimizing toxicity.

To date, there is no medication that halts or even slows a human neurodegenerative disease. T e development of drugs designed to inhibit the conversion of the normal precursor proteins into prions or to enhance the degradation of prions focuses on the initial step in prion accumulation. Although several drugs that cross the blood-brain barrier have been identified that prolong the lives of mice infected with scrapie prions, none have been identified that extend the lives of Tg mice that replicate human CJD prions. Despite doubling the length of incubation times in mice inoculated with scrapie prions, all of the mice eventually succumb to illness. Because all of the treated mice develop neurologic dysfunction at the same time, the mutation rate as judged by drug resistance is likely to approach 100%, which is much higher than mutation rates recorded for bacteria and viruses. Mutations in prions seem likely to represent conformational variants that are selected for in mammals where survival becomes limited by the fastest-replicating prions. T e results of these studies make it likely that cocktails of drugs that attack a variety of prion conformers will be required for the development of effective therapeutics.

SYSTEMS NEUROSCIENCE

Systems neuroscience refers to study of the functions of neural circuits and how they relate to brain function, behavior, motor activity, and cognition. Brain imaging techniques, primarily functional magnetic resonance imaging (fMRI) and position emission tomography (PET), have made it possible to investigate, noninvasively and in awake individuals, cognitive processes

www.ketabpezeshki.com (021) 66485457 - 66485438

such as perception, making judgments, paying attention, and thinking. T is has allowed insights into how networks of neurons operate to produce behavior. Many of these studies at present are based on determining the connectivity of neural circuits and how they operate, and how this can be then modeled to produce improved understanding of physiologic processes. fMRI uses contrast mechanisms related to physiologic changes in tissue, and brain perfusion can be studied by observing the time course of changes in brain water signal as a bolus of injected paramagnetic gadolinium contrast moves through the brain. More recently, to study intrinsic contrast-related local changes in blood oxygenation with brain activity, blood-oxygen-level-dependent (BOLD) contrast has been used to provide a rapid noninvasive approach for functional assessment. T ese techniques have been reliably used in the field of both behavior and cognitive sciences. One example is the use of fMRI to demonstrate mirror neuron systems, imitative pathways activated when observing actions of others. Mirror neurons are thought to be important for social conditioning and for many forms of learning, and abnormalities in mirror neurons may underlie some autism disorders.

Both structural and functional connectivity methods show large-scale network dysfunction in AD and frontotemporal dementia. T e networks targeted have been defined as the default network in AD and the salience network in frontotemporal dementia. T e default network is characterized by an area of reduced glucose metabolism in the temporoparietal cortex, which precedes the onset of dementia and which is an area preferentially affected by amyloid deposition. T ese networks are now thought to be pathways accounting for the spread of abnormally templated proteins (prions; see above), including b-amyloid, tau, and α-synuclein.

Other examples of the use of fMRI include the study of memory, revealing that not only is hippocampal activity correlated with declarative memory consolidation, but it also involves activation in the ventral medial prefrontal cortex. Consolidation of memory over time results in decreased activity of the hippocampus and progressively stronger activation in the ventral medial prefrontal region associated with retrieval of consolidated memories. fMRI has also been used to identify sequences of brain activation involved in normal movements and alterations in their activation associated with both injury and recovery, to plan neurosurgical operations, and remarkably, to reconstruct actual visual images from the occipital cortex. Noninvasive brain-computer interfaces have extraordinary potential to advance the development of robotics and exoskeleton devices guided by brain activity for patients with a variety of nervous system af ictions. Diffusion tensor imaging is a recently developed MRI technique that can measure macroscopic axonal organization in nervous system tissues; it appears to be useful in assessing myelin and axonal injuries as well as brain development. Advances in understanding neural processing have led to the development of the ability to demonstrate that humans have online voluntary control of human temporal lobe neurons.

Multitasking capabilities, including attention to tasks when faced with distractions, decline as we age due to a decline in medial prefrontal cognitive control system. When faced with a multitasking challenge, video game training can improve cognitive control capabilities by augmenting prefrontal suppression of the default network and, as measured by electroencephalography and fMRI, result in improved performance that is sustained and, importantly, transfers to other cognitive tasks not associated with the training paradigm.

A significant recent advance in neuropathology has discovered that sodium dodecyl sulfate (SDS) detergent treatment can render the brain transparent (CLARITY), removing lipids while preserving most protein and structural elements and providing opportunities to identify brain structures and neural networks with unprecedented detail.

A therapeutic technology that has long-reaching implications for the development of novel interventions for neurologic, including behavioral, conditions has been the development of deep-brain stimulation as a highly effective therapeutic intervention for treating excessively firing neurons in the subthalamic nucleus of patients with Parkinson's disease and the precingulate cortex in patients with depression.

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES (BRAIN) INITIATIVE

T e BRAIN initiative, grand in scope, was launched in 2013 to speed development of advances to understand, treat, repair, and prevent common neurologic disorders that, in aggregate, affect more than 1 billion people worldwide. T e initial goal of BRAIN is to bring together experts in neurobiology (including optogenetics), engineering, information technology, and other fields to develop novel visualization and electrophysiologic methods to better define and understand neural circuits and all the connections among individual neurons. T e announcement of the BRAIN initiative followed just weeks after a similarly ambitious program, the Human Brain Project (HBP), was unveiled by the European Union. T e HBP seeks to model individual neurons, neural circuits, and ultimately the entire brain using computer technologies. Its architects also envision layering clinical and biomarker data from large

www.ketabpezeshki.com (021) 66485457 - 66485438

health care databases to identify biosignatures associated with human phenotypes, possibly leading to a fundamental reclassification of disease, a concept also proposed by others, including in a 2011 report of the National Academy of Sciences (Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease). T ese two ambitious projects are expected to be complementary and over time will hopefully become increasingly integrated. Emerging discoveries are also certain to stimulate a range of ethical questions, many of which are not unique to the neurosciences but do come into sharpest focus in this area. T ese include possible risks to the privacy of personal information about our health, cognitive capabilities, or behavioral attributes; the sanctity of our private thoughts; as well as concerns regarding neuroenhancement technologies, including their potential military use. Both the BRAIN and HBP initiatives have put into place strong ethical components to ensure that these programs are carried out, from the outset and to the fullest extent possible, consistent with guiding ethical principles that include respect for individuals, public beneficence, justice and fairness, democratic deliberation, and transparency.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 31

SEIZURES AND EPILEPSY

Daniel H. Lowenstein

A seizure (from the Latin sacire, "to take possession of") is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. Depending on the distribution of discharges, this abnormal brain activity can have various manifestations, ranging from dramatic convulsive activity to experiential phenomena not readily discernible by an observer. Although a variety of factors influence the incidence and prevalence of seizures, ~5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.

The meaning of the term seizure needs to be carefully distinguished from that of epilepsy. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. This definition implies that a person with a single seizure, or recurrent seizures due to correctable or avoidable circumstances, does not necessarily have epilepsy. Epilepsy refers to a clinical phenomenon rather than a single disease entity, because there are many forms and causes of epilepsy. However, among the many causes of epilepsy there are various epilepsy syndromes in which the clinical and pathologic characteristics are distinctive and suggest a specific underlying etiology.

Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is ~0.3–0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5–30 persons per 1000.

CLASSIFICATION OF SEIZURES

Determining the type of seizure that has occurred is essential for focusing the diagnostic approach on particular etiologies, selecting the appropriate therapy, and providing potentially vital information regarding prognosis. The International League against Epilepsy (ILAE) Commission on Classification and Terminology, 2005–2009 has provided an updated approach to classification of seizures **(Table 31-1)**. This system is based on the clinical features of seizures and associated electroencephalographic findings. Other potentially distinctive features such as etiology or cellular substrate are not considered in this classification system, although this will undoubtedly change in the future as more is learned about the pathophysiologic mechanisms that underlie specific seizure types.

A fundamental principle is that seizures may be either focal or generalized. Focal seizures originate within networks limited to one cerebral hemisphere (note that the term partial seizures is no longer used). Generalized seizures arise within and rapidly engage networks distributed across both cerebral hemispheres. Focal seizures are usually associated with structural abnormalities of the brain. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution. There are clear exceptions in both cases, however.

TABLE 31-1

CLASSIFICATION OF SEIZURES

1. **Focal seizures**
   (Can be further described as having motor, sensory, autonomic, cognitive, or other features)
2. **Generalized seizures**
   a. Absence
      Typical
      Atypical
   b. Tonic clonic
   c. Clonic
   d. Tonic
   e. Atonic
   f. Myoclonic
3. **May be focal, generalized, or unclear**
   Epileptic spasms

www.ketabpezeshki.com (021) 66485457 - 66485438

FOCAL SEIZURES

Focal seizures arise from a neuronal network either discretely localized within one cerebral hemisphere or more broadly distributed but still within the hemisphere. With the new classification system, the subcategories of "simple focal seizures" and "complex focal seizures" have been eliminated. Instead, depending on the presence of cognitive impairment, they can be described as focal seizures with or without dyscognitive features. Focal seizures can also evolve into generalized seizures. In the past this was referred to as *f*ocal seizures with secondary generalization, but the new system relies on specific descriptions of the type of generalized seizures that evolve from the focal seizure.

The routine interictal (i.e., between seizures) electroencephalogram (EEG) in patients with focal seizures is often normal or may show brief discharges termed epilepti*f*orm spikes, or sharp waves. Because focal seizures can arise from the medial temporal lobe or inferior frontal lobe (i.e., regions distant from the scalp), the EEG recorded during the seizure may be nonlocalizing. However, the seizure focus is often detected using sphenoidal or surgically placed intracranial electrodes.

Focal seizures without dyscognitive features

Focal seizures can cause motor, sensory, autonomic, or psychic symptoms without impairment of cognition. For example, a patient having a focal motor seizure arising from the right primary motor cortex near the area controlling hand movement will note the onset of involuntary movements of the contralateral, left hand. These movements are typically clonic (i.e., repetitive, flexion/extension movements) at a frequency of ~2–3 Hz; pure tonic posturing may be seen as well. Since the cortical region controlling hand movement is immediately adjacent to the region for facial expression, the seizure may also cause abnormal movements of the face synchronous with the movements of the hand. The EEG recorded with scalp electrodes during the seizure (i.e., an ictal EEG) may show abnormal discharges in a very limited region over the appropriate area of cerebral cortex if the seizure focus involves the cerebral convexity. Seizure activity occurring within deeper brain structures is sometimes not detected by the standard EEG, however, and may require intracranial electrodes for its detection.

Three additional features of focal motor seizures are worth noting. First, in some patients, the abnormal motor movements may begin in a very restricted region such as the fingers and gradually progress (over seconds to minutes) to include a larger portion of the extremity. This phenomenon, described by Hughlings Jackson and known as a "Jacksonian march," represents the spread of seizure activity over a progressively larger region of motor cortex. Second, patients may experience a localized paresis (Todd's paralysis) for minutes to many hours in the involved region following the seizure. Third, in rare instances, the seizure may continue for hours or days. This condition, termed epilepsia partialis continua, is often refractory to medical therapy.

Focal seizures may also manifest as changes in somatic sensation (e.g., paresthesias), vision (flashing lights or formed hallucinations), equilibrium (sensation of falling or vertigo), or autonomic function (flushing, sweating, piloerection). Focal seizures arising from the temporal or frontal cortex may also cause alterations in hearing, olfaction, or higher cortical function (psychic symptoms). This includes the sensation of unusual, intense odors (e.g., burning rubber or kerosene) or sounds (crude or highly complex sounds), or an epigastric sensation that rises from the stomach or chest to the head. Some patients describe odd, internal feelings such as fear, a sense of impending change, detachment, depersonalization, déjá vu, or illusions that objects are growing smaller (micropsia) or larger (macropsia). These subjective, "internal" events that are not directly observable by someone else are referred to as auras.

Focal seizures with dyscognitive features

Focal seizures may also be accompanied by a transient impairment of the patient's ability to maintain normal contact with the environment. The patient is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of the ictal phase. These seizures frequently begin with an aura (i.e., a focal seizure without cognitive disturbance) that is stereotypic for the patient. The start of the ictal phase is often a sudden behavioral arrest or motionless stare, which marks the onset of the period of impaired awareness. The behavioral arrest is usually accompanied by automatisms, which are involuntary, automatic behaviors that have a wide range of manifestations. Automatisms may consist of very basic behaviors such as chewing, lip smacking, swallowing, or "picking" movements of the hands, or more elaborate behaviors such as a display of emotion or running. The patient is typically confused following the seizure, and the transition to full recovery of consciousness may range from seconds up to an hour. Examination immediately following the seizure may show an anterograde amnesia or, in cases involving the dominant hemisphere, a postictal aphasia.

The range of potential clinical behaviors linked to focal seizures is so broad that extreme caution is advised before concluding that stereotypic episodes of bizarre or atypical behavior are not due to seizure activity. In such cases additional, detailed EEG studies may be helpful.

www.ketabpezeshki.com (021) 66485457 - 66485438

EVOLUTION OF FOCAL SEIZURES TO GENERALIZED SEIZURES

Focal seizures can spread to involve both cerebral hemispheres and produce a generalized seizure, usually of the tonic-clonic variety (discussed below). T is evolution is observed frequently following focal seizures arising from a focus in the frontal lobe, but may also be associated with focal seizures occurring elsewhere in the brain. A focal seizure that evolves into a generalized seizure is often dif cult to distinguish from a primary generalized-onset tonic-clonic seizure, because bystanders tend to emphasize the more dramatic, generalized convulsive phase of the seizure and overlook the more subtle, focal symptoms present at onset. In some cases, the focal onset of the seizure becomes apparent only when a careful history identifies a preceding aura. Often, however, the focal onset is not clinically evident and may be established only through careful EEG analysis. Nonetheless, distinguishing between these two entities is extremely important, because there may be substantial differences in the evaluation and treatment of epilepsies associated with focal versus generalized seizures.

GENERALIZED SEIZURES

Generalized seizures are thought to arise at some point in the brain but immediately and rapidly engage neuronal networks in both cerebral hemispheres. Several types of generalized seizures have features that place them in distinctive categories and facilitate clinical diagnosis.

Typical absence seizures

Typical absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control. T e seizure typically lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion. Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands.

Typical absence seizures are associated with a group of genetically determined epilepsies with onset usually in childhood (ages 4–8 years) or early adolescence and are the main seizure type in 15–20% of children with epilepsy. T e seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence. Because the clinical signs of the seizures are subtle, especially to parents who may not have had previous experience with seizures, it is not surprising that the first clue to absence epilepsy is often unexplained "daydreaming" and a decline in school performance recognized by a teacher.

T e electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-wave discharge that begins and ends suddenly, superimposed on a normal EEG background. Periods of spike-and-wave discharges lasting more than a few seconds usually correlate with clinical signs, but the EEG often shows many more brief bursts of abnormal cortical activity than were suspected clinically. Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.

Atypical absence seizures

Atypical absence seizures have features that deviate both clinically and electrophysiologically from typical absence seizures. For example, the lapse of consciousness is usually of longer duration and less abrupt in onset and cessation, and the seizure is accompanied by more obvious motor signs that may include focal or lateralizing features. T e EEG shows a generalized, slow spike-and-wave pattern with a frequency of ≤2.5 per second, as well as other abnormal activity. Atypical absence seizures are usually associated with diffuse or multifocal structural abnormalities of the brain and therefore may accompany other signs of neurologic dysfunction such as mental retardation. Furthermore, the seizures are less responsive to anticonvulsants compared to typical absence seizures.

Generalized, tonic-clonic seizures

Generalized-onset tonic-clonic seizures are the main seizure type in ~10% of all persons with epilepsy. T ey are also the most common seizure type resulting from metabolic derangements and are therefore frequently encountered in many different clinical settings. T e seizure usually begins abruptly without warning, although some patients describe vague premonitory symptoms in the hours leading up to the seizure. T is prodrome is distinct from the stereotypic auras associated with focal seizures that generalize. T e initial phase of the seizure is usually tonic contraction of muscles throughout the body, accounting for a number of the classic features of the event. Tonic contraction of the muscles of expiration and the larynx at the onset will produce a loud moan or "ictal cry." Respirations are impaired, secretions pool in the oropharynx, and cyanosis develops. Contraction of the jaw muscles may cause biting of the tongue. A marked enhancement of sympathetic tone leads to increases in heart rate, blood pressure, and pupillary size. After 10–20 s, the tonic phase of the seizure typically evolves into the clonic phase, produced by

www.ketabpezeshki.com (021) 66485457 - 66485438

the superimposition of periods of muscle relaxation on the tonic muscle contraction. T e periods of relaxation progressively increase until the end of the ictal phase, which usually lasts no more than 1 min. T e postictal phase is characterized by unresponsiveness, muscular flaccidity, and excessive salivation that can cause stridorous breathing and partial airway obstruction. Bladder or bowel incontinence may occur at this point. Patients gradually regain consciousness over minutes to hours, and during this transition, there is typically a period of postictal confusion. Patients subsequently complain of headache, fatigue, and muscle ache that can last for many hours. T e duration of impaired consciousness in the postictal phase can be extremely long (i.e., many hours) in patients with prolonged seizures or underlying central nervous system (CNS) diseases such as alcoholic cerebral atrophy.

T e EEG during the tonic phase of the seizure shows a progressive increase in generalized low-voltage fast activity, followed by generalized high-amplitude, polyspike discharges. In the clonic phase, the high-amplitude activity is typically interrupted by slow waves to create a spike-and-wave pattern. T e postictal EEG shows diffuse slowing that gradually recovers as the patient awakens.

T ere are a number of variants of the generalized tonic-clonic seizure, including pure tonic and pure clonic seizures. Brief tonic seizures lasting only a few seconds are especially noteworthy since they are usually associated with specific epileptic syndromes having mixed seizure phenotypes, such as the Lennox-Gastaut syndrome (discussed below).

Atonic seizures

Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1–2 s. Consciousness is briefly impaired, but there is usually no postictal confusion. A very brief seizure may cause only a quick head drop or nodding movement, whereas a longer seizure will cause the patient to collapse. T is can be extremely dangerous, because there is a substantial risk of direct head injury with the fall. T e EEG shows brief, generalized spike-and-wave discharges followed immediately by diffuse slow waves that correlate with the loss of muscle tone. Similar to pure tonic seizures, atonic seizures are usually seen in association with known epilepsy syndromes.

Myoclonic seizures

Myoclonus is a sudden and brief muscle contraction that may involve one part of the body or the entire body. A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep. Pathologic myoclonus is most commonly seen in association with metabolic disorders, degenerative CNS diseases, or anoxic brain injury **(Chap. 33)**. Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events because they are caused by cortical (versus subcortical or spinal) dysfunction. T e EEG may show bilaterally synchronous spike-and-wave discharges synchronized with the myoclonus, although these can be obscured by movement artifact. Myoclonic seizures usually coexist with other forms of generalized seizures but are the predominant feature of juvenile myoclonic epilepsy (discussed below).

CURRENTLY UNCLASSIFIABLE SEIZURES

Not all seizure types can be designated as focal or generalized, and they should therefore be labeled as "unclassifiable" until additional evidence allows a valid classification. Epileptic spasms are such an example. T ese are characterized by a briefly sustained flexion or extension of predominantly proximal muscles, including truncal muscles. T e EEG in these patients usually shows hypsarrhythmias, which consist of diffuse, giant slow waves with a chaotic background of irregular, multifocal spikes and sharp waves. During the clinical spasm, there is a marked suppression of the EEG background (the "electrodecremental response"). T e electromyogram (EMG) also reveals a characteristic rhomboid pattern that may help distinguish spasms from brief tonic and myoclonic seizures. Epileptic spasms occur predominantly in infants and likely result from differences in neuronal function and connectivity in the immature versus mature CNS.

EPILEPSY SYNDROMES

Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is suf cient evidence (e.g., through clinical, EEG, radiologic, or genetic observations) to suggest a common underlying mechanism. T ree important epilepsy syndromes are listed below; additional examples with a known genetic basis are shown in **Table 31-2**.

JUVENILE MYOCLONIC EPILEPSY

Juvenile myoclonic epilepsy (JME) is a generalized seizure disorder of unknown cause that appears in early adolescence and is usually characterized by bilateral myoclonic jerks that may be single or repetitive. T e myoclonic seizures are most frequent in the morning after awakening and can be provoked by sleep

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 31-2

EXAMPLES OF GENES ASSOCIATED WITH EPILEPSY SYNDROMES[a]

GENE (LOCUS)	FUNCTION OF GENE	CLINICAL SYNDROME	COMMENTS
CHRNA4 (20q13.2)	Nicotinic acetylcholine receptor subunit; mutations cause alterations in Ca^{2+} flux through the receptor; this may reduce amount of GABA release in presynaptic terminals	Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE); childhood onset; brief, nighttime seizures with prominent motor movements; often misdiagnosed as primary sleep disorder	Rare; first identified in a large Australian family; other families found to have mutations in CHRNA2 or CHRNB2, and some families appear to have mutations at other loci
KCNQ2 (20q13.3)	Voltage-gated potassium channel subunits; mutation in pore regions may cause a 20–40% reduction of potassium currents, which will lead to impaired repolarization	Benign familial neonatal seizures (BFNS); autosomal dominant inheritance; onset in 1st week of life in infants who are otherwise normal; remission usually within weeks to months; long-term epilepsy in 10–15%	Rare; other families found to have mutations in KCNQ3 or an inversion in chromosomal 5; sequence and functional homology to KCNQ1, mutations of which cause long QT syndrome and a cardiac-auditory syndrome
SCN1A (2q24.3)	α-Subunit of a voltage-gated sodium channel; numerous mutations affecting sodium currents that cause either gain or loss of function; network effects appear related to expression in excitatory or inhibitory cells	Generalized epilepsy with febrile seizures plus (GEFS+); autosomal dominant inheritance; presents with febrile seizures at median 1 year, which may persist >6 years, then variable seizure types not associated with fever; numerous other syndromes, including almost 80% of patients with Dravet's syndrome (severe myoclonic epilepsy of infancy) and some cases of Lennox-Gastaut syndrome	Incidence uncertain; GEFS+ identified in other families with mutations in other sodium channel subunits (SCN2B and SCN2A) and $GABA_A$ receptor subunit (GABRG2 and GABRA1); significant phenotypic heterogeneity within same family, including members with febrile seizures only
LGI1 (10q24)	Leucine-rich glioma-inactivated 1 gene; previous evidence for role in glial tumor progression; recent studies suggest an influence in the postnatal development of glutamatergic circuits in the hippocampus	Autosomal dominant partial epilepsy with auditory features (ADPEAF); a form of idiopathic lateral temporal lobe epilepsy with auditory symptoms or aphasia as a major focal seizure manifestation; age of onset usually between 10 and 25 years	Mutations found in up to 50% of families containing two or more subjects with idiopathic localization-related epilepsy with ictal auditory symptoms, suggesting that at least one other gene may underlie this syndrome.
DEPDC5 (22q12.2)	Disheveled, Egl-10 and pleckstrin domain containing protein 5; exerts an inhibitory effect on mammalian target of rapamycin (mTOR)-mediated processes, such as cell growth and proliferation	Autosomal dominant familial focal epilepsy with variable foci (FFEVF); family members have seizures originating from different cortical regions; neuroimaging usually normal but may harbor subtle malformations; recent studies also suggest association with benign epilepsy with centrotemporal spikes	Study of families with limited number of affected members revealed mutations in approximately 12% of families; thus may be a relatively common cause of lesion-negative focal epilepsies with suspected genetic basis
CSTB (21q22.3)	Cystatin B, a noncaspase cysteine protease inhibitor; normal protein may block neuronal apoptosis by inhibiting caspases directly or indirectly (via cathepsins), or controlling proteolysis	Progressive myoclonus epilepsy (PME) (Unverricht-Lundborg disease); autosomal recessive inheritance; age of onset between 6 and 15 years, myoclonic seizures, ataxia, and progressive cognitive decline; brain shows neuronal degeneration	Overall rare, but relatively common in Finland and Western Mediterranean (>1 in 20,000); precise role of cystatin B in human disease unknown, although mice with null mutations of cystatin B have similar syndrome
EPM2A (6q24)	Laforin, a protein tyrosine phosphatase (PTP); involved in glycogen metabolism and may have antiapoptotic activity	Progressive myoclonus epilepsy (Lafora's disease); autosomal recessive inheritance; age of onset 6–19 years, death within 10 years; brain degeneration associated with polyglucosan intracellular inclusion bodies in numerous organs	Most common PME in Southern Europe, Middle East, Northern Africa, and Indian subcontinent; genetic heterogeneity; unknown whether seizure phenotype due to degeneration or direct effects of abnormal laforin expression

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 31-2

EXAMPLES OF GENES ASSOCIATED WITH EPILEPSY SYNDROMES[a] (CONTINUED)

GENE (LOCUS)	FUNCTION OF GENE	CLINICAL SYNDROME	COMMENTS
Doublecortin (Xq21-24)	Doublecortin, expressed primarily in frontal lobes; directly regulates microtubule polymerization and bundling	Classic lissencephaly associated with severe mental retardation and seizures in males; subcortical band heterotopia with more subtle findings in females (presumably due to random X-inactivation); X-linked dominant	Relatively rare but of uncertain incidence; recent increased ascertainment due to improved imaging techniques; relationship between migration defect and seizure phenotype unknown

[a]The first five syndromes listed in the table (ADNFLE, BFNC, GEFS+, ADPEAF, and FFEVF) are examples of idiopathic epilepsies associated with identified gene mutations. The last three syndromes are examples of the numerous Mendelian disorders in which seizures are one part of the phenotype.
Abbreviations: GABA, γ-aminobutyric acid; PME, progressive myoclonus epilepsy.

deprivation. Consciousness is preserved unless the myoclonus is especially severe. Many patients also experience generalized tonic-clonic seizures, and up to one-third have absence seizures. Although complete remission is relatively uncommon, the seizures usually respond well to appropriate anticonvulsant medication. There is often a family history of epilepsy, and genetic linkage studies suggest a polygenic cause.

LENNOX-GASTAUT SYNDROME

Lennox-Gastaut syndrome occurs in children and is defined by the following triad: (1) multiple seizure types (usually including generalized tonic-clonic, atonic, and atypical absence seizures); (2) an EEG showing slow (<3 Hz) spike-and-wave discharges and a variety of other abnormalities; and (3) impaired cognitive function in most but not all cases. Lennox-Gastaut syndrome is associated with CNS disease or dysfunction from a variety of causes, including de novo mutations, developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury. Unfortunately, many patients have a poor prognosis due to the underlying CNS disease and the physical and psychosocial consequences of severe, poorly controlled epilepsy.

MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

Mesial temporal lobe epilepsy (MTLE) is the most common syndrome associated with focal seizures with dyscognitive features and is an example of an epilepsy syndrome with distinctive clinical, electroencephalographic, and pathologic features **(Table 31-3)**. High-resolution magnetic resonance imaging (MRI) can detect the characteristic hippocampal sclerosis that appears to be essential in the pathophysiology of MTLE for many patients **(Fig. 31-1)**. Recognition of this syndrome is especially important because it tends to be refractory to treatment with anticonvulsants but responds well to surgical intervention. Advances in the understanding of basic mechanisms of epilepsy have come through studies of experimental models of MTLE, discussed below.

TABLE 31-3

CHARACTERISTICS OF THE MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

History	
History of febrile seizures	Rare generalized seizures
Family history of epilepsy	Seizures may remit and reappear
Early onset	Seizures often intractable
Clinical Observations	
Aura common	Postictal disorientation
Behavioral arrest/stare	Memory loss
Complex automatisms	Dysphasia (with focus in dominant hemisphere)
Unilateral posturing	
Laboratory Studies	
Unilateral or bilateral anterior temporal spikes on EEG	
Hypometabolism on interictal PET	
Hypoperfusion on interictal SPECT	
Material-specific memory deficits on intracranial amobarbital (Wada) test	
MRI Findings	
Small hippocampus with increased signal on T2-weighted sequences	
Small temporal lobe	
Enlarged temporal horn	
Pathologic Findings	
Highly selective loss of specific cell populations within hippocampus in most cases	

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 31-1
Mesial temporal lobe epilepsy. The electroencephalogram and seizure semiology were consistent with a left temporal lobe focus. This coronal high-resolution T2-weighted fast spin echo magnetic resonance image obtained at 3 tesla is at the level of the hippocampal bodies, and shows abnormal high signal intensity, blurring of internal laminar architecture, and reduced size of the left hippocampus (arrow) relative to the right. This triad of imaging findings is consistent with hippocampal sclerosis.

THE CAUSES OF SEIZURES AND EPILEPSY

Seizures are a result of a shift in the normal balance of excitation and inhibition within the CNS. Given the numerous properties that control neuronal excitability, it is not surprising that there are many different ways to perturb this normal balance, and therefore many different causes of both seizures and epilepsy. T ree clinical observations emphasize how a variety of factors determine why certain conditions may cause seizures or epilepsy in a given patient.

1. T e normal brain is capable *of* having a seizure under the appropriate circumstances, and there are di*f*ferences between individuals in the susceptibility or threshold *f*or seizures. For example, seizures may be induced by high fevers in children who are otherwise normal and who never develop other neurologic problems, including epilepsy. However, febrile seizures occur only in a relatively small proportion of children. T is implies there are various underlying endogenous *f*actors that influence the threshold for having a seizure. Some of these factors are genetic, as a family history of epilepsy has a clear influence on the likelihood of seizures occurring in otherwise normal individuals. Normal development also plays an important role, because the brain appears to have different seizure thresholds at different maturational stages.
2. T ere are a variety o*f* conditions that have an extremely high likelihood o*f* resulting in a chronic seizure disorder. One of the best examples of this is severe, penetrating head trauma, which is associated with up to a 45% risk of subsequent epilepsy. T e high propensity for severe traumatic brain injury to lead to epilepsy suggests that the injury results in a long-lasting pathologic change in the CNS that transforms a presumably normal neural network into one that is abnormally hyperexcitable. T is process is known as epileptogenesis, and the specific changes that result in a lowered seizure threshold can be considered epileptogenic *f*actors. Other processes associated with epileptogenesis include stroke, infections, and abnormalities of CNS development. Likewise, the genetic abnormalities associated with epilepsy likely involve processes that trigger the appearance of specific sets of epileptogenic factors.
3. Seizures are episodic. Patients with epilepsy have seizures intermittently and, depending on the underlying cause, many patients are completely normal for months or even years between seizures. T is implies there are important provocative or precipitating *f*actors that induce seizures in patients with epilepsy. Similarly, precipitating factors are responsible for causing the single seizure in someone without epilepsy. Precipitants include those due to intrinsic physiologic processes such as psychological or physical stress, sleep deprivation, or hormonal changes associated with the menstrual cycle. T ey also include exogenous factors such as exposure to toxic substances and certain medications.

T ese observations emphasize the concept that the many causes of seizures and epilepsy result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors. T e potential role of each needs to be carefully considered when determining the appropriate management of a patient with seizures. For example, the identification of predisposing factors (e.g., family history of epilepsy) in a patient with febrile seizures may increase the necessity for closer follow-up and a more aggressive diagnostic evaluation. Finding an epileptogenic lesion may help in the estimation of seizure recurrence and duration of therapy. Finally, removal or modification of a precipitating factor may be an effective and safer method for preventing further seizures than the prophylactic use of anticonvulsant drugs.

www.ketabpezeshki.com (021) 66485457 - 66485438

CAUSES ACCORDING TO AGE

In practice, it is useful to consider the etiologies of seizures based on the age of the patient, because age is one of the most important factors determining both the incidence and the likely causes of seizures or epilepsy **(Table 31-4)**. During the neonatal period and early infancy, potential causes include hypoxic-ischemic encephalopathy, trauma, CNS infection, congenital CNS abnormalities, and metabolic disorders. Babies born to mothers using neurotoxic drugs such as cocaine, heroin, or ethanol are susceptible to drug-withdrawal seizures in the first few days after delivery. Hypoglycemia and hypocalcemia, which can occur as secondary complications of perinatal injury, are also causes of seizures early after delivery. Seizures due to inborn errors of metabolism usually present once regular feeding begins, typically 2–3 days after birth. Pyridoxine (vitamin B_6) deficiency, an important cause of neonatal seizures, can be effectively treated with pyridoxine replacement. The idiopathic or inherited forms of benign neonatal convulsions are also seen during this time period.

The most common seizures arising in late infancy and early childhood are febrile seizures, which are seizures associated with fevers but without evidence of CNS infection or other defined causes. The overall prevalence is 3–5% and even higher in some parts of the world such as Asia. Patients often have a family history of febrile seizures or epilepsy. Febrile seizures usually occur between 3 months and 5 years of age and have a peak incidence between 18 and 24 months. The typical scenario is a child who has a generalized, tonic-clonic seizure during a febrile illness in the setting of a common childhood infection such as otitis media, respiratory infection, or gastroenteritis. The seizure is likely to occur during the rising phase of the temperature curve (i.e., during the first day) rather than well into the course of the illness. A simple febrile seizure is a single, isolated event, brief, and symmetric in appearance. Complex febrile seizures are characterized by repeated seizure activity, duration >15 minutes, or by focal features. Approximately one-third of patients with febrile seizures will have a recurrence, but <10% have three or more episodes. Recurrences are much more likely when the febrile seizure occurs in the first year of life. Simple febrile seizures are not associated with an increase in the risk of developing epilepsy, while complex febrile seizures have a risk of 2–5%; other risk factors include the presence of preexisting neurologic deficits and a family history of nonfebrile seizures.

Childhood marks the age at which many of the well-defined epilepsy syndromes present. Some children who are otherwise normal develop idiopathic, generalized tonic-clonic seizures without other features that fit into specific syndromes. Temporal lobe epilepsy usually presents in childhood and may be related to mesial temporal lobe sclerosis (as part of the MTLE syndrome) or other focal abnormalities such as cortical dysgenesis. Other types of focal seizures, including those that evolve into generalized seizures, may be the relatively late manifestation of a developmental disorder, an acquired lesion such as head trauma, CNS infection (especially viral encephalitis), or very rarely a CNS tumor.

The period of adolescence and early adulthood is one of transition during which the idiopathic or genetically based epilepsy syndromes, including JME and juvenile absence epilepsy, become less common, while epilepsies secondary to acquired CNS lesions begin to predominate. Seizures that arise in patients in this age range may be associated with head trauma, CNS infections (including parasitic infections such as cysticercosis), brain tumors, congenital CNS abnormalities,

TABLE 31-4

CAUSES OF SEIZURES	
Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer's disease and other degenerative CNS diseases Autoantibodies

Abbreviation: CNS, central nervous system.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 31-5

DRUGS AND OTHER SUBSTANCES THAT CAN CAUSE SEIZURES

Alkylating agents (e.g., busulfan, chlorambucil)
Antimalarials (chloroquine, mefloquine)
Antimicrobials/antivirals

β-lactam and related compounds
Quinolones

Acyclovir
Isoniazid
Ganciclovir
Anesthetics and analgesics
Meperidine
Fentanyl
Tramadol
Local anesthetics
Dietary supplements
Ephedra (ma huang)
Gingko
Immunomodulatory drugs
Cyclosporine
OKT3 (monoclonal antibodies to T cells)
Tacrolimus
Interferons
Psychotropics

Antidepressants (e.g., bupropion)
Antipsychotics (e.g., clozapine)
Lithium

Radiographic contrast agents
Drug withdrawal
Alcohol
Baclofen
Barbiturates (short-acting)
Benzodiazepines (short-acting)
Zolpidem
Drugs of abuse
Amphetamine
Cocaine
Phencyclidine
Methylphenidate
Flumazenil[a]

[a]In benzodiazepine-dependent patients.

illicit drug use, or alcohol withdrawal. Autoantibodies directed against CNS antigens such as potassium channels or glutamate receptors are a newly recognized cause of epilepsy that also begins to appear in this age group (although cases of autoimmunity are being increasingly described in the pediatric population), including patients without an identifiable cancer. T is etiology should be suspected when a previously normal individual presents with a particularly aggressive seizure pattern developing over weeks to months and characterized by increasingly frequent and prolonged seizures combined with cognitive decline **(Chap. 50)**.

Head trauma is a common cause of epilepsy in adolescents and adults. T e head injury can be caused by a variety of mechanisms, and the likelihood of developing epilepsy is strongly correlated with the severity of the injury. A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia has a 30–50% risk of developing epilepsy, whereas a patient with a closed head injury and cerebral contusion has a 5–25% risk. Recurrent seizures usually develop within 1 year after head trauma, although intervals of >10 years are well known. In controlled studies, mild head injury, defined as a concussion with amnesia or loss of consciousness of <30 min, was found to be associated with only a slightly increased likelihood of epilepsy. Nonetheless, most epileptologists know of patients who have focal seizures within hours or days of a mild head injury and subsequently develop chronic seizures of the same type; such cases may represent rare examples of chronic epilepsy resulting from mild head injury.

T e causes of seizures in older adults include cerebrovascular disease, trauma (including subdural hematoma), CNS tumors, and degenerative diseases. Cerebrovascular disease may account for ~50% of new cases of epilepsy in patients older than age 65. Acute seizures (i.e., occurring at the time of the stroke) are seen more often with embolic rather than hemorrhagic or thrombotic stroke. Chronic seizures typically appear months to years after the initial event and are associated with all forms of stroke.

Metabolic disturbances such as electrolyte imbalance, hypo- or hyperglycemia, renal failure, and hepatic failure may cause seizures at any age. Similarly, endocrine disorders, hematologic disorders, vasculitides, and many other systemic diseases may cause seizures over a broad age range. A wide variety of medications and abused substances are known to precipitate seizures as well **(Table 31-5)**.

BASIC MECHANISMS

MECHANISMS OF SEIZURE INITIATION AND PROPAGATION

Focal seizure activity can begin in a very discrete region of cortex and then slowly invade the surrounding regions. T e hallmark of an established seizure is typically an electrographic "spike" due to intense near-simultaneous firing of a large number of local excitatory neurons, resulting in an apparent hypersynchronization of the excitatory bursts across a relatively large cortical region. T e bursting activity in individual neurons (the "paroxysmal depolarization shift") is caused by a relatively long-lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the opening of voltage-dependent sodium (Na^+) channels, influx of Na^+, and generation of repetitive action potentials. T is is followed by a hyperpolarizing afterpotential mediated by γ-aminobutyric acid (GABA) receptors or potassium (K^+) channels, depending on the cell type. T e synchronized bursts from a suf cient number of neurons result in a so-called spike discharge on the EEG.

T e spreading seizure wavefront is slowed and ultimately halted by intact hyperpolarization and a "surround" inhibition created by feedforward activation of inhibitory neurons. With suf cient activation, there is a recruitment of surrounding neurons via a number of

www.ketabpezeshki.com (021) 66485457 - 66485438

synaptic and nonsynaptic mechanisms, including: (1) an increase in extracellular K^+, which blunts hyperpolarization and depolarizes neighboring neurons; (2) accumulation of Ca^{2+} in presynaptic terminals, leading to enhanced neurotransmitter release; (3) depolarization-induced activation of the N-methyl-d-aspartate (NMDA) subtype of the excitatory amino acid receptor, which causes additional Ca^{2+} influx and neuronal activation; and (4) ephaptic interactions related to changes in tissue osmolarity and cell swelling. T e recruitment of a suf cient number of neurons leads to the propagation of excitatory currents into contiguous areas via local cortical connections and to more distant areas via long commissural pathways such as the corpus callosum.

Many factors control neuronal excitability, and thus there are many potential mechanisms for altering a neuron's propensity to have bursting activity. Mechanisms intrinsic to the neuron include changes in the conductance of ion channels, response characteristics of membrane receptors, cytoplasmic buffering, second-messenger systems, and protein expression as determined by gene transcription, translation, and posttranslational modification. Mechanisms extrinsic to the neuron include changes in the amount or type of neurotransmitters present at the synapse, modulation of receptors by extracellular ions and other molecules, and temporal and spatial properties of synaptic and nonsynaptic input. Nonneural cells, such as astrocytes and oligodendrocytes, have an important role in many of these mechanisms as well.

Certain recognized causes of seizures are explained by these mechanisms. For example, accidental ingestion of domoic acid, which is an analogue of glutamate (the principal excitatory neurotransmitter in the brain), causes profound seizures via direct activation of excitatory amino acid receptors throughout the CNS. Penicillin, which can lower the seizure threshold in humans and is a potent convulsant in experimental models, reduces inhibition by antagonizing the effects of GABA at its receptor. T e basic mechanisms of other precipitating factors of seizures such as sleep deprivation, fever, alcohol withdrawal, hypoxia, and infection, are not as well understood but presumably involve analogous perturbations in neuronal excitability. Similarly, the endogenous factors that determine an individual's seizure threshold may relate to these properties as well.

Knowledge of the mechanisms responsible for initiation and propagation of most generalized seizures (including tonic-clonic, myoclonic, and atonic types) remains rudimentary and reflects the limited understanding of the connectivity of the brain at a systems level. Much more is understood about the origin of generalized spike-and-wave discharges in absence seizures. T ese appear to be related to oscillatory rhythms normally generated during sleep by circuits connecting the thalamus and cortex. T is oscillatory behavior involves an interaction between $GABA_B$ receptors, T-type Ca^{2+} channels, and K^+ channels located within the thalamus. Pharmacologic studies indicate that modulation of these receptors and channels can induce absence seizures, and there is good evidence that the genetic forms of absence epilepsy may be associated with mutations of components of this system.

MECHANISMS OF EPILEPTOGENESIS

Epileptogenesis refers to the transformation of a normal neuronal network into one that is chronically hyperexcitable. T ere is often a delay of months to years between an initial CNS injury such as trauma, stroke, or infection and the first seizure. T e injury appears to initiate a process that gradually lowers the seizure threshold in the affected region until a spontaneous seizure occurs. In many genetic and idiopathic forms of epilepsy, epileptogenesis is presumably determined by developmentally regulated events.

Pathologic studies of the hippocampus from patients with temporal lobe epilepsy have led to the suggestion that some forms of epileptogenesis are related to structural changes in neuronal networks. For example, many patients with MTLE have a highly selective loss of neurons that may contribute to inhibition of the main excitatory neurons within the dentate gyrus. T ere is also evidence that, in response to the loss of neurons, there is reorganization or "sprouting" of surviving neurons in a way that affects the excitability of the network. Some of these changes can be seen in experimental models of prolonged electrical seizures or traumatic brain injury. T us, an initial injury such as head injury may lead to a very focal, confined region of structural change that causes local hyperexcitability. T e local hyperexcitability leads to further structural changes that evolve over time until the focal lesion produces clinically evident seizures. Similar models have provided strong evidence for long-term alterations in intrinsic, biochemical properties *of* cells within the network such as chronic changes in glutamate or GABA receptor function. Recent work has suggested that induction of inflammatory cascades may be a critical factor in these processes as well.

GENETIC CAUSES OF EPILEPSY

T e most important recent progress in epilepsy research has been the identification of genetic mutations associated with a variety of epilepsy syndromes (Table 31-2). Although most of the mutations identified to date cause rare forms of epilepsy, their discovery has led to extremely important conceptual advances.

www.ketabpezeshki.com (021) 66485457 - 66485438

For example, it appears that many of the inherited, idiopathic epilepsies (i.e., the relatively "pure" forms of epilepsy in which seizures are the phenotypic abnormality and brain structure and function are otherwise normal) are due to mutations affecting ion channel function. T ese syndromes are therefore part of the larger group of channelopathies causing paroxysmal disorders such as cardiac arrhythmias, episodic ataxia, periodic weakness, and familial hemiplegic migraine. In contrast, gene mutations observed in symptomatic epilepsies (i.e., disorders in which other neurologic abnormalities such as cognitive impairment coexist with seizures) are proving to be associated with pathways influencing CNS development or neuronal homeostasis. De novo mutations may explain a significant proportion of these syndromes, especially those with onset in early childhood. A current challenge is to identify the multiple susceptibility genes that underlie the more common forms of idiopathic epilepsies. Recent studies suggest that ion channel mutations and copy number variants may contribute to causation in a subset of these patients.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

Antiepileptic drugs appear to act primarily by blocking the initiation or spread of seizures. T is occurs through a variety of mechanisms that modify the activity of ion channels or neurotransmitters, and in most cases, the drugs have pleiotropic effects. T e mechanisms include inhibition of Na^+-dependent action potentials in a frequency-dependent manner (e.g., phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide, lacosamide, rufinamide), inhibition of voltage-gated Ca^{2+} channels (phenytoin, gabapentin, pregabalin), facilitating the opening of potassium channels (ezogabine), attenuation of glutamate activity (lamotrigine, topiramate, felbamate), potentiation of GABA receptor function (benzodiazepines and barbiturates), increase in the availability of GABA (valproic acid, gabapentin, tiagabine), and modulation of release of synaptic vesicles (levetiracetam). T e two most effective drugs for absence seizures, ethosuximide and valproic acid, probably act by inhibiting T-type Ca^{2+} channels in thalamic neurons.

In contrast to the relatively large number of antiepileptic drugs that can attenuate seizure activity, there are currently no drugs known to prevent the formation of a seizure focus following CNS injury. T e eventual development of such "antiepileptogenic" drugs will provide an important means of preventing the emergence of epilepsy following injuries such as head trauma, stroke, and CNS infection.

APPROACH TO THE PATIENT: Seizure

When a patient presents shortly after a seizure, the first priorities are attention to vital signs, respiratory and cardiovascular support, and treatment of seizures if they resume (see "Treatment: Seizures and Epilepsy"). Life-threatening conditions such as CNS infection, metabolic derangement, or drug toxicity must be recognized and managed appropriately.

When the patient is not acutely ill, the evaluation will initially focus on whether there is a history of earlier seizures **(Fig. 31-2)**. If this is the first seizure, then the emphasis will be to: (1) establish whether the reported episode was a seizure rather than another paroxysmal event, (2) determine the cause of the seizure by identifying risk factors and precipitating events, and (3) decide whether anticonvulsant therapy is required in addition to treatment for any underlying illness.

In the patient with prior seizures or a known history of epilepsy, the evaluation is directed toward: (1) identification of the underlying cause and precipitating factors, and (2) determination of the adequacy of the patient's current therapy.

HISTORY AND EXAMINATION

T e first goal is to determine whether the event was truly a seizure. An in-depth history is essential, because in many cases the diagnosis *of* a seizure is based solely on clinical grounds—the examination and laboratory studies are of en normal. Questions should focus on the symptoms before, during, and after the episode in order to differentiate a seizure from other paroxysmal events (see "Differential Diagnosis of Seizures" below). Seizures frequently occur out-of-hospital, and the patient may be unaware of the ictal and immediate postictal phases; thus, witnesses to the event should be interviewed carefully.

T e history should also focus on risk factors and predisposing events. Clues for a predisposition to seizures include a history of febrile seizures, earlier auras or brief seizures not recognized as such, and a family history of seizures. Epileptogenic factors such as prior head trauma, stroke, tumor, or CNS infection should be identified. In children, a careful assessment of developmental milestones may provide evidence for underlying CNS disease. Precipitating factors such as sleep deprivation, systemic diseases, electrolyte or metabolic derangements, acute infection, drugs that lower the seizure threshold (Table 31-5), or alcohol or illicit drug use should also be identified.

T e general physical examination includes a search for signs of infection or systemic illness. Careful examination of the skin may reveal signs of neurocutaneous

www.ketabpezeshki.com (021) 66485457 - 66485438

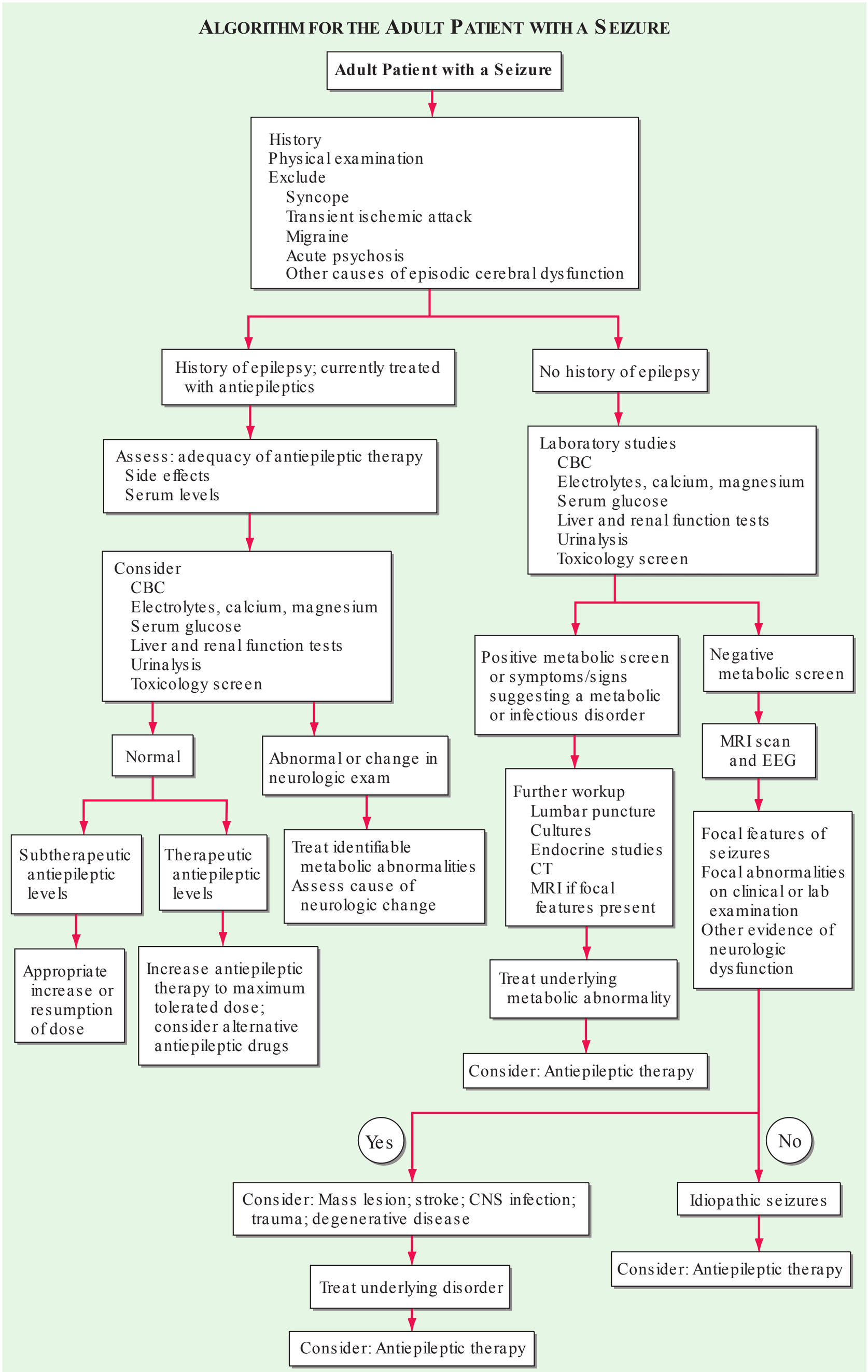


FIGURE 31-2

Evaluation of the adult patient with a seizure. CBC, complete blood count; CNS, central nervous system; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

www.ketabpezeshki.com (021) 66485457 - 66485438

disorders such as tuberous sclerosis or neurofibromatosis, or chronic liver or renal disease. A finding of organomegaly may indicate a metabolic storage disease, and limb asymmetry may provide a clue to brain injury early in development. Signs of head trauma and use of alcohol or illicit drugs should be sought. Auscultation of the heart and carotid arteries may identify an abnormality that predisposes to cerebrovascular disease.

All patients require a complete neurologic examination, with particular emphasis on eliciting signs of cerebral hemispheric disease **(Chap. 1)**. Careful assessment of mental status (including memory, language function, and abstract thinking) may suggest lesions in the anterior frontal, parietal, or temporal lobes. Testing of visual fields will help screen for lesions in the optic pathways and occipital lobes. Screening tests of motor function such as pronator drift, deep tendon reflexes, gait, and coordination may suggest lesions in motor (frontal) cortex, and cortical sensory testing (e.g., double simultaneous stimulation) may detect lesions in the parietal cortex.

LABORATORY STUDIES

Routine blood studies are indicated to identify the more common metabolic causes of seizures such as abnormalities in electrolytes, glucose, calcium, or magnesium, and hepatic or renal disease. A screen for toxins in blood and urine should also be obtained from all patients in appropriate risk groups, especially when no clear precipitating factor has been identified. A lumbar puncture is indicated if there is any suspicion of meningitis or encephalitis, and it is mandatory in all patients infected with HIV, even in the absence of symptoms or signs suggesting infection. Testing for autoantibodies in the serum and cerebrospinal fluid (CSF) should be considered in patients presenting with a seemingly aggressive form of epilepsy associated with other abnormalities such as cognitive disturbances.

ELECTROPHYSIOLOGIC STUDIES

All patients who have a possible seizure disorder should be evaluated with an EEG as soon as possible. **Details about the EEG are covered in Chap. 6.**

In the evaluation of a patient with suspected epilepsy, the presence of electrographic seizure activity during the clinically evident event (i.e., abnormal, repetitive, rhythmic activity having a discrete onset and termination) clearly establishes the diagnosis. T e absence of electrographic seizure activity does not exclude a seizure disorder, however, because focal seizures may originate from a region of the cortex that cannot be detected by standard scalp electrodes. T e EEG is always abnormal during generalized tonic-clonic seizures. Because seizures are typically infrequent and unpredictable, it is often not possible to obtain the EEG during a clinical event. Continuous monitoring for prolonged periods in video-EEG telemetry units for hospitalized patients or the use of portable equipment to record the EEG continuously for ≥24 h in ambulatory patients has made it easier to capture the electrophysiologic accompaniments of clinical events. In particular, video-EEG telemetry is now a routine approach for the accurate diagnosis of epilepsy in patients with poorly characterized events or seizures that are dif cult to control.

T e EEG may also be helpful in the interictal period by showing certain abnormalities that are highly supportive of the diagnosis of epilepsy. Such epilepti*f*orm activity consists of bursts of abnormal discharges containing spikes or sharp waves. T e presence of epileptiform activity is not specific for epilepsy, but it has a much greater prevalence in patients with epilepsy than in normal individuals. However, even in an individual who is known to have epilepsy, the initial routine interictal EEG may be normal up to 60% of the time. T us, the EEG cannot establish the diagnosis of epilepsy in many cases.

T e EEG is also used for classifying seizure disorders and aiding in the selection of anticonvulsant medications. For example, episodic generalized spike-wave activity is usually seen in patients with typical absence epilepsy and may be seen with other generalized epilepsy syndromes. Focal interictal epileptiform discharges would support the diagnosis of a focal seizure disorder such as temporal lobe epilepsy or frontal lobe seizures, depending on the location of the discharges.

T e routine scalp-recorded EEG may also be used to assess the prognosis of seizure disorders; in general, a normal EEG implies a better prognosis, whereas an abnormal background or profuse epileptiform activity suggests a poor outcome. Unfortunately, the EEG has not proved to be useful in predicting which patients with predisposing conditions such as head injury or brain tumor will go on to develop epilepsy, because in such circumstances epileptiform activity is commonly encountered regardless of whether seizures occur.

Magnetoencephalography (MEG) provides another way of looking noninvasively at cortical activity. Instead of measuring electrical activity of the brain, it measures the small magnetic fields that are generated by this activity. T e source of epileptiform activity seen on MEG can be analyzed, and its source in the brain can be estimated using a variety of mathematical techniques. T ese source estimates can then be plotted on an anatomic image of the brain such as an MRI (discussed below), to generate a magnetic source image (MSI). MSI can be useful to localize potential seizure foci.

BRAIN IMAGING

Almost all patients with new-onset seizures should have a brain imaging study to determine whether there is an underlying structural abnormality that is responsible.

www.ketabpezeshki.com (021) 66485457 - 66485438

T e only potential exception to this rule is children who have an unambiguous history and examination suggestive of a benign, generalized seizure disorder such as absence epilepsy. MRI has been shown to be superior to computed tomography (CT) for the detection of cerebral lesions associated with epilepsy. In some cases, MRI will identify lesions such as tumors, vascular malformations, or other pathologies that need urgent therapy. T e availability of newer MRI methods such as 3-tesla scanners, parallel imaging with multichannel head coils, three-dimensional structural imaging at submillimeter resolution, and widespread use of pulse sequences such as fluid-attenuated inversion recovery (FLAIR), has increased the sensitivity for detection of abnormalities of cortical architecture, including hippocampal atrophy associated with mesial temporal sclerosis, as well as abnormalities of cortical neuronal migration. In such cases, the findings may not lead to immediate therapy, but they do provide an explanation for the patient's seizures and point to the need for chronic antiepileptic drug therapy or possible surgical resection.

In the patient with a suspected CNS infection or mass lesion, CT scanning should be performed emergently when MRI is not immediately available. Otherwise, it is usually appropriate to obtain an MRI study within a few days of the initial evaluation. Functional imaging procedures such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are also used to evaluate certain patients with medically refractory seizures (discussed below).

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Disorders that may mimic seizures are listed in **Table 31-6**. In most cases, seizures can be distinguished from other conditions by meticulous attention to the history and relevant laboratory studies. On occasion, additional studies such as video-EEG monitoring, sleep studies, tilt-table analysis, or cardiac electrophysiology, may be required to reach a correct diagnosis. Two of the more common nonepileptic syndromes in the differential diagnosis are detailed below.

SYNCOPE

(See also Chap. 11) T e diagnostic dilemma encountered most frequently is the distinction between a generalized seizure and syncope. Observations by the patient and bystanders that can help differentiate between the two are listed in **Table 31-7**. Characteristics of a seizure include the presence of an aura, cyanosis, unconsciousness, motor manifestations lasting >15 s, postictal disorientation, muscle soreness, and

TABLE 31-6

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Syncope	**Transient ischemic attack (TIA)**
Vasovagal syncope	Basilar artery TIA
Cardiac arrhythmia	**Sleep disorders**
Valvular heart disease	Narcolepsy/cataplexy
Cardiac failure	Benign sleep myoclonus
Orthostatic hypotension	**Movement disorders**
Psychological disorders	Tics
Psychogenic seizure	Nonepileptic myoclonus
Hyperventilation	Paroxysmal choreoathetosis
Panic attack	**Special considerations in children**
Metabolic disturbances	Breath-holding spells
Alcoholic blackouts	Migraine with recurrent abdominal pain and cyclic vomiting
Delirium tremens	Benign paroxysmal vertigo
Hypoglycemia	Apnea
Hypoxia	Night terrors
Psychoactive drugs (e.g., hallucinogens)	Sleepwalking
Migraine	
Confusional migraine	
Basilar migraine	

TABLE 31-7

FEATURES THAT DISTINGUISH GENERALIZED TONIC-CLONIC SEIZURE FROM SYNCOPE

FEATURES	SEIZURE	SYNCOPE
Immediate precipitating factors	Usually none	Emotional stress, Valsalva, orthostatic hypotension, cardiac etiologies
Premonitory symptoms	None or aura (e.g., odd odor)	Tiredness, nausea, diaphoresis, tunneling of vision
Posture at onset	Variable	Usually erect
Transition to unconsciousness	Often immediate	Gradual over seconds[a]
Duration of unconsciousness	Minutes	Seconds
Duration of tonic or clonic movements	30–60 s	Never more than 15 s
Facial appearance during event	Cyanosis, frothing at mouth	Pallor
Disorientation and sleepiness after event	Many minutes to hours	<5 min
Aching of muscles after event	Often	Sometimes
Biting of tongue	Sometimes	Rarely
Incontinence	Sometimes	Sometimes
Headache	Sometimes	Rarely

[a]May be sudden with certain cardiac arrhythmias.

www.ketabpezeshki.com (021) 66485457 - 66485438

sleepiness. In contrast, a syncopal episode is more likely if the event was provoked by acute pain or anxiety or occurred immediately after arising from the lying or sitting position. Patients with syncope often describe a stereotyped transition from consciousness to unconsciousness that includes tiredness, sweating, nausea, and tunneling of vision, and they experience a relatively brief loss of consciousness. Headache or incontinence usually suggests a seizure but may on occasion also occur with syncope. A brief period (i.e., 1–10 s) of convulsive motor activity is frequently seen immediately at the onset of a syncopal episode, especially if the patient remains in an upright posture after fainting (e.g., in a dentist's chair) and therefore has a sustained decrease in cerebral perfusion. Rarely, a syncopal episode can induce a full tonic-clonic seizure. In such cases, the evaluation must focus on both the cause of the syncopal event as well as the possibility that the patient has a propensity for recurrent seizures.

PSYCHOGENIC SEIZURES

Psychogenic seizures are nonepileptic behaviors that resemble seizures. T ey are often part of a conversion reaction precipitated by underlying psychological distress. Certain behaviors such as side-to-side turning of the head, asymmetric and large-amplitude shaking movements of the limbs, twitching of all four extremities without loss of consciousness, and pelvic thrusting are more commonly associated with psychogenic rather than epileptic seizures. Psychogenic seizures often last longer than epileptic seizures and may wax and wane over minutes to hours. However, the distinction is sometimes dif cult on clinical grounds alone, and there are many examples of diagnostic errors made by experienced epileptologists. T is is especially true for psychogenic seizures that resemble focal seizures with dyscognitive features, because the behavioral manifestations of focal seizures (especially of frontal lobe origin) can be extremely unusual, and in both cases, the routine surface EEG may be normal. Video-EEG monitoring is very useful when historic features are nondiagnostic. Generalized tonic-clonic seizures always produce marked EEG abnormalities during and after the seizure. For suspected focal seizures of temporal lobe origin, the use of additional electrodes beyond the standard scalp locations (e.g., sphenoidal electrodes) may be required to localize a seizure focus. Measurement of serum prolactin levels may also help to distinguish between organic and psychogenic seizures, because most generalized seizures and some focal seizures are accompanied by rises in serum prolactin (during the immediate 30-min postictal period), whereas psychogenic seizures are not. T e diagnosis of psychogenic seizures does not exclude a concurrent diagnosis of epilepsy, because the two often coexist.

TREATMENT Seizures and Epilepsy

T erapy for a patient with a seizure disorder is almost always multimodal and includes treatment of underlying conditions that cause or contribute to the seizures, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy with antiepileptic medications or surgery, and addressing a variety of psychological and social issues. Treatment plans must be individualized, given the many different types and causes of seizures as well as the differences in ef cacy and toxicity of antiepileptic medications for each patient. In almost all cases, a neurologist with experience in the treatment of epilepsy should design and oversee implementation of the treatment strategy. Furthermore, patients with refractory epilepsy or those who require polypharmacy with antiepileptic drugs should remain under the regular care of a neurologist.

TREATMENT OF UNDERLYING CONDITIONS If the sole cause of a seizure is a metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence. T erapy with antiepileptic drugs is usually unnecessary unless the metabolic disorder cannot be corrected promptly and the patient is at risk of having further seizures. If the apparent cause of a seizure was a medication (e.g., theophylline) or illicit drug use (e.g., cocaine), then appropriate therapy is avoidance of the drug; there is usually no need for antiepileptic medications unless subsequent seizures occur in the absence of these precipitants.

Seizures caused by a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess may not recur after appropriate treatment of the underlying lesion. However, despite removal of the structural lesion, there is a risk that the seizure focus will remain in the surrounding tissue or develop de novo as a result of gliosis and other processes induced by surgery, radiation, or other therapies. Most patients are therefore maintained on an antiepileptic medication for at least 1 year, and an attempt is made to withdraw medications only if the patient has been completely seizure free. If seizures are refractory to medication, the patient may benefit from surgical removal of the epileptic brain region (see below).

AVOIDANCE OF PRECIPITATING FACTORS Unfortunately, little is known about the specific factors that determine precisely when a seizure will occur in a patient with epilepsy. Some patients can identify particular situations that appear to lower their seizure threshold; these situations should be avoided. For example, a patient who has seizures in the setting of sleep deprivation should obviously be advised to maintain a normal sleep schedule. Many patients note an association between alcohol intake and seizures, and they should be encouraged to modify their drinking habits accordingly. T ere are also relatively rare cases of patients with seizures that are induced by highly specific stimuli such as a video

www.ketabpezeshki.com (021) 66485457 - 66485438

game monitor, music, or an individual's voice ("reflex epilepsy"). Because there is often an association between stress and seizures, stress reduction techniques such as physical exercise, meditation, or counseling may be helpful.

ANTIEPILEPTIC DRUG THERAPY Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. Seizure classification is an important element in designing the treatment plan, because some antiepileptic drugs have different activities against various seizure types. However, there is considerable overlap between many antiepileptic drugs such that the choice of therapy is often determined more by the patient's specific needs, especially his or her assessment of side effects.

When to initiate antiepileptic drug therapy Antiepileptic drug therapy should be started in any patient with recurrent seizures of unknown etiology or a known cause that cannot be reversed. Whether to initiate therapy in a patient with a single seizure is controversial. Patients with a single seizure due to an identified lesion such as a CNS tumor, infection, or trauma, in which there is strong evidence that the lesion is epileptogenic, should be treated. The risk of seizure recurrence in a patient with an apparently unprovoked or idiopathic seizure is uncertain, with estimates ranging from 31 to 71% in the first 12 months after the initial seizure. This uncertainty arises from differences in the underlying seizure types and etiologies in various published epidemiologic studies. Generally accepted risk factors associated with recurrent seizures include the following: (1) an abnormal neurologic examination, (2) seizures presenting as status epilepticus, (3) postictal Todd's paralysis, (4) a strong family history of seizures, or (5) an abnormal EEG. Most patients with one or more of these risk factors should be treated. Issues such as employment or driving may influence the decision whether to start medications as well. For example, a patient with a single, idiopathic seizure whose job depends on driving may prefer taking antiepileptic drugs rather than risk a seizure recurrence and the potential loss of driving privileges.

Selection of antiepileptic drugs Antiepileptic drugs available in the United States are shown in **Table 31-8**, and the main pharmacologic characteristics of commonly used drugs are listed in **Table 31-9**. Worldwide, older medications such as phenytoin, valproic acid, carbamazepine, phenobarbital, and ethosuximide are generally used as first-line therapy for most seizure disorders because, overall, they are as effective as recently marketed drugs and significantly less expensive overall. Most of the new drugs that have become available in the past decade are used as add-on or alternative therapy, although many are now being used as first-line monotherapy.

In addition to efficacy, factors influencing the choice of an initial medication include the convenience of dosing (e.g., once daily versus three or four times daily) and potential side effects. In this regard, a number of the newer drugs have the advantage of reduced drug-drug interactions and easier dosing. Almost all of the commonly used antiepileptic drugs can cause similar, dose-related side effects such as sedation, ataxia, and diplopia. Long-term use of some agents in adults, especially the elderly, can lead to osteoporosis. Close follow-up is required to ensure these side effects are promptly recognized and reversed. Most of the older drugs and some of the newer ones can also cause idiosyncratic toxicity such as rash, bone marrow suppression, or hepatotoxicity. Although rare, these side effects should be considered during drug selection, and patients must be instructed about symptoms or signs that should signal the need to alert their health care provider. For some drugs, laboratory tests (e.g., complete blood count and liver function tests) are recommended prior to the institution of therapy (to establish baseline values) and during initial dosing and titration of the agent. Importantly, studies have shown that Asian individuals carrying the human leukocyte antigen allele, HLA-B*1502, are at particularly high risk of developing serious skin reactions from carbamazepine and phenytoin. As a result, racial background and genotype are additional factors to consider in drug selection.

Antiepileptic drug selection for focal seizures Carbamazepine (or a related drug, oxcarbazepine), lamotrigine, phenytoin, and levetiracetam are currently the drugs of choice approved for the initial treatment of focal seizures, including those that evolve into generalized seizures. Overall they have very similar efficacy, but differences in pharmacokinetics and toxicity are the main determinants for use in a given patient. For example,

TABLE 31-8

SELECTION OF ANTIEPILEPTIC DRUGS

GENERALIZED-ONSET TONIC-CLONIC	FOCAL	TYPICAL ABSENCE	ATYPICAL ABSENCE, MYOCLONIC, ATONIC
First-Line			
Lamotrigine	Lamotrigine	Valproic acid	Valproic acid
Valproic acid	Carbamazepine	Ethosuximide	Lamotrigine
	Oxcarbazepine	Lamotrigine	Topiramate
	Phenytoin		
	Levetiracetam		
Alternatives			
Zonisamide[a]	Topiramate	Lamotrigine	Clonazepam
Phenytoin	Zonisamide[a]	Clonazepam	Felbamate
Carbamazepine	Valproic acid		Clobazam
Oxcarbazepine	Tiagabine[a]		Rufinamide
Topiramate	Gabapentin[a]		
Phenobarbital	Lacosamide[a]		
Primidone	Exogabine[a]		
Felbamate	Phenobarbital		
	Primidone		
	Felbamate		

[a] As adjunctive therapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 31-9

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS[a]
						NEUROLOGIC	SYSTEMIC	
Carbamazepine	Tegretol[c]	Tonic-clonic Focal-onset	600–1800 mg/d (15–35 mg/kg, child); bid (capsules or tablets), tid-qid (oral suspension)	10–17 h (variable due to autoinduction: complete 3–5 wk after initiation)	4–12 µg/mL	Ataxia Dizziness Diplopia Vertigo	Aplastic anemia Leukopenia Gastrointestinal irritation Hepatotoxicity Hyponatremia	Level decreased by enzyme-inducing drugs[b] Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine
Clobazam	Onfi	Lennox-Gastaut syndrome	10–40 mg/d (5–20 mg/d for patients <30 kg body weight); bid	36–42 h (71–82 h for less active metabolite)	Not established	Fatigue Sedation Ataxia Aggression Insomnia	Constipation Anorexia Skin rash	Level increased by CYP2C19 inhibitors
Clonazepam	Klonopin	Absence Atypical absence Myoclonic	1–12 mg/d; qd-tid	24–48 h	10–70 ng/mL	Ataxia Sedation Lethargy	Anorexia	Level decreased by enzyme-inducing drugs[b]
Ethosuximide	Zarontin	Absence	750–1250 mg/d (20-40 mg/kg); qd-bid	60 h, adult 30 h, child	40–100 µg/mL	Ataxia Lethargy Headache	Gastrointestinal irritation Skin rash Bone marrow suppression	Level decreased by enzyme-inducing drugs[b] Level increased by valproic acid
Ezogabine	Potiga	Focal-onset	800–1200 mg/d; tid	7–11 h	Not established	Dizziness Fatigue Sedation Confusion Vertigo Tremor	Retinal abnormalities Skin discoloration Cardiac conduction (QT interval prolongation) Urinary retention	Level decreased by enzyme-inducing drugs[b]
Felbamate	Felbatol	Focal-onset Lennox-Gastaut syndrome Tonic-clonic	2400–3600 mg/d, tid-qid	16–22 h	30–60 µg/mL	Insomnia Dizziness Sedation Headache	Aplastic anemia Hepatic failure Weight loss Gastrointestinal irritation	Increases phenytoin, valproic acid, active carbamazepine metabolite
Gabapentin	Neurontin	Focal-onset	900–2400 mg/d; tid-qid	5–9 h	2–20 µg/mL	Sedation Dizziness Ataxia Fatigue	Gastrointestinal irritation Weight gain Edema	No known significant interactions

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485458

TABLE 31-9

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (CONTINUED)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS[a]
						NEUROLOGIC	SYSTEMIC	
Lacosamide	Vimpat	Focal-onset	200–400 mg/d; bid	13 h	Not established	Dizziness Ataxia Diplopia Vertigo	Gastrointestinal irritation Cardiac conduction (PR interval prolongation)	Level decreased by enzyme-inducing drugs[b]
Lamotrigine	Lamictal[c]	Focal-onset Tonic-clonic Atypical absence Myoclonic Lennox-Gastaut syndrome	150–500 mg/d; bid (immediate release), daily (extended release) (lower daily dose for regimens with valproic acid; higher daily dose for regimens with an enzyme inducer)	25 h 14 h (with enzyme-inducers), 59 h (with valproic acid)	2.5–20 µg/mL	Dizziness Diplopia Sedation Ataxia Headache	Skin rash Stevens-Johnson syndrome	Level decreased by enzyme-inducing drugs[b] and oral contraceptives Level increased by valproic acid
Levetiracetam	Kepprac	Focal-onset	1000–3000 mg/d; bid (immediate release), daily (extended release)	6–8 h	5–45 µg/mL	Sedation Fatigue Incoordination Mood changes	Anemia Leukopenia	No known significant interactions
Oxcarbazepinec	Trileptal	Focal-onset Tonic-clonic	900–2400 mg/d (30–45 mg/kg, child); bid	10–17 h (for active metabolite)	10–35 µg/mL	Fatigue Ataxia Dizziness Diplopia Vertigo Headache	See carbamazepine	Level decreased by enzyme-inducing drugsb May increase phenytoin
Phenobarbital	Luminal	Tonic-clonic Focal-onset	60–180 mg/d; qd-tid	90 h	10–40 µg/mL	Sedation Ataxia Confusion Dizziness Decreased libido Depression	Skin rash	Level increased by valproic acid, phenytoin

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 31-9

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (CONTINUED)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS[a]
						NEUROLOGIC	SYSTEMIC	
Phenytoin (diphenylhydantoin)	Dilantin	Tonic-clonic Focal-onset	300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); qd-tid	24 h (wide variation, dose-dependent)	10–20 µg/mL	Dizziness Diplopia Ataxia Incoordination Confusion	Gingival hyperplasia Lymphadenopathy Hirsutism Osteomalacia Facial coarsening Skin rash	Level increased by isoniazid, sulfonamides, fluoxetine Level decreased by enzyme-inducing drugs[b] Altered folate metabolism
Primidone	Mysoline	Tonic-clonic Focal-onset	750–1000 mg/d; bid-tid	Primidone, 8–15 h Phenobarbital, 90 h	Primidone, 4–12 µg/mL Phenobarbital, 10–40 µg/mL	Same as phenobarbital		Level increased by valproic acid Level decreased by phenytoin (increased conversion to phenobarbital)
Rufinamide	Banzel	Lennox-Gastaut syndrome	3200 mg/d (45 mg/kg, child); bid	6–10 h	Not established	Sedation Fatigue Dizziness Ataxia Headache Diplopia	Gastrointestinal irritation Leukopenia Cardiac conduction (QT interval shortening)	Level decreased by enzyme-inducing drugs[b] Level increased by valproic acid May increase phenytoin
Tiagabine	Gabitril	Focal-onset	32–56 mg/d; bid-qid (as adjunct to enzyme-inducing antiepileptic drug regimen)	2–5 h (with enzyme inducer), 7–9 h (without enzyme inducer)	Not established	Confusion Sedation Depression Dizziness Speech or language problems Paresthesias Psychosis	Gastrointestinal irritation	Level decreased by enzyme-inducing drugs[b]
Topiramate	Topamax	Focal-onset Tonic-clonic Lennox-Gastaut syndrome	200–400 mg/d; bid (immediate release), daily (extended release)	20 h (immediate release), 30 h (extended release)	2–20 µg/mL	Psychomotor slowing Sedation Speech or language problems Fatigue Paresthesias	Renal stones (avoid use with other carbonic anhydrase inhibitors) Glaucoma Weight loss Hypohidrosis	Level decreased by enzyme-inducing drugs[b]

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485458

TABLE 31-9

DOSAGE AND ADVERSE EFFECTS OF COMMONLY USED ANTIEPILEPTIC DRUGS (CONTINUED)

GENERIC NAME	TRADE NAME	PRINCIPAL USES	TYPICAL DOSE; DOSE INTERVAL	HALF-LIFE	THERAPEUTIC RANGE	ADVERSE EFFECTS		DRUG INTERACTIONS[a]
						NEUROLOGIC	SYSTEMIC	
Valproic acid (valproate sodium, divalproex sodium)	Depakene Depakotec	Tonic-clonic Absence Atypical absence Myoclonic Focal-onset Atonic	750–2000 mg/d (20–60 mg/kg); bid-qid (immediate and delayed release), daily (extended release)	15 h	50–125 µg/mL	Ataxia Sedation Tremor	Hepatotoxicity Thrombocytopenia Gastrointestinal irritation Weight gain Transient alopecia Hyperammonemia	Level decreased by enzyme-inducing drugs[b]
Zonisamide	Zonegran	Focal-onset Tonic-clonic	200–400 mg/d; qd-bid	50–68 h	10–40 µg/mL	Sedation Dizziness Confusion Headache Psychosis	Anorexia Renal stones Hypohidrosis	Level decreased by enzyme-inducing drugs[b]

[a]Examples only; please refer to other sources for comprehensive listings of all potential drug-drug interactions.
[b]Phenytoin, carbamazepine, phenobarbital.
[c]Extended-release product available.

www.ketabpezeshki.com (021) 66485457 - 66485438

an advantage of carbamazepine (which is also available in an extended-release form) is that its metabolism follows first-order pharmacokinetics, which allows for a linear relationship between drug dose, serum levels, and toxicity. Carbamazepine can cause leukopenia, aplastic anemia, or hepatotoxicity and would therefore be contraindicated in patients with predispositions to these problems. Oxcarbazepine has the advantage of being metabolized in a way that avoids an intermediate metabolite associated with some of the side effects of carbamazepine. Oxcarbazepine also has fewer drug interactions than carbamazepine. Lamotrigine tends to be well tolerated in terms of side effects. However, patients need to be particularly vigilant about the possibility of a skin rash during the initiation of therapy. T is can be extremely severe and lead to Stevens-Johnson syndrome if unrecognized and if the medication is not discontinued immediately. T is risk can be reduced by the use of low initial doses and slow titration. Lamotrigine must be started at lower initial doses when used as add-on therapy with valproic acid, because valproic acid inhibits lamotrigine metabolism and results in a substantially prolonged half-life. Phenytoin has a relatively long half-life and offers the advantage of once or twice daily dosing compared to two or three times daily dosing for many of the other drugs. However, phenytoin shows properties of nonlinear kinetics, such that small increases in phenytoin doses above a standard maintenance dose can precipitate marked side effects. T is is one of the main causes of acute phenytoin toxicity. Long-term use of phenytoin is associated with untoward cosmetic effects (e.g., hirsutism, coarsening of facial features, gingival hypertrophy) and effects on bone metabolism. Due to these side effects, phenytoin is often avoided in young patients who are likely to require the drug for many years. Levetiracetam has the advantage of having no known drug-drug interactions, making it especially useful in the elderly and patients on other medications. However, a significant number of patients taking levetiracetam complain of irritability, anxiety, and other psychiatric symptoms. Topiramate can be used for both focal and generalized seizures. Similar to some of the other antiepileptic drugs, topiramate can cause significant psychomotor slowing and other cognitive problems. Additionally, it should not be used in patients at risk for the development of glaucoma or renal stones.

Valproic acid is an effective alternative for some patients with focal seizures, especially when the seizures generalize. Gastrointestinal side effects are fewer when using the delayed-release formulation (Depakote). Laboratory testing is required to monitor toxicity because valproic acid can rarely cause reversible bone marrow suppression and hepatotoxicity. T is drug should generally be avoided in patients with preexisting bone marrow or liver disease. Irreversible, fatal hepatic failure appearing as an idiosyncratic rather than dose-related side effect is a relatively rare complication; its risk is highest in children <2 years old, especially those taking other antiepileptic drugs or with inborn errors of metabolism.

Zonisamide, tiagabine, gabapentin, lacosamide, and ezogabine are additional drugs currently used for the treatment of focal seizures with or without evolution into generalized seizures. Phenobarbital and other barbiturate compounds were commonly used in the past as first-line therapy for many forms of epilepsy. However, the barbiturates frequently cause sedation in adults, hyperactivity in children, and other more subtle cognitive changes; thus, their use should be limited to situations in which no other suitable treatment alternatives exist.

Antiepileptic drug selection for generalized seizures Lamotrigine and valproic acid are currently considered the best initial choice for the treatment of primary generalized, tonic-clonic seizures. Topiramate, zonisamide, phenytoin, carbamazepine, and oxcarbazepine are suitable alternatives. Valproic acid is also particularly effective in absence, myoclonic, and atonic seizures. It is therefore the drug of choice in patients with generalized epilepsy syndromes having mixed seizure types. Importantly, carbamazepine, oxcarbazepine, and phenytoin can worsen certain types of generalized seizures, including absence, myoclonic, tonic, and atonic seizures. Ethosuximide is a particularly effective drug for the treatment of uncomplicated absence seizures, but it is not useful for tonic-clonic or focal seizures. Periodic monitoring of blood cell counts is required since ethosuximide rarely causes bone marrow suppression. Lamotrigine appears to be particularly effective in epilepsy syndromes with mixed, generalized seizure types such as JME and Lennox-Gastaut syndrome. Topiramate, zonisamide, and felbamate may have similar broad ef cacy.

Initiation and monitoring of therapy Because the response to any antiepileptic drug is unpredictable, patients should be carefully educated about the approach to therapy. T e goal is to prevent seizures and minimize the side effects of treatment; determination of the optimal dose is often a matter of trial and error. T is process may take months or longer if the baseline seizure frequency is low. Most antiepileptic drugs need to be introduced relatively slowly to minimize side effects. Patients should expect that minor side effects such as mild sedation, slight changes in cognition, or imbalance will typically resolve within a few days. Starting doses are usually the lowest value listed under the dosage column in Table 31-9. Subsequent increases should be made only after achieving a steady state with the previous dose (i.e., after an interval of five or more half-lives).

Monitoring of serum antiepileptic drug levels can be very useful for establishing the initial dosing schedule. However, the published therapeutic ranges of serum drug concentrations are only an approximate guide for determining the proper dose for a given patient. T e key determinants are the clinical measures of seizure frequency and presence of side effects, not the laboratory values. Conventional assays of serum drug levels measure the total drug (i.e., both free and protein bound). However, it is the concentration of free drug that reflects extracellular levels in the brain and correlates best with ef cacy. T us, patients with decreased levels of serum proteins (e.g., decreased serum albumin due to impaired liver or renal function) may have an increased ratio of free to bound drug, yet the concentration of free drug may

www.ketabpezeshki.com (021) 66485457 - 66485438

be adequate for seizure control. T ese patients may have a "subtherapeutic" drug level, but the dose should be changed only if seizures remain uncontrolled, not just to achieve a "therapeutic" level. It is also useful to monitor free drug levels in such patients. In practice, other than during the initiation or modification of therapy, monitoring of antiepileptic drug levels is most useful for documenting adherence.

If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it becomes necessary to switch to another antiepileptic drug. T is is usually done by maintaining the patient on the first drug while a second drug is added. T e dose of the second drug should be adjusted to decrease seizure frequency without causing toxicity. Once this is achieved, the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). T e dose of the second drug is then further optimized based on seizure response and side effects. Monotherapy should be the goal whenever possible.

When to discontinue therapy Overall, about 70% of children and 60% of adults who have their seizures completely controlled with antiepileptic drugs can eventually discontinue therapy. T e following patient profile yields the greatest chance of remaining seizure free after drug withdrawal: (1) complete medical control of seizures for 1–5 years; (2) single seizure type, either focal or generalized; (3) normal neurologic examination, including intelligence; and (4) normal EEG. T e appropriate seizure-free interval is unknown and undoubtedly varies for different forms of epilepsy. However, it seems reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the above criteria, is motivated to discontinue the medication, and clearly understands the potential risks and benefits. In most cases, it is preferable to reduce the dose of the drug gradually over 2–3 months. Most recurrences occur in the first 3 months after discontinuing therapy, and patients should be advised to avoid potentially dangerous situations such as driving or swimming during this period.

Treatment of refractory epilepsy Approximately one-third of patients with epilepsy do not respond to treatment with a single antiepileptic drug, and it becomes necessary to try a combination of drugs to control seizures. Patients who have focal epilepsy related to an underlying structural lesion or those with multiple seizure types and developmental delay are particularly likely to require multiple drugs. T ere are currently no clear guidelines for rational polypharmacy, although in theory a combination of drugs with different mechanisms of action may be most useful. In most cases, the initial combination therapy combines first-line drugs (i.e., carbamazepine, oxcarbazepine, lamotrigine, valproic acid, levetiracetam, and phenytoin). If these drugs are unsuccessful, then the addition of other drugs such as topiramate, zonisamide, lacosamide, or tiagabine is indicated. Patients with myoclonic seizures resistant to valproic acid may benefit from the addition of clonazepam or clobazam, and those with absence seizures may respond to a combination of valproic acid and ethosuximide. T e same principles concerning the monitoring of therapeutic response, toxicity, and serum levels for monotherapy apply to polypharmacy, and potential drug interactions need to be recognized. If there is no improvement, a third drug can be added while the first two are maintained. If there is a response, the less effective or less well tolerated of the first two drugs should be gradually withdrawn.

SURGICAL TREATMENT OF REFRACTORY EPILEPSY Approximately 20–30% of patients with epilepsy continue to have seizures despite efforts to find an effective combination of antiepileptic drugs. For some, surgery can be extremely effective in substantially reducing seizure frequency and even providing complete seizure control. Understanding the potential value of surgery is especially important when a patient's seizures are not controlled with initial treatment, as such patients often do not respond to subsequent medication trials. Rather than submitting the patient to years of unsuccessful medical therapy and the psychosocial trauma and increased mortality associated with ongoing seizures, the patient should have an ef cient but relatively brief attempt at medical therapy and then be referred for surgical evaluation.

T e most common surgical procedure for patients with temporal lobe epilepsy involves resection of the anteromedial temporal lobe (temporal lobectomy) or a more limited removal of the underlying hippocampus and amygdala (amygdalohippocampectomy). Focal seizures arising from extratemporal regions may be abolished by a focal neocortical resection with precise removal of an identified lesion (lesionectomy). Localized neocortical resection without a clear lesion identified on MRI is also possible when other tests (e.g. MEG, PET, SPECT) implicate a focal cortical region as a seizure onset zone. When the cortical region cannot be removed, multiple subpial transection, which disrupts intracortical connections, is sometimes used to prevent seizure spread. Hemispherectomy or multilobar resection is useful for some patients with severe seizures due to hemispheric abnormalities such as hemimegalencephaly or other dysplastic abnormalities, and corpus callosotomy has been shown to be effective for disabling tonic or atonic seizures, usually when they are part of a mixed-seizure syndrome (e.g., Lennox-Gastaut syndrome).

Presurgical evaluation is designed to identify the functional and structural basis of the patient's seizure disorder. Inpatient video-EEG monitoring is used to define the anatomic location of the seizure focus and to correlate the abnormal electrophysiologic activity with behavioral manifestations of the seizure. Routine scalp or scalp-sphenoidal recordings and a high-resolution MRI scan are usually sufficient for localization of the epileptogenic focus, especially when the findings are concordant. Functional imaging studies such as SPECT, PET, and MEG are adjunctive tests that may help to reveal or verify the localization of an apparent epileptogenic region. Once the presumed location of the seizure onset is identified, additional studies, including neuropsychological testing, the intracarotid amobarbital test (Wada

www.ketabpezeshki.com (021) 66485457 - 66485438

test), and functional MRI may be used to assess language and memory localization and to determine the possible functional consequences of surgical removal of the epileptogenic region. In some cases, standard noninvasive evaluation is not sufficient to localize the seizure onset zone, and invasive electrophysiologic monitoring, such as implanted depth or subdural electrodes, is required for more definitive localization. The exact extent of the resection to be undertaken can also be determined by performing cortical mapping at the time of the surgical procedure, allowing for a tailored resection. This involves electrocorticographic recordings made with electrodes on the surface of the brain to identify the extent of epileptiform disturbances. If the region to be resected is within or near brain regions suspected of having sensorimotor or language function, electrical cortical stimulation mapping is performed on the awake patient to determine the function of cortical regions in question in order to avoid resection of so-called eloquent cortex and thereby minimize postsurgical deficits.

Advances in presurgical evaluation and microsurgical techniques have led to a steady increase in the success of epilepsy surgery. Clinically significant complications of surgery are <5%, and the use of functional mapping procedures has markedly reduced the neurologic sequelae due to removal or sectioning of brain tissue. For example, about 70% of patients treated with temporal lobectomy will become seizure free, and another 15–25% will have at least a 90% reduction in seizure frequency. Marked improvement is also usually seen in patients treated with hemispherectomy for catastrophic seizure disorders due to large hemispheric abnormalities. Postoperatively, patients generally need to remain on antiepileptic drug therapy, but the marked reduction of seizures following resective surgery can have a very beneficial effect on quality of life.

Not all medically refractory patients are suitable candidates for resective surgery. For example, some patients have seizures arising from more than one location, making the risk of ongoing seizures or potential harm from the surgery unacceptably high. Vagus nerve stimulation (VNS) has been used in some of these cases, although the results are limited and it is difficult to predict who will benefit. A new implantable device that can detect the onset of a seizure (in some instances before the seizure becomes clinically apparent) and deliver an electrical stimulation (Responsive NeuroStimulation) has recently been approved and may be of benefit in selected patients. Studies are currently evaluating the efficacy of stereotactic radiosurgery, laser thermoablation, and deep brain stimulation (DBS) as other options for surgical treatment of refractory epilepsy.

STATUS EPILEPTICUS

Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the interictal period. Status epilepticus has numerous subtypes, including generalized convulsive status epilepticus (GCSE) (e.g., persistent, generalized electrographic seizures, coma, and tonic-clonic movements) and nonconvulsive status epilepticus (e.g., persistent absence seizures or focal seizures with confusion or partially impaired consciousness, and minimal motor abnormalities). The duration of seizure activity sufficient to meet the definition of status epilepticus has traditionally been specified as 15–30 min. However, a more practical definition is to consider status epilepticus as a situation in which the duration of seizures prompts the acute use of anticonvulsant therapy. For GCSE, this is typically when seizures last beyond 5 min.

GCSE is an emergency and must be treated immediately, because cardiorespiratory dysfunction, hyperthermia, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury. Furthermore, CNS injury can occur even when the patient is paralyzed with neuromuscular blockade but continues to have electrographic seizures. The most common causes of GCSE are anticonvulsant withdrawal or noncompliance, metabolic disturbances, drug toxicity, CNS infection, CNS tumors, refractory epilepsy, and head trauma.

GCSE is obvious when the patient is having overt convulsions. However, after 30–45 min of uninterrupted seizures, the signs may become increasingly subtle. Patients may have mild clonic movements of only the fingers or fine, rapid movements of the eyes. There may be paroxysmal episodes of tachycardia, hypertension, and pupillary dilation. In such cases, the EEG may be the only method of establishing the diagnosis. Thus, if the patient stops having overt seizures, yet remains comatose, an EEG should be performed to rule out ongoing status epilepticus. This is obviously also essential when a patient with GCSE has been paralyzed with neuromuscular blockade in the process of protecting the airway.

The first steps in the management of a patient in GCSE are to attend to any acute cardiorespiratory problems or hyperthermia, perform a brief medical and neurologic examination, establish venous access, and send samples for laboratory studies to identify metabolic abnormalities. Anticonvulsant therapy should then begin without delay; a treatment approach is shown in **Fig. 31-3**.

The treatment of nonconvulsive status epilepticus is thought to be less urgent than GCSE, because the ongoing seizures are not accompanied by the severe metabolic disturbances seen with GCSE. However, evidence suggests that nonconvulsive status epilepticus, especially that caused by ongoing, focal seizure activity, is associated with cellular injury in the region of the seizure focus; therefore this condition should be treated as promptly as possible using the general approach described for GCSE.

www.ketabpezeshki.com (021) 66485457 - 66485438

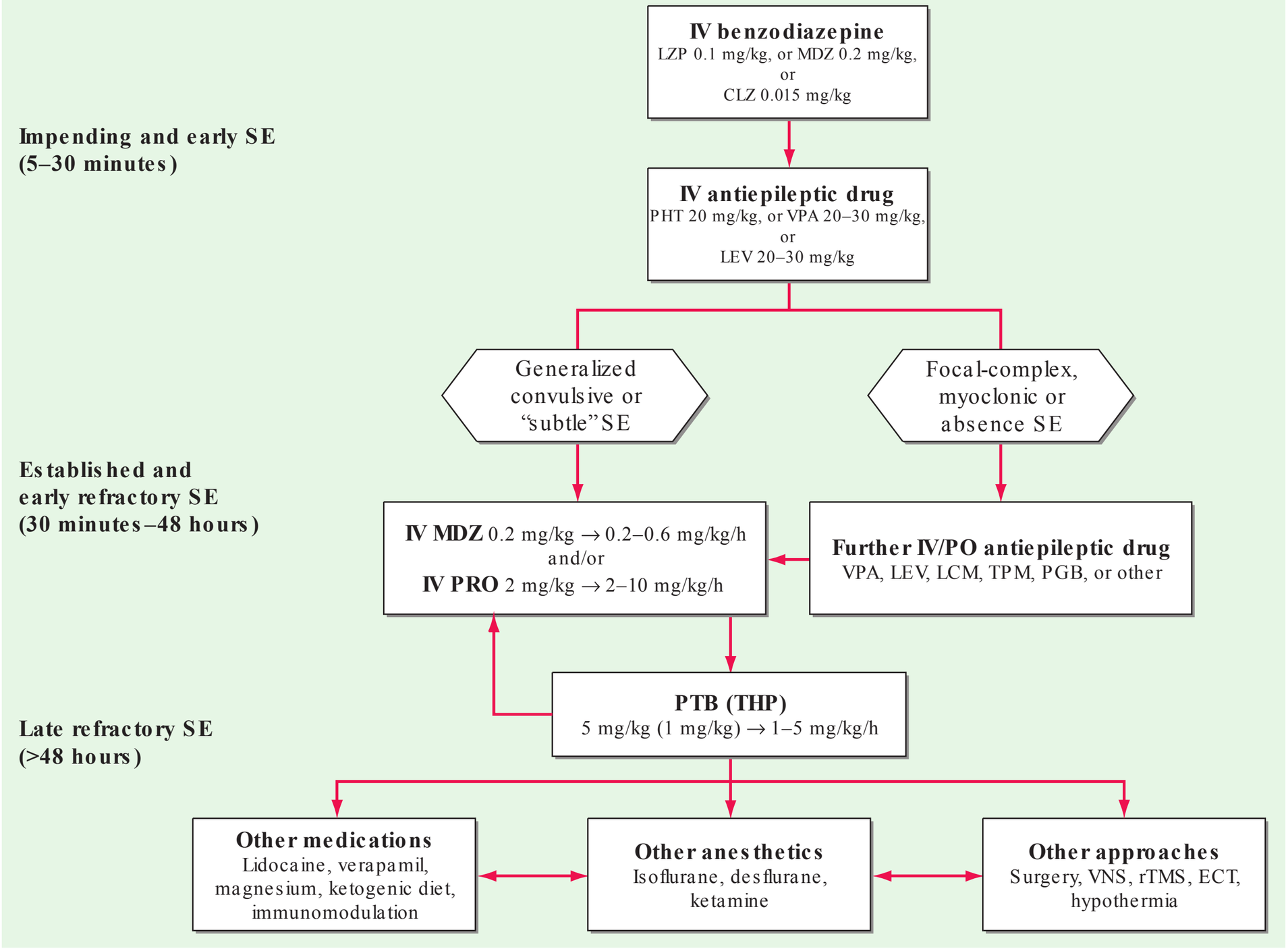


FIGURE 31-3
Pharmacologic treatment of generalized tonic-clonic status epilepticus (SE) in adults. CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fos-phenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. (From AO Rossetti, DH Lowenstein: Lancet Neurol 10:922, 2011.)

BEYOND SEIZURES: OTHER MANAGEMENT ISSUES

INTERICTAL BEHAVIOR

The adverse effects of epilepsy often go beyond clinical seizures, and the extent of these effects largely depends on the etiology of epilepsy, seizure frequency and severity, and side effects from antiepileptic therapy. Many epilepsy patients are completely normal between seizures and live highly successful and productive lives. In contrast, patients with seizures secondary to developmental abnormalities or acquired brain injury may have impaired cognitive function and other neurologic deficits. Frequent interictal EEG abnormalities are associated with subtle dysfunction of memory and attention. Patients with many seizures, especially those emanating from the temporal lobe, often note an impairment of short-term memory that may progress over time.

Patients with epilepsy are at risk of developing a variety of psychiatric problems, including depression, anxiety, and psychosis. This risk varies considerably depending on many factors, including the etiology, frequency, and severity of seizures and the patient's age and previous personal or family history of psychiatric disorder. Depression occurs in ~20% of patients, and the incidence of suicide is higher in patients with epilepsy than in the general population. Depression should be treated through counseling or medication. The selective serotonin reuptake inhibitors (SSRIs) typically have minimal effect on seizures, whereas tricyclic antidepressants may lower the seizure threshold. Anxiety can be a seizure symptom, and anxious or psychotic behavior can occur during a postictal delirium. Postictal psychosis is a rare phenomenon that typically occurs after a period of increased seizure frequency. There is usually a brief lucid interval lasting up to a week, followed by days to weeks of agitated, psychotic behavior. The psychosis usually resolves spontaneously but frequently

www.ketabpezeshki.com (021) 66485457 - 66485438

will require short-term treatment with antipsychotic or anxiolytic medications.

T ere is ongoing controversy as to whether some patients with epilepsy (especially temporal lobe epilepsy) have a stereotypical "interictal personality." T e predominant view is that atypical personality traits occur in diverse epilepsies (e.g., generalized and frontal lobe epilepsy) and may result from an underlying structural brain lesion, antiepileptic drug effects, and psychosocial factors related to suffering from a chronic disease, as well as the epilepsy itself.

MORTALITY OF EPILEPSY

Patients with epilepsy have a risk of death that is roughly two to three times greater than expected in a matched population without epilepsy. Most of the increased mortality is due to the underlying etiology of epilepsy (e.g., tumors or strokes in older adults). However, a significant number of patients die from accidents, status epilepticus, and a syndrome known as sudden unexpected death in epilepsy (SUDEP), which usually affects young people with convulsive seizures and tends to occur at night. T e cause of SUDEP is unknown; it may result from brainstem-mediated effects of seizures on pulmonary, cardiac, and arousal functions. Recent studies suggest that, in some cases, a genetic mutation may be the cause of both epilepsy and a cardiac conduction defect that gives rise to sudden death.

PSYCHOSOCIAL ISSUES

T ere continues to be a cultural stigma about epilepsy, although it is slowly declining in societies with effective health education programs. Many patients with epilepsy harbor fears such as the fear of becoming mentally retarded or dying during a seizure. T ese issues need to be carefully addressed by educating the patient about epilepsy and by ensuring that family members, teachers, fellow employees, and other associates are equally well informed. http://www.epilepsyfoundation.org A useful source of educational material is the Web site www.epilepsy.com.

EMPLOYMENT, DRIVING, AND OTHER ACTIVITIES

Many patients with epilepsy face dif culty in obtaining or maintaining employment, even when their seizures are well controlled. Federal and state legislation is designed to prevent employers from discriminating against patients with epilepsy, and patients should be encouraged to understand and claim their legal rights. Patients in these circumstances also benefit greatly from the assistance of health providers who act as strong patient advocates.

Loss of driving privileges is one of the most disruptive social consequences of epilepsy. Physicians should be very clear about local regulations concerning driving and epilepsy, because the laws vary considerably among states and countries. In all cases, it is the physician's responsibility to warn patients of the danger imposed on themselves and others while driving if their seizures are uncontrolled (unless the seizures are not associated with impairment of consciousness or motor control). In general, most states allow patients to drive after a seizure-free interval (on or off medications) of between 3 months and 2 years.

Patients with incompletely controlled seizures must also contend with the risk of being in other situations where an impairment of consciousness or loss of motor control could lead to major injury or death. T us, depending on the type and frequency of seizures, many patients need to be instructed to avoid working at heights or with machinery or to have someone close by for activities such as bathing and swimming.

SPECIAL ISSUES RELATED TO WOMEN AND EPILEPSY

CATAMENIAL EPILEPSY

Some women experience a marked increase in seizure frequency around the time of menses. T is is believed to be mediated by either the effects of estrogen and progesterone on neuronal excitability or changes in antiepileptic drug levels due to altered protein binding or metabolism. Some patients may benefit from increases in antiepileptic drug dosages during menses. Natural progestins or intramuscular medroxyprogesterone may be of benefit to a subset of women.

PREGNANCY

Most women with epilepsy who become pregnant will have an uncomplicated gestation and deliver a normal baby. However, epilepsy poses some important risks to a pregnancy. Seizure frequency during pregnancy will remain unchanged in ~50% of women, increase in 30%, and decrease in 20%. Changes in seizure frequency are attributed to endocrine effects on the CNS, variations in antiepileptic drug pharmacokinetics (such as acceleration of hepatic drug metabolism or effects on plasma protein binding), and changes in medication compliance. It is useful to see patients at frequent intervals during pregnancy and monitor serum antiepileptic drug levels. Measurement of the unbound drug

www.ketabpezeshki.com (021) 66485457 - 66485438

concentrations may be useful if there is an increase in seizure frequency or worsening of side effects of antiepileptic drugs.

The overall incidence of fetal abnormalities in children born to mothers with epilepsy is 5–6%, compared to 2–3% in healthy women. Part of the higher incidence is due to teratogenic effects of antiepileptic drugs, and the risk increases with the number of medications used (e.g., 10–20% risk of malformations with three drugs) and possibly with higher doses. A meta-analysis of published pregnancy registries and cohorts found that the most common malformations were defects in the cardiovascular and musculoskeletal system (1.4–1.8%). Valproic acid is strongly associated with an increased risk of adverse fetal outcomes (7–20%). Recent findings from a large pregnancy registry suggest that, other than topiramate, the newer antiepileptic drugs are far safer than valproic acid.

Because the potential harm of uncontrolled convulsive seizures on the mother and fetus is considered greater than the teratogenic effects of antiepileptic drugs, it is currently recommended that pregnant women be maintained on effective drug therapy. When possible, it seems prudent to have the patient on monotherapy at the lowest effective dose, especially during the first trimester. For some women, however, the type and frequency of their seizures may allow for them to safely wean off antiepileptic drugs prior to conception. Patients should also take folate (1–4 mg/d), because the antifolate effects of anticonvulsants are thought to play a role in the development of neural tube defects, although the benefits of this treatment remain unproved in this setting.

Enzyme-inducing drugs such as phenytoin, carbamazepine, oxcarbazepine, topiramate, phenobarbital, and primidone cause a transient and reversible deficiency of vitamin K–dependent clotting factors in ~50% of newborn infants. Although neonatal hemorrhage is uncommon, the mother should be treated with oral vitamin K (20 mg/d, phylloquinone) in the last 2 weeks of pregnancy, and the infant should receive intramuscular vitamin K (1 mg) at birth.

CONTRACEPTION

Special care should be taken when prescribing antiepileptic medications for women who are taking oral contraceptive agents. Drugs such as carbamazepine, phenytoin, phenobarbital, and topiramate can significantly decrease the efficacy of oral contraceptives via enzyme induction and other mechanisms. Patients should be advised to consider alternative forms of contraception, or their contraceptive medications should be modified to offset the effects of the antiepileptic medications.

BREAST-FEEDING

Antiepileptic medications are excreted into breast milk to a variable degree. The ratio of drug concentration in breast milk relative to serum ranges from ~5% (valproic acid) to 300% (levetiracetam). Given the overall benefits of breast-feeding and the lack of evidence for long-term harm to the infant by being exposed to antiepileptic drugs, mothers with epilepsy can be encouraged to breast-feed. This should be reconsidered, however, if there is any evidence of drug effects on the infant such as lethargy or poor feeding.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 32

CEREBROVASCULAR DISEASES

Wade S. Smith ■ S. Claiborne Johnston ■ J. Claude Hemphill

Cerebrovascular diseases include some of the most common and devastating disorders: ischemic stroke and hemorrhagic stroke. Stroke is the second leading cause of death worldwide, causing 6.2 million deaths in 2011, and is double the rate of heart disease in China. Strokes cause ~200,000 deaths each year in the United States and are a major cause of disability. The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030. A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. If the cessation of flow lasts for more than a few minutes, infarction or death of brain tissue results. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient: this is called a transient ischemic attack (TIA). The definition of TIA requires that all neurologic signs and symptoms resolve within 24 h without evidence of brain infarction on brain imaging. Stroke has occurred if the neurologic signs and symptoms last for >24 h or brain infarction is demonstrated. A generalized reduction in cerebral blood flow due to systemic hypotension (e.g., cardiac arrhythmia, myocardial infarction, or hemorrhagic shock) usually produces syncope **(Chap. 11)**. If low cerebral blood flow persists for a longer duration, then infarction in the border zones between the major cerebral artery distributions may develop. In more severe instances, global hypoxia-ischemia causes widespread brain injury; the constellation of cognitive sequelae that ensues is called hypoxic-ischemic encephalopathy **(Chap. 33)**. Focal ischemia or infarction, conversely, is usually caused by thrombosis of the cerebral vessels themselves or by emboli from a proximal arterial source or the heart. Intracranial hemorrhage is caused by bleeding directly into or around the brain; it produces neurologic symptoms by producing a mass effect on neural structures, from the toxic effects of blood itself, or by increasing intracranial pressure.

APPROACH TO THE PATIENT: Cerebrovascular Disease

Rapid evaluation is essential for use of time-sensitive treatments such as thrombolysis. However, patients with acute stroke often do not seek medical assistance on their own because they are rarely in pain and also may lose the appreciation that something is wrong (anosognosia); it is often a family member or a bystander who calls for help. Therefore, patients and their family members should be counseled to call emergency medical services immediately if they experience or witness the sudden onset of any of the following: loss of sensory and/or motor function on one side of the body (nearly 85% of ischemic stroke patients have hemiparesis); change in vision, gait, or ability to speak or understand; or a sudden, severe headache.

Other causes of sudden-onset neurologic symptoms that may mimic stroke include seizure, intracranial tumor, migraine, and metabolic encephalopathy. An adequate history from an observer that no convulsive activity occurred at the onset usually excludes seizure, although ongoing complex partial seizures without tonic-clonic activity can on occasion mimic stroke. Tumors may present with acute neurologic symptoms due to hemorrhage, seizure,

www.ketabpezeshki.com (021) 66485457 - 66485438

or hydrocephalus. Surprisingly, migraine **(Chap. 34)** can mimic stroke, even in patients without a significant migraine history. When migraine develops without head pain (acephalgic migraine), the diagnosis can be especially difficult. Patients without any prior history of migraine may develop acephalgic migraine even after age 65. A sensory disturbance is often prominent, and the sensory deficit, as well as any motor deficits, tends to migrate slowly across a limb, over minutes rather than seconds as with stroke. T e diagnosis of migraine becomes more secure as the cortical disturbance begins to cross vascular boundaries or if typical visual symptoms are present such as scintillating scotomata. At times it may be impossible to make the diagnosis of migraine until there have been multiple episodes with no residual symptoms or signs and no changes on brain magnetic resonance imaging (MRI). Metabolic encephalopathies typically produce fluctuating mental status changes without focal neurologic findings. However, in the setting of prior stroke or brain injury, a patient with fever or sepsis may manifest a recurrent hemiparesis, which clears rapidly when the infection is treated. T e metabolic process serves to "unmask" a prior deficit.

Once the diagnosis of stroke is made, a brain imaging study is necessary to determine if the cause of stroke is ischemia or hemorrhage **(Fig. 32-1)**. Computed tomography (CT) imaging of the brain is the standard imaging modality to detect the presence or absence of intracranial hemorrhage (see "Imaging Studies," below). If the stroke is ischemic, administration of recombinant tissue plasminogen activator (rtPA) or endovascular mechanical thrombectomy may be beneficial in restoring cerebral perfusion (see "Treatment: Acute Ischemic Stroke"). Medical management to reduce the risk of complications becomes the next priority, followed by plans for secondary prevention. For ischemic stroke, several strategies can reduce the risk of subsequent stroke in all patients, while other strategies are effective for patients with specific causes of stroke such as cardiac embolus and carotid atherosclerosis. For hemorrhagic stroke, aneurysmal subarachnoid hemorrhage (SAH) and hypertensive intracerebral hemorrhage are two important causes. T e treatment and prevention of hypertensive intracerebral hemorrhage are discussed later in this chapter. **SAH is discussed in Chap. 33.**

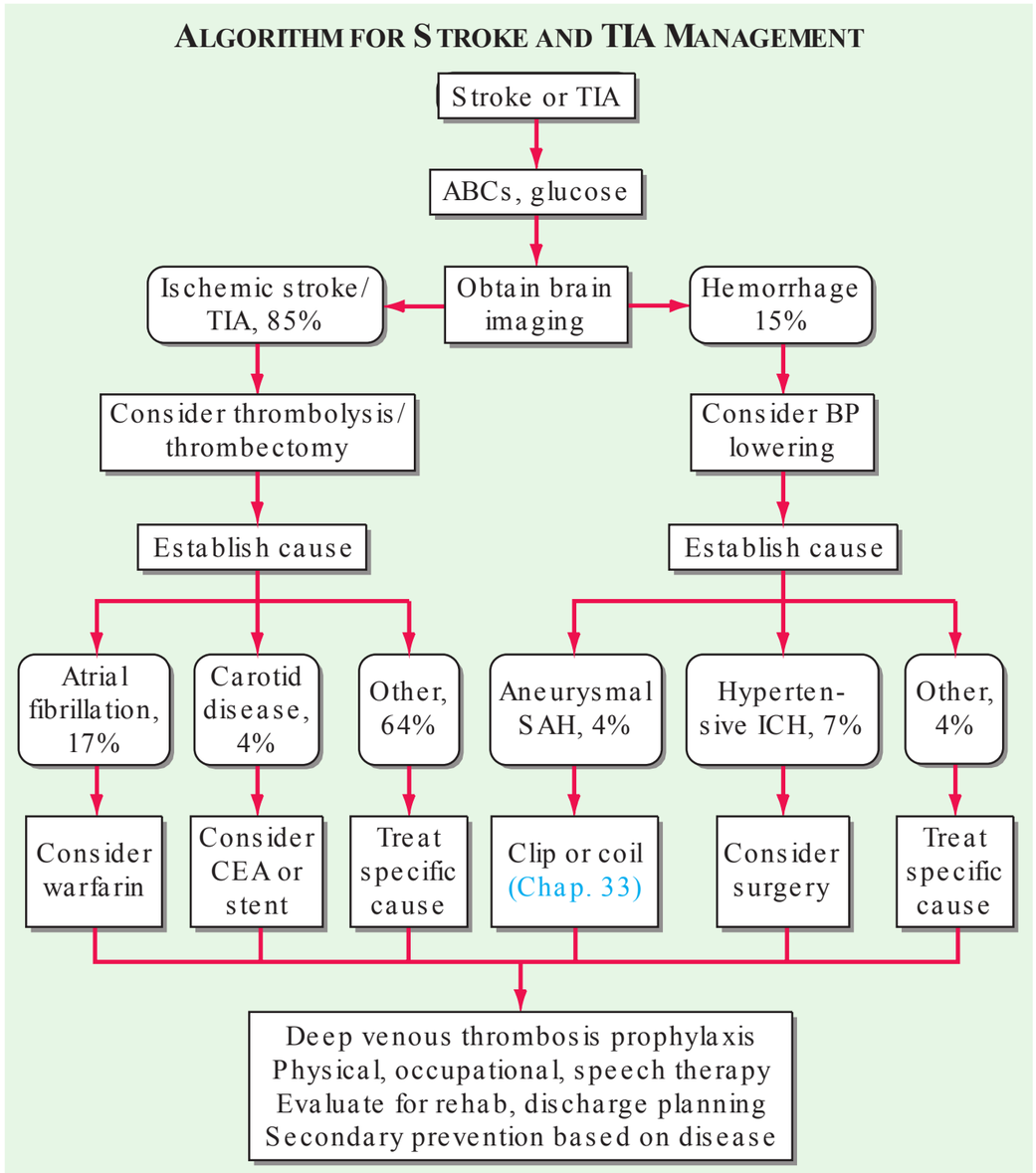


FIGURE 32-1
Medical management of stroke and TIA. Rounded boxes are diagnoses; rectangles are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; BP, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

ISCHEMIC STROKE

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies. T e magnitude of flow reduction is a function of collateral blood flow, and this depends on individual vascular anatomy (which may be altered by disease), the site of occlusion, and systemic blood pressure. A decrease in cerebral blood flow to zero causes death of brain tissue within 4–10 min; values <16–18 mL/100 g tissue per minute cause infarction within an hour; and values <20 mL/100 g tissue per minute cause ischemia without infarction unless prolonged for several hours or days. If blood flow is restored to ischemic tissue before significant infarction develops, the patient may experience only transient symptoms, and the clinical syndrome is called a TIA. Another important concept is the ischemic penumbra, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction. T e penumbra can be imaged by perfusion-diffusion imaging using MRI or CT (see below and Figs. 32-15 and 32-16). T e ischemic penumbra will eventually progress to infarction if no change in flow occurs, and hence saving the ischemic penumbra is the goal of revascularization therapies.

Focal cerebral infarction occurs via two distinct pathways **(Fig. 32-2)**: (1) a necrotic pathway in which cellular cytoskeletal breakdown is rapid, due principally to energy failure of the cell; and (2) an apoptotic pathway in which cells become programmed to die. Ischemia produces necrosis by starving neurons of glucose

www.ketabpezeshki.com (021) 66485457 - 66485438

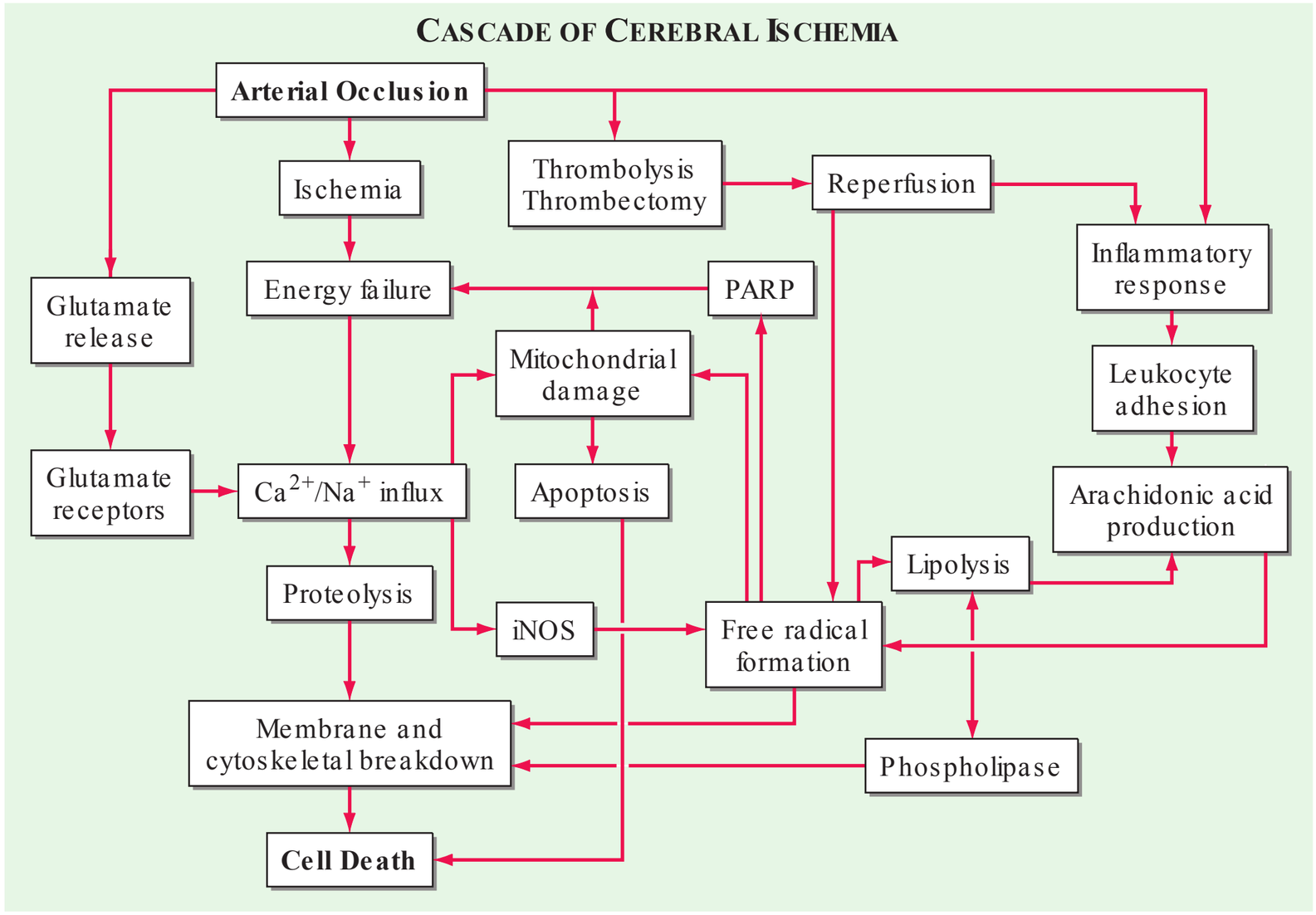


FIGURE 32-2
Major steps in the cascade of cerebral ischemia. See text for details. iNOS, inducible nitric oxide synthase; PARP, poly-A ribose polymerase.

and oxygen, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps stop functioning and neurons depolarize, allowing intracellular calcium to rise. Cellular depolarization also causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors that increase neuronal calcium influx. Free radicals are produced by degradation of membrane lipids and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death causing cells to die days to weeks later. Fever dramatically worsens brain injury during ischemia, as does hyperglycemia (glucose >11.1 mmol/L [200 mg/dL]), so it is reasonable to suppress fever and prevent hyperglycemia as much as possible. T e value of induced mild hypothermia to improve stroke outcomes is the subject of continuing clinical research.

TREATMENT Acute Ischemic Stroke

After the clinical diagnosis of stroke is made, an orderly process of evaluation and treatment should follow (Fig. 32-1). T e first goal is to prevent or reverse brain injury. Attend to the patient's airway, breathing, and circulation (ABCs), and treat hypoglycemia or hyperglycemia if identified. Perform an emergency noncontrast head CT scan to differentiate between ischemic stroke and hemorrhagic stroke; there are no reliable clinical findings that conclusively separate ischemia from hemorrhage, although a more depressed level of consciousness, higher initial blood pressure, or worsening of symptoms after onset favor hemorrhage, and a deficit that is maximal at onset, or remits, suggests ischemia. Treatments designed to reverse or lessen the amount of tissue infarction and improve clinical outcome fall within six categories: (1) medical support, (2) IV thrombolysis, (3) endovascular revascularization, (4) antithrombotic treatment, (5) neuroprotection, and (6) stroke centers and rehabilitation.

MEDICAL SUPPORT When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra. Attention is also directed toward preventing the common complications of bedridden patients—infections (pneumonia, urinary, and skin) and deep venous thrombosis (DVT) with pulmonary embolism. Subcutaneous heparin (unfractionated and low-molecular-weight) is safe and can be used concomitantly. Use of pneumatic compression stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin.

Because collateral blood flow within the ischemic brain may be blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely. Blood pressure should be lowered if there is malignant hypertension or concomitant myocardial ischemia, or if blood pressure is >185/110 mmHg and thrombolytic therapy is anticipated. When faced with the competing demands of myocardium

www.ketabpezeshki.com (021) 66485457 - 66485438

and brain, lowering the heart rate with a β_1-adrenergic blocker (such as esmolol) can be a first step to decrease cardiac work and maintain blood pressure. Routine lowering of blood pressure has been found to worsen outcomes. Fever is detrimental and should be treated with antipyretics and surface cooling. Serum glucose should be monitored and kept at <10.0 mmol/L (180 mg/dL) using an insulin infusion if necessary.

Between 5 and 10% of patients develop enough cerebral edema to cause obtundation or brain herniation. Edema peaks on the second or third day but can cause mass effect for ~10 days. T e larger the infarct, the greater the likelihood that clinically significant edema will develop. Water restriction and IV mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided because this may contribute to hypotension and worsening infarction. Combined analysis of three randomized European trials of hemicraniectomy (craniotomy and temporary removal of part of the skull) shows that hemicraniectomy markedly reduces mortality, and the clinical outcomes of survivors are acceptable. T e size of the diffusion-weighted imaging volume of brain infarction during the acute stroke is a predictor of deterioration requiring hemicraniectomy.

Special vigilance is warranted for patients with cerebellar infarction. T ese strokes may mimic labyrinthitis because of prominent vertigo and vomiting; the presence of head or neck pain should alert the physician to consider cerebellar stroke from vertebral artery dissection. Even small amounts of cerebellar edema can acutely increase intracranial pressure (ICP) by obstructing cerebrospinal fluid (CSF) flow leading to hydrocephalus or by directly compressing the brainstem. T e resulting brainstem compression can manifest as coma and respiratory arrest and require emergency surgical decompression. Prophylactic suboccipital decompression of large cerebellar infarcts before brainstem compression, although not tested rigorously in a clinical trial, is practiced at most stroke centers.

INTRAVENOUS THROMBOLYSIS T e National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study showed a clear benefit for IV rtPA in selected patients with acute stroke. T e NINDS study used IV rtPA (0.9 mg/kg to a 90-mg maximum; 10% as a bolus, then the remainder over 60 min) versus placebo in ischemic stroke within 3 h of onset. One-half of the patients were treated within 90 min. Symptomatic intracranial hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. In the rTPA group, there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA) and a nonsignificant 4% reduction in mortality (21% on placebo and 17% on rtPA). T us, despite an increased incidence of symptomatic intracranial hemorrhage, treatment with IV rtPA within 3 h of the onset of ischemic stroke improved clinical outcome.

T ree subsequent trials of IV rtPA did not confirm this benefit, perhaps because of the dose of rtPA used, the timing of its delivery, and small sample size. When data from all randomized IV rtPA trails were combined, however, efficacy was confirmed in the <3-h time window, and efficacy likely extended to 4.5 h and possibly to 6 h. Based on these combined results, the European Cooperative Acute Stroke Study (ECASS) III explored the safety and efficacy of rtPA in the 3- to 4.5-h time window. Unlike the NINDS study, patients older than 80 years of age and diabetic patients with a previous stroke were excluded. In this 821-patient randomized study, efficacy was again confirmed, although the treatment effect was less robust than in the 0- to 3-h time window. In the rtPA group, 52.4% of patients achieved a good outcome at 90 days, compared to 45.2% of the placebo group (odds ratio [OR] 1.34, p = .04). T e symptomatic intracranial hemorrhage rate was 2.4% in the rtPA group and 0.2% in the placebo group (p = .008).

Based on these data, rtPA is approved in the 3- to 4.5-h window in Europe and Canada, but is still only approved for 0–3 h in the United States and Canada. Use of IV tPA is now considered a central component of primary stroke centers (see below). It represents the first treatment proven to improve clinical outcomes in ischemic stroke and is cost-effective and cost-saving. Advanced neuroimaging techniques (see neuroimaging section below) may help to select patients beyond the 4.5-h window who will benefit from thrombolysis, but this is currently investigational. T e time of stroke onset is defined as the time the patient's symptoms were witnessed to begin or the time the patient was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed. **Table 32-1** summarizes eligibility criteria and instructions for administration of IV rtPA.

ENDOVASCULAR REVASCULARIZATION Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels (middle cerebral artery [MCA], intracranial internal carotid artery, and the basilar artery) generally involve a large clot volume and often fail to open with IV rtPA alone. T erefore, there is growing interest in using thrombolytics via an intraarterial route to increase the concentration of drug at the clot and minimize systemic bleeding complications. T e Prolyse in Acute Cerebral T romboembolism (PROACT) II trial found benefit for intraarterial prourokinase in acute MCA occlusions up to the sixth hour following onset of stroke. Intraarterial treatment of basilar artery occlusions may also be beneficial for selected patients. Intraarterial administration of a thrombolytic agent for acute ischemic stroke (AIS) is not approved by the U.S. Food and Drug Administration (FDA); however, many stroke centers offer this treatment based on these data.

Endovascular mechanical thrombectomy has been studied as an alternative or adjunctive treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who failed to achieve vascular recanalization with IV thrombolytics (see Fig. 32-15). T e Mechanical Embolus Removal in Cerebral Ischemia

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 32-1

ADMINISTRATION OF INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA) FOR ACUTE ISCHEMIC STROKE (AIS)[a]

INDICATION	CONTRAINDICATION
Clinical diagnosis of stroke	Sustained BP >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤4.5 h[b]	Platelets <100,000; HCT <25%; glucose <50 or >400 mg/dL
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Use of heparin within 48 h and prolonged PTT, or elevated INR
Age 18 ≥ years	Rapidly improving symptoms
Consent by patient or surrogate	Prior stroke or head injury within 3 months; prior intracranial hemorrhage
	Major surgery in preceding 14 days
	Minor stroke symptoms
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction
	Coma or stupor

Administration of rtPA

IV access with two peripheral IV lines (avoid arterial or central line placement)

Review eligibility for rtPA

Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h

Frequent cuff blood pressure monitoring

No other antithrombotic treatment for 24 h

For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently

Avoid urethral catheterization for ≥2 h

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.
[b]Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.
Abbreviations: BP, blood pressure; CT, computed tomography; HCT, hematocrit; INR, international normalized ratio; MCA, middle cerebral artery; PTT, partial thromboplastin time.

(MERCI) and multi-MERCI single-arm trials found that an endovascular thrombectomy device restored patency of occluded intracranial vessels within 8 h of ischemic stroke symptoms compared with a historical control group. Recanalization of the target vessel occurred in 48–58% of treated patients and in 60–69% of patients after use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favorable outcomes. Based on these nonrandomized data, the FDA approved this device as the first device for revascularization of occluded vessels in AIS even if the patient has been given rtPA and that therapy has failed. The Penumbra Pivotal Stroke trial tested another mechanical device that showed even higher rates of recanalization and led to FDA clearance of the tested device as well. More recently, two Stentriever devices (nondetachable stents) were shown to significantly improve vascular recanalization compared to the first approved MERCI device, approaching recanalization rates of 90% in most large intracranial vessels.

In 2015, five open-label randomized control trials each demonstrated that rapid thrombectomy with Stentriever devices was superior to treatment with intravenous thrombolysis alone. These trials studied patients with proven anterior circulation large-vessel occlusions demonstrated on early vascular imaging, typically with CT angiography. Patients were treated at least up to six hours from time last seen well, and those eligible for intravenous thrombolysis received IV rtPA prior to thrombectomy. A recent meta-analysis of individual patient data from these five trials showed significantly reduced disability at 90 days with a number needed to treat of 2.6 to reduce disability by at least one level on the modified Rankin scale. Mortality at 90 days and risk of intracerebral hemorrhage did not differ between the groups.

In the setting of these results, patients with acute stroke presenting within six hours of their last time seen normal should receive vascular imaging to identify those patients with a large-vessel occlusion amenable to thrombectomy. Patients eligible for IV rtPA should receive it quickly and prior to thrombectomy. The role of perfusion imaging in patient selection remains unclear and additional trials are underway to examine this approach. Although there is not widespread availability of interventionalists who can perform these procedures, comprehensive stroke centers are now obtaining credentialing to offer this therapy in distinction to primary stroke centers that are only required to provide treatment with IV rtPA.

ANTITHROMBOTIC TREATMENT

Platelet inhibition Aspirin is the only antiplatelet agent that has been proven effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke (see below). Two large trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), found that the use of aspirin within 48 h of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin, 300 mg/d, had slightly fewer deaths within 14 days (9.0 vs 9.4%), significantly fewer recurrent ischemic strokes (2.8 vs 3.9%), no excess of hemorrhagic strokes (0.9 vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2 vs 63.5%). In CAST, 21,106 patients with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. There were very small reductions in the aspirin group in early mortality (3.3 vs 3.9%), recurrent ischemic strokes (1.6 vs 2.1%), and dependency at discharge or death (30.5 vs 31.6%). These trials demonstrate that the

www.ketabpezeshki.com (021) 66485457 - 66485438

use of aspirin in the treatment of AIS is safe and produces a small net benefit. For every 1000 acute strokes treated with aspirin, about 9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and ~13 fewer patients will be dead or dependent at 6 months.

Clopidogrel is being tested as a way to prevent stroke following TIA and minor ischemic stroke (see below).

Anticoagulation Numerous clinical trials have failed to demonstrate any benefit of anticoagulation in the primary treatment of atherothrombotic cerebral ischemia. Several trials have investigated antiplatelet versus anticoagulant medications given within 12–24 h of the initial event. The U.S. Trial of Organon 10172 in Acute Stroke Treatment (TOAST), an investigational low-molecular-weight heparin (LMWH), failed to show any benefit over aspirin. Use of SC unfractionated heparin versus aspirin was tested in IST. Heparin given SC afforded no additional benefit over aspirin and increased bleeding rates. Several trials of LMWHs have also shown no consistent benefit in AIS. Furthermore, trials generally have shown an excess risk of brain and systemic hemorrhage with acute anticoagulation. A recent meta-analysis of all forms of heparin found no benefit for acute stroke patients at high or low risk of thrombotic events. Therefore, trials do not support the use of heparin or other anticoagulants for patients with atherothrombotic stroke.

NEUROPROTECTION Neuroprotection is the concept of providing a treatment that prolongs the brain's tolerance to ischemia. Drugs that block the excitatory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple human trials, they have not yet been proven to be beneficial. Hypothermia is a powerful neuroprotective treatment in patients with cardiac arrest **(Chap. 33)** and is neuroprotective in animal models of stroke, but it has not been adequately studied in patients with ischemic stroke and is associated with an increase in pneumonia rates that could adversely impact stroke outcomes.

STROKE CENTERS AND REHABILITATION Patient care in stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality. Use of clinical pathways and staff dedicated to the stroke patient can improve care. This includes use of standardized stroke order sets. Stroke teams that provide emergency 24-h evaluation of acute stroke patients for acute medical management and consideration of thrombolysis or endovascular treatments are essential components of primary and comprehensive stroke centers, respectively.

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. It is directed toward educating the patient and family about the patient's neurologic deficit, preventing the complications of immobility (e.g., pneumonia, DVT and pulmonary embolism, pressure sores of the skin, and muscle contractures), and providing encouragement and instruction in overcoming the deficit. Use of pneumatic compression stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin. The goal of rehabilitation is to return the patient to home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient. Additionally, the use of constrained movement therapy (immobilizing the unaffected side) has been shown to improve hemiparesis following stroke, even years after the stroke, suggesting that physical therapy can recruit unused neural pathways. Newer robotic therapies appear promising as well. The human nervous system is more adaptable than previously thought, and developing physical and pharmacologic strategies to enhance long-term neural recovery is an active area of research.

ETIOLOGY OF ISCHEMIC STROKE

(Figs. 32-1 and 32-3 and Table 32-2) Although the initial management of AIS often does not depend on the etiology, establishing a cause is essential to reduce the risk of recurrence. Particular focus should be on atrial fibrillation and carotid atherosclerosis, because these etiologies have proven secondary prevention strategies. The clinical presentation and examination findings often establish the cause of stroke or narrow the possibilities to a few. Judicious use of laboratory testing and imaging studies completes the initial evaluation. Nevertheless, nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should focus on the peripheral and cervical vascular system (carotid auscultation for bruits and blood pressure), the heart (dysrhythmia, murmurs), extremities (peripheral emboli), and retina (effects of hypertension and cholesterol emboli [Hollenhorst plaques]). A complete neurologic examination is performed to localize the anatomic site of stroke. An imaging study of the brain is nearly always indicated and is required for patients being considered for thrombolysis; it may be combined with CT- or MRI-based angiography to visualize the vasculature of the neck and intracranial vessels (see "Imaging Studies," below). A chest x-ray, electrocardiogram (ECG), urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), serum electrolytes, blood urea nitrogen (BUN), creatinine, blood glucose, serum lipid profile, prothrombin time (PT), and partial thromboplastin time (PTT) are often useful and should be considered in all patients. An ECG may demonstrate arrhythmias or reveal evidence of recent myocardial infarction (MI). Of all these studies, only brain imaging, blood glucose, and perhaps PTT/international normalized ratio (INR) are necessary prior to IV rtPA; the results of other studies should not delay the rapid administration of IV rtPA if the patient is eligible.

Cardioembolic stroke

Cardioembolism is responsible for ~20% of all ischemic strokes. Stroke caused by heart disease is primarily due to embolism of thrombotic material forming on the

www.ketabpezeshki.com (021) 66485457 - 66485438

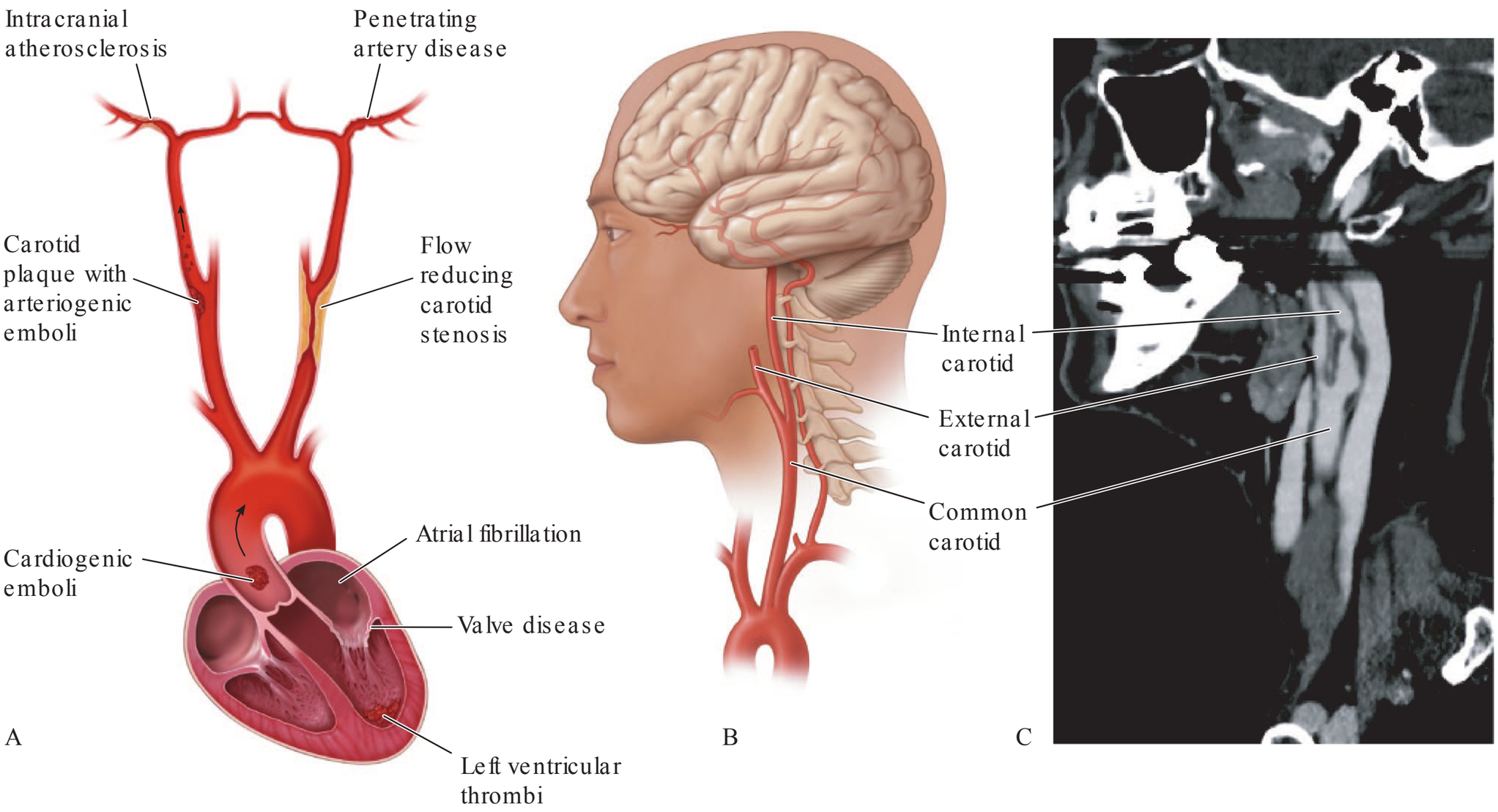


FIGURE 32-3
Pathophysiology of ischemic stroke. A. Diagram illustrating the three major mechanisms that underlie ischemic stroke: (1) occlusion of an intracranial vessel by an embolus that arises at a distant site (e.g., cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque), often affecting the large intracranial vessels; (2) in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries; (3) hypoperfusion caused by flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, often producing "watershed" ischemia. B. and C. Diagram and reformatted computed tomography angiogram of the common, internal, and external carotid arteries. High-grade stenosis of the internal carotid artery, which may be associated with either cerebral emboli or flow-limiting ischemia, was identified in this patient.

atrial or ventricular wall or the left heart valves. These thrombi then detach and embolize into the arterial circulation. The thrombus may fragment or lyse quickly, producing only a TIA. Alternatively, the arterial occlusion may last longer, producing stroke. Embolic strokes tend to occur suddenly with maximum neurologic deficit present at onset. With reperfusion following more prolonged ischemia, petechial hemorrhages can occur within the ischemic territory. These are usually of no clinical significance and should be distinguished from frank intracranial hemorrhage into a region of ischemic stroke where the mass effect from the hemorrhage can cause a significant decline in neurologic function.

Emboli from the heart most often lodge in the intracranial internal carotid artery, the MCA, the posterior cerebral artery (PCA), or one of their branches; infrequently, the anterior cerebral artery (ACA) is involved. Emboli large enough to occlude the stem of the MCA (3–4 mm) lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory depend on the extent of the collateral circulation.

The most significant causes of cardioembolic stroke in most of the world are nonrheumatic (often called nonvalvular) atrial fibrillation, MI, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopathy (Table 32-2). Cardiac disorders causing brain embolism are discussed in the chapters on heart diseases. A few pertinent aspects are highlighted here.

Nonrheumatic atrial fibrillation is the most common cause of cerebral embolism overall. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage, with subsequent embolization. Patients with atrial fibrillation have an average annual risk of stroke of ~5%. The risk of stroke can be estimated by calculating the CHADS2 score **(Table 32-3)**. Left atrial enlargement is an additional risk factor for formation of atrial thrombi. Rheumatic heart disease usually causes ischemic stroke when there is prominent mitral stenosis or atrial fibrillation. Recent MI may be a source of emboli, especially when transmural and involving the anteroapical ventricular wall, and prophylactic anticoagulation following MI has been shown to reduce stroke risk. Mitral valve prolapse is not usually a source of emboli unless the prolapse is severe.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 32-2

CAUSES OF ISCHEMIC STROKE

COMMON CAUSES	UNCOMMON CAUSES
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency[a]
Large-vessel thrombosis	Protein S deficiency[a]
Dehydration	Antithrombin III deficiency[a]
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation[a]
Carotid bifurcation	Prothrombin G20210 mutation[a]
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias[a]
Mechanical valve	Nephrotic syndrome[a]
Bacterial endocarditis	Inflammatory bowel disease[a]
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosis[b]
Patent foramen ovale	Fibromuscular dysplasia
Atrial septal aneurysm	Vasculitis
Spontaneous echo contrast	Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis)
Stimulant drugs: cocaine, amphetamine	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Noninflammatory vasculopathy
	Reversible vasoconstriction syndrome
	Fabry's disease
	Angiocentric lymphoma
	Cardiogenic
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Moyamoya disease
	Eclampsia

[a]Chiefly cause venous sinus thrombosis.
[b]May be associated with any hypercoagulable disorder.
Abbreviations: CNS, central nervous system; PAN, polyarteritis nodosa.

Paradoxical embolization occurs when venous thrombi migrate to the arterial circulation, usually via a patent foramen ovale or atrial septal defect. Bubble-contrast echocardiography (IV injection of agitated saline coupled with either transthoracic or transesophageal echocardiography) can demonstrate a right-to-left cardiac shunt, revealing the conduit for paradoxical embolization. Alternatively, a right-to-left shunt is implied if immediately following IV injection of agitated saline, the ultrasound signature of bubbles is observed during transcranial Doppler insonation of the MCA; pulmonary arteriovenous malformations should be considered if this test is positive yet an echocardiogram fails to reveal an intracardiac shunt. Both techniques are highly sensitive for detection of right-to-left shunts. Besides venous clot, fat and tumor emboli, bacterial endocarditis, IV air, and amniotic fluid emboli at childbirth may occasionally be responsible for paradoxical embolization. The importance of a patent foramen ovale (PFO) as a cause of stroke is debated, particularly because they are present in ~15% of the general population. Some studies have suggested that the risk is only elevated in the presence of a coexisting atrial septal aneurysm. The presence of a venous source of embolus, most commonly a deep venous thrombus, may provide confirmation of the importance of a PFO with an accompanying right-to-left shunt in a particular case. Three randomized trials of PFO occlusion for secondary prevention of ischemic stroke were negative, although each lacked sufficient power to be conclusive. At present, there is no supportive evidence to offer percutaneous PFO closure for stroke prevention.

Bacterial endocarditis can be a source of valvular vegetations that give rise to septic emboli. The appearance of multifocal symptoms and signs in a patient with stroke makes bacterial endocarditis more likely. Infarcts of microscopic size occur, and large septic infarcts may evolve into brain abscesses or cause hemorrhage into the infarct, which generally precludes use of anticoagulation or thrombolytics. Mycotic aneurysms caused by septic emboli may also present as SAH or intracerebral hemorrhage.

Artery-to-artery embolic stroke

Thrombus formation on atherosclerotic plaques may embolize to intracranial arteries producing an artery-to-artery embolic stroke. Less commonly, a diseased vessel may acutely thrombose. Unlike the myocardial vessels, artery-to-artery embolism, rather than local thrombosis, appears to be the dominant vascular mechanism causing large-vessel brain ischemia. Any diseased vessel may be an embolic source, including the aortic arch, common carotid, internal carotid, vertebral, and basilar arteries.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 32-3

RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS

CONDITION	RECOMMENDATION
Nonvalvular atrial fibrillation	Calculate CHADS2[a] score
• CHADS2 score 0	Aspirin or no antithrombotic
• CHADS2 score 1	Aspirin or OAC
• CHADS2 score >1	OAC
Rheumatic mitral valve disease	
• With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm	OAC
• Embolization or appendage clot despite OAC	OAC plus aspirin
Mitral valve prolapse	
• Asymptomatic	No therapy
• With otherwise cryptogenic stroke or TIA	Aspirin
• Atrial fibrillation	OAC
Mitral annular calcification	
• Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA	Aspirin
• Recurrent embolization despite aspirin	OAC
• With atrial fibrillation	OAC
Aortic valve calcification	
• Asymptomatic	No therapy
• Otherwise cryptogenic stroke or TIA	Aspirin
Aortic arch mobile atheroma	
• Otherwise cryptogenic stroke or TIA	Aspirin or OAC
Patent foramen ovale	
• Otherwise cryptogenic ischemic stroke or TIA	Aspirin
• Indication for OAC (deep venous thrombosis or hypercoagulable state)	OAC
Mechanical heart value	
• Aortic position, bileaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm	VKA INR 2.5, range 2–3
• Mitral position tilting disk or bileaflet valve	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, anterior-apical myocardial infarct or left atrial enlargement	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease	Aspirin plus VKA INR 3.0, range 2.5–3.5
• Systemic embolization despite target INR	Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4
Bioprosthetic valve	
• No other indication for VKA therapy	Aspirin
Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis	
• With systemic embolization	Full-dose unfractionated heparin or SC LMWH

[a]CHADS2 score calculated as follows: 1 point for age >75 years, 1 point for hypertension, 1 point for congestive heart failure, 1 point for diabetes, and 2 points for stroke or TIA; sum of points is the total CHADS2 score.

Note: Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Sources: Modified from DE Singer et al: Chest 133:546S, 2008; DN Salem et al: Chest 133:593S, 2008.

www.ketabpezeshki.com (021) 66485457 - 66485438

Carotid atherosclerosis

Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery; the carotid siphon (portion within the cavernous sinus) is also vulnerable to atherosclerosis. Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are risk factors for carotid disease, as they are for stroke in general **(Table 32-4)**. Carotid atherosclerosis produces an estimated 10% of ischemic stroke.

Carotid disease can be classified by whether the stenosis is symptomatic or asymptomatic and by the degree of stenosis (percent narrowing of the narrowest segment compared to a nondiseased segment). Symptomatic carotid disease implies that the patient has experienced a stroke or TIA within the vascular distribution of the artery, and it is associated with a greater risk of subsequent stroke than asymptomatic stenosis, in which the patient is symptom free and the stenosis is detected through screening. Greater degrees of arterial narrowing are generally associated with a higher risk of stroke, except that those with near occlusions are at lower risk of stroke.

Other causes of artery-to-artery embolic stroke

Intracranial atherosclerosis produces stroke either by an embolic mechanism or by in situ thrombosis of a diseased vessel. It is more common in patients of Asian and African-American descent. Recurrent stroke risk is ~15% per year, similar to symptomatic untreated carotid atherosclerosis.

Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young (age <60 years) patients. The dissection is usually painful and precedes the stroke by several hours or days. Extracranial dissections do not cause hemorrhage, presumably because of the tough adventitia of these vessels. Intracranial dissections, conversely, may produce SAH because the adventitia of intracranial vessels is thin and pseudoaneurysms may form, requiring urgent treatment to prevent rerupture. Treating asymptomatic pseudoaneurysms following dissection is likely not necessary. The cause of dissection is usually unknown, and recurrence is rare. Ehlers-Danlos type IV, Marfan's disease, cystic medial necrosis, and fibromuscular dysplasia are associated with dissections. Trauma (usually a motor vehicle accident or a sports injury) can cause carotid and vertebral artery dissections. Spinal manipulative therapy is associated with vertebral artery dissection and stroke. Most dissections heal spontaneously, and stroke or TIA is uncommon beyond 2 weeks. Recent trials comparing anticoagulation to antiplatelet agents have shown no significant differences between these approaches.

SMALL-VESSEL STROKE

The term lacunar infarction refers to infarction following atherothrombotic or lipohyalinotic occlusion of a small artery in the brain. The term small-vessel stroke denotes occlusion of such a small penetrating artery and is now the preferred term. Small-vessel strokes account for ~20% of all strokes.

Pathophysiology

The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and

TABLE 32-4

RISK FACTORS FOR STROKE

RISK FACTOR	RELATIVE RISK	RELATIVE RISK REDUCTION WITH TREATMENT	NUMBER NEEDED TO TREAT[a]	
			PRIMARY PREVENTION	SECONDARY PREVENTION
Hypertension	2–5	38%	100–300	50–100
Atrial fibrillation	1.8–2.9	68% warfarin, 21% aspirin	20–83	13
Diabetes	1.8–6	No proven effect		
Smoking	1.8	50% at 1 year, baseline risk at 5 years postcessation		
Hyperlipidemia	1.8–2.6	16–30%	560	230
Asymptomatic carotid stenosis	2.0	53%	85	N/A
Symptomatic carotid stenosis (70–99%)		65% at 2 years	N/A	12
Symptomatic carotid stenosis (50–69%)		29% at 5 years	N/A	77

[a]Number needed to treat to prevent one stroke annually. Prevention of other cardiovascular outcomes is not considered here.
Abbreviation: N/A, not applicable.

www.ketabpezeshki.com (021) 66485457 - 66485438

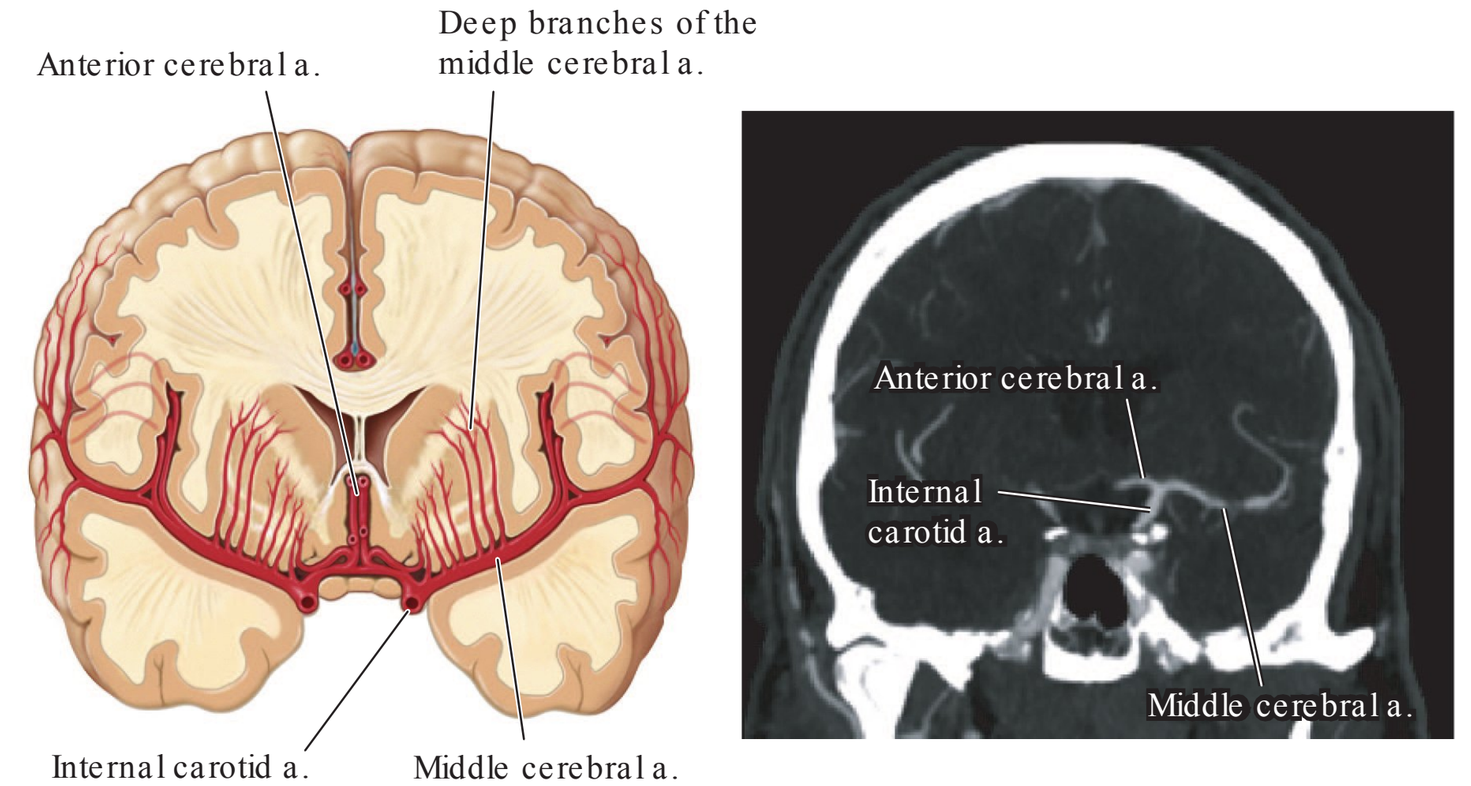


FIGURE 32-4

Diagrams and reformatted computed tomography (CT) angiograms in the coronal section illustrating the deep penetrating arteries involved in small-vessel strokes. In the anterior circulation, small penetrating arteries called lenticulostriates arise from the proximal portion of the anterior and middle cerebral arteries and supply deep subcortical structures (upper panels). In the posterior circulation, similar arteries arise directly from the vertebral and basilar arteries to supply the brainstem (lower panels). Occlusion of a single penetrating artery gives rise to a discrete area of infarct (pathologically termed a "lacune," or lake). Note that these vessels are too small to be visualized on CT angiography.

vertebral arteries all give rise to 30- to 300-μm branches that penetrate the deep gray and white matter of the cerebrum or brainstem **(Fig. 32-4)**. Each of these small branches can occlude either by atherothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as lacunes (Latin for "lake" of fluid noted at autopsy). These infarcts range in size from 3 mm to 2 cm in diameter. Hypertension and age are the principal risk factors.

Clinical manifestations

The most common small-vessel stroke syndromes are the following: (1) pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or the pons; the face, arm, and leg are almost always involved; (2) pure sensory stroke from an infarct in the ventral thalamus; (3) ataxic hemiparesis from an infarct in the ventral pons or internal capsule; (4) and dysarthria and a clumsy hand or arm due to infarction in the ventral pons or in the genu of the internal capsule.

Transient symptoms (small-vessel TIAs) may herald a small-vessel infarct; they may occur several times a day and last only a few minutes. Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is severe permanent disability.

A large-vessel source (either thrombosis or embolism) may manifest initially as a small-vessel infarction. Therefore, the search for embolic sources (carotid and heart) should not be completely

www.ketabpezeshki.com (021) 66485457 - 66485438

abandoned in the evaluation of these patients. Secondary prevention of small-vessel stroke involves risk factor modification, specifically reduction in blood pressure (see "Treatment: Primary and Secondary Prevention of Stroke and TIA," below).

LESS COMMON CAUSES OF STROKE

(Table 32-2) Hypercoagulable disorders primarily increase the risk of venous, including venous sinus, thrombosis. Systemic lupus erythematosus with Libman-Sacks endocarditis can be a cause of embolic stroke. T ese conditions overlap with the antiphospholipid syndrome, which probably requires long-term anticoagulation to prevent further stroke. Homocysteinemia may cause arterial thromboses as well; this disorder is caused by various mutations in the homocysteine pathways and responds to different forms of cobalamin depending on the mutation.

Venous sinus thrombosis of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration. It is also seen in patients with laboratory-confirmed thrombophilia including polycythemia, sickle cell anemia, deficiencies of proteins C and S, factor V Leiden mutation (resistance to activated protein C), antithrombin III deficiency, homocysteinemia, and the prothrombin G20210 mutation. Women who take oral contraceptives and have the prothrombin G20210 mutation may be at particularly high risk for sinus thrombosis. Patients present with headache and may also have focal neurologic signs (especially paraparesis) and seizures. Often, CT imaging is normal unless an intracranial venous hemorrhage has occurred, but the venous sinus occlusion is readily visualized using magnetic resonance (MR) or CT venography or conventional x-ray angiography. With greater degrees of sinus thrombosis, the patient may develop signs of increased ICP and coma. Intravenous heparin, regardless of the presence of intracranial hemorrhage, reduces morbidity and mortality, and the long-term outcome is generally good. Heparin prevents further thrombosis and reduces venous hypertension and ischemia. If an underlying hypercoagulable state is not found, many physicians treat with vitamin K antagonists (VKAs) for 3–6 months and then convert to aspirin, depending on the degree of resolution of the venous sinus thrombus. Anticoagulation is often continued indefinitely if thrombophilia is diagnosed.

Sickle cell anemia (SS disease) is a common cause of stroke in children. A subset of homozygous carriers of this hemoglobin mutation develop stroke in childhood, and this may be predicted by documenting high-velocity blood flow within the MCAs using transcranial Doppler ultrasonography. In children who are identified to have high velocities, treatment with aggressive exchange transfusion dramatically reduces risk of stroke, and if exchange transfusion is ceased, their stroke rate increases again along with MCA velocities.

Fibromuscular dysplasia affects the cervical arteries and occurs mainly in women. T e carotid or vertebral arteries show multiple rings of segmental narrowing alternating with dilatation. Vascular occlusion is usually incomplete. T e process is often asymptomatic but occasionally is associated with an audible bruit, TIAs, or stroke. Involvement of the renal arteries is common and may cause hypertension. T e cause and natural history of fibromuscular dysplasia are unknown. TIA or stroke generally occurs only when the artery is severely narrowed or dissects. Anticoagulation or antiplatelet therapy may be helpful.

*T*emporal (giant cell) arteritis is a relatively common af iction of elderly individuals in which the external carotid system, particularly the temporal arteries, undergo subacute granulomatous inflammation with giant cells. Occlusion of posterior ciliary arteries derived from the ophthalmic artery results in blindness in one or both eyes and can be prevented with glucocorticoids. It rarely causes stroke because the internal carotid artery is usually not inflamed. Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (*T*akayasu's arteritis) may cause carotid or vertebral thrombosis; it is rare in the Western Hemisphere.

Necrotizing (or granulomatous) arteritis, occurring alone or in association with generalized polyarteritis nodosa or granulomatosis with polyangiitis (Wegener's), involves the distal small branches (<2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. T e CSF often shows pleocytosis, and the protein level is elevated. Primary central nervous system vasculitis is rare; small or medium-sized vessels are usually affected, without apparent systemic vasculitis. T e differential diagnosis includes other inflammatory vasculopathies including infection (tuberculous, fungal), sarcoidosis, angiocentric lymphoma, carcinomatous meningitis, and noninflammatory causes such as atherosclerosis, emboli, connective tissue disease, vasospasm, migraine-associated vasculopathy, and drug-associated causes. Some cases develop in the postpartum period and are self-limited.

Patients with any form of vasculopathy may present with insidious progression of combined white and gray matter infarctions, prominent headache, and cognitive decline. Brain biopsy or high-resolution conventional x-ray angiography is usually required to make the diagnosis **(Fig. 32-5)**. An inflammatory profile found on lumbar puncture favors an inflammatory cause. In cases where inflammation is confirmed, aggressive

www.ketabpezeshki.com (021) 66485457 - 66485438

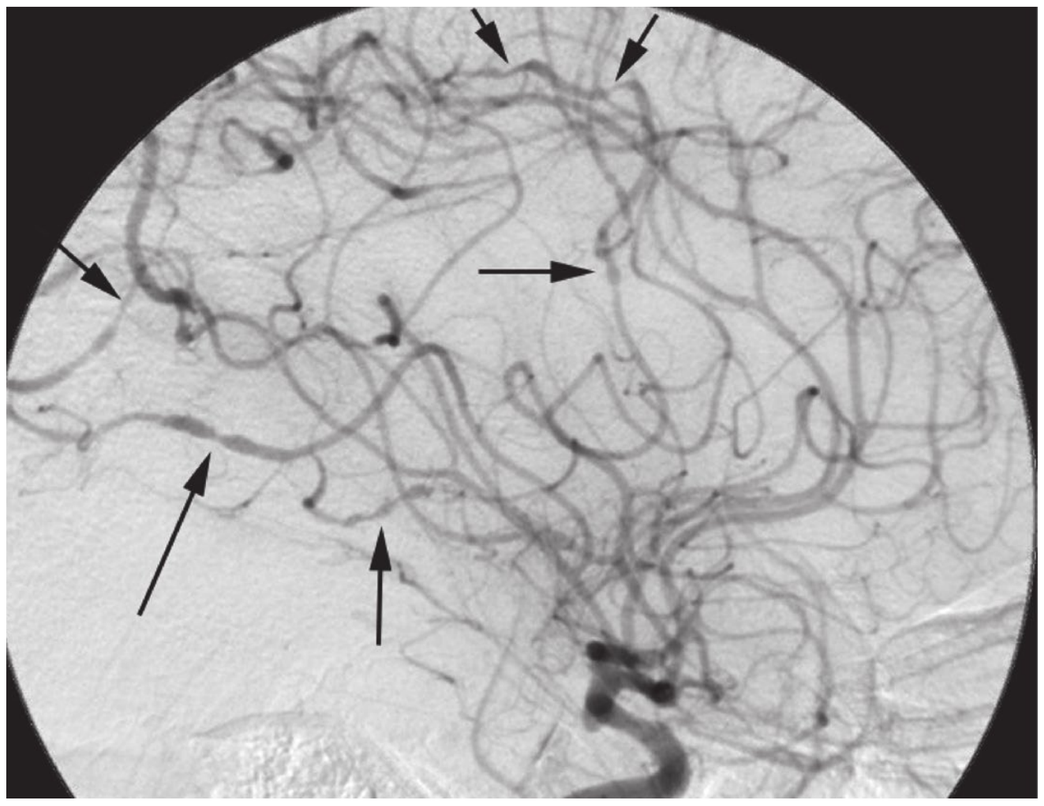


FIGURE 32-5
Cerebral angiogram from a 32-year-old male with central nervous system vasculopathy. Dramatic beading (arrows) typical of vasculopathy is seen.

immunosuppression with glucocorticoids, and often cyclophosphamide, is usually necessary to prevent progression; a diligent investigation for infectious causes such as tuberculosis is essential prior to immunosuppression. With prompt recognition and treatment, many patients can make an excellent recovery.

Drugs, in particular amphetamines and perhaps cocaine, may cause stroke on the basis of acute hypertension or drug-induced vasculopathy. No data exist on the value of any treatment. Phenylpropanolamine has been linked with intracranial hemorrhage, as has cocaine and methamphetamine, perhaps related to a drug-induced vasculopathy. Moyamoya disease is a poorly understood occlusive disease involving large intracranial arteries, especially the distal internal carotid artery and the stem of the MCA and ACA. Vascular inflammation is absent. T e lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a "puff of smoke" (moyamoya in Japanese) on conventional x-ray angiography. Other collaterals include transdural anastomoses between the cortical surface branches of the meningeal and scalp arteries. T e disease occurs mainly in Asian children or young adults, but the appearance may be identical in adults who have atherosclerosis, particularly in association with diabetes. Intracranial hemorrhage may result from rupture of the transdural and pial anastomotic channels; thus, anticoagulation is risky. Breakdown of dilated lenticulostriate arteries may produce intraparenchymal hemorrhage, and progressive occlusion of large surface arteries can occur, producing large-artery distribution strokes. Surgical bypass of extracranial carotid arteries to the dura or MCAs may prevent stroke and hemorrhage.

Posterior reversible encephalopathy syndrome (PRES) can occur with head injury, seizure, migraine, sympathomimetic drug use, eclampsia, and in the postpartum period **(Chap. 58)**. T e pathophysiology is uncertain but likely involves a hyperperfusion state with widespread segmental vasoconstriction and cerebral edema. Patients complain of headache and manifest fluctuating neurologic symptoms and signs, especially visual symptoms. Sometimes cerebral infarction ensues, but typically the clinical and imaging findings suggest that ischemia reverses completely. MRI findings are characteristic with the edema present within the occipital lobes but can be generalized and do not respect any single vascular territory. A closely related reversible cerebral vasoconstriction syndrome (RCVS) typically presents with sudden, severe headache closely mimicking SAH. Patients may experience ischemic infarction and intracerebral hemorrhage and typically have new-onset, severe hypertension. Conventional x-ray angiography reveals changes in the vascular caliber throughout the hemispheres resembling vasculitis, but the process is noninflammatory. Oral calcium channel blockers may be effective in producing remission, and recurrence is rare.

Leukoaraiosis, or periventricular white matter disease, is the result of multiple small-vessel infarcts within the subcortical white matter. It is readily seen on CT or MRI scans as areas of white matter injury surrounding the ventricles and within the corona radiata. T e pathophysiologic basis of the disease is lipohyalinosis of small penetrating arteries within the white matter, likely produced by chronic hypertension. Patients with periventricular white matter disease may develop a subcortical dementia syndrome, and it is likely that this common form of dementia may be delayed or prevented with antihypertensive medications **(Chap. 35)**.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited disorder that presents as small-vessel strokes, progressive dementia, and extensive symmetric white matter changes often including the anterior temporal lobes visualized by MRI. Approximately 40% of patients have migraine with aura, often manifest as transient motor or sensory deficits. Onset is usually in the fourth or fifth decade of life. T is autosomal dominant condition is caused by one of several mutations in Notch-3, a member of a highly conserved gene family characterized by epidermal growth factor repeats in its extracellular domain. Other monogenic ischemic stroke syndromes include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). Fabry's disease also produces both a large-vessel arteriopathy and small-vessel infarctions.

www.ketabpezeshki.com (021) 66485457 - 66485438

TRANSIENT ISCHEMIC ATTACKS

TIAs are episodes of stroke symptoms that last only briefly; the standard definition of duration is <24 h, but most TIAs last <1 h. If a relevant brain infarction is identified on brain imaging, the clinical entity is now classified as stroke regardless of the duration of symptoms. The causes of TIA are similar to the causes of ischemic stroke, but because TIAs may herald stroke, they are an important risk factor that should be considered separately and urgently. TIAs may arise from emboli to the brain or from in situ thrombosis of an intracranial vessel. With a TIA, the occluded blood vessel reopens and neurologic function is restored.

T e risk of stroke after a TIA is ~10–15% in the first 3 months, with most events occurring in the first 2 days. T is risk can be directly estimated using the well-validated ABCD^2 score **(Table 32-5)**. T erefore, urgent evaluation and treatment are justified. Because etiologies for stroke and TIA are identical, evaluation for TIA should parallel that of stroke (Figs. 32-1 and 32-3). T e improvement characteristic of TIA is a contraindication to thrombolysis. However, because the risk of subsequent stroke in the first few days after a TIA is high, the opportunity to give rtPA rapidly if a stroke occurs may justify hospital admission for most patients. T e combination of aspirin and clopidogrel has been recently reported to prevent stroke following TIA better than aspirin alone in a large Chinese randomized trial and is undergoing similar evaluation in an ongoing National Institutes of Health (NIH)-sponsored trial (POINT study).

TABLE 32-5

RISK OF STROKE FOLLOWING TRANSIENT ISCHEMIC ATTACK: THE ABCD^2 SCORE

CLINICAL FACTOR	SCORE
A: Age ≥60 years	1
B: SBP >140 mmHg or DBP >90 mmHg	1
C: Clinical symptoms	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
>60 min	2
10–59 min	1
D: Diabetes (oral medications or insulin)	1
Total Score	**Sum Each Category**
ABCD^2 Score Total	3-Month Rate of Stroke (%)[a]
0	0
1	2
2	3
3	3
4	8
5	12
6	17
7	22

[a]Data ranges are from five cohorts.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
Source: SC Johnston et al: Validation and refinement of score to predict very early stroke risk after transient ischaemic attack. Lancet 369:283, 2007.

TREATMENT Primary and Secondary Prevention of Stroke and TIA

GENERAL PRINCIPLES A number of medical and surgical interventions, as well as lifestyle modifications, are available for preventing stroke. Some of these can be widely applied because of their low cost and minimal risk; others are expensive and carry substantial risk but may be valuable for selected high-risk patients. Identification and control of modifiable risk factors, and especially hypertension, is the best strategy to reduce the burden of stroke, and the total number of strokes could be reduced substantially by these means (Table 32-4).

ATHEROSCLEROSIS RISK FACTORS Older age, diabetes mellitus, hypertension, tobacco smoking, abnormal blood cholesterol (particularly, low high-density lipoprotein [HDL] and/or elevated low-density lipoprotein [LDL]), and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Risk of stroke is much greater in those with prior stroke or TIA. Many cardiac conditions predispose to stroke, including atrial fibrillation and recent MI. Oral contraceptives and hormone replacement therapy increase stroke risk, and although rare, certain inherited and acquired hypercoagulable states predispose to stroke.

Hypertension is the most significant of the risk factors; in general, all hypertension should be treated to a target of less than 140–150/90 mmHg. However, many vascular neurologists recommend that guidelines for secondary prevention of stroke should aim for blood pressure reduction to 130/80 mmHg or lower. T e presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension. Also, the value of treating systolic hypertension in older patients has been clearly established. Lowering blood pressure to levels below those traditionally defining hypertension appears to reduce the risk of stroke even further. Data are particularly strong in support of thiazide diuretics and angiotensin-converting enzyme inhibitors.

www.ketabpezeshki.com (021) 66485457 - 66485438

Several trials have confirmed that statin drugs reduce the risk of stroke even in patients without elevated LDL or low HDL. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed benefit in secondary stroke reduction for patients with recent stroke or TIA who were prescribed atorvastatin, 80 mg/d. The primary prevention trial, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), found that patients with low LDL (<130 mg/dL) caused by elevated C-reactive protein benefitted by daily use of this statin. Primary stroke occurrence was reduced by 51% (hazard ratio 0.49, p = .004), and there was no increase in the rates of intracranial hemorrhage. Meta-analysis has also supported a primary treatment effect for statins given acutely for ischemic stroke. Therefore, a statin should be considered in all patients with prior ischemic stroke. Tobacco smoking should be discouraged in all patients **(Chap. 66)**. The use of pioglitazone (an agonist of peroxisome proliferator-activated receptor gamma) in patients with type 2 diabetes and previous stroke may lower risk of recurrent stroke, MI, or vascular death.

ANTIPLATELET AGENTS Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting the formation of intraarterial platelet aggregates. These can form on diseased arteries, induce thrombus formation, and occlude or embolize into the distal circulation. Aspirin, clopidogrel, and the combination of aspirin plus extended-release dipyridamole are the antiplatelet agents most commonly used for this purpose. Ticlopidine has been largely abandoned because of its adverse effects but may be used as an alternative to clopidogrel.

Aspirin is the most widely studied antiplatelet agent. Aspirin acetylates platelet cyclooxygenase, which irreversibly inhibits the formation in platelets of thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiaggregating and vasodilating prostaglandin. This effect is transient. As soon as aspirin is cleared from the blood, the nucleated endothelial cells again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A_2 in platelets without substantially inhibiting prostacyclin formation. Higher doses of aspirin have not been proven to be more effective than lower doses.

Ticlopidine and clopidogrel block the adenosine diphosphate (ADP) receptor on platelets and thus prevent the cascade resulting in activation of the glycoprotein IIb/IIIa receptor that leads to fibrinogen binding to the platelet and consequent platelet aggregation. Ticlopidine is more effective than aspirin; however, it has the disadvantage of causing diarrhea, skin rash, and, in rare instances, neutropenia and thrombotic thrombocytopenic purpura (TTP). Clopidogrel rarely causes TTP but does not cause neutropenia. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, which led to FDA approval, found that it was only marginally more effective than aspirin in reducing risk of stroke. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial was a large multicenter, randomized, double-blind study that compared clopidogrel in combination with aspirin to clopidogrel alone in the secondary prevention of TIA or stroke. The MATCH trial found no difference in TIA or stroke prevention with this combination, but did show a small but significant increase in major bleeding complications (3 vs 1%). In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which included a subgroup of patients with prior stroke or TIA along with other groups at high risk of cardiovascular events, there was no benefit of clopidogrel combined with aspirin compared to aspirin alone. Lastly, the SPS3 trial looked at the long-term combination of clopidogrel and aspirin versus clopidogrel alone in small-vessel stroke and found no improvement in stroke prevention and a significant increase in both hemorrhage and death. Thus, the long-term use of clopidogrel in combination with aspirin is not recommended for stroke prevention.

The short-term combination of clopidogrel with aspirin may be effective in preventing second stroke, however. A trial of 5170 Chinese patients enrolled within 24 h of TIA or minor ischemic stroke found that a clopidogrel-aspirin regimen (clopidogrel 300 mg load then 75 mg/d with aspirin 75 mg for the first 21 days) was superior to aspirin (75 mg/d) alone, with 90-day stroke risk decreased from 11.7 to 8.2% (p < .001) and no increase in major hemorrhage. An international NIH-sponsored trial of similar design is ongoing.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of aggregation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggregatory effects of prostacyclin and nitric oxide produced by the endothelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting elevation in cyclic AMP inhibits aggregation of platelets. Dipyridamole is erratically absorbed depending on stomach pH, but a newer formulation combines timed-release dipyridamole, 200 mg, with aspirin, 25 mg, and has better oral bioavailability. This combination drug was studied in three trials. The European Stroke Prevention Study (ESPS) II showed efficacy of both 50 mg/d of aspirin and extended-release dipyridamole in preventing stroke, and a significantly better risk reduction when the two agents were combined. The open-label ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) trial confirmed the ESPS-II results. After 3.5 years of follow-up, 13% of patients on aspirin and dipyridamole and 16% on aspirin alone (hazard ratio 0.80, 95% confidence index [CI] 0.66–0.98) met the primary outcome of death from all vascular causes. In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, the combination of extended-release dipyridamole and aspirin

www.ketabpezeshki.com (021) 66485457 - 66485438

was compared directly with clopidogrel with and without the angiotensin receptor blocker telmisartan; there were no differences in the rates of second stroke (9% each) or degree of disability in patients with median follow-up of 2.4 years. Telmisartan also had no effect on these outcomes. T is suggests that these antiplatelet regimens are similar and also raises questions about default prescription of agents to block the angiotensin pathway in all stroke patients. T e principal side effect of dipyridamole is headache. T e combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke.

Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular atherothrombotic events (i.e., ischemic stroke, MI, and death due to all vascular causes) in patients at risk for these events. T e overall relative reduction in risk of nonfatal stroke is about 25–30% and of all vascular events is about 25%. T e absolute reduction varies considerably, depending on the particular patient's risk. Individuals at very low risk for stroke seem to experience the same relative reduction, but their risks may be so low that the "benefit" is meaningless. Conversely, individuals with a 10–15% risk of vascular events per year experience a reduction to about 7.5–11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life threatening. Consequently, not every 40- or 50-year-old should be advised to take aspirin regularly because the risk of atherothrombotic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke or TIA and has no contraindication should be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%; another few percent will experience an MI or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment.

T e choice of antiplatelet agent and dose must balance the risk of stroke, the expected benefit, and the risk and cost of treatment. However, there are no definitive data, and opinions vary. Many authorities believe low-dose (30–75 mg/d) and high-dose (650–1300 mg/d) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 81–325 mg/d, whereas most Europeans recommend 50–100 mg. Clopidogrel and extended-release dipyridamole plus aspirin are being increasingly recommended as first-line drugs for secondary prevention. Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher, and this is likely to affect long-term patient adherence. T e use of platelet aggregation studies in individual patients taking aspirin is controversial because of limited data.

ANTICOAGULATION THERAPY AND EMBOLIC STROKE Several trials have shown that anticoagulation (INR range, 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with a VKA reduces the risk by about 67%, which clearly outweighs the 1–3% risk per year of a major bleeding complication. VKAs are difficult to dose, their effects vary with dietary intake of vitamin K, and they require frequent blood monitoring of the PTT/INR. Several newer oral anticoagulants (OACs) have recently been shown to be more convenient and efficacious for stroke prevention in NVAF. A randomized trial compared the oral thrombin inhibitor dabigatran to VKAs in a noninferiority trial to prevent stroke or systemic embolization in NVAF. Two doses of dabigatran were used: 110 mg/d and 150 mg/d. Both dose tiers of dabigatran were noninferior to VKAs in preventing second stroke and systemic embolization, and the higher dose tier was superior (relative risk 0.66; 95% CI 0.53–0.82; $p < .001$) and the rate of major bleeding was lower in the lower dose tier of dabigatran compared to VKAs. Dabigatran requires no blood monitoring to titrate the dose, and its effect is independent of oral intake of vitamin K. Newer oral factor Xa inhibitors have also been found to be equivalent or safer and more effective than VKAs in NVAF stroke prevention. In the Apixaban for Reduction in Stroke and Other T romboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, patients were randomized between apixaban, 5 mg twice daily, and dose-adjusted warfarin (INR 2–3). T e combined endpoint of ischemic or hemorrhagic stroke or system embolism occurred in 1.27% of patients in the apixaban group and in 1.6% in the warfarin group ($p < .001$ for noninferiority and $p < .01$ for superiority). Major bleeding was 1% less, favoring apixaban ($p < .001$). Similar results were obtained in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). Here, patients with NVAF were randomized to rivaroxaban versus warfarin: 1.7% of the factor Xa group and 2.2% of the warfarin group reached the endpoint of stroke and systemic embolism ($p < .001$ for noninferiority); intracranial hemorrhage was also lower with rivaroxaban. Finally, the factor Xa inhibitor edoxaban was also found to be noninferior to warfarin. T us, oral factor Xa inhibitors are at least a suitable alternative to VKAs, and likely are superior both in efficacy and perhaps compliance.

For patients who cannot take anticoagulant medications, clopidogrel plus aspirin was compared to aspirin alone in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A). Clopidogrel combined with aspirin was more effective than aspirin alone in preventing vascular events, principally stroke, but increased the risk of major bleeding (relative risk 1.57, $p < .001$).

T e decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 32-3). T e history of a TIA or stroke tips the balance in favor of anticoagulation regardless of other risk factors. Intermittent

www.ketabpezeshki.com (021) 66485457 - 66485438

atrial fibrillation carries the same risk of stroke as chronic atrial fibrillation, and several ambulatory studies of seemingly "cryptogenic" stroke have found evidence of intermittent atrial fibrillation in nearly 20% of patients monitored for a few weeks. Interrogation of implanted pacemakers also confirms an association between subclinical atrial fibrillation and stroke risk. T erefore, for patients with otherwise cryptogenic embolic stroke (no evidence of any other cause for stroke), ambulatory monitoring for 3–4 weeks is a reasonable strategy to determine the best prophylactic therapy.

Because of the high annual stroke risk in untreated rheumatic heart disease with atrial fibrillation, primary prophylaxis against stroke has not been studied in a double-blind fashion. T ese patients generally should receive long-term anticoagulation. Dabigatran and the oral Xa inhibitors have not been studied in this population.

Anticoagulation also reduces the risk of embolism in acute MI. Most clinicians recommend a 3-month course of anticoagulation when there is anterior Q-wave infarction, substantial left ventricular dysfunction, congestive heart failure, mural thrombosis, or atrial fibrillation. OACs are recommended long-term if atrial fibrillation persists.

Stroke secondary to thromboembolism is one of the most serious complications of prosthetic heart valve implantation. T e intensity of anticoagulation and/or antiplatelet therapy is dictated by the type of prosthetic valve and its location. Dabigatran may be less effective than warfarin, and the oral Xa inhibitors have not been studied in this population.

If the embolic source cannot be eliminated, anticoagulation should in most cases be continued indefinitely. Many neurologists recommend combining antiplatelet agents with anticoagulants for patients who "fail" anticoagulation (i.e., have another stroke or TIA), but the evidence basis for this is lacking.

ANTICOAGULATION THERAPY AND NONCARDIOGENIC STROKE Data do not support the use of long-term VKAs for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease. T e Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no benefit of warfarin sodium (INR 1.4–2.8) over aspirin, 325 mg, for secondary prevention of stroke but did find a slightly higher bleeding rate in the warfarin group; a European study confirmed this finding. T e Warfarin and Aspirin for Symptomatic Intracranial Disease (WASID) study (see below) demonstrated no benefit of warfarin (INR 2–3) over aspirin in patients with symptomatic intracranial atherosclerosis and also found a higher rate of bleeding complications.

TREATMENT Carotid Atherosclerosis

Carotid atherosclerosis can be removed surgically (endarterectomy) or mitigated with endovascular stenting with or without balloon angioplasty. Anticoagulation has not been directly compared with antiplatelet therapy for carotid disease.

SURGICAL THERAPY Symptomatic carotid stenosis was studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). Both showed a substantial benefit for surgery in patients with stenosis of ≥70%. In NASCET, the average cumulative ipsilateral stroke risk at 2 years was 26% for patients treated medically and 9% for those receiving the same medical treatment plus a carotid endarterectomy. T is 17% absolute reduction in the surgical group is a 65% relative risk reduction favoring surgery (Table 32-4). NASCET also showed a significant, although less robust, benefit for patients with 50–70% stenosis. ECST found harm for patients with stenosis <30% treated surgically.

A patient's risk of stroke and possible benefit from surgery are related to the presence of retinal versus hemispheric symptoms, degree of arterial stenosis, extent of associated medical conditions (of note, NASCET and ECST excluded "high-risk" patients with significant cardiac, pulmonary, or renal disease), institutional surgical morbidity and mortality, timing of surgery relative to symptoms, and other factors. A recent meta-analysis of the NASCET and ECST trials demonstrated that endarterectomy is most beneficial when performed within 2 weeks of symptom onset. In addition, benefit is more pronounced in patients >75 years, and men appear to benefit more than women.

In summary, a patient with recent symptomatic hemispheric ischemia, high-grade stenosis in the appropriate internal carotid artery, and an institutional perioperative morbidity and mortality rate of ≤6% generally should undergo carotid endarterectomy. If the perioperative stroke rate is >6% for any particular surgeon, however, the benefits of carotid endarterectomy are questionable.

T e indications for surgical treatment of asymptomatic carotid disease have been clarified by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST). ACAS randomized asymptomatic patients with ≥60% stenosis to medical treatment with aspirin or the same medical treatment plus carotid endarterectomy. T e surgical group had a risk over 5 years for ipsilateral stroke (and any perioperative stroke or death) of 5.1%, compared to a risk in the medical group of 11%. Although this demonstrates a 53% relative risk reduction, the absolute risk reduction is only 5.9% over 5 years, or 1.2% annually (Table 32-4). Nearly one-half of the strokes in the surgery group were caused by preoperative angiograms. ACST randomized asymptomatic patients with >60% carotid stenosis to endarterectomy or medical therapy. T e 5-year risk of stroke in the surgical group (including perioperative stroke or death) was 6.4%, compared to 11.8% in the medically treated group (46% relative risk reduction and 5.4% absolute risk reduction).

In both ACAS and ACST, the perioperative complication rate was higher in women, perhaps negating any benefit in the reduction of stroke risk within 5 years. It is possible that with longer follow-up, a clear benefit in women will emerge. At present, carotid endarterectomy in asymptomatic women remains particularly controversial.

www.ketabpezeshki.com (021) 66485457 - 66485438

In summary, the natural history of asymptomatic stenosis is an ~2% per year stroke rate, whereas symptomatic patients experience a 13% per year risk of stroke. Whether to recommend carotid revascularization for an asymptomatic patient is somewhat controversial and depends on many factors, including patient preference, degree of stenosis, age, gender, and comorbidities. Medical therapy for reduction of atherosclerosis risk factors, including cholesterol-lowering agents and antiplatelet medications, is generally recommended for patients with asymptomatic carotid stenosis. As with atrial fibrillation, it is imperative to counsel the patient about TIAs so that therapy can be revised if symptoms develop.

ENDOVASCULAR THERAPY Balloon angioplasty coupled with stenting is being used with increasing frequency to open stenotic carotid arteries and maintain their patency. T ese techniques can treat carotid stenosis not only at the bifurcation but also near the skull base and in the intracranial segments. T e Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized high-risk patients (defined as patients with clinically significant coronary or pulmonary disease, contralateral carotid occlusion, restenosis after endarterectomy, contralateral laryngeal-nerve palsy, prior radical neck surgery or radiation, or age >80) with symptomatic carotid stenosis >50% or asymptomatic stenosis >80% to either stenting combined with a distal emboli-protection device or endarterectomy. T e risk of death, stroke, or MI within 30 days and ipsilateral stroke or death within 1 year was 12.2% in the stenting group and 20.1% in the endarterectomy group (p = .055), suggesting that stenting is at the very least comparable to endarterectomy as a treatment option for this patient group at high risk of surgery. However, the outcomes with both interventions may not have been better than leaving the carotid stenoses untreated, particularly for the asymptomatic patients, and much of the benefit seen in the stenting group was due to a reduction in periprocedure MI. Two randomized trials comparing stents to endarterectomy in lower-risk patients have been published. T e Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) enrolled patients with either asymptomatic or symptomatic stenosis. T e 30-day risk of stroke was 4.1% in the stent group and 2.3% in the surgical group, but the 30-day risk of MI was 1.1% in the stent group and 2.3% in the surgery group, suggesting relative equivalence of risk between the procedures. At median follow-up of 2.5 years, the combined endpoint of stroke, MI, and death was the same (7.2% stent vs 6.8% surgery). T e rate of restenosis at 2 years was also similar in both groups. T e International Carotid Stenting (ICSS) trial randomized symptomatic patients to stents versus endarterectomy and found a different result: At 120 days, the incidence of stroke, MI, or death was 8.5% in the stenting group versus 5.2% in the endarterectomy group (p = .006); longer-term follow-up is currently under way. Differences between trial designs, selection of stent, and operator experience may explain these important differences. Until more data are available, there remains controversy as to who should receive a stent or have endarterectomy; it is likely that the procedures carry similar risks if performed by experienced physicians.

BYPASS SURGERY Extracranial-to-intracranial (EC-IC) bypass surgery has been proven ineffective for atherosclerotic stenoses that are inaccessible to conventional carotid endarterectomy. In patients with recent stroke, an associated carotid occlusion, and evidence of inadequate perfusion of the brain as measured with positron emission tomography, no benefit from EC-IC bypass was found in a trial stopped for futility.

INTRACRANIAL ATHEROSCLEROSIS T e WASID trial randomized patients with symptomatic stenosis (50–99%) of a major intracranial vessel to either high-dose aspirin (1300 mg/d) or warfarin (target INR, 2.0–3.0), with a combined primary endpoint of ischemic stroke, brain hemorrhage, or death from vascular cause other than stroke. T e trial was terminated early because of an increased risk of adverse events related to warfarin anticoagulation. With a mean follow-up of 1.8 years, the primary endpoint was seen in 22.1% of patients in the aspirin group and 21.8% of the warfarin group. Death from any cause was seen in 4.3% of the aspirin group and 9.7% of the warfarin group; 3.2% of patients on aspirin experienced major hemorrhage, compared to 8.3% of patients taking warfarin.

Intracranial stenting of intracranial atherosclerosis was found to be dramatically harmful compared to aspirin in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial. T is trial enrolled newly symptomatic TIA or minor stroke patients with associated 70–99% intracranial stenosis to primary stenting with a self-expanding stent or to medical management. Both groups received clopidogrel, aspirin, statin, and aggressive control of blood pressure. T e endpoint of stroke or death occurred in 14.7% of the stented group and 5.8% of the medically treated groups (p = .002). T is low rate of second stroke was significantly lower than in the WASID trial and suggests that aggressive medical management had a marked influence on secondary stroke risk.

Dural sinus thrombosis Limited evidence exists to support short-term use of anticoagulants, regardless of the presence of intracranial hemorrhage, for venous infarction following sinus thrombosis. T e long-term outcome for most patients, even those with intracerebral hemorrhage, is excellent.

STROKE SYNDROMES

A careful history and neurologic examination can often localize the region of brain dysfunction; if this region corresponds to a particular arterial distribution, the possible causes responsible for the syndrome can be narrowed. T is is of particular importance when the patient presents with a TIA and a normal examination. For example, if a patient develops language loss and a right homonymous hemianopia, a search for causes

www.ketabpezeshki.com (021) 66485457 - 66485438

of left middle cerebral emboli should be performed. A finding of an isolated stenosis of the right internal carotid artery in that patient, for example, suggests an asymptomatic carotid stenosis, and the search for other causes of stroke should continue. The following sections describe the clinical findings of cerebral ischemia associated with cerebral vascular territories depicted in Figs. 32-4 and **32-6 through 32-14**. Stroke syndromes are divided into: (1) large-vessel stroke within the anterior circulation, (2) large-vessel stroke within the posterior circulation, and (3) small-vessel disease of either vascular bed.

Stroke within the anterior circulation

The internal carotid artery and its branches comprise the anterior circulation of the brain. These vessels can be occluded by intrinsic disease of the vessel (e.g., atherosclerosis or dissection) or by embolic occlusion from a proximal source as discussed above. Occlusion of each major intracranial vessel has distinct clinical manifestations.

Middle cerebral artery

Occlusion of the proximal MCA or one of its major branches is most often due to an embolus (artery-to-artery, cardiac, or of unknown source) rather than intracranial atherothrombosis. Atherosclerosis of the proximal MCA may cause distal emboli to the middle cerebral territory or, less commonly, may produce low-flow TIAs. Collateral formation via leptomeningeal vessels often prevents MCA stenosis from becoming symptomatic.

The cortical branches of the MCA supply the lateral surface of the hemisphere except for (1) the frontal pole and a strip along the superomedial border of the frontal and parietal lobes supplied by the ACA, and (2) the lower temporal and occipital pole convolutions supplied by the PCA (Figs. 32-6, 32-7, 32-8, and 32-9).

The proximal MCA (M1 segment) gives rise to penetrating branches (termed lenticulostriate arteries) that supply the putamen, outer globus pallidus, posterior limb of the internal capsule, adjacent corona radiata, and most of the caudate nucleus (Fig. 32-6). In the sylvian fissure, the MCA in most patients divides into superior and inferior divisions (M2 branches). Branches of the inferior division supply the inferior parietal and temporal cortex, and those from the superior division supply the frontal and superior parietal cortex (Fig. 32-7).

If the entire MCA is occluded at its origin (blocking both its penetrating and cortical branches) and the distal collaterals are limited, the clinical findings are contralateral hemiplegia, hemianesthesia, homonymous hemianopia, and a day or two of gaze preference to the ipsilateral side. Dysarthria is common because of facial weakness. When the dominant hemisphere is involved,

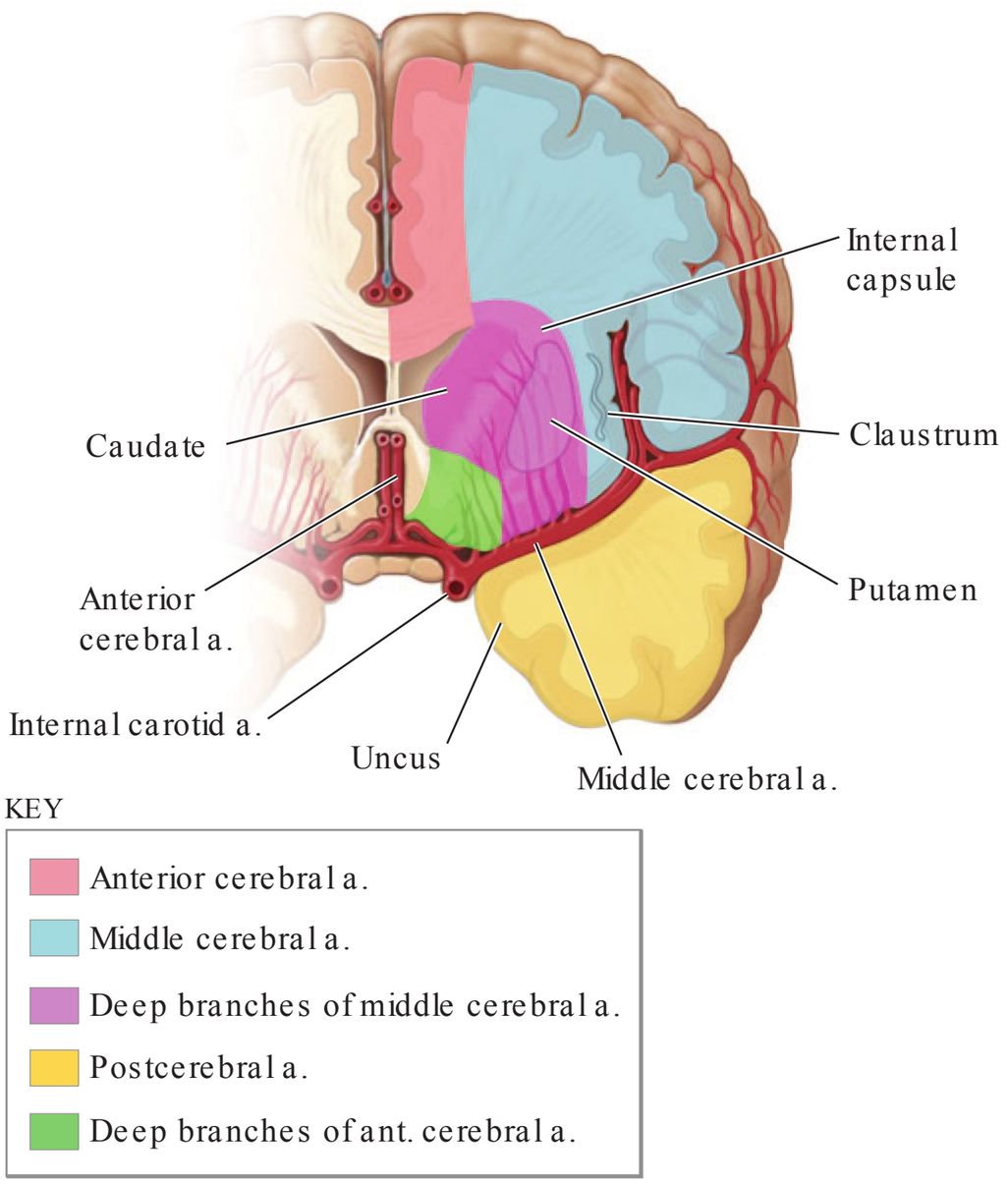


FIGURE 32-6
Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels that branch from the internal carotid arteries.

global aphasia is present also, and when the nondominant hemisphere is affected, anosognosia, constructional apraxia, and neglect are found **(Chap. 22)**.

Complete MCA syndromes occur most often when an embolus occludes the stem of the artery. Cortical collateral blood flow and differing arterial configurations are probably responsible for the development of many partial syndromes. Partial syndromes may also be due to emboli that enter the proximal MCA without complete occlusion, occlude distal MCA branches, or fragment and move distally.

Partial syndromes due to embolic occlusion of a single branch include hand, or arm and hand, weakness alone (brachial syndrome) or facial weakness with nonfluent (Broca) aphasia **(Chap. 22)**, with or without arm weakness (frontal opercular syndrome). A combination of sensory disturbance, motor weakness, and nonfluent aphasia suggests that an embolus has occluded the proximal superior division and infarcted large portions of the frontal and parietal cortices (Fig. 32-7). If a fluent (Wernicke's) aphasia occurs without weakness, the inferior division of the MCA supplying the posterior part (temporal cortex) of the dominant hemisphere is probably involved. Jargon speech and an inability to comprehend written and spoken language are prominent features, often accompanied by a contralateral, homonymous superior quadrantanopia. Hemineglect or spatial

www.ketabpezeshki.com (021) 66485457 - 66485438

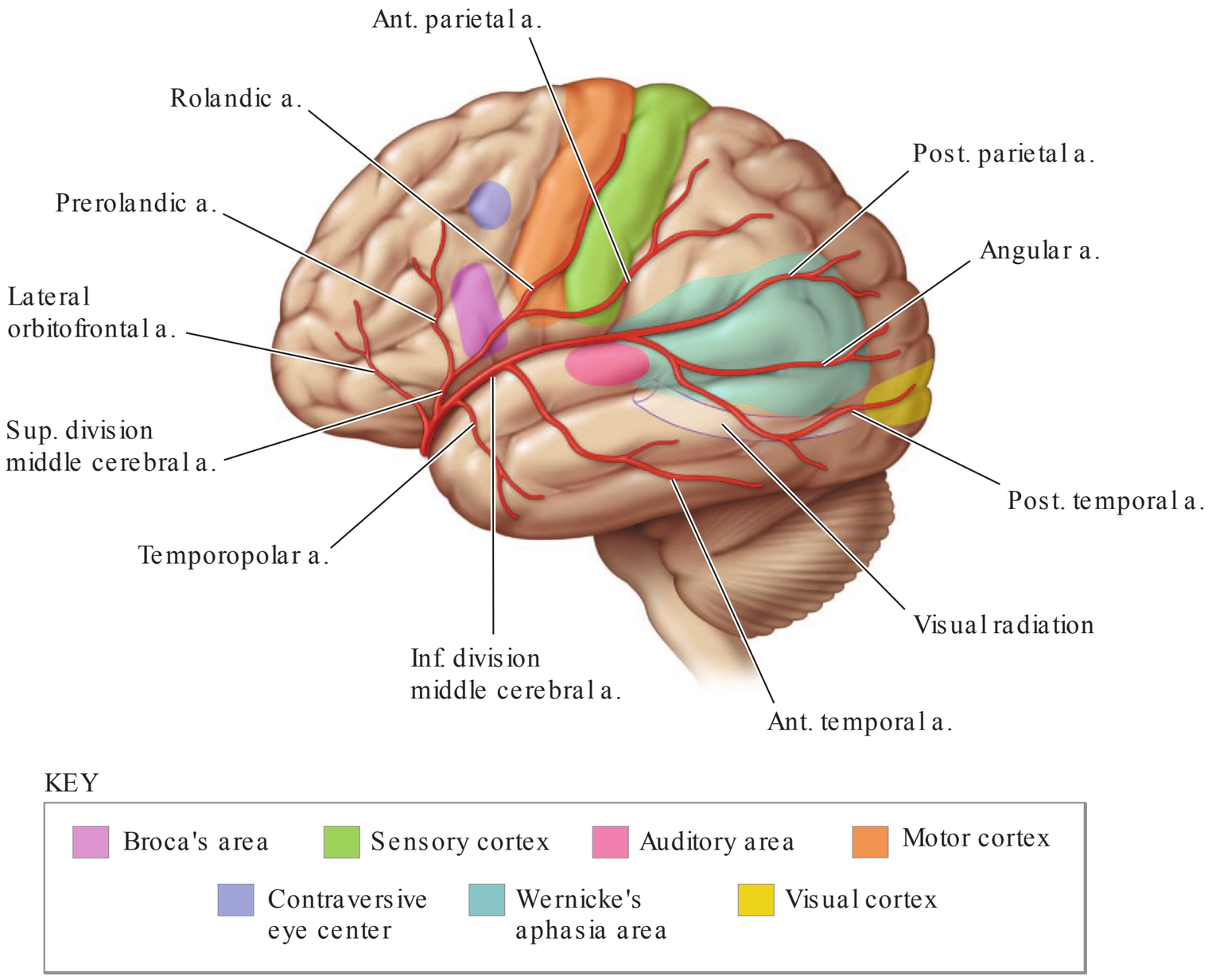


FIGURE 32-7

Diagram of a cerebral hemisphere, lateral aspect, showing the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization. Note the bifurcation of the middle cerebral artery into a superior and inferior division. Signs and symptoms: Structures involved

Paralysis of the contralateral face, arm, and leg; sensory impairment over the same area (pinprick, cotton touch, vibration, position, two-point discrimination, stereognosis, tactile localization, barognosis, cutaneographia): Somatic motor area for face and arm and the fibers descending from the leg area to enter the corona radiata and corresponding somatic sensory system

Motor aphasia: Motor speech area of the dominant hemisphere

Central aphasia, word deafness, anomia, jargon speech, sensory agraphia, acalculia, alexia, finger agnosia, right-left confusion (the last four comprise the Gerstmann syndrome): Central, suprasylvian speech area and parietooccipital cortex of the dominant hemisphere

Conduction aphasia: Central speech area (parietal operculum)

Apractagnosia of the nondominant hemisphere, anosognosia, hemiasomatognosia, unilateral neglect, agnosia for the left half of external space, dressing "apraxia," constructional "apraxia," distortion of visual coordinates, inaccurate localization in the half field, impaired ability to judge distance, upside-down reading, visual illusions (e.g., it may appear that another person walks through a table): Nondominant parietal lobe (area corresponding to speech area in dominant hemisphere); loss of topographic memory is usually due to a nondominant lesion, occasionally to a dominant one

Homonymous hemianopia (often homonymous inferior quadrantanopia): Optic radiation deep to second temporal convolution

Paralysis of conjugate gaze to the opposite side: Frontal contraversive eye field or projecting fibers

agnosia without weakness indicates that the inferior division of the MCA in the nondominant hemisphere is involved.

Occlusion of a lenticulostriate vessel produces small-vessel (lacunar) stroke within the internal capsule (Fig. 32-6). The is produces pure motor stroke or sensory-motor stroke contralateral to the lesion. Ischemia within the genu of the internal capsule causes primarily facial weakness followed by arm and then leg weakness as the ischemia moves posterior within the capsule. Alternatively, the contralateral hand may become ataxic, and dysarthria will be prominent (clumsy hand, dysarthria lacunar syndrome). Lacunar infarction affecting the globus pallidus and putamen often has few clinical signs, but parkinsonism and hemiballismus have been reported.

Anterior cerebral artery

The ACA is divided into two segments: the precommunal (A1) circle of Willis, or stem, which connects the internal carotid artery to the anterior communicating artery, and the postcommunal (A2) segment distal to the anterior communicating artery (Figs. 32-4, 32-6, and 32-8). The A1 segment gives rise to several deep penetrating branches that supply the anterior limb of the internal capsule, the anterior perforate substance, amygdala, anterior hypothalamus, and the inferior part of the head of the caudate nucleus (Fig. 32-6).

www.ketabpezeshki.com (021) 66485457 - 66485438

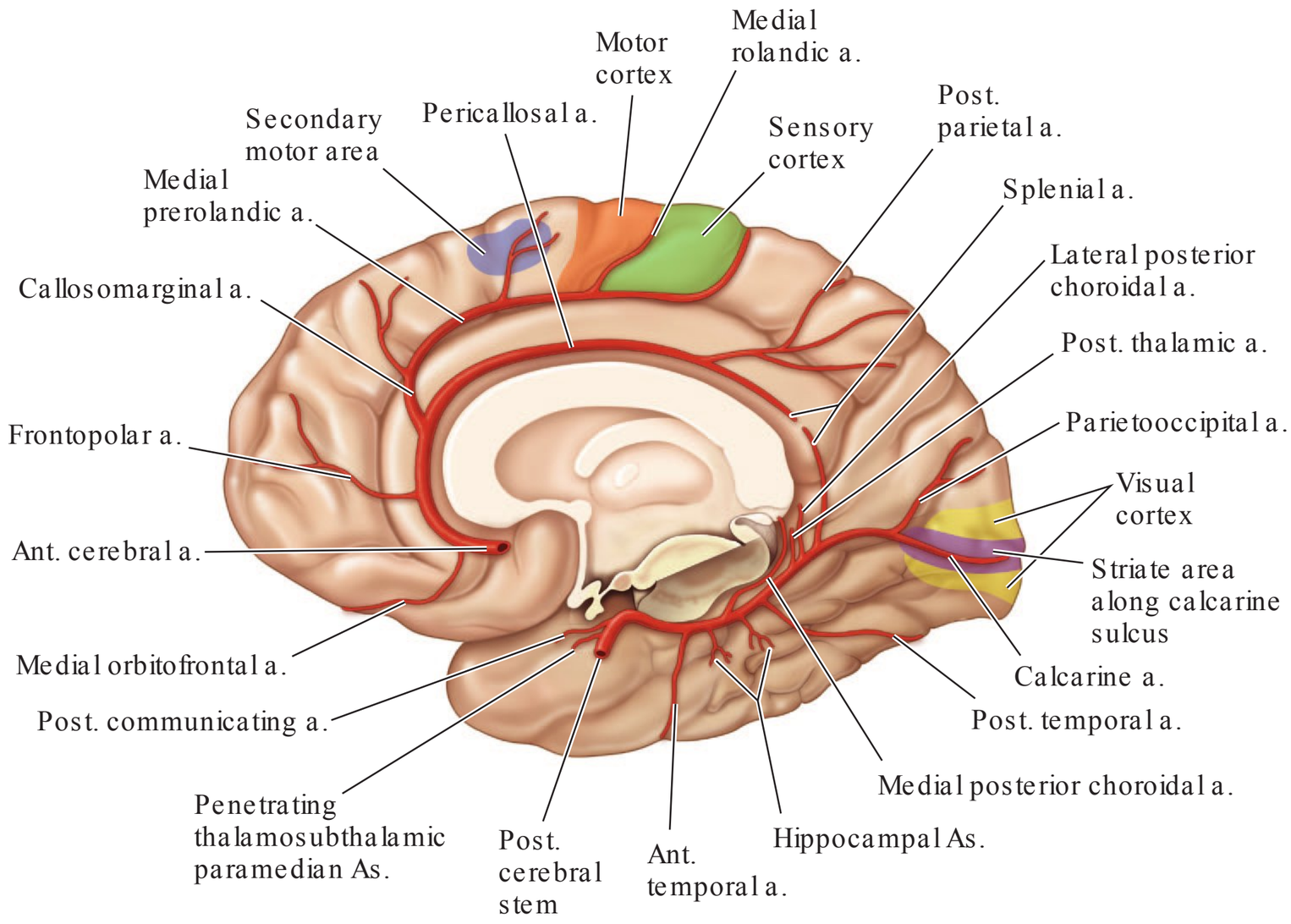


FIGURE 32-8

Diagram of a cerebral hemisphere, medial aspect, showing the branches and distribution of the anterior cerebral artery and the principal regions of cerebral localization.

Signs and symptoms: Structures involved

Paralysis of opposite foot and leg: Motor leg area

A lesser degree of paresis of opposite arm: Arm area of cortex or fibers descending to corona radiata

Cortical sensory loss over toes, foot, and leg: Sensory area for foot and leg

Urinary incontinence: Sensorimotor area in paracentral lobule

Contralateral grasp reflex, sucking reflex, gegenhalten (paratonic rigidity): Medial surface of the posterior frontal lobe; likely supplemental motor area

Abulia (akinetic mutism), slowness, delay, intermittent interruption, lack of spontaneity, whispering, reflex distraction to sights and sounds: Uncertain localization—probably cingulate gyrus and medial inferior portion of frontal, parietal, and temporal lobes

Impairment of gait and stance (gait apraxia): Frontal cortex near leg motor area

Dyspraxia of left limbs, tactile aphasia in left limbs: Corpus callosum

Occlusion of the proximal ACA is usually well tolerated because of collateral flow through the anterior communicating artery and collaterals through the MCA and PCA. Occlusion of a single A2 segment results in the contralateral symptoms noted in Fig. 32-8. If both A2 segments arise from a single anterior cerebral stem (contralateral A1 segment atresia), the occlusion may affect both hemispheres. Profound abulia (a delay in verbal and motor response) and bilateral pyramidal signs with paraparesis or quadriparesis and urinary incontinence result.

Anterior choroidal artery

This artery arises from the internal carotid artery and supplies the posterior limb of the internal capsule and the white matter posterolateral to it, through which pass some of the geniculocalcarine fibers (Fig. 32-9). The complete syndrome of anterior choroidal artery occlusion consists of contralateral hemiplegia, hemianesthesia (hypesthesia), and homonymous hemianopia. However, because this territory is also supplied by penetrating vessels of the proximal MCA and the posterior communicating and posterior choroidal arteries, minimal deficits may occur, and patients frequently recover substantially. Anterior choroidal strokes are usually the result of in situ thrombosis of the vessel, and the vessel is particularly vulnerable to iatrogenic occlusion during surgical clipping of aneurysms arising from the internal carotid artery.

Internal carotid artery

The clinical picture of internal carotid occlusion varies depending on whether the cause of ischemia is propagated thrombus, embolism, or low flow. The cortex supplied by the MCA territory is affected most often. With a competent circle of Willis, occlusion may go unnoticed. If the thrombus propagates up the internal carotid artery into the MCA or embolizes it, symptoms are identical to proximal MCA occlusion (see above). Sometimes there is massive infarction of the entire deep

www.ketabpezeshki.com (021) 66485457 - 66485438

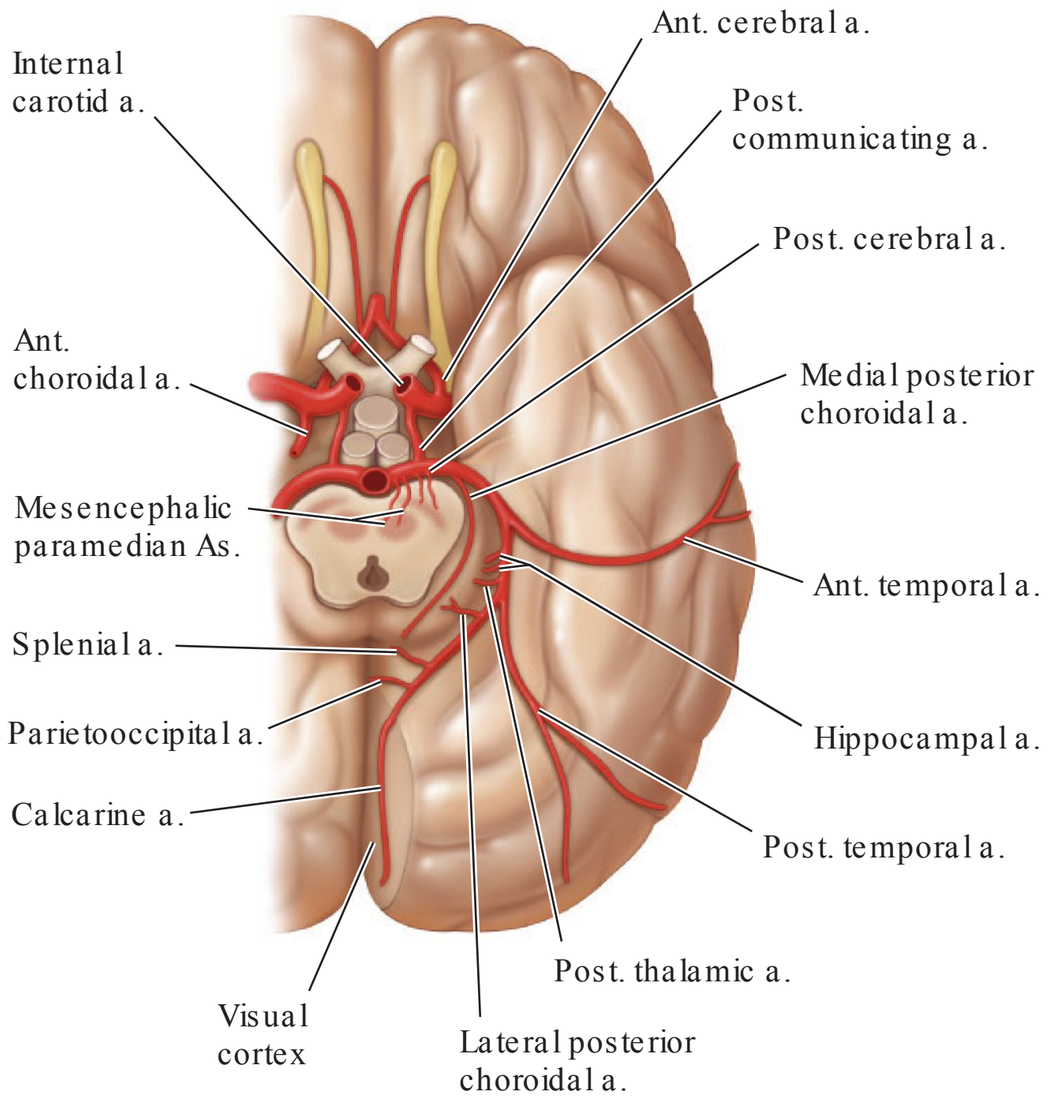


FIGURE 32-9

Inferior aspect of the brain with the branches and distribution of the posterior cerebral artery and the principal anatomic structures shown.

Signs and symptoms: Structures involved

Peripheral territory (see also Fig. 32-12). Homonymous hemianopia (often upper quadrantic): Calcarine cortex or optic radiation nearby. Bilateral homonymous hemianopia, cortical blindness, awareness or denial of blindness; tactile naming, achromatopia (color blindness), failure to see to-and-fro movements, inability to perceive objects not centrally located, apraxia of ocular movements, inability to count or enumerate objects, tendency to run into things that the patient sees and tries to avoid: Bilateral occipital lobe with possibly the parietal lobe involved. Verbal dyslexia without agraphia, color anomia: Dominant calcarine lesion and posterior part of corpus callosum. Memory defect: Hippocampal lesion bilaterally or on the dominant side only. Topographic disorientation and prosopagnosia: Usually with lesions of nondominant, calcarine, and lingual gyrus. Simultanagnosia, hemivisual neglect: Dominant visual cortex, contralateral hemisphere. Unformed visual hallucinations, peduncular hallucinosis, metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, central photophobia: Calcarine cortex. Complex hallucinations: Usually nondominant hemisphere.

Central territory. Thalamic syndrome: sensory loss (all modalities), spontaneous pain and dysesthesias, choreoathetosis, intention tremor, spasms of hand, mild hemiparesis: Posteroventral nucleus of thalamus; involvement of the adjacent subthalamus body or its afferent tracts. Thalamoperforate syndrome: crossed cerebellar ataxia with ipsilateral third nerve palsy (Claude's syndrome): Dentatothalamic tract and issuing third nerve. Weber's syndrome: third nerve palsy and contralateral hemiplegia: Third nerve and cerebral peduncle. Contralateral hemiplegia: Cerebral peduncle. Paralysis or paresis of vertical eye movement, skew deviation, sluggish pupillary responses to light, slight miosis and ptosis (retraction nystagmus and "tucking" of the eyelids may be associated): Supranuclear fibers to third nerve, interstitial nucleus of Cajal, nucleus of Darkschewitsch, and posterior commissure. Contralateral rhythmic, ataxic action tremor; rhythmic postural or "holding" tremor (rubral tremor): Dentatothalamic tract.

white matter and cortical surface. When the origins of both the ACA and MCA are occluded at the top of the carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and aphasia or anosognosia. When the PCA arises from the internal carotid artery (a configuration called a fetal posterior cerebral artery), it may also become occluded and give rise to symptoms referable to its peripheral territory (Figs. 32-8 and 32-9).

In addition to supplying the ipsilateral brain, the internal carotid artery perfuses the optic nerve and retina via the ophthalmic artery. In ~25% of symptomatic internal carotid disease, recurrent transient monocular blindness (amaurosis fugax) warns of the lesion. Patients typically describe a horizontal shade that sweeps down or up across the field of vision. T ey may also complain that their vision was blurred in that eye or that the upper or lower half of vision disappeared. In most cases, these symptoms last only a few minutes. Rarely, ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

A high-pitched prolonged carotid bruit fading into diastole is often associated with tightly stenotic lesions. As the stenosis grows tighter and flow distal to the stenosis becomes reduced, the bruit becomes fainter and may disappear when occlusion is imminent.

www.ketabpezeshki.com (021) 66485457 - 66485438

Common carotid artery

All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery. Jaw claudication may result from low flow in the external carotid branches. Bilateral common carotid artery occlusions at their origin may occur in Takayasu's arteritis.

Stroke within the posterior circulation

The posterior circulation is composed of the paired vertebral arteries, the basilar artery, and the paired posterior cerebral arteries. The vertebral arteries join to form the basilar artery at the pontomedullary junction. The basilar artery divides into two posterior cerebral arteries in the interpeduncular fossa (Figs. 32-4, 32-8, and 32-9). These major arteries give rise to long and short circumferential branches and to smaller deep penetrating branches that supply the cerebellum, medulla, pons, midbrain, subthalamus, thalamus, hippocampus, and medial temporal and occipital lobes. Occlusion of each vessel produces its own distinctive syndrome.

Posterior cerebral artery

In 75% of cases, both PCAs arise from the bifurcation of the basilar artery; in 20%, one has its origin from the ipsilateral internal carotid artery via the posterior communicating artery; in 5%, both originate from the respective ipsilateral internal carotid arteries (Figs. 32-8 and 32-9). The precommunal, or P1, segment of the true posterior cerebral artery is atretic in such cases.

PCA syndromes usually result from atheroma formation or emboli that lodge at the top of the basilar artery; posterior circulation disease may also be caused by dissection of either vertebral artery or fibromuscular dysplasia.

Two clinical syndromes are commonly observed with occlusion of the PCA: (1) P1 syndrome: midbrain, subthalamic, and thalamic signs, which are due to disease of the proximal P1 segment of the PCA or its penetrating branches (thalamogeniculate, Percheron, and posterior choroidal arteries); and (2) P2 syndrome: cortical temporal and occipital lobe signs, due to occlusion of the P2 segment distal to the junction of the PCA with the posterior communicating artery.

P1 syndromes

Infarction usually occurs in the ipsilateral subthalamus and medial thalamus and in the ipsilateral cerebral peduncle and midbrain (Figs. 32-9 and 32-14). A third nerve palsy with contralateral ataxia (Claude's syndrome) or with contralateral hemiplegia (Weber's syndrome) may result. The ataxia indicates involvement of the red nucleus or dentatorubrothalamic tract; the hemiplegia is localized to the cerebral peduncle (Fig. 32-14). If the subthalamic nucleus is involved, contralateral hemiballismus may occur. Occlusion of the artery of Percheron produces paresis of upward gaze and drowsiness and often abulia. Extensive infarction in the midbrain and subthalamus occurring with bilateral proximal PCA occlusion presents as coma, unreactive pupils, bilateral pyramidal signs, and decerebrate rigidity.

Occlusion of the penetrating branches of thalamic and thalamogeniculate arteries produces less extensive thalamic and thalamocapsular lacunar syndromes. The thalamic Déjérine-Roussy syndrome consists of contralateral hemisensory loss followed later by an agonizing, searing or burning pain in the affected areas. It is persistent and responds poorly to analgesics. Anticonvulsants (carbamazepine or gabapentin) or tricyclic antidepressants may be beneficial.

P2 syndromes

(Figs. 32-8 and 32-9) Occlusion of the distal PCA causes infarction of the medial temporal and occipital lobes. Contralateral homonymous hemianopia with macula sparing is the usual manifestation. Occasionally, only the upper quadrant of visual field is involved. If the visual association areas are spared and only the calcarine cortex is involved, the patient may be aware of visual defects. Medial temporal lobe and hippocampal involvement may cause an acute disturbance in memory, particularly if it occurs in the dominant hemisphere. The defect usually clears because memory has bilateral representation. If the dominant hemisphere is affected and the infarct extends to involve the splenium of the corpus callosum, the patient may demonstrate alexia without agraphia. Visual agnosia for faces, objects, mathematical symbols, and colors and anomia with paraphasic errors (amnestic aphasia) may also occur, even without callosal involvement. Occlusion of the posterior cerebral artery can produce peduncular hallucinosis (visual hallucinations of brightly colored scenes and objects).

Bilateral infarction in the distal PCAs produces cortical blindness (blindness with preserved pupillary light reaction). The patient is often unaware of the blindness or may even deny it (Anton's syndrome). Tiny islands of vision may persist, and the patient may report that vision fluctuates as images are captured in the preserved portions. Rarely, only peripheral vision is lost and central vision is spared, resulting in "gun-barrel" vision. Bilateral visual association area lesions may result in Balint's syndrome, a disorder of the orderly visual scanning of the environment **(Chap. 22)**, usually resulting from infarctions secondary to low flow in the "watershed" between the distal PCA and MCA territories, as occurs after cardiac arrest. Patients may experience persistence of a visual image for several minutes despite gazing at another scene (palinopsia) or an inability to

www.ketabpezeshki.com (021) 66485457 - 66485438

synthesize the whole of an image (asimultanagnosia). Embolic occlusion of the top of the basilar artery can produce any or all of the central or peripheral territory symptoms. The hallmark is the sudden onset of bilateral signs, including ptosis, pupillary asymmetry or lack of reaction to light, and somnolence.

Vertebral and posterior inferior cerebellar arteries

The vertebral artery, which arises from the innominate artery on the right and the subclavian artery on the left, consists of four segments. The first (V1) extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen. The second segment (V2) traverses the vertebral foramina from C6 to C2. The third (V3) passes through the transverse foramen and circles around the arch of the atlas to pierce the dura at the foramen magnum. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery; only the fourth segment gives rise to branches that supply the brainstem and cerebellum. The posterior inferior cerebellar artery (PICA) in its proximal segment supplies the lateral medulla and, in its distal branches, the inferior surface of the cerebellum.

Atherothrombotic lesions have a predilection for V1 and V4 segments of the vertebral artery. The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli; collateral flow from the contralateral vertebral artery or the ascending cervical, thyrocervical, or occipital arteries is usually sufficient to prevent low-flow TIAs or stroke. When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient (Figs. 32-4 and 32-9). In this setting, low-flow TIAs may occur, consisting of syncope, vertigo, and alternating hemiplegia; this state also sets the stage for thrombosis. Disease of the distal fourth segment of the vertebral artery can promote thrombus formation manifest as embolism or with propagation as basilar artery thrombosis. Stenosis proximal to the origin of the PICA can threaten the lateral medulla and posterior inferior surface of the cerebellum.

If the subclavian artery is occluded proximal to the origin of the vertebral artery, there is a reversal in the direction of blood flow in the ipsilateral vertebral artery. Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulation TIAs, or "subclavian steal."

Although atheromatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection, fibromuscular dysplasia, and, rarely, encroachment by osteophytic spurs within the vertebral foramina.

Embolic occlusion or thrombosis of a V4 segment causes ischemia of the lateral medulla. The constellation of vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the lateral medullary (or Wallenberg's) syndrome **(Fig. 32-10)**. Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. Hemiparesis is not a *feature of* vertebral artery occlusion; however, quadriparesis may result *from* occlusion *of* the anterior spinal artery.

Rarely, a medial medullary syndrome occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. If the medial lemniscus and emerging hypoglossal nerve fibers are involved, contralateral loss of joint position sense and ipsilateral tongue weakness occur.

Cerebellar infarction with edema can lead to sudden respiratory arrest due to raised ICP in the posterior fossa. Drowsiness, Babinski signs, dysarthria, and bifacial weakness may be absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, headache, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome. Separating these symptoms from those of viral labyrinthitis can be a challenge, but headache, neck stiffness, and unilateral dysmetria favor stroke.

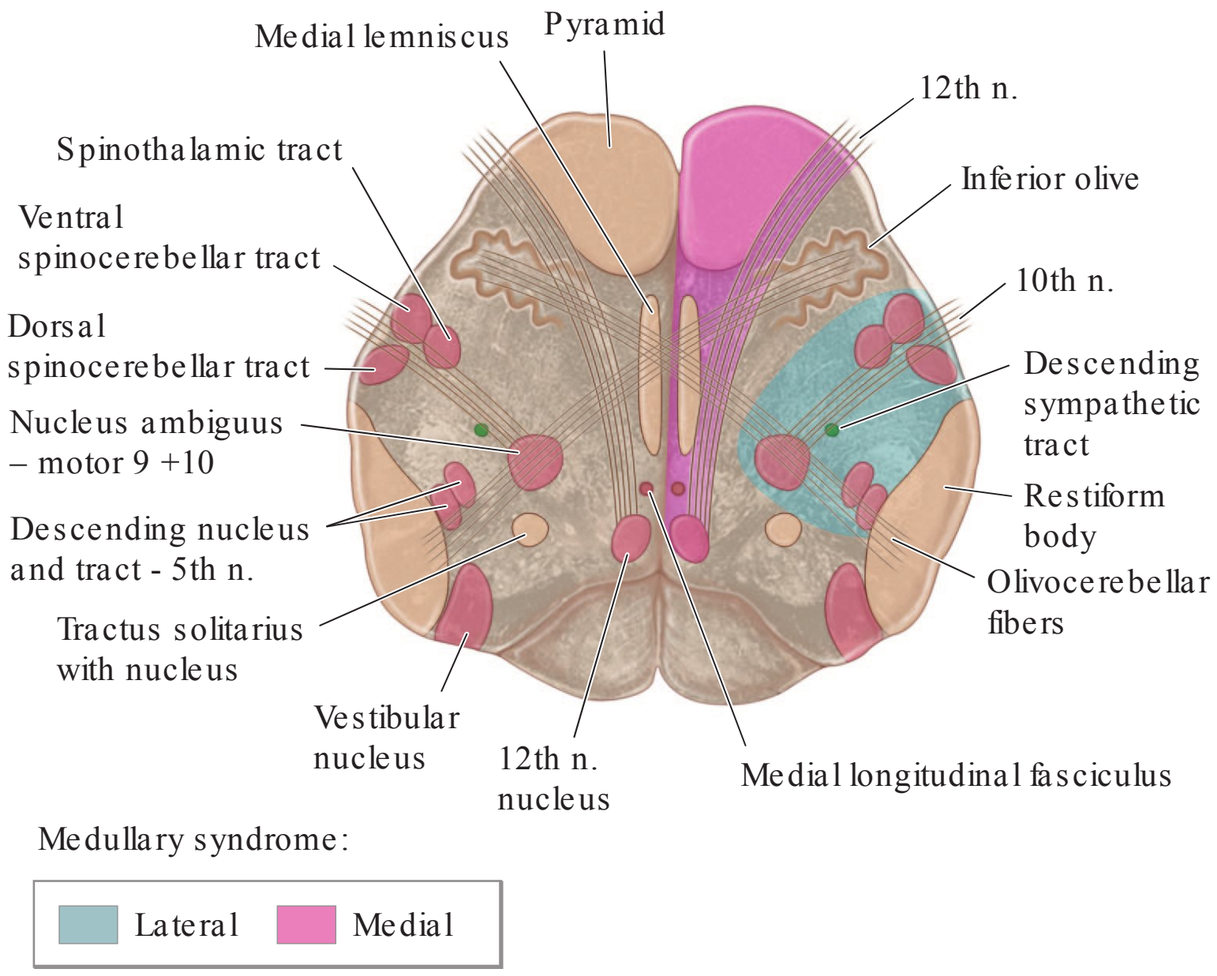
Basilar artery

Branches of the basilar artery supply the base of the pons and superior cerebellum and fall into three groups: (1) paramedian, 7–10 in number, which supply a wedge of pons on either side of the midline; (2) short circumferential, 5–7 in number, that supply the lateral two-thirds of the pons and middle and superior cerebellar peduncles; and (3) bilateral long circumferential (superior cerebellar and anterior inferior cerebellar arteries), which course around the pons to supply the cerebellar hemispheres.

Atheromatous lesions can occur anywhere along the basilar trunk but are most frequent in the proximal basilar and distal vertebral segments. Typically, lesions occlude either the proximal basilar and one or both vertebral arteries. The clinical picture varies depending on the availability of retrograde collateral flow from the posterior communicating arteries. Rarely, dissection of a vertebral artery may involve the basilar artery and, depending on the location of true and false lumen, may produce multiple penetrating artery strokes.

Although atherothrombosis occasionally occludes the distal portion of the basilar artery, emboli from the heart or proximal vertebral or basilar segments are more commonly responsible for "top of the basilar" syndromes.

www.ketabpezeshki.com (021) 66485457 - 66485438



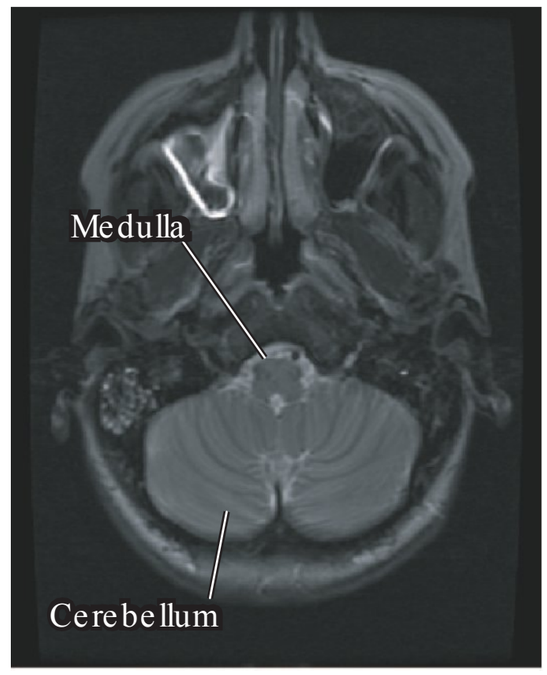


FIGURE 32-10

Axial section at the level of the medulla, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Note that in Figs. 32-10 through 32-14, all drawings are oriented with the dorsal surface at the bottom, matching the orientation of the brainstem that is commonly seen in all modern neuroimaging studies. Approximate regions involved in medial and lateral medullary stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial medullary syndrome (occlusion of vertebral artery or of branch of vertebral or lower basilar artery)
   On side of lesion
   Paralysis with atrophy of one-half half the tongue: Ipsilateral twelfth nerve
   On side opposite lesion
   Paralysis of arm and leg, sparing face; impaired tactile and proprioceptive sense over one-half the body: Contralateral pyramidal tract and medial lemniscus
2. Lateral medullary syndrome (occlusion of any of five vessels may be responsible—vertebral, posterior inferior cerebellar, superior, middle, or inferior lateral medullary arteries)
   On side of lesion
   Pain, numbness, impaired sensation over one-half the face: Descending tract and nucleus fifth nerve
   Ataxia of limbs, falling to side of lesion: Uncertain—restiform body, cerebellar hemisphere, cerebellar fibers, spinocerebellar tract (?)
   Nystagmus, diplopia, oscillopsia, vertigo, nausea, vomiting: Vestibular nucleus
   Horner's syndrome (miosis, ptosis, decreased sweating): Descending sympathetic tract
   Dysphagia, hoarseness, paralysis of palate, paralysis of vocal cord, diminished gag reflex: Issuing fibers ninth and tenth nerves
   Loss of taste: Nucleus and tractus solitarius
   Numbness of ipsilateral arm, trunk, or leg: Cuneate and gracile nuclei
   Weakness of lower face: Genuflected upper motor neuron fibers to ipsilateral facial nucleus
   On side opposite lesion
   Impaired pain and thermal sense over half the body, sometimes face: Spinothalamic tract
3. Total unilateral medullary syndrome (occlusion of vertebral artery): Combination of medial and lateral syndromes
4. Lateral pontomedullary syndrome (occlusion of vertebral artery): Combination of lateral medullary and lateral inferior pontine syndrome
5. Basilar artery syndrome (the syndrome of the lone vertebral artery is equivalent): A combination of the various brainstem syndromes plus those arising in the posterior cerebral artery distribution.
   Bilateral long tract signs (sensory and motor; cerebellar and peripheral cranial nerve abnormalities): Bilateral long tract; cerebellar and peripheral cranial nerves
   Paralysis or weakness of all extremities, plus all bulbar musculature: Corticobulbar and corticospinal tracts bilaterally

Because the brainstem contains many structures in close apposition, a diversity of clinical syndromes may emerge with ischemia, reflecting involvement of the corticospinal and corticobulbar tracts, ascending sensory tracts, and cranial nerve nuclei (Figs. 32-11, 32-12, 32-13, and 32-14).

The symptoms of transient ischemia or infarction in the territory of the basilar artery often do not indicate whether the basilar artery itself or one of its branches is diseased, yet this distinction has important implications for therapy. The picture of complete basilar occlusion, however, is easy to recognize as a constellation of bilateral long

www.ketabpezeshki.com (021) 66485457 - 66485438

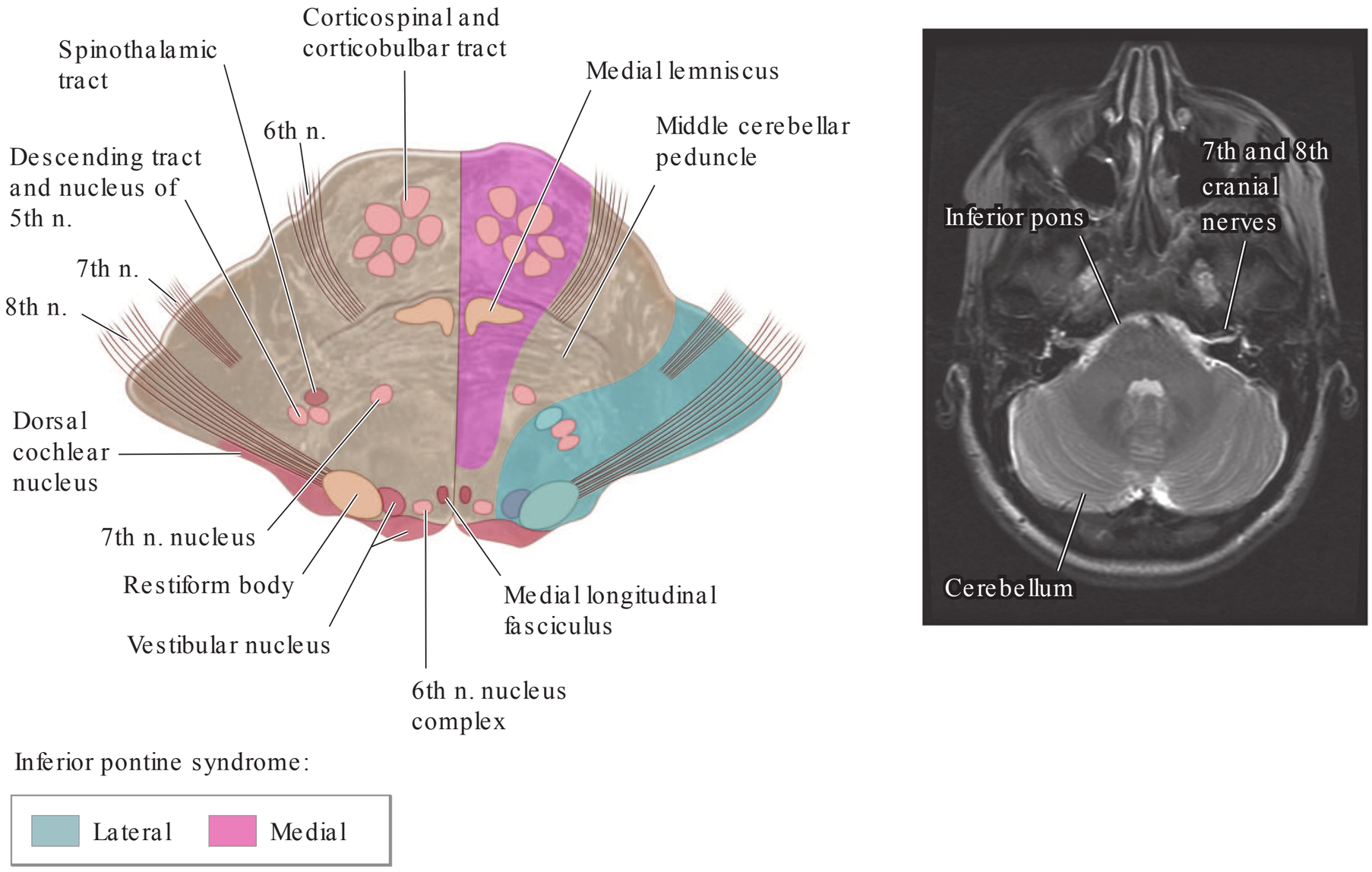


FIGURE 32-11

Axial section at the level of the inferior pons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral inferior pontine stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial inferior pontine syndrome (occlusion of paramedian branch of basilar artery)
   On side of lesion
      Paralysis of conjugate gaze to side of lesion (preservation of convergence): Center *f*or conjugate lateral gaze
   Nystagmus: Vestibular nucleus
      Ataxia of limbs and gait: Likely middle cerebellar peduncle
      Diplopia on lateral gaze: Abducens nerve
   On side opposite lesion
      Paralysis of face, arm, and leg: Corticobulbar and corticospinal tract in lower pons
      Impaired tactile and proprioceptive sense over one-half of the body: Medial lemniscus
2. Lateral inferior pontine syndrome (occlusion of anterior inferior cerebellar artery)
   On side of lesion
      Horizontal and vertical nystagmus, vertigo, nausea, vomiting, oscillopsia: Vestibular nerve or nucleus
      Facial paralysis: Seventh nerve
   Paralysis of conjugate gaze to side of lesion: Center *f*or conjugate lateral gaze
      Deafness, tinnitus: Auditory nerve or cochlear nucleus
      Ataxia: Middle cerebellar peduncle and cerebellar hemisphere
      Impaired sensation over face: Descending tract and nucleus *fif*th nerve
   On side opposite lesion
      Impaired pain and thermal sense over one-half the body (may include face): Spinothalamic tract

tract signs (sensory and motor) with signs *of* cranial nerve and cerebellar dys*f*unction. A "locked-in" state of preserved consciousness with quadriplegia and cranial nerve signs suggests complete pontine and lower midbrain infarction. T e therapeutic goal is to identify impending basilar occlusion before devastating infarction occurs. A series of TIAs and a slowly progressive, fluctuating stroke are extremely significant, because they often herald an atherothrombotic occlusion of the distal vertebral or proximal basilar artery.

TIAs in the proximal basilar distribution may produce vertigo (often described by patients as "swimming," "swaying," "moving," "unsteadiness," or "lightheadedness"). Other symptoms that warn of basilar thrombosis include diplopia, dysarthria, facial or circumoral numbness, and hemisensory symptoms. In general, symptoms of basilar branch TIAs affect one side of the brainstem, whereas symptoms of basilar artery TIAs usually affect both sides, although a "herald" hemiparesis has been emphasized as an initial symptom of basilar occlusion. Most often, TIAs, whether due to impending occlusion of the basilar artery or a basilar branch, are short lived (5–30 min) and repetitive, occurring several times a day. T e pattern suggests intermittent reduction of flow. Many neurologists treat with heparin to prevent clot propagation.

Atherothrombotic occlusion of the basilar artery with infarction usually causes bilateral brainstem signs. A gaze paresis or internuclear ophthalmoplegia associated with

www.ketabpezeshki.com (021) 66485457 - 66485438

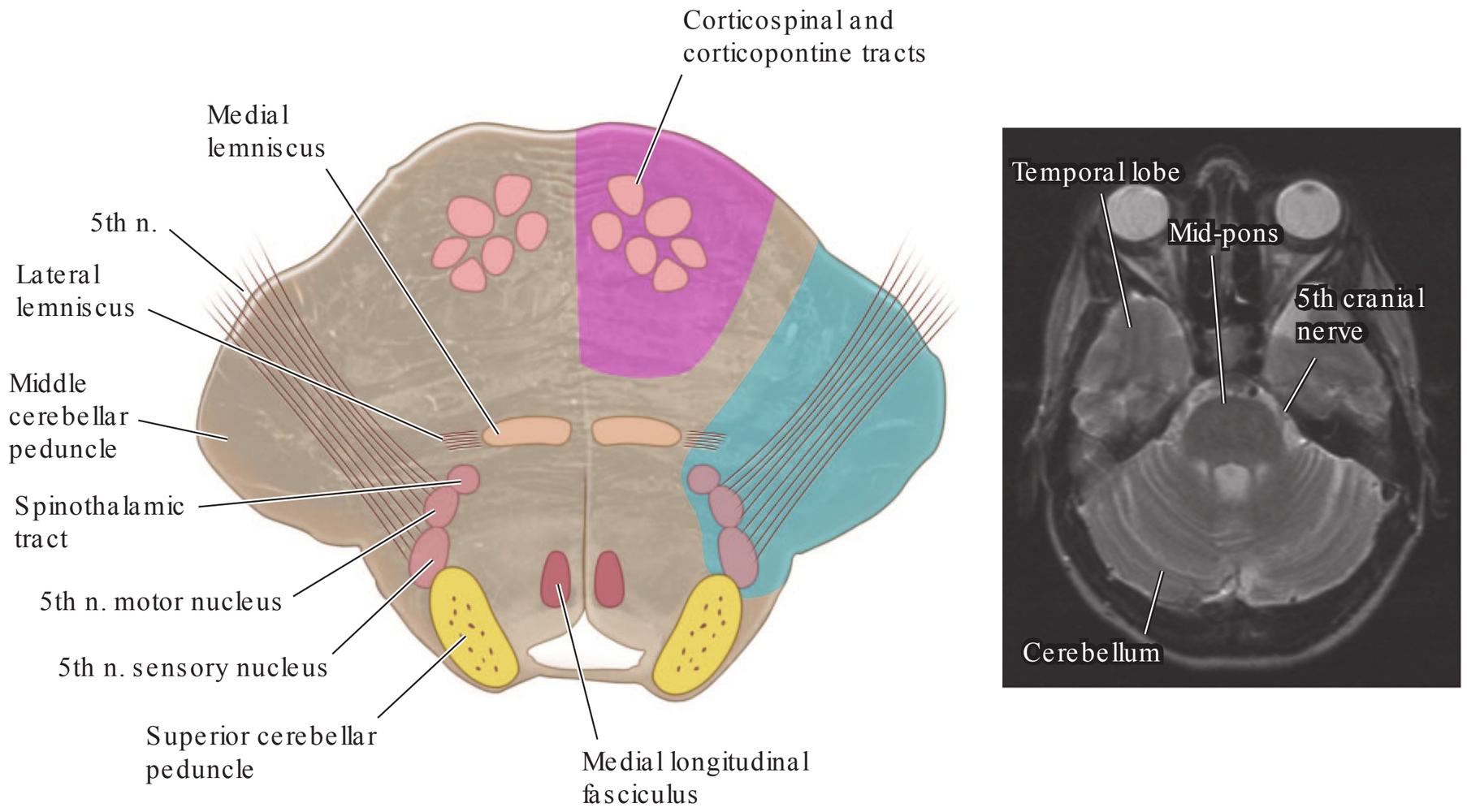


FIGURE 32-12

Axial section at the level of the midpons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral midpontine stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial midpontine syndrome (paramedian branch of midbasilar artery)
   On side of lesion
   Ataxia of limbs and gait (more prominent in bilateral involvement): Pontine nuclei
   On side opposite lesion
   Paralysis of face, arm, and leg: Corticobulbar and corticospinal tract
   Variable impaired touch and proprioception when lesion extends posteriorly: Medial lemniscus
2. Lateral midpontine syndrome (short circumferential artery)
   On side of lesion
   Ataxia of limbs: Middle cerebellar peduncle
   Paralysis of muscles of mastication: Motor fibers or nucleus of fifth nerve
   Impaired sensation over side of face: Sensory fibers or nucleus of fifth nerve
   On side opposite lesion
   Impaired pain and thermal sense on limbs and trunk: Spinothalamic tract

ipsilateral hemiparesis may be the only manifestation of bilateral brainstem ischemia. More often, unequivocal signs of bilateral pontine disease are present. Complete basilar thrombosis carries a high mortality.

Occlusion of a branch of the basilar artery usually causes unilateral symptoms and signs involving motor, sensory, and cranial nerves. As long as symptoms remain unilateral, concern over pending basilar occlusion should be reduced.

Occlusion of the superior cerebellar artery results in severe ipsilateral cerebellar ataxia, nausea and vomiting, dysarthria, and contralateral loss of pain and temperature sensation over the extremities, body, and face (spino- and trigeminothalamic tract). Partial deafness, ataxic tremor of the ipsilateral upper extremity, Horner's syndrome, and palatal myoclonus may occur rarely. Partial syndromes occur frequently (Fig. 32-13). With large strokes, swelling and mass effects may compress the midbrain or produce hydrocephalus; these symptoms may evolve rapidly. Neurosurgical intervention may be lifesaving in such cases.

Occlusion of the anterior inferior cerebellar artery produces variable degrees of infarction because the size of this artery and the territory it supplies vary inversely with those of the PICA. The principal symptoms include: (1) ipsilateral deafness, facial weakness, vertigo, nausea and vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner's syndrome, and paresis of conjugate lateral gaze; and (2) contralateral loss of pain and temperature sensation. An occlusion close to the origin of the artery may cause corticospinal tract signs (Fig. 32-11).

Occlusion of one of the short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and middle or superior cerebellar

www.ketabpezeshki.com (021) 66485457 - 66485438

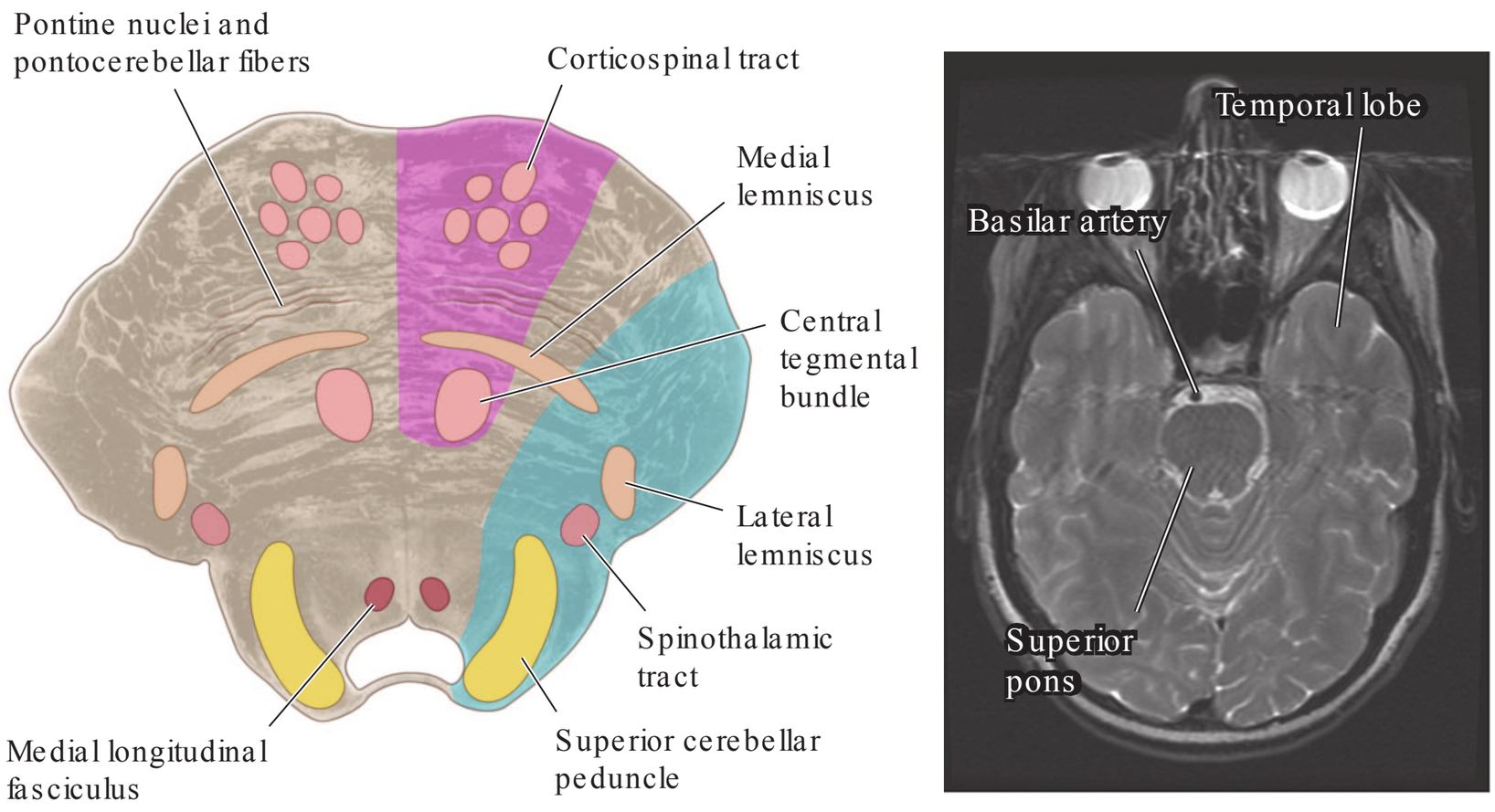


FIGURE 32-13

Axial section at the level of the superior pons, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral superior pontine stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial superior pontine syndrome (paramedian branches of upper basilar artery)
   On side of lesion
   Cerebellar ataxia (probably): Superior and/or middle cerebellar peduncle
   Internuclear ophthalmoplegia: Medial longitudinal fasciculus
   Myoclonic syndrome, palate, pharynx, vocal cords, respiratory apparatus, face, oculomotor apparatus, etc.: Localization uncertain—central tegmental bundle, dentate projection, inferior olivary nucleus
   On side opposite lesion
   Paralysis of face, arm, and leg: Corticobulbar and corticospinal tract
   Rarely touch, vibration, and position are affected: Medial lemniscus
2. Lateral superior pontine syndrome (syndrome of superior cerebellar artery)
   On side of lesion
   Ataxia of limbs and gait, falling to side of lesion: Middle and superior cerebellar peduncles, superior surface of cerebellum, dentate nucleus
   Dizziness, nausea, vomiting; horizontal nystagmus: Vestibular nucleus
   Paresis of conjugate gaze (ipsilateral): Pontine contralateral gaze
   Skew deviation: Uncertain
   Miosis, ptosis, decreased sweating over face (Horner's syndrome): Descending sympathetic fibers
   Tremor: Localization unclear—Dentate nucleus, superior cerebellar peduncle
   On side opposite lesion
   Impaired pain and thermal sense on face, limbs, and trunk: Spinothalamic tract
   Impaired touch, vibration, and position sense, more in leg than arm (there is a tendency to incongruity of pain and touch deficits): Medial lemniscus (lateral portion)

peduncle, whereas occlusion of one of the paramedian branches affects a wedge-shaped area on either side of the medial pons (Figs. 32-11 through 32-13).

IMAGING STUDIES

See also Chap. 4.

CT Scans

CT radiographic images identify or exclude hemorrhage as the cause of stroke, and they identify extraparenchymal hemorrhages, neoplasms, abscesses, and other conditions masquerading as stroke. Brain CT scans obtained in the first several hours after an infarction generally show no abnormality, and the infarct may not be seen reliably for 24–48 h. CT may fail to show small ischemic strokes in the posterior fossa because of bone artifact; small infarcts on the cortical surface may also be missed.

Contrast-enhanced CT scans add specificity by showing contrast enhancement of subacute infarcts and allow visualization of venous structures. Coupled with multidetector scanners, CT angiography (CTA) can be performed with administration of IV iodinated

www.ketabpezeshki.com (021) 66485457 - 66485438

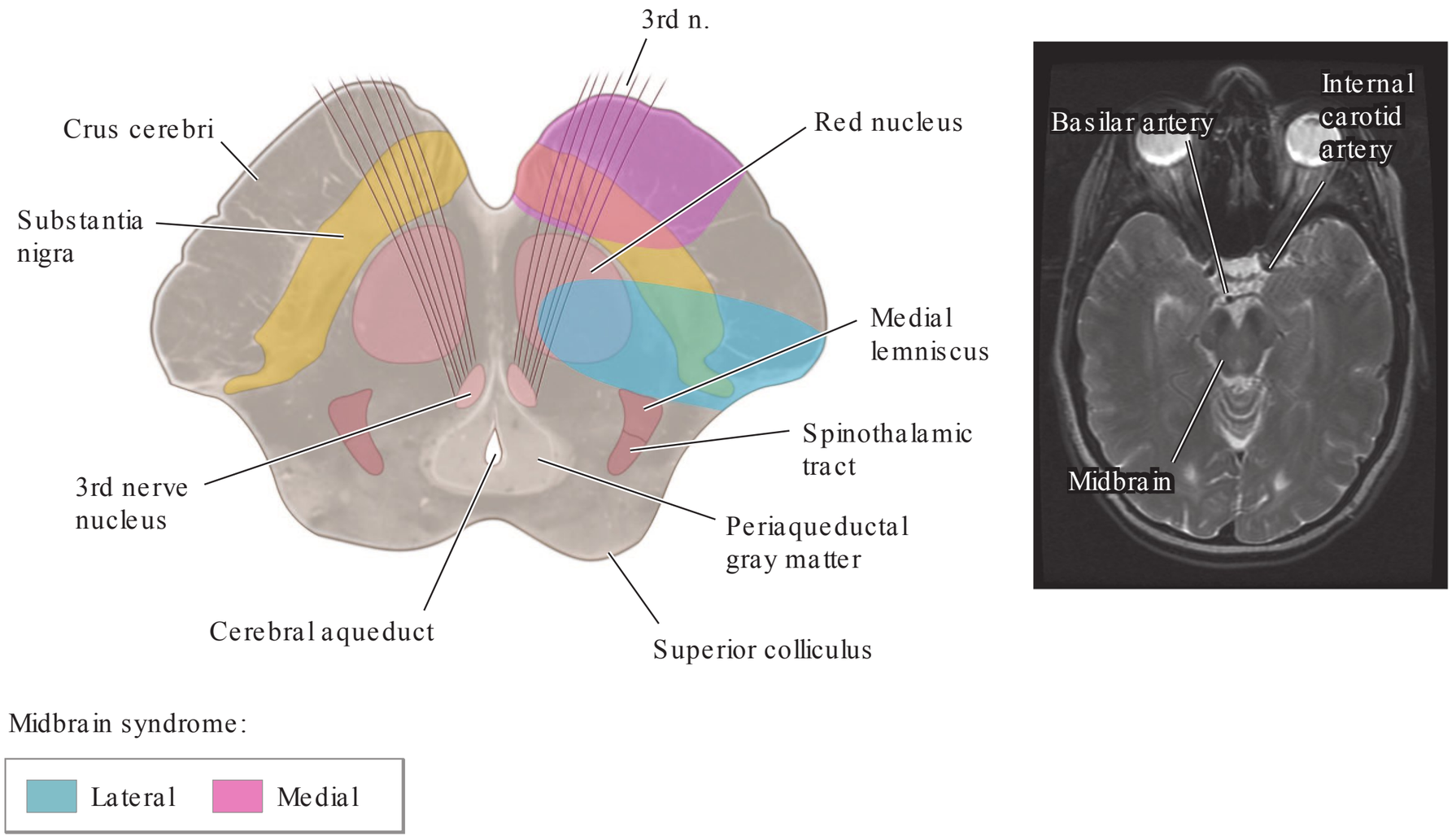


FIGURE 32-14

Axial section at the level of the midbrain, depicted schematically on the left, with a corresponding magnetic resonance image on the right. Approximate regions involved in medial and lateral midbrain stroke syndromes are shown.

Signs and symptoms: Structures involved

1. Medial midbrain syndrome (paramedian branches of upper basilar and proximal posterior cerebral arteries)
   On side of lesion
   Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: Third nerve *fi*bers
   On side opposite lesion
   Paralysis of face, arm, and leg: Corticobulbar and corticospinal tract descending in crus cerebri
2. Lateral midbrain syndrome (syndrome of small penetrating arteries arising from posterior cerebral artery)
   On side of lesion
   Eye "down and out" secondary to unopposed action of fourth and sixth cranial nerves, with dilated and unresponsive pupil: Third nerve *fi*bers and/or third nerve nucleus
   On side opposite lesion
   Hemiataxia, hyperkinesias, tremor: Red nucleus, dentatorubrothalamic pathway

contrast allowing visualization of the cervical and intracranial arteries, intracranial veins, aortic arch, and even the coronary arteries in one imaging session. Carotid disease and intracranial vascular occlusions are readily identified with this method (Fig. 32-3). After an IV bolus of contrast, deficits in brain perfusion produced by vascular occlusion can also be demonstrated **(Fig. 32-15)** and used to predict the region of infarcted brain and the brain at risk of further infarction (i.e., the ischemic penumbra, see "Pathophysiology of Ischemic Stroke" above). CT imaging is also sensitive for detecting SAH (although by itself does not rule it out), and CTA can readily identify intracranial aneurysms **(Chap. 33)**. Because of its speed and wide availability, noncontrast head CT is the imaging modality of choice in patients with acute stroke (Fig. 32-1), and CTA and CT perfusion imaging may also be useful and convenient adjuncts.

MRI

MRI reliably documents the extent and location of infarction in all areas of the brain, including the posterior fossa and cortical surface. It also identifies intracranial hemorrhage and other abnormalities and, using special sequences, can be as sensitive as CT for detecting acute intracerebral hemorrhage. MRI scanners with magnets of higher field strength produce more reliable and precise images. Diffusion-weighted imaging is more sensitive for early brain infarction than standard MR sequences or CT **(Fig. 32-16)**, as is fluid-attenuated inversion recovery (FLAIR) imaging **(Chap. 4)**. Using IV administration of gadolinium contrast, MR perfusion studies can be performed. Brain regions showing poor perfusion but no abnormality on diffusion provide, compared to CT, an equivalent measure of the ischemic penumbra. MR angiography

www.ketabpezeshki.com (021) 66485457 - 66485438

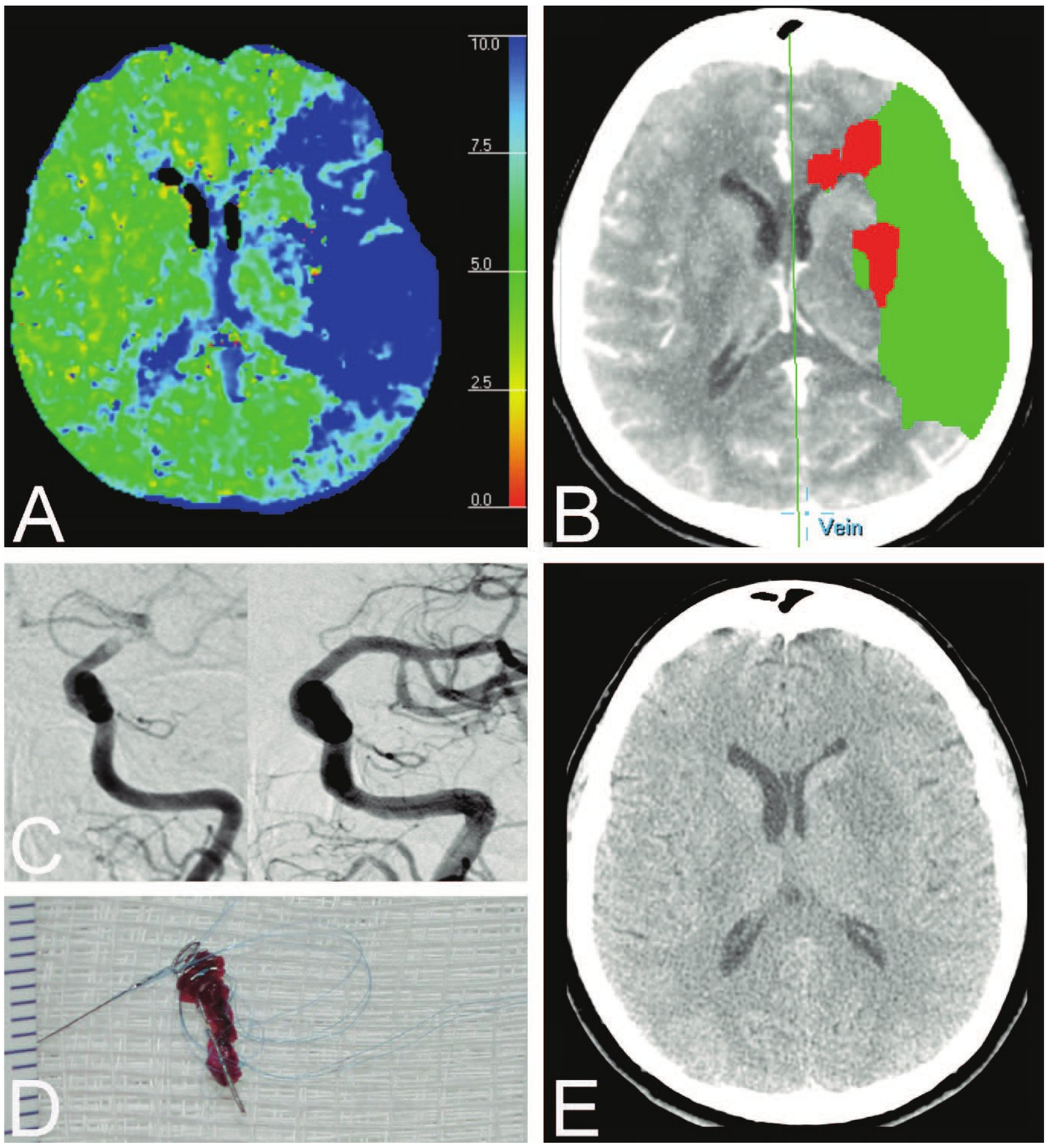


FIGURE 32-15
Acute left middle cerebral artery (MCA) stroke with right hemiplegia but preserved language. A. Computed tomography (CT) perfusion mean-transit time map showing delayed perfusion of the left MCA distribution (blue). B. Predicted region of infarct (red) and penumbra (green) based on CT perfusion data. C. Conventional angiogram showing occlusion of the left internal carotid–MCA bifurcation (left panel), and revascularization of the vessels following successful thrombectomy 8 h after stroke symptom onset (right panel). D. The clot removed with a thrombectomy device (L5, Concentric Medical, Inc.). E. CT scan of the brain 2 days later; note infarction in the region predicted in B but preservation of the penumbral region by successful revascularization.

is highly sensitive for stenosis of extracranial internal carotid arteries and of large intracranial vessels. With higher degrees of stenosis, MR angiography tends to overestimate the degree of stenosis when compared to conventional x-ray angiography. MRI with fat saturation is an imaging sequence used to visualize extra or intracranial arterial dissection. T is sensitive technique images clotted blood within the dissected vessel wall. Iron-sensitive imaging (ISI) is helpful to detect cerebral microbleeds that may be present in cerebral amyloid angiopathy and other hemorrhagic disorders.

MRI is more expensive and time consuming than CT and less readily available. Claustrophobia and the logistics of imaging acutely critically ill patients also limit its application. Most acute stroke protocols use CT because of these limitations. However, MRI is useful outside the acute period by more clearly defining the extent of tissue injury and discriminating new from old regions of brain infarction. MRI may have particular utility in patients with TIA, because it is also more likely to identify new infarction, which is a strong predictor of subsequent stroke.

Cerebral angiography

Conventional x-ray cerebral angiography is the gold standard for identifying and quantifying atherosclerotic stenoses of the cerebral arteries and for identifying and characterizing other pathologies, including aneurysms, vasospasm, intraluminal thrombi, fibromuscular dysplasia, arteriovenous fistulae, vasculitis, and collateral channels of blood flow. Conventional angiography carries risks of arterial damage, groin hemorrhage, embolic stroke, and renal failure from contrast nephropathy, so it should be reserved for situations where less invasive means are inadequate. As reviewed earlier in this

www.ketabpezeshki.com (021) 66485457 - 66485438

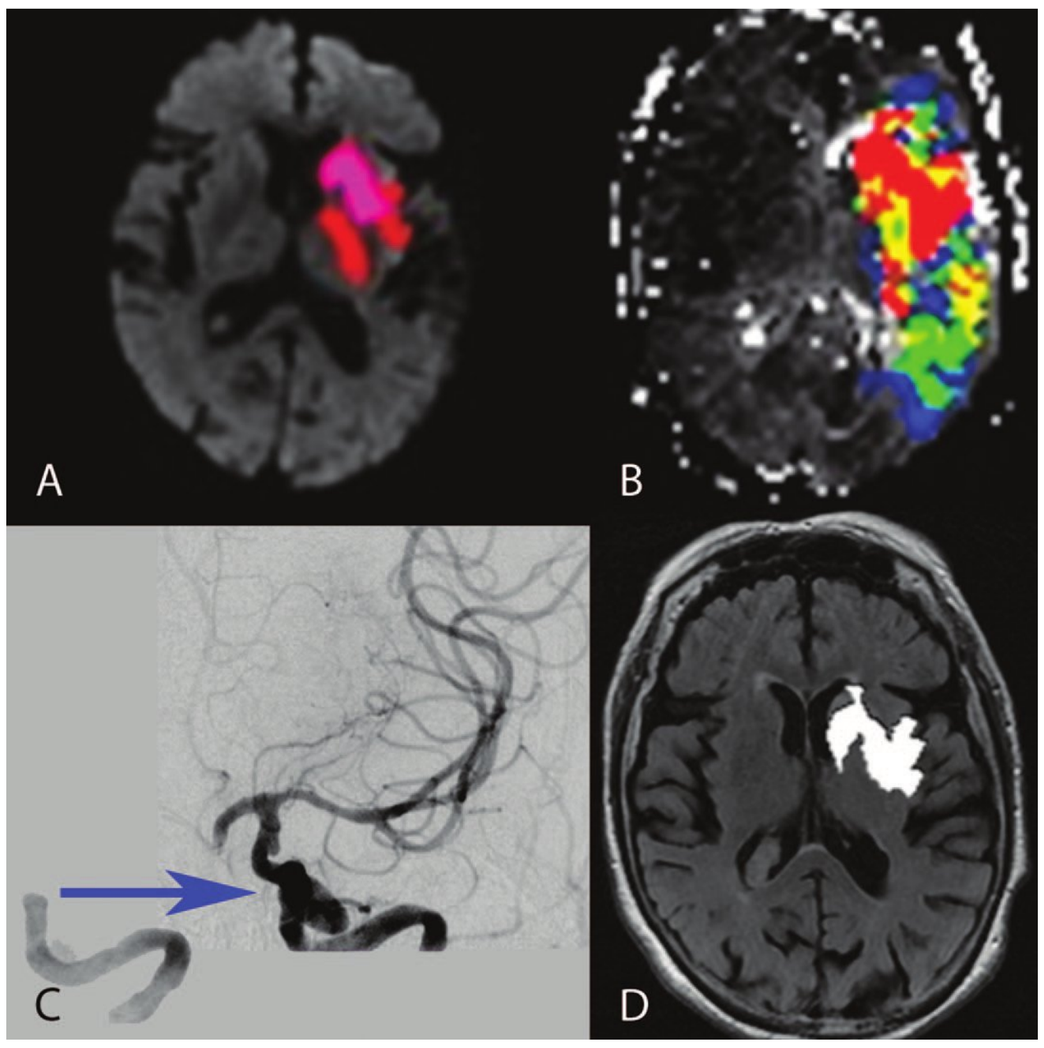


FIGURE 32-16
Magnetic resonance imaging (MRI) of acute stroke. A. MRI diffusion-weighted image (DWI) of an 82-year-old woman 2.5 h after onset of right-sided weakness and aphasia reveals restricted diffusion within the left basal ganglia and internal capsule (colored regions). B. Perfusion defect within the left hemisphere (colored signal) imaged after administration of an IV bolus of gadolinium contrast. The discrepancy between the region of poor perfusion shown in B and the diffusion deficit shown in A is called diffusion-perfusion mismatch and provides an estimate of the ischemic penumbra. Without specific therapy, the region of infarction will expand into much or all of the perfusion deficit. C. Cerebral angiogram of the left internal carotid artery in this patient before (left) and after (right) successful endovascular embolectomy. The occlusion is within the carotid terminus. D. Fluid-attenuated inversion recovery image obtained 3 days later showing a region of infarction (coded as white) that corresponds to the initial DWI image in A, but not the entire area at risk shown in B, suggesting that successful embolectomy saved a large region of brain tissue from infarction. (Courtesy of Gregory Albers, MD, Stanford University; with permission.)

chapter, endovascular stroke therapy has not been proven effective in three randomized trials, and this remains an area of ongoing investigation.

Ultrasound techniques

Stenosis at the origin of the internal carotid artery can be identified and quantified reliably by ultrasonography that combines a B-mode ultrasound image with a Doppler ultrasound assessment of flow velocity ("duplex" ultrasound). Transcranial Doppler (TCD) assessment of MCA, ACA, and PCA flow and of vertebrobasilar flow is also useful. T is latter technique can detect stenotic lesions in the large intracranial arteries because such lesions increase systolic flow velocity. TCD can assist thrombolysis and improve large artery recanalization following rtPA administration; the potential clinical benefit of this treatment is the subject of ongoing study. TCD can also detect microemboli from otherwise asymptomatic carotid plaques. In many cases, MR angiography combined with carotid and transcranial ultrasound studies eliminates the need for conventional x-ray angiography in evaluating vascular stenosis. Alternatively, CT angiography of the entire head and neck can be performed during the initial imaging of acute stroke. Because this images the entire arterial system relevant to stroke, with the exception of the heart, much of the clinician's stroke workup can be completed with this single imaging study.

Perfusion techniques

Both xenon techniques (principally xenon-CT) and positron emission tomography (PET) can quantify cerebral blood flow. T ese tools are generally used for research **(Chap. 4)** but can be useful for determining the significance of arterial stenosis and planning for revascularization surgery. Single-photon emission computed tomography (SPECT) and MR perfusion techniques report relative cerebral blood flow. As noted above, CT imaging is used as the initial imaging modality for acute stroke, and some centers combine both CT angiography and CT perfusion imaging together with the noncontrast CT scan. CT perfusion imaging increases the sensitivity for detecting ischemia and can measure the ischemic penumbra (Fig. 32-15). Alternatively, MR perfusion can be combined with MR diffusion imaging to identify the ischemic penumbra as the mismatch between these two imaging sequences (Fig. 32-16).

INTRACRANIAL HEMORRHAGE

Hemorrhages are classified by their location and the underlying vascular pathology. Bleeding into subdural and epidural spaces is principally produced by trauma. SAH results from trauma or the rupture of an intracranial aneurysm or arteriovenous malformation (AVM) **(Chap. 33)**. Intracerebral and intraventricular hemorrhage will be considered here.

DIAGNOSIS

Intracranial hemorrhage is often discovered on noncontrast CT imaging of the brain during the acute evaluation of stroke. Because CT is more widely available and may be logistically easier, CT imaging is the preferred method for acute stroke evaluation (Fig. 32-1). T e location of the hemorrhage narrows the differential diagnosis to a few entities. **Table 32-6** lists the causes and anatomic spaces involved in hemorrhages.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 32-6

CAUSES OF INTRACRANIAL HEMORRHAGE

CAUSE	LOCATION	COMMENTS
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural)	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~30–100 μm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion
Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–3% per year for bleeding if previously unruptured
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; associated with dementia, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in KRIT1, CCM2, and PDCD10 genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

EMERGENCY MANAGEMENT

Close attention should be paid to airway management because a reduction in the level of consciousness is common and often progressive. The initial blood pressure should be maintained until the results of the CT scan are reviewed and demonstrate an intracerebral hemorrhage (ICH). In theory, a higher blood pressure should promote hematoma expansion, but it remains unclear if lowering of blood pressure reduces hematoma growth. Recent clinical trials have shown that systolic blood pressure (SBP) can be safely lowered acutely and rapidly to <140 mmHg in patients with spontaneous ICH whose initial SBP was 150–220 mmHg. The INTERACT2 trial is the only large phase 3 clinical trial to address the effect of acute blood pressure lowering on ICH functional outcome. INTERACT2 randomized patients with spontaneous ICH within 6 h of onset and a baseline SBP of 150–220 mmHg to two different SBP targets (<140 mmHg and <180 mmHg). In those with the target SBP <140 mmHg, 52% had an outcome of death or major disability at 90 days compared with 55.6% of those with a target SBP <180 mmHg ($p = .06$). There was a significant shift to improved outcomes in the lower blood pressure arm, whereas both groups had a similar mortality. This study shows that it is not harmful, and may be modestly beneficial, to lower blood pressure in acute ICH. Thus, it is reasonable to target an SBP <140 mmHg initially in this group of patients. In patients who have higher SBP on presentation or who are deeply comatose with possible elevated ICP, it is unclear whether the INTERACT2 results apply. In patients who have ICP monitors in place, current recommendations are to maintain the cerebral perfusion pressure (mean arterial pressure [MAP] minus ICP) above 60 mmHg. Blood pressure should be lowered with nonvasodilating IV drugs such as nicardipine, labetalol, or esmolol. Patients with cerebellar hemorrhages or with depressed mental status and radiographic evidence of hydrocephalus should undergo urgent neurosurgical evaluation; these patients require close monitoring because they can deteriorate rapidly. Based on the clinical examination and CT findings, further imaging studies may be necessary, including MRI or conventional x-ray angiography. Stuporous or comatose patients with clinical and imaging signs of herniation are generally treated presumptively for elevated ICP, with tracheal intubation, administration of osmotic diuretics such as mannitol or hypertonic saline, and elevation of the head of the bed while surgical consultation is obtained **(Chap. 33)**. Reversal of coagulopathy and consideration of surgical evacuation of the hematoma (detailed below) are two other principal aspects of initial emergency management.

www.ketabpezeshki.com (021) 66485457 - 66485438

INTRACEREBRAL HEMORRHAGE

ICH accounts for ~10% of all strokes, and about 35–45% of patients die within the first month. Incidence rates are particularly high in Asians and blacks. Hypertension, coagulopathy, sympathomimetic drugs (cocaine, methamphetamine), and cerebral amyloid angiopathy cause the majority of these hemorrhages. Advanced age and heavy alcohol consumption increase the risk, and cocaine and methamphetamine use is one of the most important causes in the young.

Hypertensive intracerebral hemorrhage

Pathophysiology

Hypertensive ICH usually results from spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (especially the putamen), thalamus, cerebellum, and pons. The small arteries in these areas seem most prone to hypertension-induced vascular injury. When hemorrhages occur in other brain areas or in nonhypertensive patients, greater consideration should be given to other causes such as hemorrhagic disorders, neoplasms, vascular malformations, and cerebral amyloid angiopathy. The hemorrhage may be small, or a large clot may form and compress adjacent tissue, causing herniation and death. Blood may also dissect into the ventricular space, which substantially increases morbidity and may cause hydrocephalus.

Most hypertensive ICHs initially develop over 30–90 min, whereas those associated with anticoagulant therapy may evolve for as long as 24–48 h. However, it is now recognized that about a third of patients even with no coagulopathy may have significant hematoma expansion with the first day. Within 48 h, macrophages begin to phagocytize the hemorrhage at its outer surface. After 1–6 months, the hemorrhage is generally resolved to a slitlike orange cavity lined with glial scar and hemosiderin-laden macrophages.

Clinical manifestations

ICH generally presents as the abrupt onset of a focal neurologic deficit. Seizures are uncommon. Although clinical symptoms may be maximal at onset, commonly the focal deficit worsens over 30–90 min and is associated with a diminishing level of consciousness and signs of increased ICP such as headache and vomiting.

The putamen is the most common site for hypertensive hemorrhage, and the adjacent internal capsule is usually damaged **(Fig. 32-17)**. Contralateral hemiparesis is therefore the sentinel sign. When mild, the face sags on one side over 5–30 min, speech becomes slurred, the arm and leg gradually weaken, and the eyes deviate away from the side of the hemiparesis. The paralysis may worsen until the affected limbs become flaccid or

FIGURE 32-17
Hypertensive hemorrhage. Transaxial noncontrast computed tomography scan through the region of the basal ganglia reveals a hematoma involving the left putamen in a patient with rapidly progressive onset of right hemiparesis.

extend rigidly. When hemorrhages are large, drowsiness gives way to stupor as signs of upper brainstem compression appear. Coma ensues, accompanied by deep, irregular, or intermittent respiration, a dilated and fixed ipsilateral pupil, and decerebrate rigidity. In milder cases, edema in adjacent brain tissue may cause progressive deterioration over 12–72 h.

Thalamic hemorrhages also produce a contralateral hemiplegia or hemiparesis from pressure on, or dissection into, the adjacent internal capsule. A prominent sensory deficit involving all modalities is usually present. Aphasia, often with preserved verbal repetition, may occur after hemorrhage into the dominant thalamus, and constructional apraxia or mutism occurs in some cases of nondominant hemorrhage. There may also be a homonymous visual field defect. Thalamic hemorrhages cause several typical ocular disturbances by virtue of extension inferiorly into the upper midbrain. These include deviation of the eyes downward and inward so that they appear to be looking at the nose, unequal pupils with absence of light reaction, skew deviation with the eye opposite the hemorrhage displaced downward and medially, ipsilateral Horner's syndrome, absence of convergence, paralysis of vertical gaze, and retraction nystagmus. Patients may later develop a chronic, contralateral pain syndrome (Déjérine-Roussy syndrome).

In pontine hemorrhages, deep coma with quadriplegia often occurs over a few minutes. Typically, there is prominent decerebrate rigidity and "pinpoint" (1 mm) pupils that react to light. There is impairment of reflex

www.ketabpezeshki.com (021) 66485457 - 66485438

horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water **(Chap. 19)**. Hyperpnea, severe hypertension, and hyperhidrosis are common. Most patients with deep coma from pontine hemorrhage ultimately die, but small hemorrhages are compatible with survival.

Cerebellar hemorrhages usually develop over several hours and are characterized by occipital headache, repeated vomiting, and ataxia of gait. In mild cases, there may be no other neurologic signs except for gait ataxia. Dizziness or vertigo may be prominent. T ere is often paresis of conjugate lateral gaze toward the side of the hemorrhage, forced deviation of the eyes to the opposite side, or an ipsilateral sixth nerve palsy. Less frequent ocular signs include blepharospasm, involuntary closure of one eye, ocular bobbing, and skew deviation. Dysarthria and dysphagia may occur. As the hours pass, the patient often becomes stuporous and then comatose from brainstem compression or obstructive hydrocephalus; immediate surgical evacuation before brainstem compression occurs may be lifesaving. Hydrocephalus from fourth ventricle compression can be relieved by external ventricular drainage, but definitive hematoma evacuation is recommended. If the deep cerebellar nuclei are spared, full recovery is common.

Lobar hemorrhage

T e major neurologic deficit with an occipital hemorrhage is hemianopia; with a left temporal hemorrhage, aphasia and delirium; with a parietal hemorrhage, hemisensory loss; and with frontal hemorrhage, arm weakness. Large hemorrhages may be associated with stupor or coma if they compress the thalamus or midbrain. Most patients with lobar hemorrhages have focal headaches, and more than one-half vomit or are drowsy. Stiff neck and seizures are uncommon.

Other causes of intracerebral hemorrhage

Cerebral amyloid angiopathy is a disease of the elderly in which arteriolar degeneration occurs and amyloid is deposited in the walls of the cerebral arteries. Amyloid angiopathy causes both single and recurrent lobar hemorrhages and is probably the most common cause of lobar hemorrhage in the elderly. It accounts for some intracranial hemorrhages associated with IV thrombolysis given for MI. T is disorder can be suspected in patients who present with multiple hemorrhages (and infarcts) over several months or years or in patients with "microbleeds" seen on brain MRI sequences sensitive for hemosiderin (iron-sensitive imaging), but it is definitively diagnosed by pathologic demonstration of Congo red staining of amyloid in cerebral vessels. T e ε2 and ε4 allelic variations of the apolipoprotein E gene are associated with increased risk of recurrent lobar hemorrhage and may therefore be markers of amyloid angiopathy. Currently, there is no specific therapy. OACs are typically avoided.

Cocaine and methamphetamine are frequent causes of stroke in young (age <45 years) patients. ICH, ischemic stroke, and SAH are all associated with stimulant use. Angiographic findings vary from completely normal arteries to large-vessel occlusion or stenosis, vasospasm, or changes consistent with vasculopathy. T e mechanism of sympathomimetic-related stroke is not known, but cocaine enhances sympathetic activity causing acute, sometimes severe, hypertension, and this may lead to hemorrhage. Slightly more than one-half of stimulant-related intracranial hemorrhages are intracerebral, and the rest are subarachnoid. In cases of SAH, a saccular aneurysm is usually identified. Presumably, acute hypertension causes aneurysmal rupture.

Head injury often causes intracranial bleeding. T e common sites are intraparenchymal (especially temporal and inferior frontal lobes) and into the subarachnoid, subdural, and epidural spaces. Trauma must be considered in any patient with an unexplained acute neurologic deficit (hemiparesis, stupor, or confusion), particularly if the deficit occurred in the context of a fall **(Chap. 44)**.

Intracranial hemorrhages associated with anticoagulant therapy can occur at any location; they are often lobar or subdural. Anticoagulant-related ICHs may continue to evolve over 24–48 h, especially if coagulopathy is insufficiently reversed. Coagulopathy and thrombocytopenia should be reversed rapidly, as discussed below. ICH associated with hematologic disorders (leukemia, aplastic anemia, thrombocytopenic purpura) can occur at any site and may present as multiple ICHs. Skin and mucous membrane bleeding may be evident and offers a diagnostic clue.

Hemorrhage into a brain tumor may be the first manifestation of neoplasm. Choriocarcinoma, malignant melanoma, renal cell carcinoma, and bronchogenic carcinoma are among the most common metastatic tumors associated with ICH. Glioblastoma multiforme in adults and medulloblastoma in children may also have areas of ICH.

Hypertensive encephalopathy is a complication of malignant hypertension. In this acute syndrome, severe hypertension is associated with headache, nausea, vomiting, convulsions, confusion, stupor, and coma. Focal or lateralizing neurologic signs, either transitory or permanent, may occur but are infrequent and therefore suggest some other vascular disease (hemorrhage, embolism, or atherosclerotic thrombosis). T ere are retinal hemorrhages, exudates, papilledema (hypertensive retinopathy), and evidence of renal and cardiac disease. In most cases, ICP and CSF protein levels are

www.ketabpezeshki.com (021) 66485457 - 66485438

elevated. MRI brain imaging shows a pattern of typically posterior (occipital > frontal) brain edema that is reversible and termed reversible posterior leukoencephalopathy. T e hypertension may be essential or due to chronic renal disease, acute glomerulonephritis, acute toxemia of pregnancy, pheochromocytoma, or other causes. Lowering the blood pressure reverses the process, but stroke can occur, especially if blood pressure is lowered too rapidly. Neuropathologic examination reveals multifocal to diffuse cerebral edema and hemorrhages of various sizes from petechial to massive. Microscopically, there are necrosis of arterioles, minute cerebral infarcts, and hemorrhages. T e term hypertensive encephalopathy should be reserved for this syndrome and not for chronic recurrent headaches, dizziness, recurrent TIAs, or small strokes that often occur in association with high blood pressure.

Primary intraventricular hemorrhage is rare and should prompt investigation for an underlying vascular anomaly. Sometimes bleeding begins within the periventricular substance of the brain and dissects into the ventricular system without leaving signs of intraparenchymal hemorrhage. Alternatively, bleeding can arise from periependymal veins. Vasculitis, usually polyarteritis nodosa or lupus erythematosus, can produce hemorrhage in any region of the central nervous system; most hemorrhages are associated with hypertension, but the arteritis itself may cause bleeding by disrupting the vessel wall. Nearly one-half of patients with primary intraventricular hemorrhage have identifiable bleeding sources seen using conventional angiography.

Sepsis can cause small petechial hemorrhages throughout the cerebral white matter. Moyamoya disease, mainly an occlusive arterial disease that causes ischemic symptoms, may on occasion produce ICH, particularly in the young. Hemorrhages into the spinal cord are usually the result of an AVM, cavernous malformation, or metastatic tumor. Epidural spinal hemorrhage produces a rapidly evolving syndrome of spinal cord or nerve root compression **(Chap. 43)**. Spinal hemorrhages usually present with sudden back pain and some manifestation of myelopathy.

Laboratory and imaging evaluation

Patients should have routine blood chemistries and hematologic studies. Specific attention to the platelet count and PT/PTT/INR is important to identify coagulopathy. CT imaging reliably detects acute focal hemorrhages in the supratentorial space. Rarely very small pontine or medullary hemorrhages may not be well delineated because of motion and bone-induced artifact that obscure structures in the posterior fossa. After the first 2 weeks, x-ray attenuation values of clotted blood diminish until they become isodense with surrounding brain. Mass effect and edema may remain. In some cases, a surrounding rim of contrast enhancement appears after 2–4 weeks and may persist for months. MRI, although more sensitive for delineating posterior fossa lesions, is generally not necessary for primary diagnosis in most instances. Images of flowing blood on MRI scan may identify AVMs as the cause of the hemorrhage. MRI, CT angiography (CTA), and conventional x-ray angiography are used when the cause of intracranial hemorrhage is uncertain, particularly if the patient is young or not hypertensive and the hematoma is not in one of the usual sites for hypertensive hemorrhage. CTA or postcontrast CT imaging may reveal one or more small areas of enhancement within a hematoma; this "spot sign" is thought to represent ongoing bleeding. T e presence of a spot sign is associated with an increased risk of hematoma expansion, increased mortality, and lower likelihood of favorable functional outcome. Some centers routinely perform CT with CTA and postcontrast CT at the time of initial imaging to rapidly identify any macrovascular etiology of the hemorrhage and provide prognostic information at the same time. Because patients typically have focal neurologic signs and obtundation and often show signs of increased ICP, a lumbar puncture is generally unnecessary and should usually be avoided because it may induce cerebral herniation.

TREATMENT Intracerebral Hemorrhage

ACUTE MANAGEMENT Although about 40% of patients with a hypertensive ICH die, others have a good to complete recovery if they survive the initial hemorrhage. T e ICH Score **(Table 32-7)** is a validated clinical grading scale that is useful for stratification of mortality risk and clinical outcome. Any identified coagulopathy should be corrected as soon as possible. For patients taking VKAs, rapid correction of coagulopathy can be achieved by infusing prothrombin complex concentrates (PCC), which can be administered quickly, with vitamin K administered concurrently. Fresh frozen plasma is an alternative but generally requires larger fluid volumes and longer time to achieve adequate reversal than PCC. Recently idarucizumab has been approved to rapidly reverse bleeding associated with the oral direct thrombin inhibitor dibigatran and should be used for ICH in this setting. PCC may partially reverse the effects of oral factor Xa inhibitors and are reasonable to administer if available. When ICH is associated with thrombocytopenia (platelet count <50,000/μL), transfusion of fresh platelets is indicated. Platelet transfusions are not recommended empirically based on recent trial data, but the use of urgent platelet inhibition assays remains unclear.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 32-7

THE ICH SCORE

CLINICAL OR IMAGING FACTOR	POINT SCORE
Age	
<80 years	0
≥80 years	1
Hematoma Volume	
<30 cc	0
≥30 cc	1
Intraventricular Hemorrhage Present	
No	0
Yes	1
Infratentorial Origin of Hemorrhage	
No	0
Yes	1
Glasgow Coma Scale Score	
13–15	0
5–12	1
3–4	2
Total Score	Sum of each category above

ICH SCORE TOTAL	% MORTALITY AT 30 DAYS (95% CI)	% WALK INDEPENDENTLY AT 12 MONTHS (95% CI)
0	0 (0–13)	70 (53–84)
1	13 (4–29)	60 (47–73)
2	26 (11–46)	33 (21–48)
3	72 (53–86)	13 (5–25)
4	97 (82–100)	3 (0–16)
5	100 (54–100)	8 (0–38)

Note: Although an ICH Score of 6 is possible with the scale, this is rarely observed and is considered highly likely to be fatal.
Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage.
Sources: JC Hemphill et al: Stroke 32:891, 2001; JC Hemphill et al: Neurology 73:1088, 2009.

Hematomas may expand for several hours following the initial hemorrhage, even in patients without coagulopathy. However, the precise mechanism is unclear. A phase 3 trial of treatment with recombinant factor VIIa reduced hematoma expansion; however, clinical outcomes were not improved, so use of this drug cannot be advocated at present. The theoretical risk of acutely elevated blood pressure on hematoma expansion forms the basis of the consideration for recently completed and ongoing clinical trials of acute blood pressure lowering.

Evacuation of supratentorial hematomas does not appear to improve outcome for most patients. The International Surgical Trial in Intracerebral Haemorrhage (STICH) randomized patients with supratentorial ICH to either early surgical evacuation or initial medical management. No benefit was found in the early surgery arm, although analysis was complicated by the fact that 26% of patients in the initial medical management group ultimately had surgery for neurologic deterioration. The follow-up study STICH-II found that surgery within 24 h of lobar, supratentorial hemorrhage did not improve overall outcome, but might have a role in select severely affected patients. Therefore, existing data do not support routine surgical evacuation of supratentorial hemorrhages in stable patients. However, many centers still consider surgery for patients deemed salvageable and who are having progressive neurologic deterioration due to herniation. Surgical techniques continue to evolve, and minimally invasive endoscopic hematoma evacuation is currently being investigated in clinical trials.

For cerebellar hemorrhages, a neurosurgeon should be consulted immediately to assist with the evaluation; most cerebellar hematomas >3 cm in diameter will require surgical evacuation. If the patient is alert without focal brainstem signs and if the hematoma is <1 cm in diameter, surgical removal is usually unnecessary. Patients with hematomas between 1 and 3 cm require careful observation for signs of impaired consciousness, progressive hydrocephalus, and precipitous respiratory failure. Hydrocephalus due to cerebellar hematoma should not be treated solely with ventricular drainage.

Tissue surrounding hematomas is displaced and compressed but not necessarily infarcted. Hence, in survivors, major improvement commonly occurs as the hematoma is reabsorbed and the adjacent tissue regains its function. Careful management of the patient during the acute phase of the hemorrhage can lead to considerable recovery.

Surprisingly, ICP is often normal even with large ICHs. However, if the hematoma causes marked midline shift of structures with consequent obtundation, coma, or hydrocephalus, osmotic agents can be instituted in preparation for placement of a ventriculostomy or parenchymal ICP monitor **(Chap. 33)**. Once ICP is recorded, CSF drainage (if available), osmotic therapy, and blood pressure management can be tailored to the individual patient to keep cerebral perfusion pressure (MAP minus ICP) above 60 mmHg. For example, if ICP is found to be high, CSF can be drained from the ventricular space and osmotic therapy continued; persistent or progressive elevation in ICP may prompt surgical evacuation of the clot. Alternately, if ICP is normal or only mildly elevated, interventions such as osmotic therapy may be tapered. Because hyperventilation may actually produce ischemia by cerebral vasoconstriction, induced hyperventilation should be limited to acute resuscitation of the patient with presumptive high ICP and eliminated once other treatments (osmotic therapy or surgical treatments) have been instituted. Glucocorticoids are not helpful for the edema from intracerebral hematoma.

PREVENTION Hypertension is the leading cause of primary ICH. Prevention is aimed at reducing chronic hypertension, eliminating excessive alcohol use, and discontinuing use of

www.ketabpezeshki.com (021) 66485457 - 66485438

illicit drugs such as cocaine and amphetamines. Patients with amyloid angiopathy should generally avoid OACs, but antiplatelet agents may be administered if there is an indication based on atherothrombotic vascular disease.

VASCULAR ANOMALIES

Vascular anomalies can be divided into congenital vascular malformations and acquired vascular lesions.

CONGENITAL VASCULAR MALFORMATIONS

True arteriovenous mal*f*ormations (AVMs), venous anomalies, and capillary telangiectasias are lesions that usually remain clinically silent through life. AVMs are probably congenital, but cases of acquired lesions have been reported.

True AVMs are congenital shunts between the arterial and venous systems that may present with headache, seizures, and intracranial hemorrhage. AVMs consist of a tangle of abnormal vessels across the cortical surface or deep within the brain substance. AVMs vary in size from a small blemish a few millimeters in diameter to a large mass of tortuous channels composing an arteriovenous shunt of sufficient magnitude to raise cardiac output and precipitate heart failure. Blood vessels forming the tangle interposed between arteries and veins are usually abnormally thin and histologically resemble both arteries and veins. AVMs occur in all parts of the cerebral hemispheres, brainstem, and spinal cord, but the largest ones are most frequently in the posterior half of the hemispheres, commonly forming a wedge-shaped lesion extending from the cortex to the ventricle.

Bleeding, headache, and seizures are most common between the ages of 10 and 30, occasionally as late as the fifties. AVMs are more frequent in men, and rare familial cases have been described. Familial AVM may be a part of the autosomal dominant syndrome of hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome due to mutations in either endoglin or activin receptor-like kinase 1, both involved in transforming growth factor (TGF) signaling and angiogenesis.

Headache (without bleeding) may be hemicranial and throbbing, like migraine, or diffuse. Focal seizures, with or without generalization, occur in ~30% of cases. One-half of AVMs become evident as ICHs. In most, the hemorrhage is mainly intraparenchymal with extension into the subarachnoid space in some cases. Blood is usually not deposited in the basal cisterns, and symptomatic cerebral vasospasm is rare. T e risk of AVM rupture is strongly influenced by a history of prior rupture. Although unruptured AVMs have a hemorrhage rate of ~2–4% per year, previously ruptured AVMs may have a rate as high as 17% a year, at least for the first year. Hemorrhages may be massive, leading to death, or may be as small as 1 cm in diameter, leading to minor focal symptoms or no deficit. T e AVM may be large enough to steal blood away from adjacent normal brain tissue or to increase venous pressure significantly to produce venous ischemia locally and in remote areas of the brain. T is is seen most often with large AVMs in the territory of the MCA.

Large AVMs of the anterior circulation may be associated with a systolic and diastolic bruit (sometimes self-audible) over the eye, forehead, or neck and a bounding carotid pulse. Headache at the onset of AVM rupture is generally not as explosive as with aneurysmal rupture. MRI is better than CT for diagnosis, although noncontrast CT scanning sometimes detects calcification of the AVM and contrast may demonstrate the abnormal blood vessels. Once identified, conventional x-ray angiography is the gold standard for evaluating the precise anatomy of the AVM.

Surgical treatment of AVMs presenting with hemorrhage often done in conjunction with preoperative embolization to reduce operative bleeding is usually indicated for accessible lesions. Stereotaxic radiation, an alternative to surgery, can produce a slow sclerosis of the AVM over 2–3 years.

Several angiographic features can be used to help predict future bleeding risk. Paradoxically, smaller lesions seem to have a higher hemorrhage rate. T e presence of deep venous drainage, venous outflow stenosis, and intranidal aneurysms may increase rupture risk. Because of the relatively low annual rate of hemorrhage and the risk of complications due to surgical or endovascular treatment, the indication for surgery in asymptomatic AVMs is debated. T e ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial randomized patients to medical management versus intervention (surgery, endovascular embolization, combination embolization and surgery, or gamma-knife). T e trial was stopped prematurely for harm, with the medical arm achieving the combined endpoint of death or symptomatic stroke in 10.1% of patients compared to 30.7% in the intervention group at an average follow-up time of 33 months. T is highly significant finding argues against routine intervention for patients presenting without hemorrhage, although debate ensues regarding the generalizability of these results.

Venous anomalies are the result of development of anomalous cerebral, cerebellar, or brainstem venous drainage. T ese structures, unlike AVMs, are functional venous channels. T ey are of little clinical significance and should be ignored if found incidentally on brain imaging studies. Surgical resection of these anomalies may result in venous infarction and hemorrhage.

www.ketabpezeshki.com (021) 66485457 - 66485438

Venous anomalies may be associated with cavernous malformations (see below), which do carry some bleeding risk.

Capillary telangiectasias are true capillary malformations that often form extensive vascular networks through an otherwise normal brain structure. T e pons and deep cerebral white matter are typical locations, and these capillary malformations can be seen in patients with hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) syndrome. If bleeding does occur, it rarely produces mass effect or significant symptoms. No treatment options exist.

ACQUIRED VASCULAR LESIONS

Cavernous angiomas are tufts of capillary sinusoids that form within the deep hemispheric white matter and brainstem with no normal intervening neural structures. T e pathogenesis is unclear. Familial cavernous angiomas have been mapped to several different genes: KRI*T*1, CCM2, and PDCD10. Both KRI*T*1 and CCM2 have roles in blood vessel formation, whereas PDCD10 is an apoptotic gene. Cavernous angiomas are typically <1 cm in diameter and are often associated with a venous anomaly. Bleeding is usually of small volume, causing slight mass effect only. T e bleeding risk for single cavernous malformations is 0.7–1.5% per year and may be higher for patients with prior clinical hemorrhage or multiple malformations. Seizures may occur if the malformation is located near the cerebral cortex. Surgical resection eliminates bleeding risk and may reduce seizure risk, but it is usually reserved for those malformations that form near the brain surface. Radiation treatment has not been shown to be of benefit.

Dural arteriovenous f stulas are acquired connections usually from a dural artery to a dural sinus. Patients may complain of a pulse-synchronous cephalic bruit ("pulsatile tinnitus") and headache. Depending on the magnitude of the shunt, venous pressures may rise high enough to cause cortical ischemia or venous hypertension and hemorrhage, particularly SAH. Surgical and endovascular techniques are usually curative. T ese fistulas may form because of trauma, but most are idiopathic. T ere is an association between fistulas and dural sinus thrombosis. Fistulas have been observed to appear months to years following venous sinus thrombosis, suggesting that angiogenesis factors elaborated from the thrombotic process may cause these anomalous connections to form. Alternatively, dural arteriovenous fistulas can produce venous sinus occlusion over time, perhaps from the high pressure and high flow through a venous structure.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 33

NEUROLOGIC CRITICAL CARE, INCLUDING HYPOXIC-ISCHEMIC ENCEPHALOPATHY, AND SUBARACHNOID HEMORRHAGE

J. Claude Hemphill, III ■ Wade S. Smith ■ Daryl R. Gress

Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a consequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest **(Table 33-1)**. Neurologic critical care focuses on preservation of neurologic tissue and prevention of secondary brain injury caused by ischemia, hemorrhage, edema, herniation, and elevated intracranial pressure (ICP). Management of other organ systems proceeds concurrently and may need to be modified in order to maintain the overall focus on neurologic issues.

PATHOPHYSIOLOGY

Brain edema

Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. Vasogenic edema refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms. The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements. Vasogenic edema results from abnormal permeability of the BBB, and typically develops rapidly following injury. Cytotoxic edema results from cellular swelling, membrane breakdown, and ultimately cell death. Clinically significant brain edema usually represents a combination of vasogenic and cytotoxic components. Edema can lead to increased ICP as well as tissue shifts and brain displacement or herniation from focal processes **(Chap. 19)**. These tissue shifts can cause injury by mechanical distention and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP.

Ischemic cascade and cellular injury

When delivery of substrates, principally oxygen and glucose, is inadequate to sustain cellular function, a series of interrelated biochemical reactions known as the ischemic cascade is initiated **(see Fig. 32-2)**. The release of excitatory amino acids, especially glutamate, leads to influx of calcium and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases, which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain injury.

Penumbra refers to areas of ischemic brain tissue that have not yet undergone irreversible infarction, implying that these regions are potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellular metabolism, outstripping compensatory processes. Clinically, these events are known as secondary brain insults because they lead to exacerbation of the primary brain injury. Prevention, identification, and treatment of secondary brain insults are fundamental goals of management.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 33-1

NEUROLOGIC DISORDERS IN CRITICAL ILLNESS

LOCALIZATION ALONG NEUROAXIS	SYNDROME
Central Nervous System	
Brain: Cerebral hemispheres	Global encephalopathy Delirium Sepsis Organ failure—hepatic, renal Medication related—sedatives, hypnotics, analgesics, H_2 blockers, antihypertensives Drug overdose Electrolyte disturbance—hyponatremia, hypoglycemia Hypotension/hypoperfusion Hypoxia Meningitis Subarachnoid hemorrhage Wernicke's disease Seizure—postictal or nonconvulsive status Hypertensive encephalopathy Hypothyroidism—myxedema Focal deficits Ischemic stroke Tumor Abscess, subdural empyema Intraparenchymal hemorrhage Subdural/epidural hematoma
Brainstem/ cerebellum	Mass effect and compression Basilar artery thrombosis Intraparenchymal hemorrhage Central pontine myelinolysis Mass effect and compression
Spinal cord	Disk herniation Epidural hematoma Ischemia—hypotension/embolic Epidural abscess Trauma Myelitis
Peripheral Nervous System	
Peripheral nerve Axonal	Critical illness polyneuropathy Neuromuscular blocking agent complications Metabolic disturbances, uremia, hyperglycemia Medication effects—chemotherapeutic, antiretroviral
Demyelinating	Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy
Neuromuscular junction	Prolonged effect of neuromuscular blockade Medication effects—aminoglycosides Myasthenia gravis, Lambert-Eaton syndrome, botulism
Muscle	Critical illness myopathy Cachectic myopathy Acute necrotizing myopathy Thick-filament myopathy Electrolyte disturbances—hypokalemia/ hyperkalemia, hypophosphatemia Rhabdomyolysis

An alternative pathway of cellular injury is apoptosis. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, traumatic brain injury, and possibly intracerebral hemorrhage. Apoptotic cell death can be distinguished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways; apoptotic cell death occurs without cerebral edema and therefore is often not seen on brain imaging. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia.

Excitotoxicity and mechanisms of cell death are discussed in more detail in Chap. 30.

Cerebral perfusion and autoregulation

Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pressure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. Autoregulation refers to the physiologic response whereby cerebral blood flow (CBF) is regulated via alterations in cerebrovascular resistance in order to maintain perfusion over wide physiologic changes such as neuronal activation or changes in hemodynamic function. If systemic blood pressure drops, cerebral perfusion is preserved through vasodilation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion, resulting in fairly constant perfusion across a wide range of systemic blood pressures **(Fig. 33-1)**. At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the microcirculation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and $Paco_2$. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis because of pH related changes in cerebral vascular resistance. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in both CBF and intracranial blood volume. Cerebral autoregulation is a complex process critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

Cerebrospinal fluid and intracranial pressure

The cranial contents consist essentially of brain, cerebrospinal fluid (CSF), and blood. CSF is produced

www.ketabpezeshki.com (021) 66485457 - 66485438

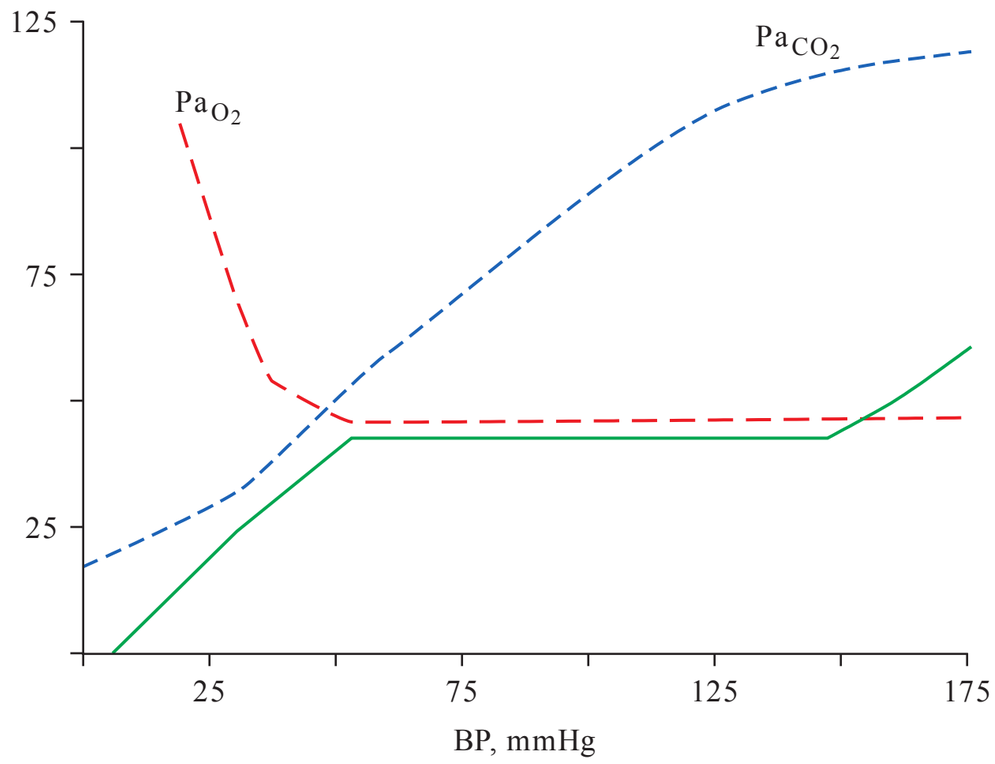


FIGURE 33-1
Autoregulation of cerebral blood flow (solid line). Cerebral perfusion is constant over a wide range of systemic blood pressure. Perfusion is increased in the setting of hypoxia or hypercarbia. BP, blood pressure; CBF, cerebral blood flow. (Reprinted with permission from HM Shapiro: Anesthesiology 43:447, 1975. Copyright 1975, Lippincott Company.).

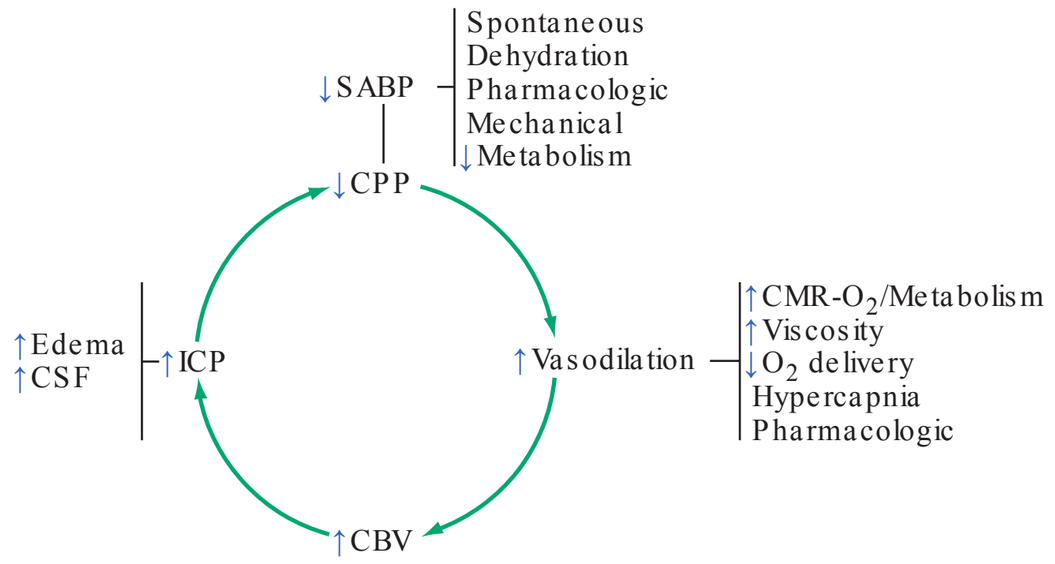


FIGURE 33-2
Ischemia and vasodilatation. Reduced cerebral perfusion pressure (CPP) leads to increased ischemia, vasodilation, increased intracranial pressure (ICP), and further reductions in CPP, a cycle leading to further neurologic injury. CBV, cerebral blood volume; CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; SABP, systolic arterial blood pressure. (Adapted from MJ Rosner et al: J Neurosurg 83:949, 1995; with permission.)

principally in the choroid plexus of each lateral ventricle, exits the brain via the foramens of Luschka and Magendie, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. In adults, approximately 150 mL of CSF are contained within the ventricles and surrounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF outflow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia **(Fig. 33-2)**. This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts.

APPROACH TO THE PATIENT: Severe Central Nervous System Dysfunction

Critically ill patients with severe central nervous system (CNS) dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evaluation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or paralytic agents to facilitate procedures.

An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, process is implicated. Examples of diffuse processes include metabolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemorrhagic stroke and traumatic brain injury, especially with intracranial hematomas. Because these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. **The approach to the comatose patient is discussed in Chap. 19; etiologies are listed in Table 19-1**.

Minor focal deficits may be present on the neurologic examination in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or paraplegia should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. Computed tomography (CT) scanning is usually the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. Magnetic resonance imaging (MRI) may provide more specific information in some situations,

www.ketabpezeshki.com (021) 66485457 - 66485438

such as acute ischemic stroke (diffusion-weighted imaging [DWI]) and cerebral venous sinus thrombosis (magnetic resonance venography [MRV]). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervical spine injury and prompt an imaging evaluation using plain x-rays, CT, or MRI.

Acute brainstem ischemia due to basilar artery thrombosis may cause brief episodes of spontaneous extensor posturing superficially resembling generalized seizures. Coma of sudden onset, accompanied by these movements and cranial nerve abnormalities, necessitates emergency imaging. A noncontrast CT scan of the brain may reveal a hyperdense basilar artery indicating thrombus in the vessel, and subsequent CT or MR angiography can assess basilar artery patency.

Other diagnostic studies are best used in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. T e EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inapparent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious or inflammatory processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed first or antibiotics may be empirically administered before the diagnostic studies are completed. Standard laboratory evaluation of critically ill patients should include assessment of serum electrolytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encephalopathy of unknown cause. EEG, LP, and other specific laboratory tests are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed in clear-cut cases of stroke or traumatic brain injury.

Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Included are patients with the following: severe traumatic brain injury (Glasgow Coma Scale [GCS] score ≤8 **[see Table 44-2]**); large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydrocephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in the brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more dif - cult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) **(Fig. 33-3)**.

TREATMENT OF ELEVATED ICP Elevated ICP may occur in a wide range of disorders, including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs, intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. T is is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg.

Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP **(Table 33-2)**. For example, in hydrocephalus from SAH, the principal cause of elevated ICP is impairment of CSF

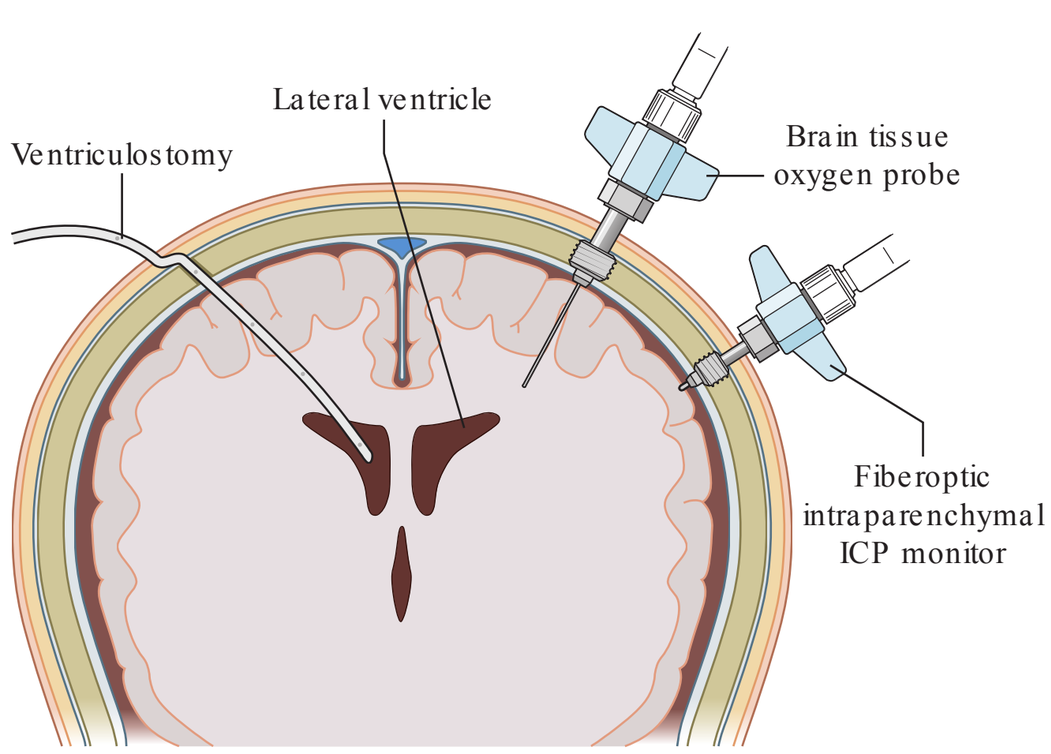


FIGURE 33-3
Intracranial pressure and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fuid to treat elevated intracranial pressure (ICP). Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood fow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 33-2

STEPWISE APPROACH TO TREATMENT OF ELEVATED INTRACRANIAL PRESSURE (ICP)[a]

Insert ICP monitor—ventriculostomy versus parenchymal device

General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg.

For ICP >20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to $PaCO_2$ 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP
   a. Decompressive craniectomy
   b. High-dose barbiturate therapy ("pentobarb coma")
   c. Hypothermia to 33°C

[a]Throughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP.

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; $Paco_2$, arterial partial pressure of carbon dioxide.

drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic agents such as mannitol or hypertonic saline becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase mean arterial pressure may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume.

Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate intervention. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstriction and reduces cerebral blood volume. To avoid provoking or worsening cerebral ischemia, hyperventilation, if used at all, is best administered only for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperventilation on ICP are short-lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examination lessens and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompressive hemicraniectomy, and hypothermia are sometimes used for refractory elevations of ICP, although these have significant side effects and have not been proven to improve outcome.

SECONDARY BRAIN INSULTS Patients with primary brain injuries, whether due to trauma or stroke, are at risk for ongoing secondary ischemic brain injury. Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. Although elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury limiting eventual recovery, which manifests as a higher mortality rate or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent secondary ischemia. Avoiding hypotension and hypoxia is critical, as significant hypotensive events (systolic blood pressure <90 mmHg) as short as 10 min in duration have been shown to adversely influence outcome after traumatic brain injury. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation <90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normothermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management

www.ketabpezeshki.com (021) 66485457 - 66485438

of refractory fever is under investigation. T e use of IV insulin infusion is encouraged for control of hyperglycemia because this allows better regulation of serum glucose levels than SC insulin. A reasonable goal is to maintain the serum glucose level at <10.0 mmol/L (<180 mg/dL), although episodes of hypoglycemia appear equally detrimental and the optimal targets remain uncertain. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, and metabolism (via microdialysis) may further improve the management of secondary brain injury.

CRITICAL CARE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

T is occurs from lack of delivery of oxygen to the brain because of extreme hypotension (hypoxia-ischemia) or hypoxia due to respiratory failure. Causes include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are sometimes termed histotoxic hypoxia because they cause a direct impairment of the respiratory chain.

Clinical manifestations

Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage usually results. Except in extreme cases, it may be dif cult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 8–10 min of global cerebral ischemia. T e brain is more tolerant to pure hypoxia than it is to hypoxia-ischemia. For example, a Pao_2 as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, whereas short durations of very low or absent cerebral circulation usually result in permanent impairment.

Clinical examination at different time points after a hypoxic-ischemic insult (especially cardiac arrest) is useful in assessing prognosis for long-term neurologic outcome. T e prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (doll's eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A low likelihood of a favorable outcome from hypoxic-ischemic coma is strongly suggested by an absent pupillary light reflex or extensor or absent motor response to pain on day 3 following the injury, excluding patients with metabolic disturbances and those treated with high-dose barbiturates or hypothermia, which confound interpretation of these signs. Electrophysiologically, the bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) in the first several days also conveys a poor prognosis. A very elevated serum level (>33 μg/L) of the biochemical marker neuron-specific enolase (NSE) is indicative of brain damage after resuscitation from cardiac arrest and predicts a poor outcome. However, at present, SSEPs and NSE levels may be dif cult to obtain in a timely fashion, with SSEP testing requiring substantial expertise in interpretation and NSE measurements not yet standardized. Recent studies suggest that the administration of mild hypothermia after cardiac arrest (see "Treatment") may affect the time points when these clinical and electrophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery. For example, the false-positive rate for incorrect prediction of poor neurologic outcome may be as high as 21% (95% confidence interval [CI] 8–43%) for patients treated with mild hypothermia who exhibit 3-day motor function no better than extensor posturing. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or a vegetative state **(Chap. 19)**, dementia, visual agnosia **(Chap. 22)**, parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus.

Pathology

Principal histologic findings are extensive multifocal or diffuse laminar cortical necrosis **(Fig. 33-4)**, with frequent involvement of the hippocampus. T e hippocampal CA1 neurons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect pathways that mediate arousal, and this pathology may be responsible for the persistent vegetative state. A specific form of hypoxic-ischemic encephalopathy, so-called watershed infarcts, occurs at the distal territories between the major cerebral arteries and can cause cognitive deficits, including visual agnosia, and weakness that is greater in proximal than in distal muscle groups.

www.ketabpezeshki.com (021) 66485457 - 66485438

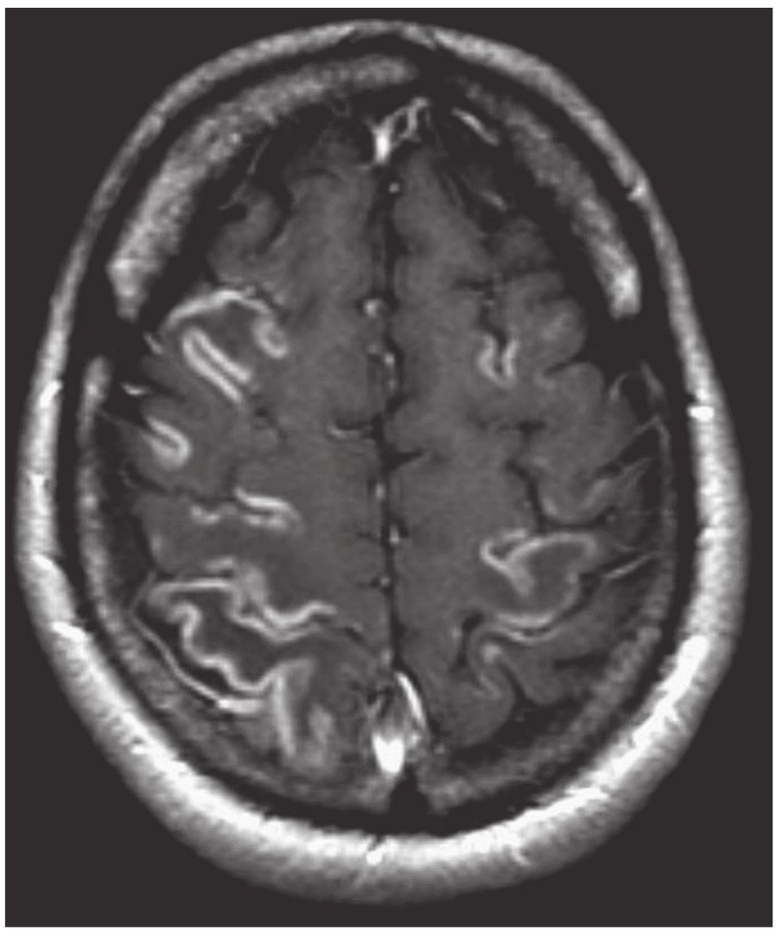


FIGURE 33-4
Cortical laminar necrosis in hypoxic-ischemic encephalopathy. T1-weighted postcontrast magnetic resonance imaging shows cortical enhancement in a watershed distribution consistent with laminar necrosis.

Diagnosis

Diagnosis is based on the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or Pao_2 <40 mmHg is usually necessary, although both absolute levels and duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the venous blood and skin, although the latter is an inconsistent clinical finding.

TREATMENT Hypoxic-Ischemic Encephalopathy

Treatment should be directed at restoration of normal cardiorespiratory function. T is includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluid, pressors, or cardiac pacing. Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. In two trials, mild hypothermia (33°C) improved functional outcome in patients who remained comatose after resuscitation from a cardiac arrest. Treatment was initiated within minutes of cardiac resuscitation and continued for 12 h in one study and 24 h in the other. Potential complications of hypothermia include coagulopathy and an increased risk of infection. Based on these studies, the International Liaison Committee on Resuscitation issued the following advisory statement: "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°–34°C for 12–24 h when the initial rhythm was ventricular fibrillation. Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest."

Severe carbon monoxide intoxication may be treated with hyperbaric oxygen. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Posthypoxic myoclonus may respond to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg daily in divided doses. Myoclonic status epilepticus within 24 h after a primary circulatory arrest generally portends a very poor prognosis, even if seizures are controlled.

Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impairment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT and MRI.

METABOLIC ENCEPHALOPATHIES

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium, a confusional state characterized by disordered perception, frequent hallucinations, delusions, and sleep disturbance. T is is often attributed to medication effects, sleep deprivation, pain, and anxiety. T e presence of delirium is associated with worsened outcome in critically ill patients, even in those without an identifiable CNS pathology such as stroke or brain trauma. In these patients, the cause of delirium is often multifactorial, resulting from organ dysfunction, sepsis, and especially the use of medications given to treat pain, agitation, or anxiety. Critically ill patients are often treated with a variety of sedative and analgesic medications, including opiates, benzodiazepines, neuroleptics, and sedative-anesthetic medications, such as propofol. In critically ill patients requiring sedation, use of the centrally acting α_2 agonist dexmedetomidine may reduce delirium and shorten the duration of mechanical ventilation compared to the use of benzodiazepines such as lorazepam or midazolam. T e presence of family members in the ICU may also help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics (e.g., haloperidol 0.5–1 mg) can be useful. Current strategies focus on limiting the use of sedative medications when this can be done safely.

In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most

www.ketabpezeshki.com (021) 66485457 - 66485438

frequently in patients with a history of chronic CO_2 retention who are receiving oxygen therapy for emphysema or chronic pulmonary disease. The elevated $Paco_2$ leading to CO_2 narcosis may have a direct anesthetic effect, and cerebral vasodilation from increased $Paco_2$ can lead to increased ICP. Hepatic encephalopathy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hallmarks of acute Wernicke's disease (see below).

SEPSIS-ASSOCIATED ENCEPHALOPATHY

Pathogenesis

In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory mediators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed sepsis-associated encephalopathy. Although the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor, interleukin (IL)-1, IL-2, and IL-6 are thought to play a role in this syndrome.

Diagnosis

Sepsis-associated encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alertness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex **(Chap. 22)** can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Sepsis-associated encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunction in critically ill patients and requires exclusion of structural, metabolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality rate of patients with sepsis-associated encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is not a direct result of the encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. Successful treatment of the underlying critical illness almost always results in substantial improvement of the encephalopathy. However, although severe disability to the level of chronic vegetative or minimally conscious states is uncommon, long-term cognitive dysfunction clinically similar to dementia is being increasingly recognized in some survivors.

CENTRAL PONTINE MYELINOLYSIS

This disorder typically presents in a devastating fashion as quadriplegia and pseudobulbar palsy. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states. The pathology consists of demyelination without inflammation in the base of the pons, with relative sparing of axons and nerve cells. MRI is useful in establishing the diagnosis **(Fig. 33-5)** and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze without quadriplegia. Occasional cases present with lesions outside of the brainstem. Therapeutic guidelines for the restoration of severe hyponatremia should aim for gradual correction, i.e., by ≤10 mmol/L (10 meq/L) within 24 h and 20 mmol/L (20 meq/L) within 48 h.

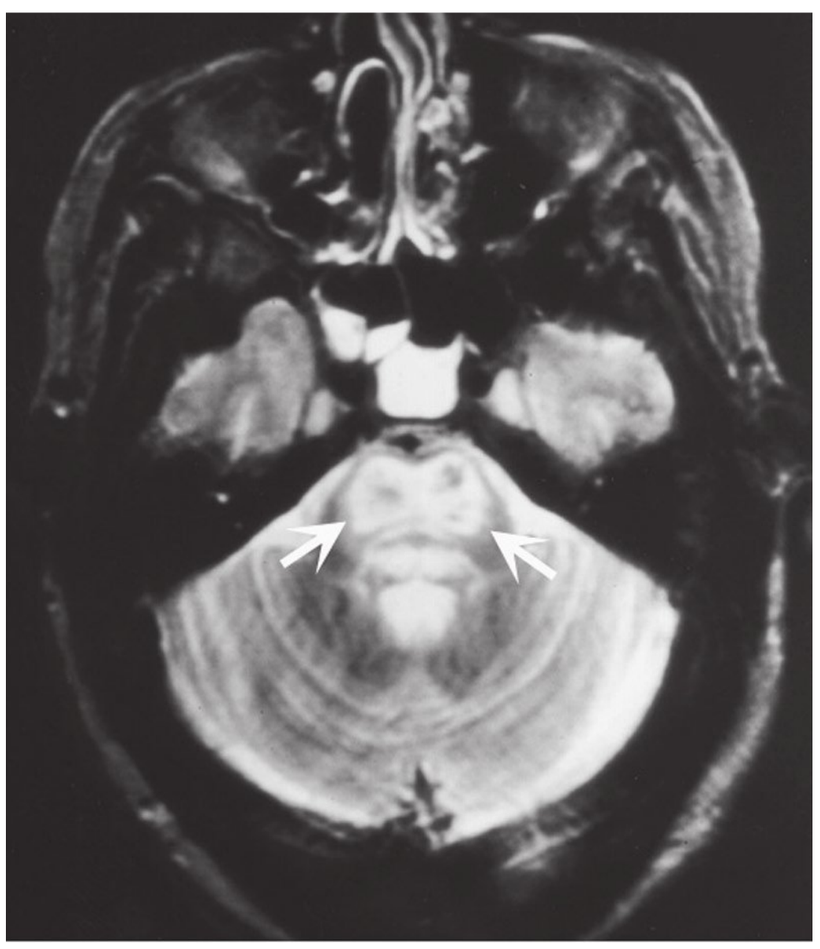


FIGURE 33-5
Central pontine myelinolysis. Axial T2-weighted magnetic resonance scan through the pons reveals a symmetric area of abnormal high signal intensity within the basis pontis (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

WERNICKE'S DISEASE

Wernicke's disease is a common and preventable disorder due to a deficiency of thiamine. In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, starvation, renal dialysis, cancer, AIDS, or rarely gastric surgery are also at risk. The characteristic clinical triad is that of ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease.

Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (Korsakoff's psychosis). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing.

Pathology

Periventricular lesions surround the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mammillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelination, and some neuronal loss. These changes may be detected by MRI scanning **(Fig. 33-6)**. The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus.

Pathogenesis

Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates due to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.

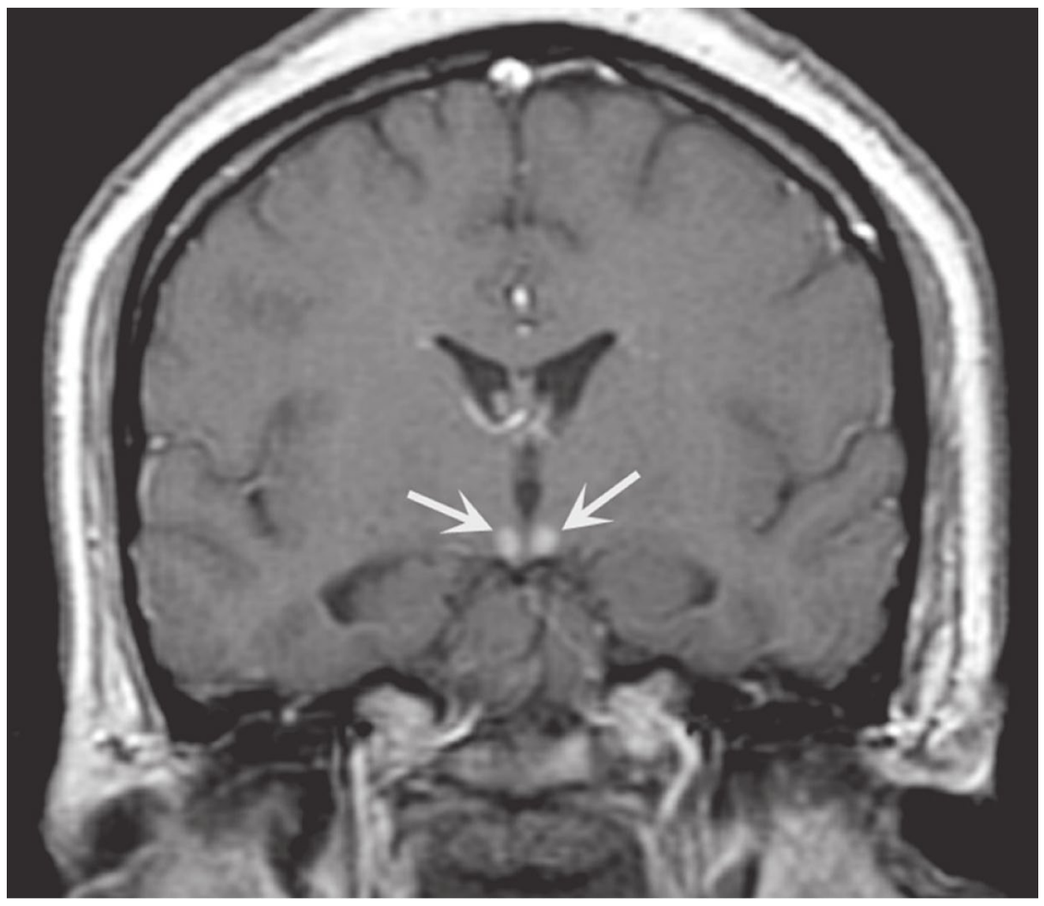


FIGURE 33-6
Wernicke's disease. Coronal T1-weighted postcontrast magnetic resonance imaging reveals abnormal enhancement of the mammillary bodies (arrows), typical of acute Wernicke's encephalopathy.

TREATMENT Wernicke's Disease

Wernicke's disease is a medical emergency and requires immediate administration of thiamine, in a dose of 100 mg either IV or IM. The dose should be given daily until the patient resumes a normal diet and should be begun prior to treatment with IV glucose solutions. Larger doses, 100 mg four times a day or more, have been advocated by some. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM

Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventilation, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome **(Chap. 54)**,

www.ketabpezeshki.com (021) 66485457 - 66485438

neuromuscular junction disorders including myasthenia gravis **(Chap. 55)** and botulism, and primary muscle disorders such as polymyositis **(Chap. 56)**. T e latter result either from the systemic disease itself or as a consequence of interventions.

General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to <–25 cmH_2O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspiration. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventilation should be undertaken based on clinical assessment rather than waiting until oxygen saturation drops or CO_2 retention develops from hypoventilation. Noninvasive mechanical ventilation may be considered initially in lieu of endotracheal intubation but is generally insuf cient in patients with severe bulbar weakness or ventilatory failure with hypercarbia.

NEUROPATHY

Although encephalopathy may be the most obvious neurologic dysfunction in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. Critical illness polyneuropathy refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged critical illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have confirmed axonal degeneration. T e precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cytokines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Aggressive glycemic control with insulin infusions appears to decrease the risk of critical illness polyneuropathy. Treatment is otherwise supportive, with specific intervention directed at treating the underlying illness. Although spontaneous recovery is usually seen, the time course may extend over weeks to months and necessitate long-term ventilatory support and care even after the underlying critical illness has resolved.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Botulism may be acquired by ingesting botulinum toxin from improperly stored food or may arise from an anaerobic abscess from Clostridium botulinum (wound botulism). Infants can present with generalized weakness from gut-derived Clostridium infection, especially if they are fed honey. Diplopia and dysphagia are early signs of foodborne botulism. Treatment is mostly supportive, although use of antitoxin early in the course may limit the duration of the neuromuscular blockade. General ICU care is similar to patients with Guillain-Barré syndrome or myasthenia gravis with focused care to avoid ulcer formation at pressure points, deep venous thromboprophylaxis, and infection prevention. Public health of cers should be rapidly informed when the diagnosis is made to prevent further exposure to others from the tainted food or source of wound botulism (such as injection drug use).

Undiagnosed myasthenia gravis **(Chap. 55)** may be a consideration in weak ICU patients; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neuromuscular transmission; these include antibiotics, especially aminoglycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and cisatracurium. T ey are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use persistent neuromuscular blockade may result in weakness even after discontinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure.

Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should

www.ketabpezeshki.com (021) 66485457 - 66485438

be used to achieve the desired result and, when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function.

MYOPATHY

Critically ill patients, especially those with sepsis, frequently develop muscle weakness and wasting, often in the face of seemingly adequate nutritional support. Critical illness myopathy is an overall term that describes several different discrete muscle disorders that may occur in critically ill patients. T e assumption has been that a catabolic myopathy may develop as a result of multiple factors, including elevated cortisol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as cachectic myopathy, serum creatine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. T is less common acute necrotizing intensive care myopathy is characterized clinically by weakness progressing to a profound level over just a few days. T ere may be associated elevations in serum creatine kinase and urine myoglobin. Both EMG and muscle biopsy may be normal initially but eventually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Acute rhabdomyolysis can occur from alcohol ingestion or from compartment syndromes.

A thick-f lament myopathy may occur in the setting of glucocorticoid and nd-NMBA use. T e most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocorticoids and nd-NMBA to facilitate mechanical ventilation. T is muscle disorder is not due to prolonged action of nd-NMBAs at the neuromuscular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use or sepsis alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be loss of thick (myosin) filaments. T ick-filament critical illness myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheotomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy.

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) renders the brain critically ill from both primary and secondary brain insults. Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Some idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

SACCULAR ("BERRY") ANEURYSM

Autopsy and angiography studies have found that about 2% of adults harbor intracranial aneurysms, for a prevalence of 4 million persons in the United States; the aneurysm will rupture, producing SAH, in 25,000–30,000 cases per year. For patients who arrive alive at hospital, the mortality rate over the next month is about 45%. Of those who survive, more than half are left with major neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is about 20% in the first 2 weeks, 30% in the first month, and about 3% per year afterward. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the SAH.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. T e annual risk of rupture for aneurysms <10 mm in size is ~0.1%, and for aneurysms ≥10 mm in size is ~0.5–1%; the surgical morbidity rate far exceeds these percentages. Because of the longer length of exposure to risk of rupture, younger patients with aneurysms >10 mm in size may benefit from prophylactic treatment. As with the treatment of asymptomatic carotid stenosis, this risk-benefit ratio strongly depends on the complication rate of treatment.

Giant aneurysms, those >2.5 cm in diameter, occur at the same sites (see below) as small aneurysms and account for 5% of cases. T e three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the

www.ketabpezeshki.com (021) 66485457 - 66485438

basilar artery. Their risk of rupture is ~6% in the first year after identification and may remain high indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilation and rupture. Whether these lesions should be sought and repaired prior to rupture or left to heal spontaneously with antibiotic treatment is controversial.

Pathophysiology

Saccular aneurysms occur at the bifurcations of the large- to medium-sized intracranial arteries; rupture is into the subarachnoid space in the basal cisterns and often into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are important factors in planning neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth-muscle cells. At the site of rupture (most often the dome), the wall thins, and the tear that allows bleeding is often ≤0.5 mm long. Aneurysm size and site are important in predicting risk of rupture. Those >7 mm in diameter and those at the top of the basilar artery and at the origin of the posterior communicating artery are at greater risk of rupture.

Clinical manifestations

Most unruptured intracranial aneurysms are completely asymptomatic. Symptoms are usually due to rupture and resultant SAH, although some unruptured aneurysms present with mass effect on cranial nerves or brain parenchyma. At the moment of aneurysmal rupture with major SAH, the ICP suddenly rises. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In ~45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache "the worst headache of my life"; however, the most important characteristic is sudden onset. Occasionally, these ruptures may present as headache of only moderate intensity or as a change in the patient's usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or MCA bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The deficits that result can include hemiparesis, aphasia, and abulia.

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy, particularly when associated with pupillary dilation, loss of ipsilateral (but retained contralateral) light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm **(Chap. 32)**. Pain in or behind the eye and in the low temple can occur with an expanding MCA aneurysm. The underclap headache is a variant of migraine that simulates an SAH. Before concluding that a patient with sudden, severe headache has thunderclap migraine, a definitive workup for aneurysm or other intracranial pathology is required.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called sentinel bleeds. Sudden unexplained headache at any location should raise suspicion of SAH and be investigated, because a major hemorrhage may be imminent.

The initial clinical manifestations of SAH can be graded using the Hunt-Hess or World Federation of Neurosurgical Societies classification schemes **(Table 33-3)**. For ruptured aneurysms, prognosis for good outcomes falls as the grade increases. For example, it is unusual for a Hunt-Hess grade 1 patient to die if the aneurysm is treated, but the mortality rate for grade 4 and 5 patients may be as high as 80%.

Delayed neurologic deficits

There are four major causes of delayed neurologic deficits: rerupture, hydrocephalus, vasospasm, and hyponatremia.

1. Rerupture. The incidence of rerupture of an untreated aneurysm in the first month following SAH is ~30%, with the peak in the first 7 days. Rerupture is associated with a 60% mortality rate and poor outcome. Early treatment eliminates this risk.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 33-3

GRADING SCALES FOR SUBARACHNOID HEMORRHAGE

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS[a] score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3–6, with or without motor deficits

[a]Glasgow Coma Scale; see **Table 44-1**.

2. Hydrocephalus. Acute hydrocephalus can cause stupor and coma and can be mitigated by placement of an external ventricular drain. More often, subacute hydrocephalus may develop over a few days or weeks and causes progressive drowsiness or slowed mentation (abulia) with incontinence. Hydrocephalus is differentiated from cerebral vasospasm with a CT scan, CT angiogram, transcranial Doppler (TCD) ultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.
3. Vasospasm. Narrowing of the arteries at the base of the brain following SAH causes symptomatic ischemia and infarction in ~30% of patients and is the major cause of delayed morbidity and death. Signs of ischemia appear 4–14 days after the hemorrhage, most often at 7 days. The severity and distribution of vasospasm determine whether infarction will occur.

   Delayed vasospasm is believed to result from direct effects of clotted blood and its breakdown products on the arteries within the subarachnoid space. In general, the more blood that surrounds the arteries, the greater the chance of symptomatic vasospasm. Spasm of major arteries produces symptoms referable to the appropriate vascular territory **(Chap. 32)**. All of these focal symptoms may present abruptly, fluctuate, or develop over a few days. In most cases, focal spasm is preceded by a decline in mental status.

   Vasospasm can be detected reliably with conventional x-ray angiography, but this invasive procedure is expensive and carries the risk of stroke and other complications. TCD ultrasound is based on the principle that the velocity of blood flow within an artery will rise as the lumen diameter is narrowed. By directing the probe along the MCA and proximal anterior cerebral artery (ACA), carotid terminus, and vertebral and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected and treatments initiated to prevent cerebral ischemia (see below). CT angiography is another method that can detect vasospasm.

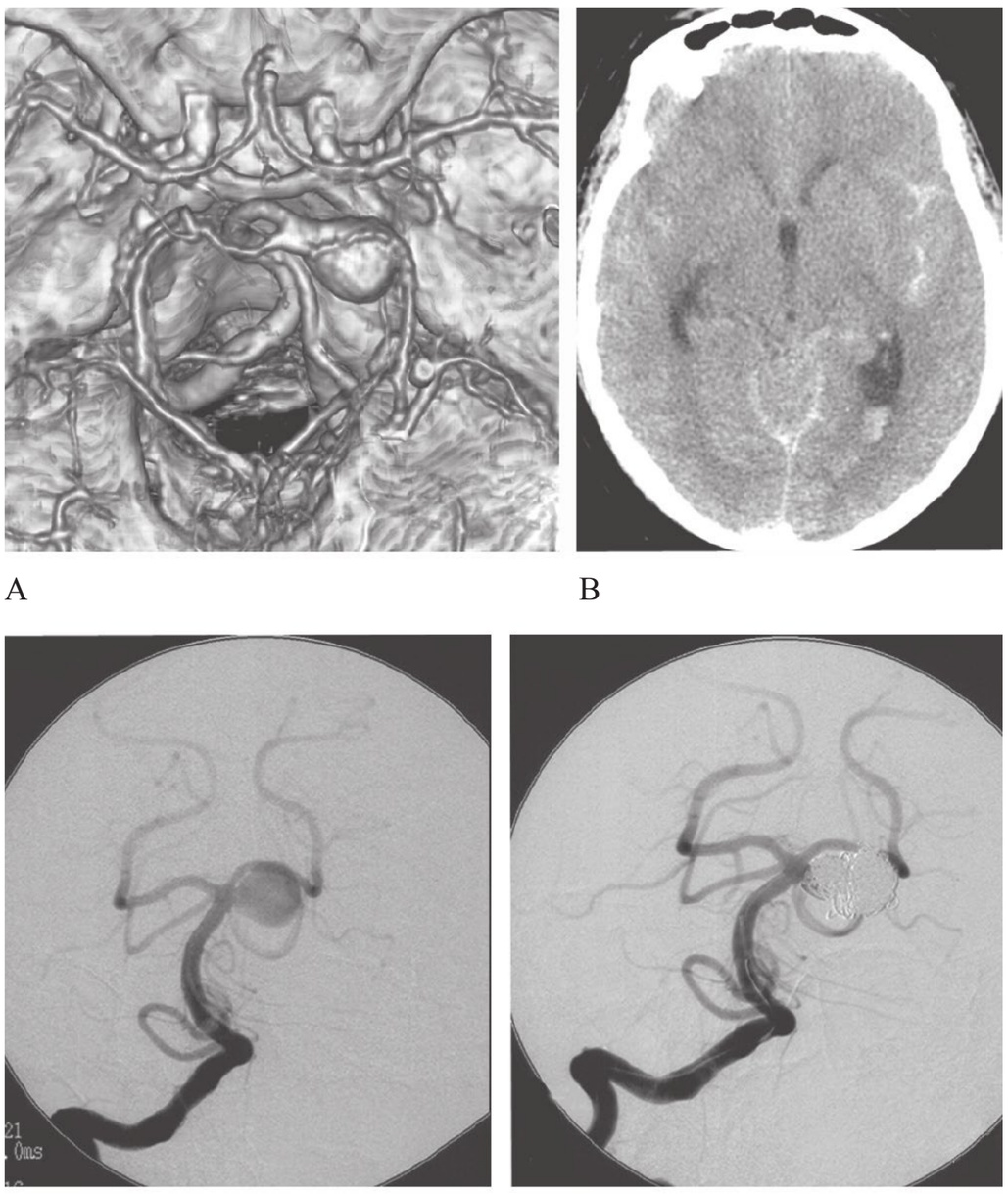
   Severe cerebral edema in patients with infarction from vasospasm may increase the ICP enough to reduce cerebral perfusion pressure. Treatment may include mannitol, hyperventilation, and hemicraniectomy; moderate hypothermia may have a role as well.
4. Hyponatremia. Hyponatremia may be profound and can develop quickly in the first 2 weeks following SAH. There is both natriuresis and volume depletion with SAH, so that patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this "cerebral salt-wasting syndrome." Typically, it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free-water restriction as this may increase the risk of stroke (see below).

Laboratory evaluation and imaging

(Fig. 33-7) The hallmark of aneurysmal rupture is blood in the CSF. More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h. If the scan fails to establish the diagnosis of SAH and no mass lesion or obstructive hydrocephalus is found, a lumbar puncture should be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. It is xanthochromic spinal fluid peaks in intensity at 48 h and lasts for 1–4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on a noncontrast CT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit, and predict delayed vasospasm. A high incidence of symptomatic vasospasm in the MCA and ACA has been found when early CT scans show subarachnoid clots >5 × 3 mm in the basal cisterns, or layers of blood >1 mm thick in the cerebral fissures. CT scans less

www.ketabpezeshki.com (021) 66485457 - 66485438



A B C D

FIGURE 33-7
Subarachnoid hemorrhage. A. Computed tomography (CT) angiography revealing an aneurysm of the left superior cerebellar artery. B. Noncontrast CT scan at the level of the third ventricle revealing subarachnoid blood (bright) in the left sylvian fissure and within the left lateral ventricle. C. Conventional anteroposterior x-ray angiogram of the right vertebral and basilar artery showing the large aneurysm. D. Conventional angiogram following coil embolization of the aneurysm, whereby the aneurysm body is filled with platinum coils delivered through a microcatheter navigated from the femoral artery into the aneurysm neck.

reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

Lumbar puncture prior to an imaging procedure is indicated only if a CT scan is not available at the time of the suspected SAH. Once the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (both carotids and both vertebrals) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist **(Fig. 33-7C)**. At some centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiogram as a way to expedite treatment and minimize the number of invasive procedures. CT angiography is an alternative method for locating the aneurysm and may be suf cient to plan definitive therapy.

Close monitoring (daily or twice daily) of electrolytes is important because hyponatremia can occur precipitously during the first 2 weeks following SAH (see above).

T e electrocardiogram (ECG) frequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. A prolonged QRS complex, increased QT interval, and prominent "peaked" or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. T ere is evidence that structural myocardial lesions produced by circulating catecholamines and excessive discharge of sympathetic neurons may occur after SAH, causing these ECG changes and a reversible cardiomyopathy suf - cient to cause shock or congestive heart failure. Echocardiography reveals a pattern of regional wall motion abnormalities that follow the distribution of sympathetic nerves rather than the major coronary arteries, with relative sparing of the ventricular wall apex. T e sympathetic nerves themselves appear to be injured by direct toxicity from the excessive catecholamine release. An asymptomatic troponin elevation is common. Serious ventricular dysrhythmias occurring in-hospital are unusual.

TREATMENT Subarachnoid Hemorrhage

Early aneurysm repair prevents rerupture and allows the safe application of techniques to improve blood flow (e.g., induced hypertension) should symptomatic vasospasm develop. An aneurysm can be "clipped" by a neurosurgeon or "coiled" by an endovascular surgeon. Surgical repair involves placing a metal clip across the aneurysm neck, thereby immediately eliminating the risk of rebleeding. T is approach requires craniotomy and brain retraction, which is associated with neurologic morbidity. Endovascular techniques involve placing platinum coils, or other embolic material, within the aneurysm via a catheter that is passed from the femoral artery. T e aneurysm is packed tightly to enhance thrombosis and over time is walled off from the circulation **(Fig. 33-7D)**. T ere have been two prospective randomized trials of surgery versus endovascular treatment for ruptured aneurysms: the first was the International Subarachnoid Aneurysm Trial (ISAT), which was terminated early when 24% of patients treated with endovascular therapy were dead or dependent at 1 year compared to 31% treated with surgery, a significant 23% relative reduction. After 5 years, risk of death was lower in the coiling group, although the proportion of survivors who were independent was the same in both groups. Risk of rebleeding was low, but more common in the coiling group. T ese results favoring coiling at 1 year were confirmed in a second trial, although the differences in functional outcome were no longer significant at 3 years. Because some aneurysms have a morphology that is not amenable to endovascular treatment, surgery remains an important treatment option. Centers that combine both endovascular and neurosurgical expertise likely offer the best outcomes for patients, and there are reliable data showing that specialized aneurysm treatment centers can improve mortality rates.

www.ketabpezeshki.com (021) 66485457 - 66485438

T e medical management of SAH focuses on protecting the airway, managing blood pressure before and after aneurysm treatment, preventing rebleeding prior to treatment, managing vasospasm, treating hydrocephalus, treating hyponatremia, limiting secondary brain insults, and preventing pulmonary embolus (PE).

Intracranial hypertension following aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to measure ICP and to treat high ICP in order to prevent cerebral ischemia. Medical therapies designed to combat raised ICP (e.g., osmotic therapy and sedation) can also be used as needed. High ICP refractory to treatment is a poor prognostic sign.

Prior to definitive treatment of the ruptured aneurysm, care is required to maintain adequate cerebral perfusion pressure while avoiding excessive elevation of arterial pressure. If the patient is alert, it is reasonable to lower the systolic blood pressure to below 160 mmHg using nicardipine, labetalol, or esmolol. If the patient has a depressed level of consciousness, ICP should be measured and the cerebral perfusion pressure targeted to 60–70 mmHg. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided if possible because it can obscure the ability to clinically detect changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. T e quivering, jerking, and extensor posturing that often accompany loss of consciousness with SAH are probably related to the sharp rise in ICP rather than seizures. However, anticonvulsants are sometimes given as prophylactic therapy because a seizure could theoretically promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. T ere is no good evidence that they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is not recommended.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. T ey are associated with a reduced incidence of aneurysmal rerupture but may also increase the risk of delayed cerebral infarction and deep vein thrombosis (DVT). Several recent studies suggest that a shorter duration of use (until the aneurysm is secured or for the first 3 days) may decrease rerupture and be safer than found in earlier studies of longer duration treatment.

Vasospasm remains the leading cause of morbidity and mortality following aneurysmal SAH. Treatment with the calcium channel antagonist nimodipine (60 mg PO every 4 h) improves outcome, perhaps by preventing ischemic injury rather than reducing the risk of vasospasm. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. Symptomatic cerebral vasospasm can also be treated by increasing the cerebral perfusion pressure by raising mean arterial pressure through plasma volume expansion and the judicious use of IV vasopressor agents, usually phenylephrine or norepinephrine. Raised perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and hypervolemia generally requires monitoring of arterial and central venous pressures; it is best to infuse pressors through a central venous line as well. Volume expansion helps prevent hypotension and augments cardiac output.

If symptomatic vasospasm persists despite optimal medical therapy, intraarterial vasodilators and percutaneous transluminal angioplasty are considered. Vasodilatation by direct angioplasty appears to be permanent, allowing hypertensive therapy to be tapered sooner. T e pharmacologic vasodilators (verapamil and nicardipine) do not last more than about 24 h, and therefore multiple treatments may be required until the subarachnoid blood is reabsorbed. Although intraarterial papaverine is an effective vasodilator, there is evidence that papaverine may be neurotoxic, so its use should generally be avoided.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients with SAH at risk for vasospasm because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients also require intravenous hypertonic saline. Care must be taken not to correct serum sodium too quickly in patients with marked hyponatremia of several days' duration, as central pontine myelinolysis may occur.

All patients should have pneumatic compression stockings applied to prevent pulmonary embolism. Unfractionated heparin administered subcutaneously for DVT prophylaxis can be initiated immediately following endovascular treatment and within days following craniotomy with surgical clipping and is a useful adjunct to pneumatic compression stockings. Treatment of pulmonary embolus depends on whether the aneurysm has been treated and whether or not the patient has had a craniotomy. Systemic anticoagulation with heparin is contraindicated in patients with ruptured and untreated aneurysms. It is a relative contraindication following craniotomy for several days, and it may delay thrombosis of a coiled aneurysm. If DVT or PE occurs within the first days following craniotomy, use of an inferior vena cava filter may be considered to prevent additional pulmonary emboli, whereas systemic anticoagulation with heparin is preferred following successful endovascular treatment.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 34

MIGRAINE AND OTHER PRIMARY HEADACHE DISORDERS

Peter J. Goadsby ■ Neil H. Raskin

T e general principles around headache as a cardinal symptom are covered elsewhere **(Chap. 9)**; here we discuss disorders in which headache and associated features occur in the absence of any exogenous cause. T e most common are migraine, tension-type headache, and the trigeminal autonomic cephalalgias, notably cluster headache; the complete list is summarized in **Table 34-1**.

MIGRAINE

Migraine, the second most common cause of headache, and the most common headache-related, and indeed neurologic, cause of disability in the world, afflicts approximately 15% of women and 6% of men over a 1-year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine is a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures **(Table 34-2)**. Migraine can often be recognized by its activators, referred to as triggers.

T e brain of the migraineur is particularly sensitive to environmental and sensory stimuli; migraine-prone patients do not habituate easily to sensory stimuli. T is sensitivity is amplified in females during the menstrual cycle. Headache can be initiated or amplified by various triggers, including glare, bright lights, sounds, or other afferent stimulation; hunger; let-down from stress; physical exertion; stormy weather or barometric pressure changes; hormonal fluctuations during menses; lack of or excess sleep; and alcohol or other chemical stimulation, such as with nitrates. Knowledge of a patient's susceptibility to specific triggers can be useful in management strategies involving lifestyle adjustments.

Pathogenesis

T e sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus **(Fig. 34-1)**.

Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene–related peptide (CGRP), at vascular terminations of the trigeminal nerve and within the trigeminal nucleus. CGRP receptor antagonists, gepants, have now been shown to be effective in the acute treatment and prevention of migraine, and monoclonal antibodies to CGRP have been shown effective in multiple phase II clinical trials. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established antinociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus coeruleus in the pons and the rostroventromedial medulla.

Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as serotonin) in migraines. Approximately 60 years ago, methysergide was found to antagonize certain peripheral actions of 5-HT and was introduced as the first drug capable of preventing migraine attacks. T e triptans were designed to stimulate selectively subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. T e triptans are potent agonists of 5-HT_{1B} and 5-HT_{1D} receptors, and some are active at the 5-HT_{1F} receptors; the latter's exclusive agonists are called ditans. Triptans arrest nerve signaling in the nociceptive pathways of the trigeminovascular system, at least in the trigeminal

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-1

PRIMARY HEADACHE DISORDERS, MODIFIED FROM INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS-III-BETA (HEADACHE CLASSIFICATION COMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY, 2013)	
1. Migraine	1.1 Migraine without aura 1.2 Migraine with aura 1.2.1 Migraine with typical aura 1.2.1.1 Typical aura with headache 1.2.1.2 Typical aura without headache 1.2.2 Migraine with brainstem aura 1.2.3 Hemiplegic migraine 1.2.3.1 Familial hemiplegic migraine (FHM) 1.2.3.1.1 Familial hemiplegic migraine type 1 1.2.3.1.2 Familial hemiplegic migraine type 2 1.2.3.1.3 Familial hemiplegic migraine type 3 1.2.3.2 Sporadic hemiplegic migraine 1.2.4 Retinal migraine 1.3 Chronic migraine 1.4 Complications of migraine 1.4.1 Status migrainosus 1.4.2 Persistent aura without infarction 1.4.3 Migrainous infarction 1.4.4 Migraine aura-triggered seizure 1.5 Probable migraine 1.5.1 Probable migraine without aura 1.5.2 Probable migraine with aura 1.6 Episodic syndromes that may be associated with migraine 1.6.1 Recurrent gastrointestinal disturbance 1.6.1.1 Cyclical vomiting syndrome 1.6.1.2 Abdominal migraine 1.6.2 Benign paroxysmal vertigo 1.6.3 Benign paroxysmal torticollis
2. Tension-type headache	2.1 Infrequent episodic tension-type headache 2.2 Frequent episodic tension-type headache 2.3 Chronic tension-type headache
3. Trigeminal autonomic cephalalgias	3.1 Cluster headache 3.1.1 Episodic cluster headache 3.1.2 Chronic cluster headache 3.2 Paroxysmal hemicrania 3.2.1 Episodic paroxysmal hemicrania 3.2.2 Chronic paroxysmal hemicrania 3.3 Short-lasting unilateral neuralgiform headache attacks 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) 3.4 Hemicrania continua
4. Other primary headache disorders	4.1 Primary cough headache 4.2 Primary exercise headache 4.3 Primary headache associated with sexual activity 4.4 Primary thunderclap headache 4.5 Cold-stimulus headache 4.5.1 Headache attributed to external application of a cold stimulus 4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus 4.6 External-pressure headache 4.6.1 External-compression headache 4.6.2 External-traction headache 4.7 Primary stabbing headache 4.8 Nummular headache 4.9 Hypnic headache 4.10 New daily persistent headache (NDPH)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-2

SYMPTOMS ACCOMPANYING SEVERE MIGRAINE ATTACKS IN 500 PATIENTS

SYMPTOM	PATIENTS AFFECTED, %
Nausea	87
Photophobia	82
Lightheadedness	72
Scalp tenderness	65
Vomiting	56
Visual disturbances	36
Paresthesias	33
Vertigo	33
Photopsia	26
Alteration of consciousness	18
Diarrhea	16
Fortification spectra	10
Syncope	10
Seizure	4
Confusional state	4

Source: From NH Raskin: Headache, 2nd ed. New York, Churchill Livingston, 1988; with permission.

nucleus caudalis and trigeminal sensory thalamus, in addition to cranial vasoconstriction, while ditans, now shown conclusively to be effective in acute migraine, act only at neural targets. An interesting range of neural targets is now being actively pursed for the acute and preventive management of migraine.

Data also support a role for dopamine in the pathophysiology of migraine. Most migraine symptoms can be induced by dopaminergic stimulation. Moreover, there is dopamine receptor hypersensitivity in migraineurs, as demonstrated by the induction of yawning, nausea, vomiting, hypotension, and other symptoms of a migraine attack by dopaminergic agonists at doses that do not affect nonmigraineurs. Dopamine receptor antagonists are effective therapeutic agents in migraine, especially when given parenterally or concurrently with other antimigraine agents. Moreover, hypothalamic activation, anterior to that seen in cluster headache, has now been shown in the premonitory phase of migraine using functional imaging, and this may hold a key to understanding some part of the role of dopamine in the disorder.

Migraine genes identified by studying families with familial hemiplegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in

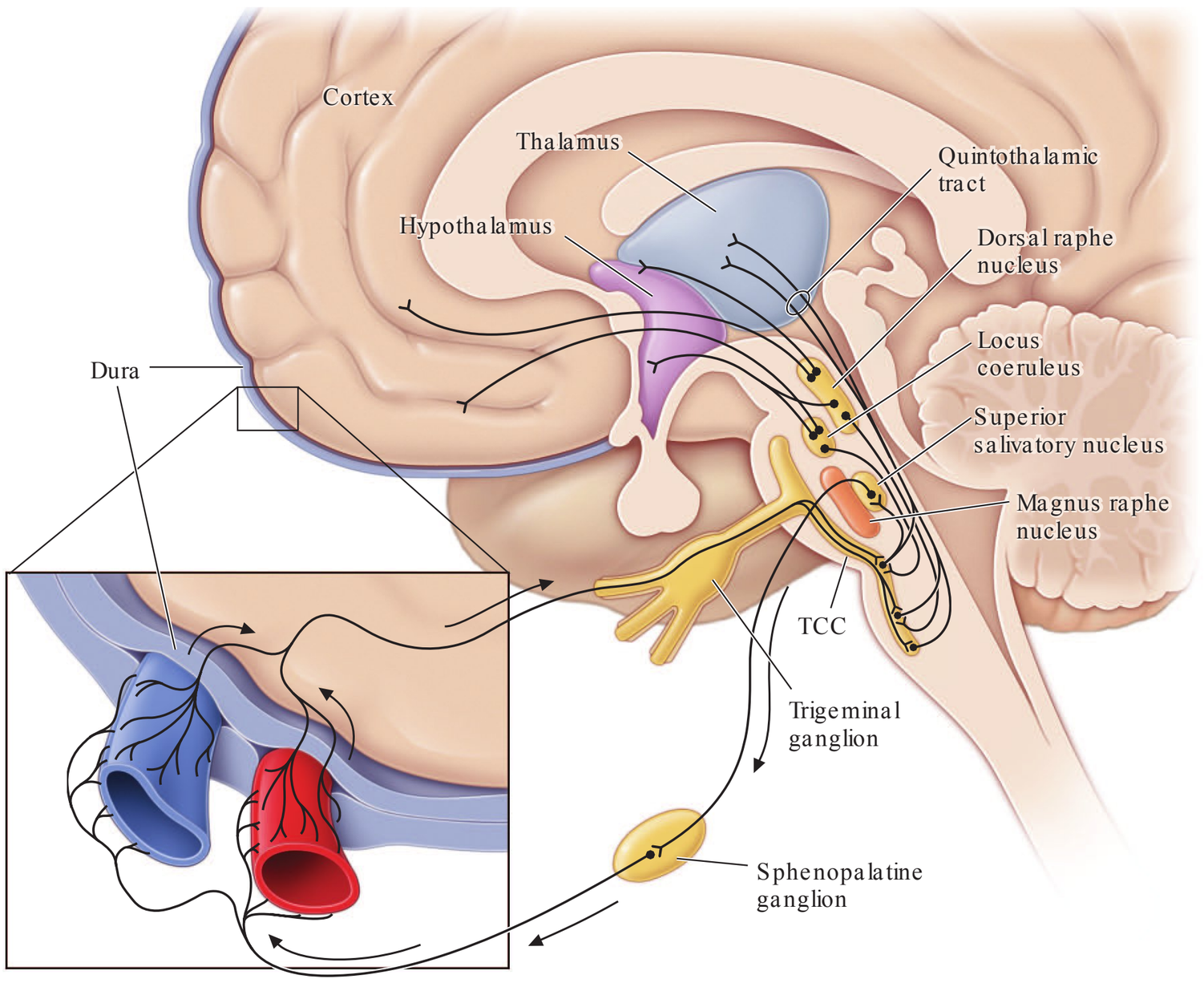


FIGURE 34-1

Brainstem pathways that modulate sensory input. The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex (TCC). These neurons in turn project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

www.ketabpezeshki.com (021) 66485457 - 66485438

membrane excitability can predispose to migraine. Mutations involving the $Ca_v2.1$ (P/Q)–type voltage-gated calcium channel CACNA1A gene are now known to cause FHM 1; this mutation is responsible for about 50% of FHMs. Mutations in the Na^+-K^+ATPase ATP1A2 gene, designated FHM 2, are responsible for about 20% of FHMs. Mutations in the neuronal voltage-gated sodium channel SCN1A cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine **(Fig. 34-2)** and the posterior hypothalamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache **(Fig. 34-3)** are good candidates for specific involvement in primary headache.

Diagnosis and clinical features

Diagnostic criteria for migraine headache are listed in **Table 34-3**. A high index of suspicion is required to diagnose migraine: the migraine aura, consisting of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms, is reported in only 20–25% of patients. A headache diary can often be helpful in making the diagnosis; this is also helpful in assessing disability and the frequency of treatment for acute attacks. Patients with episodes of migraine that occur daily or near-daily are considered to have chronic migraine **(see "Chronic Daily Headache" in Chap. 9)**. Migraine must be differentiated from tension-type headache (discussed below),

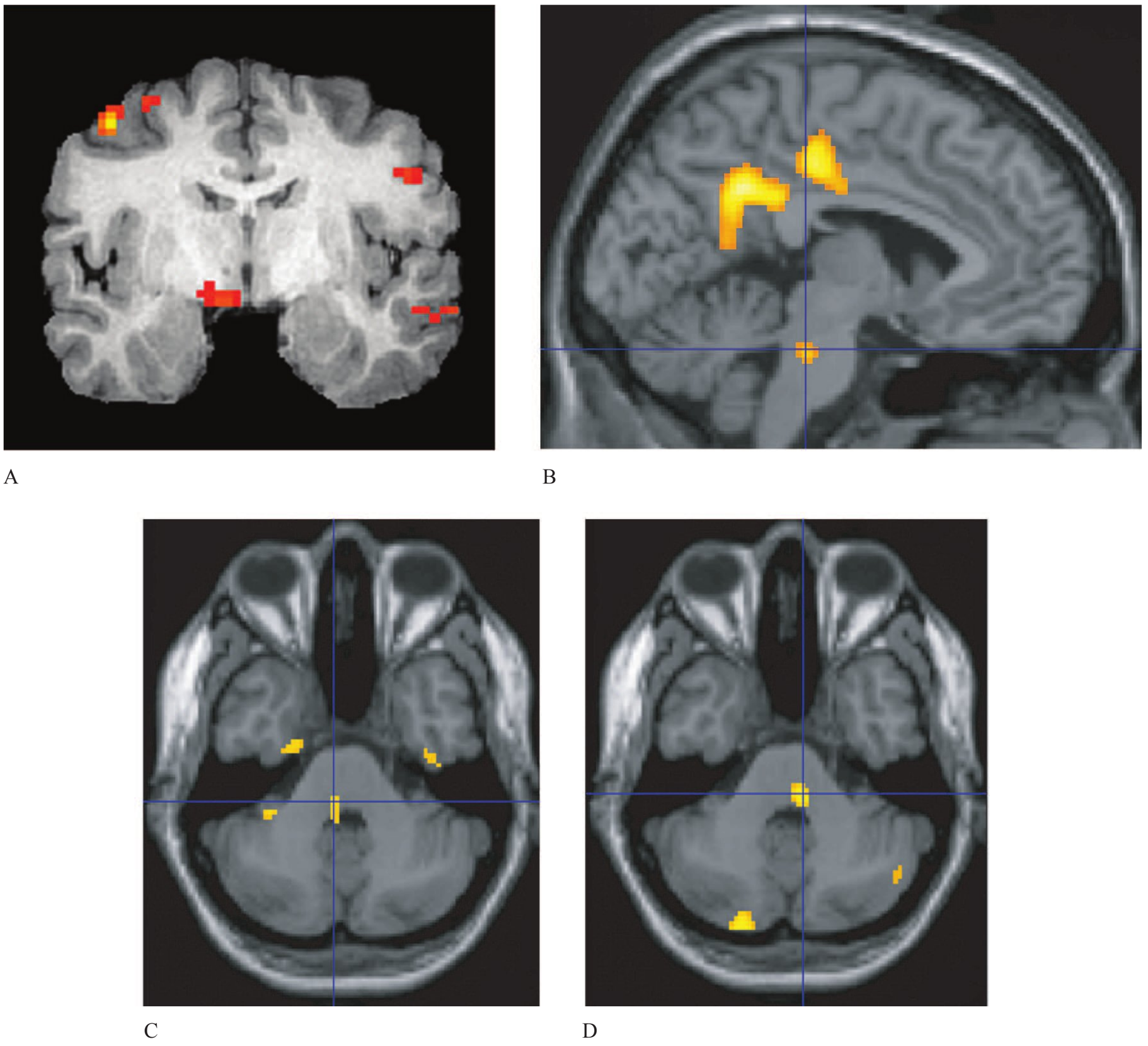
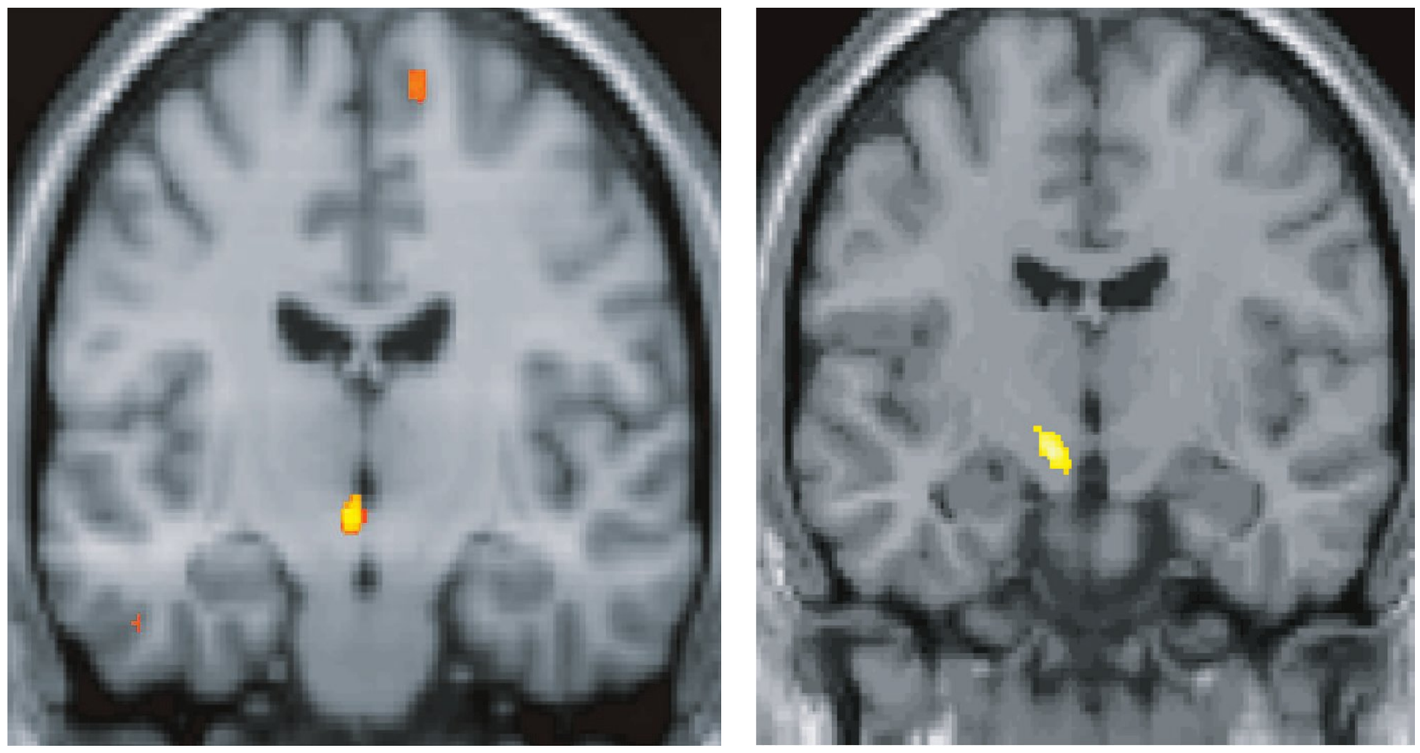


FIGURE 34-2

Positron emission tomography (PET) activation in migraine. Hypothalamic, dorsal midbrain, and dorsolateral pontine activation is seen in triggered attacks in the premonitory phase before pain, whereas in migraine attacks, dorsolateral pontine activation persists, as it does in chronic migraine (not shown). The dorsolateral pontine area, which includes the noradrenergic locus coeruleus, is fundamental to the expression of migraine. Moreover, lateralization of changes in this region of the brainstem correlates with lateralization of the head pain in hemicranial migraine; the scans shown in panels C and D are of patients with acute migraine headache on the right and left side, respectively. (Panel A *from* FH Maniyar et al: Brain 137:232, 2014; panel B *from* SK Afridi et al: Arch Neurol 2005;62:1270; Panels C and D *from* SK Afridi et al: Brain 128:932, 2005.)

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 34-3

A. Posterior hypothalamic gray matter activation by positron emission tomography in a patient with acute cluster headache. (From A May et al: Lancet 352:275, 1998.) B. High-resolution T1-weighted magnetic resonance image obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache. (From A May et al: Nat Med 5:836, 1999.)

the most common primary headache syndrome seen in the population. Migraine has several forms that have been defined (Table 34-1): migraine with and without aura and chronic migraine, the latter occurring 15 days or more a month, as the most important. Migraine at its most basic level is headache with associated features, and tension-type headache is headache that is featureless. Most patients with disabling headache probably have migraine.

Patients with acephalgic migraine (typical aura without headache, 1.2.1.2 in Table 34-1) experience recurrent neurologic symptoms, often with nausea or vomiting, but with little or no headache. Vertigo can be prominent; it has been estimated that one-third of patients referred for vertigo or dizziness have a primary diagnosis of migraine. Migraine aura can have prominent brainstem symptoms, and the terms basilar artery and basilar-type migraine have now been replaced by migraine with brainstem aura (Table 34-1).

TABLE 34-3

SIMPLIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE	
REPEATED ATTACKS OF HEADACHE LASTING 4–72 H IN PATIENTS WITH A NORMAL PHYSICAL EXAMINATION, NO OTHER REASONABLE CAUSE FOR THE HEADACHE, AND:	
AT LEAST 2 OF THE FOLLOWING FEATURES:	PLUS AT LEAST 1 OF THE FOLLOWING FEATURES:
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2013).

TREATMENT Migraine Headache

Once a diagnosis of migraine has been established, it is important to assess the extent of a patient's disease and disability. The Migraine Disability Assessment Score (MIDAS) is a well-validated, easy-to-use tool **(Fig. 34-4)**.

Patient education is an important aspect of migraine management. Information for patients is available at sites such as www.achenet.org, the website of the American Council for Headache Education (ACHE). It is helpful for patients to understand that migraine is an inherited tendency to headache; that migraine can be modified and controlled by lifestyle adjustments and medications, but it cannot be eradicated; and that, except in some occasions in women on oral estrogens or contraceptives, migraine is not associated with serious or life-threatening illnesses.

NONPHARMACOLOGIC MANAGEMENT Migraine can often be managed to some degree by a variety of nonpharmacologic approaches. Most patients benefit by the identification and avoidance of specific headache triggers. A regulated lifestyle is helpful, including a healthy diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance of acute changes in stress levels, being particularly wary of the let-down effect.

The measures that benefit a given individual should be used routinely because they provide a simple, cost-effective approach to migraine management. Patients with migraine do not encounter more stress than headache-free

www.ketabpezeshki.com (021) 66485457 - 66485438

***MIDAS Questionnaire**

INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... _____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.) ..... _____ days
3. On how many days in the last 3 months did you **not** do household work because of your headaches? ..... _____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.) ..... _____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... _____ days

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than one day, count each day.) ..... _____ days

B. On a scale of 0–10, on average how painful were these headaches? (Where 0 = no pain at all, and 10 = pain as bad as it can be.) ..... _____

*Migraine Disability Assessment Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: > 20

© Innovative Medical Research 1997

FIGURE 34-4
The Migraine Disability Assessment Score (MIDAS) Questionnaire.

individuals; over-responsiveness to changes in stress appears to be the issue. Because the stresses of everyday living cannot be eliminated, lessening one's response to stress by various techniques is helpful for many patients. T ese may include yoga, transcendental meditation, hypnosis, and conditioning techniques such as biofeedback. For most patients, this approach is, at best, an adjunct to pharmacotherapy. Nonpharmacologic measures are unlikely to prevent all migraine attacks. If these measures fail to prevent an attack, pharmacologic approaches are then needed to abort an attack.

ACUTE ATTACK THERAPIES FOR MIGRAINE T e mainstay of pharmacologic therapy is the judicious use of one or more of the many medicines that are effective in migraine **(Table 34-4)**. T e selection of the optimal regimen for a given patient depends on a number of factors, the most important of which is the severity of the attack. Mild migraine attacks can usually be managed by oral agents; the average ef cacy rate is 50–70%. Severe migraine attacks may require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of three major pharmacologic classes: nonsteroidal anti-inflammatory drugs, 5-$HT_{1B/1D}$ receptor agonists, and dopamine receptor antagonists.

In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks or a different class of drug tried as first-line treatment. Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be constantly refined until one is identified that provides the patient with rapid, complete, and consistent relief with minimal side effects **(Table 34-5)**.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Both the severity and duration of a migraine attack can be reduced significantly by NSAIDs (Table 34-4). Indeed, many undiagnosed migraineurs self-treat with nonprescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of these agents in migraine is usually less than optimal in moderate or severe migraine attacks. T e combination of acetaminophen, aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate migraine. T e combination of aspirin and metoclopramide has been shown to be comparable to a single dose of oral sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

5-$HT_{1B/1D}$ RECEPTOR AGONISTS

Oral Stimulation of 5-$HT_{1B/1D}$ receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, whereas the triptans are selective

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-4

TREATMENT OF ACUTE MIGRAINE

DRUG	TRADE NAME	DOSAGE
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg PO bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg PO q3–4h
Tolfenamic acid	Clotam Rapid	200 mg PO; may repeat ×1 after 1–2 h
Diclofenac K	Cambia	50 mg PO with water
5-HT_1 Receptor Agonists		
Oral		
Ergotamine 1 mg, caffeine 100 mg	Cafergot	One or two tablets at onset, then one tablet q½h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5-mg tablet at onset; may repeat once after 4 h
Rizatriptan	Maxalt Maxalt-MLT	5–10-mg tablet at onset; may repeat after 2 h (max 30 mg/d)
Sumatriptan	Imitrex	50–100-mg tablet at onset; may repeat after 2 h (max 200 mg/d)
Frovatriptan	Frova	2.5-mg tablet at onset, may repeat after 2 h (max 5 mg/d)
Almotriptan	Axert	12.5-mg tablet at onset, may repeat after 2 h (max 25 mg/d)
Eletriptan	Relpax	40 or 80 mg
Zolmitriptan	Zomig Zomig Rapimelt	2.5-mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray
Sumatriptan	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
Zolmitriptan	Zomig	5 mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d)
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection Alsuma Sumavel DosePro	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
Dopamine Receptor Antagonists		
Oral		
Metoclopramide	Reglan,[a] generic[a]	5–10 mg/d
Prochlorperazine	Compazine,a generic[a]	1–25 mg/d
Parenteral		
Chlorpromazine	Generic[a]	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan,[a] generic	10 mg IV
Prochlorperazine	Compazine,[a] generic[a]	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, plus dichloralphenazone, 100 mg, plus isometheptene, 65 mg	Midrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Nasal		
Butorphanol	Generic	1 mg (1 spray in 1 nostril), may repeat if necessary in 1–2 h
Parenteral		
Opioids	Generic[a]	Multiple preparations and dosages; **see Table 18-1**

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.

Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.

Abbreviations: 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-5

CLINICAL STRATIFICATION OF ACUTE SPECIFIC MIGRAINE TREATMENTS

CLINICAL SITUATION	TREATMENT OPTIONS
Failed NSAIDs/ analgesics	**First tier** Sumatriptan 50 mg or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eletriptan 40 mg PO Zolmitriptan 2.5 mg PO **Slower ef ect/better tolerability** Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO **Infrequent headache** Ergotamine/caffeine 1–2/100 mg PO Dihydroergotamine nasal spray 2 mg
Early nausea or dif - culties taking tablets	Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/ usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg
Tolerating acute treat- ments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg
Early vomiting	Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC
Menses-related headache	**Prevention** Ergotamine PO at night Estrogen patches **Treatment** Triptans Dihydroergotamine nasal spray
Very rapidly develop- ing symptoms	Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

5-$HT_{1B/1D}$ receptor agonists. A variety of triptans, 5-$HT_{1B/1D}$ receptor agonists—sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan—are now available for the treatment of migraine.

Each drug in the triptan class has similar pharmacologic properties but varies slightly in terms of clinical ef cacy. Rizatriptan and eletriptan are the most ef cacious of the triptans currently available in the United States. Sumatriptan and zolmitriptan have similar rates of ef cacy as well as time to onset, with an advantage of having multiple formulations, whereas almotriptan has a similar rate of ef cacy to sumatriptan and is better tolerated, and frovatriptan and naratriptan are somewhat slower in onset and are better tolerated. Clinical ef cacy appears to be related more to the t_{max} (time to peak plasma level) than to the potency, half-life, or bioavailability. T is observation is consistent with a large body of data indicating that faster-acting analgesics are more effective than slower-acting agents.

Unfortunately, monotherapy with a selective oral 5-$HT_{1B/1D}$ receptor agonist does not result in rapid, consistent, and complete relief of migraine in all patients. Triptans are generally not effective in migraine with aura unless given after the aura is completed and the headache initiated. Side effects are common, although often mild and transient. Moreover, 5-$HT_{1B/1D}$ receptor agonists are contraindicated in individuals with a history of cardiovascular and cerebrovascular disease. Recurrence of headache, within usual time course of an attack, is another important limitation of triptan use and occurs at least occasionally in most patients. Evidence from randomized controlled trials show that coadministration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the initial effect of sumatriptan and, importantly, reduce rates of headache recurrence.

Ergotamine preparations offer a nonselective means of stimulating 5-HT_1 receptors. A nonnauseating dose of ergotamine should be sought because a dose that provokes nausea is too high and may intensify head pain. Except for a sublingual formulation of ergotamine, oral formulations of ergotamine also contain 100 mg caffeine (theoretically to enhance ergotamine absorption and possibly to add additional analgesic activity). T e average oral ergotamine dose for a migraine attack is 2 mg. Because the clinical studies demonstrating the ef cacy of ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is dif cult to assess the clinical ef cacy of ergotamine versus the triptans. In general, ergotamine appears to have a much higher incidence of nausea than triptans but less headache recurrence.

Nasal Nasal formulations of dihydroergotamine (Migranal), zolmitriptan (Zomig nasal), or sumatriptan can be useful in patients requiring a nonoral route of administration. T e nasal sprays result in substantial blood levels within 30–60 min. Although in theory nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported ef cacy is only approximately 50–60%. Studies with a new inhalational formulation of dihydroergotamine indicate that its absorption problems can be overcome to produce rapid onset of action with good tolerability.

Parenteral Administration of drugs by injection, such as dihydroergotamine and sumatriptan, is approved by the FDA for the rapid relief of a migraine attack. Peak plasma levels of dihydroergotamine are achieved 3 min after IV dosing, 30 min after IM dosing, and 45 min after SC dosing. If an attack has not already peaked, SC or IM administration of 1 mg of dihydroergotamine suf ces for about 80–90% of patients. Sumatriptan, 4–6 mg SC, is effective in ~50–80% of patients, and can now be administered by a needle-free device.

www.ketabpezeshki.com (021) 66485457 - 66485438

DOPAMINE RECEPTOR ANTAGONISTS

Oral Oral dopamine receptor antagonists can be considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs even in the absence of nausea and is related to the severity of the attack and not its duration. T erefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine receptor antagonist, such as metoclopramide 10 mg or domperidone 10 mg (not available in the United States), should be considered to enhance gastric absorption. In addition, dopamine receptor antagonists decrease nausea/vomiting and restore normal gastric motility.

Parenteral Dopamine receptor antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) by injection can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-$HT_{1B/1D}$ receptor agonists. A common IV protocol used for the treatment of severe migraine is the administration over 2 min of a mixture of 5 mg of prochlorperazine and 0.5 mg of dihydroergotamine.

OTHER MEDICATIONS FOR ACUTE MIGRAINE

Oral T e combination of acetaminophen, dichloralphenazone, and isometheptene, one to two capsules, has been classified by the FDA as "possibly" effective in the treatment of migraine. Because the clinical studies demonstrating the ef cacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is dif cult to compare the ef cacy of this sympathomimetic compound to other agents.

Nasal A nasal preparation of butorphanol is available for the treatment of acute pain. As with all opioids, the use of nasal butorphanol has little role in migraine treatment.

Parenteral Opioids are modestly effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given frequently in the emergency room. T is regimen "works" in the sense that the pain of migraine is eliminated. However, this regimen is clearly suboptimal for patients with recurrent headache. Opioids do not treat the underlying headache mechanism; rather, they act to alter the pain sensation, and there is evidence their use may decrease the likelihood of a response to triptans in the future. Moreover, in patients taking oral opioids, such as oxycodone or hydrocodone, habituation or addiction can greatly confuse the treatment of migraine. Opioid craving and/or withdrawal can aggravate and accentuate migraine. T erefore, it is recommended that opioid use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacologic approaches or who have contraindications to other therapies.

MEDICATION-OVERUSE HEADACHE

Acute attack medications, particularly opioid or barbiturate-containing compound analgesics, have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache called medication-overuse headache. T is condition is likely not a separate headache entity but a reaction of the migraine patient to a particular medicine. Migraine patients who have two or more headache days a week should be cautioned about frequent analgesic use **(see "Chronic Daily Headache" in Chap. 9)**.

PREVENTIVE TREATMENTS FOR MIGRAINE

Patients with an increasing frequency of migraine attacks or with attacks that are either unresponsive or poorly responsive to abortive treatments are good candidates for preventive agents. In general, a preventive medication should be considered in the subset of patients with four or more attacks a month. Significant side effects are associated with the use of many of these agents; furthermore, determination of dose can be dif cult because the recommended doses have been derived for conditions other than migraine. T e mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum, to achieve clinical benefit.

Drugs that have the capacity to stabilize migraine are listed in **Table 34-6**. Drugs must be taken daily, and there is usually a lag of between 2 to 12 weeks before an effect is seen. T e drugs that have been approved by the FDA for the prophylactic treatment of migraine include propranolol, timolol, sodium valproate, topiramate, and methysergide (not available). In addition, a number of other drugs appear to display prophylactic ef cacy. T is group includes amitriptyline, nortriptyline, flunarizine, phenelzine, gabapentin, and cyproheptadine. Placebo-controlled trials of onabotulinum toxin type A in episodic migraine were negative, whereas, overall, placebo-controlled trials in chronic migraine were positive. Phenelzine and methysergide are usually reserved for recalcitrant cases because of their serious potential side effects. Phenelzine is a monoamine oxidase inhibitor (MAOI); therefore, tyramine-containing foods, decongestants, and meperidine are contraindicated. Methysergide may cause retroperitoneal or cardiac valvular fibrosis when it is used for >6 months, and thus monitoring is required for patients using this drug; the risk of fibrosis is about 1:1500 and is likely to reverse after the drug is stopped.

T e probability of success with any one of the antimigraine drugs is 50–75%. Many patients are managed adequately with low-dose amitriptyline, propranolol, candesartan, topiramate, or valproate. If these agents fail or lead to unacceptable side effects, second-line agents such as methysergide or phenelzine can be used. Once effective stabilization is achieved, the drug is continued for ~6 months and then slowly tapered to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-6

PREVENTIVE TREATMENTS IN MIGRAINE[a]

DRUG	DOSE	SELECTED SIDE EFFECTS
Pizotifen[b]	0.5–2 mg qd	Weight gain Drowsiness
Beta blocker		
Propranolol	40–120 mg bid	Reduced energy
Metoprolol	25–100 mg bid	Tiredness Postural symptoms Contraindicated in asthma
Antidepressants		
Amitriptyline	10–75 mg at night	Drowsiness
Dosulepin	25–75 mg at night	
Nortriptyline	25–75 mg at night	Note: Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required
Venlafaxine	75–150 mg/d	
Anticonvulsants		
Topiramate	25–200 mg/d	Paresthesias Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities
Serotonergic drugs		
Methysergide[c]	1–4 mg qd	Drowsiness Leg cramps Hair loss Retroperitoneal fibrosis (1-month drug holiday is required every 6 months)
Other classes		
Flunarizine[b]	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
Candesartan	16 mg daily	Dizziness
Chronic migraine		
Onabotulinum toxin type A	155 U	Loss of brow furrow
No convincing evidence from controlled trials		
Verapamil		
Controlled trials demonstrate no effect		
Nimodipine		
Clonidine		
Selective serotonin reuptake inhibitors: fluoxetine		

[a]Commonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.
[b]Not available in the United States. [c]Not currently available worldwide.

www.ketabpezeshki.com (021) 66485457 - 66485438

TENSION-TYPE HEADACHE

Clinical features

The term tension-type headache (TTH) is commonly used to describe a chronic head-pain syndrome characterized by bilateral tight, band-like discomfort. The pain typically builds slowly, fluctuates in severity, and may persist more or less continuously for many days. The headache may be episodic or chronic (present >15 days per month).

A useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement. Such an approach neatly separates migraine, which has one or more of these features and is the main differential diagnosis, from TTH. The International Headache Society's main definition of TTH allows an admixture of nausea, photophobia, or phonophobia in various combinations, although the appendix definition does not; this illustrates the difficulty in distinguishing these two clinical entities. In clinical practice, dichotomizing patients on the basis of the presence of associated features (migraine) and the absence of associated features (TTH) is highly recommended. Indeed patients whose headaches fit the TTH phenotype and who have migraine at other times, along with a family history of migraine, migrainous illnesses of childhood, or typical migraine triggers to their migraine attacks, may be biologically different from those who have TTH headache with none of the features. TTH may be infrequent (episodic) or occur on 15 days or more a month (chronic).

Pathophysiology

The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of central nervous system pain modulation alone, unlike migraine, which involves a more generalized disturbance of sensory modulation. Data suggest a genetic contribution to TTH, but this may not be a valid finding: given the current diagnostic criteria, the studies undoubtedly included many migraine patients. The name tension-type headache implies that pain is a product of nervous tension, but there is no clear evidence for tension as an etiology. Muscle contraction has been considered to be a feature that distinguishes TTH from migraine, but there appear to be no differences in contraction between the two headache types.

TREATMENT Tension-Type Headache

The pain of TTH can generally be managed with simple analgesics such as acetaminophen, aspirin, or NSAIDs. Behavioral approaches including relaxation can also be effective. Clinical studies have demonstrated that triptans in pure TTH are not helpful, although triptans are effective in TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treatment (Table 34-6); other tricyclics, selective serotonin reuptake inhibitors, and the benzodiazepines have not been shown to be effective. There is no evidence for the efficacy of acupuncture. Placebo-controlled trials of onabotulinum toxin type A in chronic TTH were negative.

TRIGEMINAL AUTONOMIC CEPHALALGIAS, INCLUDING CLUSTER HEADACHE

The trigeminal autonomic cephalalgias (TACs) describe a grouping of primary headaches including cluster headache, paroxysmal hemicrania, SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)/SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms), and hemicrania continua (Table 34-1). TACs are characterized by relatively short-lasting attacks of head pain associated with cranial autonomic symptoms, such as lacrimation, conjunctival injection, or nasal congestion **(Table 34-7)**. Pain is usually severe and may occur more than once a day. Because of the associated nasal congestion or rhinorrhea, patients are often misdiagnosed with "sinus headache" and treated with decongestants, which are ineffective.

TACs must be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia, primary stabbing headache, and hypnic headache. The cycling pattern and length, frequency, and timing of attacks are useful in classifying patients. Patients with TACs should undergo pituitary imaging and pituitary function tests because there is an excess of TAC presentations in patients with pituitary tumor–related headache.

Cluster headache

Cluster headache is a relatively rare form of primary headache with a population frequency of approximately 0.1%. The pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating, and explosive in quality. A core feature of cluster headache is periodicity. At least one of the daily attacks of pain recurs at about the same hour each day for the duration of a cluster bout. The typical cluster headache patient has daily bouts of one to two attacks of relatively short-duration unilateral pain for 8 to 10 weeks a year; this is usually followed by a pain-free interval that averages a little less than 1 year. Cluster headache is characterized as chronic when there is less than 1 month of sustained remission without treatment. Patients are generally

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-7

CLINICAL FEATURES OF THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

	CLUSTER HEADACHE	PAROXYSMAL HEMICRANIA	SUNCT/SUNA
Gender	M > F	F = M	F ~ M
Pain			
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Severity	Excruciating	Excruciating	Severe to excruciating
Site	Orbit, temple	Orbit, temple	Periorbital
Attack frequency	1/alternate day–8/d	1–20/d (>5/d for more than half the time)	3–200/d
Duration of attack	15–180 min	2–30 min	5–240 s
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)[a]
Migrainous features[b]	Yes	Yes	Yes
Alcohol trigger	Yes	No	No
Cutaneous triggers	No	No	Yes
Indomethacin effect	—	Yes[c]	—
Abortive treatment	Sumatriptan injection or nasal spray Oxygen	No effective treatment	Lidocaine (IV)
Prophylactic treatment	Verapamil Methysergide Lithium	Indomethacin	Lamotrigine Topiramate Gabapentin

[a]If conjunctival injection and tearing are not present, consider SUNA.
[b]Nausea, photophobia, or phonophobia; photophobia and phonophobia are typically unilateral on the side of the pain.
[c]Indicates complete response to indomethacin.
Abbreviations: SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

perfectly well between episodes. Onset is nocturnal in about 50% of patients, and men are affected three times more often than women. Patients with cluster headache tend to move about during attacks, pacing, rocking, or rubbing their head for relief; some may even become aggressive during attacks. T is is in sharp contrast to patients with migraine, who prefer to remain motionless during attacks.

Cluster headache is associated with ipsilateral symptoms of cranial parasympathetic autonomic activation: conjunctival injection or lacrimation, rhinorrhea or nasal congestion, or cranial sympathetic dysfunction such as ptosis. T e sympathetic deficit is peripheral and likely to be due to parasympathetic activation with injury to ascending sympathetic fibers surrounding a dilated carotid artery as it passes into the cranial cavity. When present, photophobia and phonophobia are far more likely to be unilateral and on the same side of the pain, rather than bilateral, as is seen in migraine. T is phenomenon of unilateral photophobia/phonophobia is characteristic of TACs. Cluster headache is likely to be a disorder involving central pacemaker neurons in the posterior hypothalamic region (Fig. 34-3).

TREATMENT Cluster Headache

T e most satisfactory treatment is the administration of drugs to prevent cluster attacks until the bout is over. However, treatment of acute attacks is required for all cluster headache patients at some time.

ACUTE ATTACK TREATMENT Cluster headache attacks peak rapidly, and thus a treatment with quick onset is required. Many patients with acute cluster headache respond very well to oxygen inhalation. T is should be given as 100% oxygen at 10–12 L/min for 15–20 min. It appears that high flow and high oxygen content are important. Sumatriptan 6 mg SC is rapid in onset and will usually shorten an attack to 10–15 min; there is no evidence of tachyphylaxis. Sumatriptan (20 mg) and zolmitriptan (5 mg) nasal sprays are both effective in acute cluster headache, offering a useful option for patients who may not wish to self-inject daily. Oral sumatriptan is not effective for prevention or for acute treatment of cluster headache.

PREVENTIVE TREATMENTS T e choice of a preventive treatment in cluster headache depends in part on the length of the bout **(Table 34-8)**. Patients with long bouts or those with chronic

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 34-8

PREVENTIVE MANAGEMENT OF CLUSTER HEADACHE

SHORT-TERM PREVENTION	LONG-TERM PREVENTION
EPISODIC CLUSTER HEADACHE	EPISODIC CLUSTER HEADACHE AND PROLONGED CHRONIC CLUSTER HEADACHE
Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days Methysergide 3–12 mg/d Verapamil 160–960 mg/d Greater occipital nerve injection	Verapamil 160–960 mg/d Lithium 400–800 mg/d Methysergide[a] 3–12 mg/d Topiramate[b] 100–400 mg/d Gabapentin[b] 1200–3600 mg/d Melatonin[b] 9–12 mg/d

[a]Not available worldwide.
[b]Unproven but of potential benefit.

cluster headache require medicines that are safe when taken for long periods. For patients with relatively short bouts, limited courses of oral glucocorticoids or methysergide (not available in the United States) can be very useful. A 10-day course of prednisone, beginning at 60 mg daily for 7 days and followed by a rapid taper, may interrupt the pain bout for many patients. Lithium (400–800 mg/d) appears to be particularly useful for the chronic form of the disorder.

Many experts favor verapamil as the first-line preventive treatment for patients with chronic cluster headache or prolonged bouts. While verapamil compares favorably with lithium in practice, some patients require verapamil doses far in excess of those administered for cardiac disorders. The initial dose range is 40–80 mg twice daily; effective doses may be as high as 960 mg/d. Side effects such as constipation and leg swelling can be problematic. Of paramount concern, however, is the cardiovascular safety of verapamil, particularly at high doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node, a condition that can be monitored by following the PR interval on a standard electrocardiogram (ECG). Approximately 20% of patients treated with verapamil develop ECG abnormalities, which can be observed with doses as low as 240 mg/d; these abnormalities can worsen over time in patients on stable doses. A baseline ECG is recommended for all patients. The ECG is repeated 10 days after a dose change in patients whose dose is being increased above 240 mg daily. Dose increases are usually made in 80-mg increments. For patients on long-term verapamil, ECG monitoring every 6 months is advised.

NEUROSTIMULATION THERAPY When medical therapies fail in chronic cluster headache, neurostimulation strategies can be used. Deep-brain stimulation of the region of the posterior hypothalamic gray matter has proven successful in a substantial proportion of patients, although its risk-benefit ratio makes it inappropriate with so many other options now available. Favorable results have also been reported with the less-invasive approach of occipital nerve stimulation, with sphenopalatine ganglion stimulation and with a noninvasive vagal nerve stimulator.

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania (PH) is characterized by frequent unilateral, severe, short-lasting episodes of headache. Like cluster headache, the pain tends to be retroorbital but may be experienced all over the head and is associated with autonomic phenomena such as lacrimation and nasal congestion. Patients with remissions are said to have episodic PH, whereas those with the nonremitting form are said to have chronic PH. The essential features of PH are unilateral, very severe pain; short-lasting attacks (2–45 min); very frequent attacks (usually more than five a day); marked autonomic features ipsilateral to the pain; rapid course (<72 h); and excellent response to indomethacin. In contrast to cluster headache, which predominantly affects males, the male-to-female ratio in PH is close to 1:1.

Indomethacin (25–75 mg tid), which can completely suppress attacks of PH, is the treatment of choice. Although therapy may be complicated by indomethacin-induced gastrointestinal side effects, currently there are no consistently effective alternatives. Topiramate is helpful in some cases. Piroxicam has been used, although it is not as effective as indomethacin. Verapamil, an effective treatment for cluster headache, does not appear to be useful for PH. In occasional patients, PH can coexist with trigeminal neuralgia (PH-tic syndrome); similar to cluster-tic syndrome, each component may require separate treatment.

Secondary PH has been reported with lesions in the region of the sella turcica, including arteriovenous malformation, cavernous sinus meningioma, pituitary pathology and epidermoid tumors. Secondary PH is more likely if the patient requires high doses (>200 mg/d) of indomethacin. In patients with apparent bilateral PH, raised cerebrospinal fluid (CSF) pressure should be suspected. It is important to note that indomethacin reduces CSF pressure. When a diagnosis of PH is considered, magnetic resonance imaging (MRI) is indicated to exclude a pituitary lesion.

SUNCT/SUNA

SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) is a rare primary headache syndrome characterized by severe, unilateral orbital or temporal pain that is stabbing or throbbing in quality. Diagnosis requires at least 20 attacks, lasting for 5–240 s; ipsilateral conjunctival injection and lacrimation should be present. In some

www.ketabpezeshki.com (021) 66485457 - 66485438

patients, conjunctival injection or lacrimation is missing, and the diagnosis of SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) can be made.

Diagnosis

The pain of SUNCT/SUNA is unilateral and may be located anywhere in the head. Three basic patterns can be seen: single stabs, which are usually short-lived; groups of stabs; or a longer attack comprising many stabs between which the pain does not completely resolve, thus giving a "saw-tooth" phenomenon with attacks lasting many minutes. Each pattern may be seen in the context of an underlying continuous head pain. Characteristics that lead to a suspected diagnosis of SUNCT are the cutaneous (or other) triggers of attacks, a lack of refractory period to triggering between attacks, and the lack of a response to indomethacin. Apart from trigeminal sensory disturbance, the neurologic examination is normal in primary SUNCT.

The diagnosis of SUNCT/SUNA is often confused with trigeminal neuralgia (TN) particularly in first-division TN **(Chap. 42)**. Minimal or no cranial autonomic symptoms and a clear refractory period to triggering indicate a diagnosis of TN.

Secondary (symptomatic) sunct

SUNCT can be seen with posterior fossa or pituitary lesions. All patients with SUNCT/SUNA should be evaluated with pituitary function tests and a brain MRI with pituitary views.

TREATMENT SUNCT/SUNA

ABORTIVE THERAPY Therapy of acute attacks is not a useful concept in SUNCT/SUNA because the attacks are of such short duration. However, IV lidocaine, which arrests the symptoms, can be used in hospitalized patients.

PREVENTIVE THERAPY Long-term prevention to minimize disability and hospitalization is the goal of treatment. The most effective treatment for prevention is lamotrigine, 200–400 mg/d. Topiramate and gabapentin may also be effective. Carbamazepine, 400–500 mg/d, has been reported by patients to offer modest benefit.

Surgical approaches such as microvascular decompression or destructive trigeminal procedures are seldom useful and often produce long-term complications. Greater occipital nerve injection has produced limited benefit in some patients. Occipital nerve stimulation is probably helpful in a subgroup of these patients. Complete control with deep-brain stimulation of the posterior hypothalamic region was reported in a single patient. For intractable cases, short-term prevention with IV lidocaine can be effective, as can occipital nerve stimulation.

Hemicrania continua

The essential features of hemicrania continua are moderate and continuous unilateral pain associated with fluctuations of severe pain; complete resolution of pain with indomethacin; and exacerbations that may be associated with autonomic features, including conjunctival injection, lacrimation, and photophobia on the affected side. The age of onset ranges from 11 to 58 years; women are affected twice as often as men. The cause is unknown.

TREATMENT Hemicrania Continua

Treatment consists of indomethacin; other NSAIDs appear to be of little or no benefit. The IM injection of 100 mg of indomethacin has been proposed as a diagnostic tool, and administration with a placebo injection in a blinded fashion can be very useful diagnostically. Alternatively, a trial of oral indomethacin, starting with 25 mg tid, then 50 mg tid, and then 75 mg tid, can be given. Up to 2 weeks at the maximal dose may be necessary to assess whether a dose has a useful effect. Topiramate can be helpful in some patients. Occipital nerve stimulation probably has a role in patients with hemicrania continua who are unable to tolerate indomethacin.

OTHER PRIMARY HEADACHES

Primary cough headache

Primary cough headache is a generalized headache that begins suddenly, lasts for several minutes, sometimes up to a few hours, and is precipitated by coughing; it is preventable by avoiding coughing or other precipitating events, which can include sneezing, straining, laughing, or stooping. In all patients with this syndrome, serious etiologies must be excluded before a diagnosis of "benign" primary cough headache can be established. A Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures can be the cause of the head pain. Other conditions that can present with cough or exertional headache as the initial symptom include cerebral aneurysm, carotid stenosis, and vertebrobasilar disease. Benign cough headache can resemble benign exertional headache (below), but patients with the former condition are typically older.

TREATMENT Primary Cough Headache

Indomethacin 25–50 mg two to three times daily is the treatment of choice. Some patients with cough headache obtain complete cessation of their attacks with lumbar puncture; this is a simple option when compared to prolonged use of indomethacin, and it is effective in about one-third of patients. The mechanism of this response is unclear.

www.ketabpezeshki.com (021) 66485457 - 66485438

Primary exercise headache

Primary exertional headache has features resembling both cough headache and migraine. It may be precipitated by any form of exercise; it often has the pulsatile quality of migraine. T e pain, which can last from 5 min to 24 h, is bilateral and throbbing at onset; migrainous features may develop in patients susceptible to migraine. T e duration tends to be shorter in adolescents than in older adults. Primary exertional headache can be prevented by avoiding excessive exertion, particularly in hot weather or at high altitude.

T e mechanism of primary exertional headache is unclear. Acute venous distension likely explains one syndrome—the acute onset of headache with straining and breath holding, as in weightlifter's headache. Because exertion can result in headache in a number of serious underlying conditions, these must be considered in patients with exertional headache. Pain from angina may be referred to the head, probably by central connections of vagal afferents, and may present as exertional headache (cardiac cephalgia). T e link to exercise is the main clinical clue that headache is of cardiac origin. Pheochromocytoma may occasionally cause exertional headache. Intracranial lesions and stenosis of the carotid arteries are other possible etiologies.

TREATMENT Primary Exertional Headache

Exercise regimens should begin modestly and progress gradually to higher levels of intensity. Indomethacin at daily doses from 25 to 150 mg is generally effective in benign exertional headache. Indomethacin (50 mg), ergotamine (1 mg orally), dihydroergotamine (2 mg by nasal spray), and methysergide (1–2 mg orally given 30–45 min before exercise) are useful prophylactic measures.

Primary headache associated with sexual activity

T ree types of sex headache are reported: a dull bilateral ache in the head and neck that intensifies as sexual excitement increases; a sudden, severe, explosive headache occurring at orgasm; and a postural headache developing after coitus that resembles the headache of low CSF pressure. T e last arises from vigorous sexual activity and is a form of low CSF pressure headache **(Chap. 9)**. Headaches developing at the time of orgasm are not always benign; 5–12% of cases of subarachnoid hemorrhage are precipitated by sexual intercourse. Sex headache is reported by men more often than women and may occur at any time during the years of sexual activity. It may develop on several occasions in succession and then not trouble the patient again, even without an obvious change in sexual activity. In patients who stop sexual activity when headache is first noticed, the pain may subside within a period of 5 min to 2 h. In about half of patients, sex headache will subside within 6 months. About half of patients with sex headache have a history of exertional headaches, but there is no excess of cough headache. Migraine is probably more common in patients with sex headache.

TREATMENT Primary Sex Headache

Benign sex headaches recur irregularly and infrequently. Management can often be limited to reassurance and advice about ceasing sexual activity if a mild, warning headache develops. Propranolol can be used to prevent headache that recurs regularly or frequently, but the dosage required varies from 40 to 200 mg/d. An alternative is the calcium channel–blocking agent diltiazem, 60 mg tid. Ergotamine (1 mg) or indomethacin (25–50 mg) taken 30–45 min prior to sexual activity can also be helpful.

Primary thunderclap headache

Sudden onset of severe headache may occur in the absence of any known provocation. T e differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervicocephalic arterial dissection, and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or of tyramine-containing foods in a patient who is taking MAOIs, or they may be a symptom of pheochromocytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is uncertain. When neuroimaging studies and lumbar puncture exclude subarachnoid hemorrhage, patients with thunderclap headache usually do very well over the long term. In one study of patients whose computed tomography (CT) scans and CSF findings were negative, ~15% had recurrent episodes of thunderclap headache, and nearly half subsequently developed migraine or TTH.

T e first presentation of any sudden-onset severe headache should be diligently investigated with neuroimaging (CT or, when possible, MRI with MR angiography) and CSF examination. Formal cerebral angiography should be reserved for those cases in which no primary diagnosis is forthcoming and for clinical situations that are particularly suggestive of intracranial aneurysm. Reversible segmental cerebral vasoconstriction may be seen in primary thunderclap headache without an intracranial aneurysm. In the presence of posterior leukoencephalopathy, the differential diagnosis includes cerebral angiitis, drug toxicity (cyclosporine, intrathecal methotrexate/cytarabine, pseudoephedrine, or cocaine), posttransfusion effects, and postpartum angiopathy. Treatment with nimodipine may be helpful,

www.ketabpezeshki.com (021) 66485457 - 66485438

although by definition, the vasoconstriction of primary thunderclap headache resolves spontaneously.

Cold-stimulus headache

This refers to head pain triggered by application or ingestion/inhalation of something cold. It is bought on quickly and typically resolves within 10–30 min of the stimulus being removed. It is best recognized as "brain-freeze" headache or ice-cream headache when due to ingestion. Although cold may be uncomfortable at some level for many people, it is the reliable, severe, and somewhat prolonged nature of these pains that set them apart. The transient receptor potential cation subfamily M member 8 (TRPM8) channel, a known cold temperature sensor, may be a mediator of this syndrome.

External pressure headache

External pressure from compression or traction on the head can produce a pain that may have some generalized component, although the pain is largely focused around the site of the pressure. It typically resolves within an hour of the stimulus being removed. Examples of stimuli include helmets, swimming goggles, or very long ponytails. Treatment is to recognize the problem and remove the stimulus.

Primary stabbing headache

The essential features of primary stabbing headache are stabbing pain confined to the head or, rarely, the face, lasting from 1 to many seconds or minutes and occurring as a single stab or a series of stabs; absence of associated cranial autonomic features; absence of cutaneous triggering of attacks; and a pattern of recurrence at irregular intervals (hours to days). The pains have been variously described as "ice-pick pains" or "jabs and jolts." They are more common in patients with other primary headaches, such as migraine, the TACs, and hemicrania continua.

TREATMENT Primary Stabbing Headache

The response of primary stabbing headache to indomethacin (25–50 mg two to three times daily) is usually excellent. As a general rule, the symptoms wax and wane, and after a period of control on indomethacin, it is appropriate to withdraw treatment and observe the outcome.

Nummular headache

Nummular headache is felt as a round or elliptical discomfort that is fixed in place, ranges in size from 1–6 cm, and may be continuous or intermittent. Uncommonly it may be multifocal. It may be episodic but is more often continuous during exacerbations. Accompanying the pain there may be a local sensory disturbance, such as allodynia or hypesthesia. Local dermatologic or bony lesions need to be excluded by examination and investigation. This condition can be difficult to treat; tricyclics, such as amitriptyline, or anticonvulsants, such as topiramate or valproate, are most often tried.

Hypnic headache

This headache syndrome typically begins a few hours after sleep onset. These headaches last from 15 to 30 min and are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are female, and the onset is usually after age 60 years. Headaches are bilateral in most, but may be unilateral. Photophobia, phonophobia, and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition.

TREATMENT Hypnic Headache

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). For those intolerant of lithium, verapamil (160 mg) or methysergide (1–4 mg at bedtime) may be alternative strategies. One to two cups of coffee or caffeine, 60 mg orally, at bedtime may be effective in approximately one-third of patients. Case reports also suggest that flunarizine, 5 mg nightly, can be effective.

New daily persistent headache

Primary new daily persistent headache (NDPH) occurs in both males and females. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH. Migrainous features are common and include unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients. Some patients have a previous history of migraine; however, the proportion of NDPH sufferers with preexisting migraine is no greater than the frequency of migraine in the general population. At 24 months, ~86% of patients are headache-free. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (see above). Featureless NDPH is one of the primary headache forms most refractory to treatment. Standard preventive therapies can be offered but are often ineffective. The secondary NDPHs are discussed elsewhere **(Chap. 9)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 35

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

William W. Seeley ■ Bruce L. Miller

ALZHEIMER'S DISEASE

Approximately 10% of all persons over the age of 70 years have significant memory loss, and in more than half, the cause is Alzheimer's disease (AD). It is estimated that the median annual total cost of caring for a single patient with advanced AD is >$50,000, while the emotional toll for family members and caregivers is immeasurable. AD can manifest as young as the third decade, but it is the most common cause of dementia in the elderly. Patients most often present with an insidious loss of episodic memory followed by a slowly progressive dementia that evolves over years. In typical amnestic AD, brain imaging reveals atrophy that begins in the medial temporal lobes before spreading to lateral and medial parietal and temporal lobes and lateral frontal cortex. Microscopically, there are neuritic plaques containing amyloid beta (Aβ), neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau filaments, and Aβ accumulation of in blood vessel walls in cortex and leptomeninges (see "Pathology," below). T e identification of causative mutations and susceptibility genes for AD has provided a foundation for rapid progress in understanding the biological basis of the disorder. T e major genetic risk for AD is apolipoprotein ε4 (Apo ε4). Carrying one E4 allele increases the risk for AD by 2- to 3-fold, whereas two alleles increase the risk 16-fold.

CLINICAL MANIFESTATIONS

T e cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and progressing to language and visuospatial deficits. Yet, approximately 20% of patients with AD present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In other patients, upstream visual processing dysfunction (referred to as posterior cortical atrophy syndrome) or a progressive "logopenic" aphasia are the primary manifestations of AD for years before progressing to involve memory and other cognitive domains. Still other patients may present with an asymmetric akinetic-rigid-dystonic ("corticobasal") syndrome or a dysexecutive "frontal variant" of AD.

In the early stages of typical amnestic AD, the memory loss may go unrecognized or be ascribed to benign forgetfulness of aging. Once the memory loss becomes noticeable to the patient and spouse and falls 1.5 standard deviations below normal on standardized memory tests, the term mild cognitive impairment (MCI) is applied. T is construct provides useful prognostic information, because approximately 50% of patients with MCI (roughly 12% per year) will progress to AD over 4 years. Increasingly, the MCI construct is being replaced by the notion of "early symptomatic AD" to signify that AD is considered the underlying disease (based on clinical or biomarker evidence) in a patient who remains functionally compensated. Even earlier in the course, "prodromal AD" refers to a person with biomarker evidence of AD (amyloid imaging positive with positron emission tomography or low cerebrospinal $A\beta_{42}$ and mildly elevated tau) in the absence of symptoms. T ese refinements have been developed in anticipation of early-stage treatment and prevention trials that have already begun in humans. New evidence suggests that partial and sometimes generalized seizures herald AD and can occur even prior to dementia onset.

Eventually, with AD, the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (anosognosia), but most remain acutely attuned to their deficits. Changes in environment (travel, relocation, hospitalization) tend to destabilize the patient. Over time patients become lost on walks or while driving. Social graces, routine behavior, and superficial conversation may be surprisingly intact, even into the later stages of the illness.

www.ketabpezeshki.com (021) 66485457 - 66485438

In the middle stages of AD, the patient is unable to work, is easily lost and confused, and requires daily supervision. Language becomes impaired—first naming, then comprehension, and finally fluency. Word-finding difficulties and circumlocution can be evident in the early stages, even when formal testing demonstrates intact naming and fluency. Apraxia emerges, and patients have trouble performing learned sequential motor tasks. Visuospatial deficits begin to interfere with dressing, eating, or even walking, and patients fail to solve simple puzzles or copy geometric figures. Simple calculations and clock reading become difficult in parallel.

In the late stages, some persons remain ambulatory, wandering aimlessly. Loss of judgment and reasoning is inevitable. Delusions are common, usually simple, with common themes of theft, infidelity, or misidentification. Approximately 10% of AD patients develop Capgras' syndrome, believing that a caregiver has been replaced by an impostor. In contrast to dementia with Lewy bodies (DLB), where Capgras' syndrome is an early feature, in AD this syndrome emerges late. Disinhibition and uncharacteristic belligerence may occur and alternate with passivity and withdrawal. Sleep-wake patterns are disrupted, and nighttime wandering becomes disturbing to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of movement. Patients often look parkinsonian **(Chap. 36)** but rarely have a high-amplitude, low-frequency tremor at rest. T ere is a strong overlap between Parkinson's disease (PD) and AD, and some AD patients develop more classical PD features.

In the end stages, AD patients become rigid, mute, incontinent, and bedridden, and help is needed with eating, dressing, and toileting. Hyperactive tendon reflexes and myoclonic jerks (sudden brief contractions of various muscles or the whole body) may occur spontaneously or in response to physical or auditory stimulation. Often death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. T e typical duration of AD is 8–10 years, but the course ranges from 1 to 25 years. For unknown reasons, some patients with AD show a steady decline in function while others have prolonged plateaus without major deterioration.

DIFFERENTIAL DIAGNOSIS

Early in the disease course, other etiologies of dementia should be excluded **(see Tables 35-1, 35-3, and 35-4)**. Neuroimaging studies (computed tomography [CT] and magnetic resonance imaging [MRI]) do not show a single specific pattern with AD and may be normal early in the disease. As AD progresses, more distributed but usually posterior-predominant cortical atrophy becomes apparent, along with atrophy of the medial temporal memory structures (**see Chap. 21,** Fig. 35-1). T e main purpose of imaging is to exclude other disorders, such as primary and secondary neoplasms, vascular dementia, dif use white matter disease, and normal-pressure hydrocephalus (NPH). Imaging also helps to distinguish AD from other degenerative disorders, such as frontotemporal dementia (FTD) or Creutzfeldt-Jacob disease (CJD), which feature distinctive imaging patterns. Functional imaging studies, such as positron emission tomography (PET), reveal hypometabolism in the posterior temporal-parietal cortex in AD (see Fig. 35-1). PET can also be used to detect the presence of fibrillar amyloid in the brain (see Fig. 35-4), and amyloid PET positivity is becoming required for entry into treatment trials for AD. Barriers to interpretation continue, however, to limit the use of amyloid PET in routine clinical evaluation. Although amyloid binding with PET is typical for AD, many asymptomatic healthy older individuals show amyloid uptake, and the likelihood that these individuals will convert to clinical AD is still under study. Similarly, dementia due to a non-AD disorder can be the underlying etiology in a patient who is amyloid positive on imaging. Electroencephalogram (EEG) is normal or shows nonspecific slowing; prolonged EEG can be used to seek out intermittent nonconvulsive seizures. Routine spinal fluid examination is also normal. Cerebrospinal fluid (CSF) $A\beta_{42}$ level is reduced, whereas the tau protein is elevated, but the test characteristics of these assays still make interpretation challenging in individual patients. Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or C*T* scan showing only distributed or posteriorly predominant cortical and hippocampal atrophy are highly suggestive o*f* AD. A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy about 90% of the time, with misdiagnosed cases usually representing one of the other dementing disorders described later in this chapter, a mixture of AD with vascular pathology, or DLB.

Simple clinical clues are useful in the dif erential diagnosis. Early prominent gait disturbance with only mild memory loss suggests vascular dementia or, rarely, NPH (see below). Resting tremor with stooped posture, bradykinesia, and masked facies suggest PD **(Chap. 36)**. When dementia occurs after a well-established diagnosis of PD, PD dementia (PDD) is usually the correct diagnosis, but many patients with this diagnosis will show a mixture of AD and Lewy body disease at autopsy. T e early appearance of parkinsonian features in association with fluctuating alertness, visual hallucinations, or delusional misidentification suggests

www.ketabpezeshki.com (021) 66485457 - 66485438

DLB. Chronic alcoholism should prompt the search for vitamin deficiency. Loss of joint position and vibration sensibility accompanied by Babinski signs suggests vitamin B_{12} deficiency **(Chap. 43)**. Early onset of a focal seizure suggests a metastatic or primary brain neoplasm **(Chap. 49)**. Previous or ongoing depression raises suspicion for depression-related cognitive impairment, although AD can feature a depressive prodrome. A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with rigidity and myoclonus suggests CJD **(Chap. 40)**. Prominent behavioral changes with intact navigation and focal anterior-predominant atrophy on brain imaging are typical of FTD. A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as FTD (see below), HD (see below), prion disease **(Chap. 40)**, or rare hereditary ataxias **(Chap. 37)**.

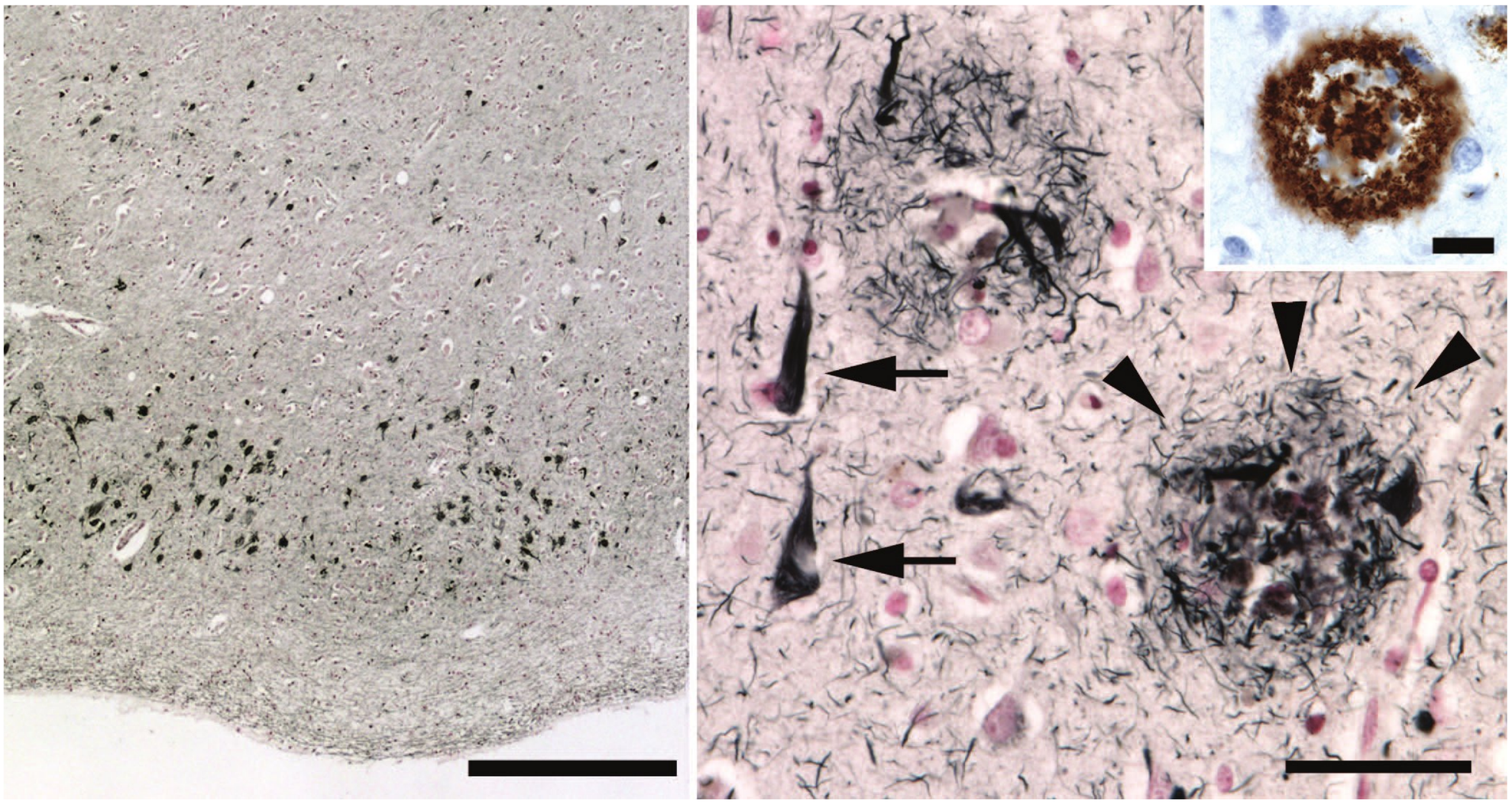
EPIDEMIOLOGY

T e most important risk factors for AD are old age and a positive family history. T e prevalence of AD increases with each decade of adult life, reaching 20–40% of the population over the age of 85. A positive family history of dementia suggests a genetic contribution to AD, although autosomal dominant inheritance occurs in only 2% of patients. Female sex is a risk factor independent of the greater longevity of women, and women who carry an Apo ε4 allele are more susceptible than are male ε4 carriers. A history of head trauma with concussion increases the risk for AD. AD is more common in groups with low educational attainment, but education influences test-taking ability, and it is clear that AD can af ect persons of all intellectual levels. One study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Numerous environmental factors, including aluminum, mercury, and viruses, have been proposed as causes of AD, but rigorous studies have failed to demonstrate to a significant role for any of these exposures. Similarly, several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a decreased risk of AD, but this risk has not been confirmed in large prospective studies. Vascular disease, and stroke in particular, seems to lower the threshold for the clinical expression of AD. Also, in many patients with AD, amyloid angiopathy can lead to microhemorrhages, large lobar hemorrhages, ischemic infarctions most often in the subcortical white matter, or in rare cases an inflammatory leukoencephalopathy. Diabetes increases the risk of AD threefold. Elevated homocysteine and cholesterol levels; hypertension; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; and low levels of exercise are all being explored as potential risk factors for AD.

PATHOLOGY

At autopsy, the earliest and most severe degeneration is usually found in the medial temporal lobe (entorhinal/perirhinal cortex and hippocampus), lateral temporal cortex, and nucleus basalis of Meynert. T e characteristic microscopic findings are neuritic plaques and NFTs **(Fig. 35-1)**. T ese lesions may accumulate in small numbers during normal brain aging but dominate the picture in AD. Increasing evidence suggests that soluble amyloid species called oligomers may cause cellular dysfunction and represent the early toxic molecule in AD. Eventually, further amyloid polymerization and fibril formation lead to neuritic plaques, which contain a central core of amyloid, proteoglycans, Apo ε4, α-antichymotrypsin, and other proteins. Aβ is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein, amyloid precursor protein (APP), when APP is cleaved by β and γ secretases **(Fig. 35-2)**. T e normal function of the Aβ peptides remains uncertain. APP has neurotrophic and neuroprotective properties. T e plaque core is surrounded by a halo, which contains dystrophic, tau-immunoreactive neurites and activated microglia. T e accumulation of Aβ in cerebral arterioles is termed amyloid angiopathy. NFTs are composed of silver-staining neuronal cytoplasmic fibrils composed of abnormally phosphorylated tau protein; they appear as paired helical filaments by electron microscopy. Tau binds to and stabilizes microtubules, supporting axonal transport of organelles, glycoproteins, neurotransmitters, and other important cargoes throughout the neuron. Once hyperphosphorylated, tau can no longer bind properly to microtubules and redistributes from the axon to throughout the neuronal cytoplasm and distal dendrites, compromising function. Finally, patients with AD often show comorbid DLB or vascular pathology. In animal models of AD, diminishing neuronal tau ameliorates the cognitive deficits and seizures, even though $A\beta_{42}$ continues to accumulate, raising hope for tau-lowering therapies in humans. Biochemically, AD is associated with a decrease in the cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors. Reduction of acetylcholine reflects degeneration of cholinergic neurons in the nucleus basalis of Meynert that project throughout the cortex. T ere is also noradrenergic and serotonergic depletion due to degeneration of brainstem nuclei such as the locus coeruleus and dorsal raphe, where tau-immunoreactive neuronal cytoplasmic inclusions can be identified even in individuals lacking entorhinal cortex NFTs.

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 35-1
Neuropathology of Alzheimer's disease. A. Early neurofibrillary degeneration, consisting of neurofibrillary tangles and neuropil threads, preferentially affects the medial temporal lobes, especially the stellate pyramidal neurons that compose the layer 2 islands of entorhinal cortex, as shown. B. Higher magnification view reveals the fibrillary nature of tangles (arrows) and the complex structure of neuritic plaques (arrowheads), whose major component is Aβ (inset shows immunohistochemistry for Aβ). Scale bars are 500 μM in A, 50 μM in B, and 20 μM in B inset.

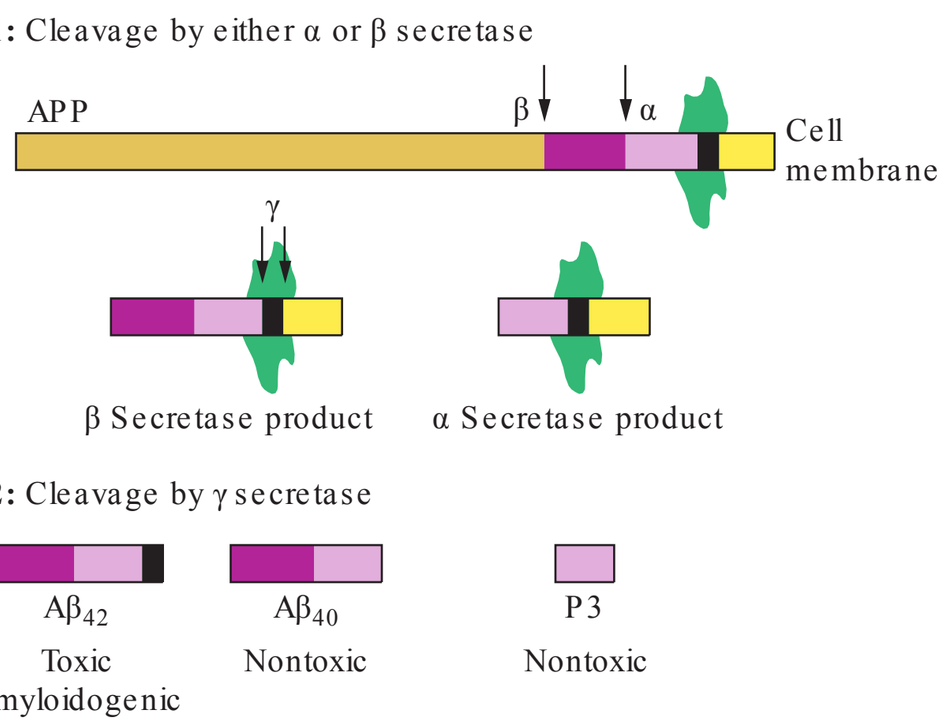


FIGURE 35-2
Amyloid precursor protein (APP) is catabolized by α, β, and γ secretases. A key initial step is the digestion by either β secretase (BASE) or α secretase (ADAM10 or ADAM17 [TACE]), producing smaller nontoxic products. Cleavage of the β secretase product by γ secretase (Step 2) results in either the toxic $A\beta_{42}$ or the nontoxic $A\beta_{40}$ peptide; cleavage of the α secretase product by γ secretase produces the nontoxic P3 peptide. Excess production of $A\beta_{42}$ is a key initiator of cellular damage in Alzheimer's disease (AD). Therapeutics for AD have focused on attempts to reduce accumulation of $A\beta_{42}$ by antagonizing β or γ secretases, promoting α secretase, or clearing $A\beta_{42}$ that has already formed by use of specific antibodies.

GENETIC CONSIDERATIONS

Several genes play an important role in the pathogenesis of AD. One is the APP gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40 years, and many develop a progressive dementia superimposed on their baseline mental retardation. T e extra dose of the APP gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome and results in excess cerebral amyloid production. Supporting this hypothesis, some families with early age-of-onset familial AD (FAD) have point mutations in APP. Although very rare, these families were the first examples of single-gene autosomal dominant transmission of AD.

Investigation of large families with multigenerational FAD led to the discovery of two additional AD-causing genes, the presenilins. Presenilin-1 (PS-1) is on chromosome 14 and encodes a protein called S182. Mutations in this gene cause an early-age-of-onset AD, with onset before the age of 60 and often before age 50, transmitted in an autosomal dominant, highly penetrant fashion. More than 100 dif erent mutations have been found in the PS-1 gene in families from a wide range of ethnic backgrounds. Presenilin-2 (PS-2) is on chromosome 1 and encodes a protein called STM2. A

www.ketabpezeshki.com (021) 66485457 - 66485438

mutation in the PS-2 gene was first found in a group of American families with Volga German ethnic background. Mutations in PS-1 are much more common than those in PS-2. The presenilins are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation STM), but subsequent studies have suggested eight such domains, with a ninth submembrane region. Both S182 and STM2 are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. They are homologous to a cell-trafficking protein, sel 12, found in the nematode Caenorhabditis elegans. Patients with mutations in the presenilin genes have elevated plasma levels of $A\beta_{42}$, and PS-1 mutations produce increased $A\beta_{42}$ in the media in cell culture. There is evidence that PS-1 is involved in the cleavage of APP at the γ secretase site and mutations in either gene (PS-1 or APP) may disturb γ secretase cleavage. Mutations in PS-1 are the most common cause of early-age-of-onset FAD, representing perhaps 40–70% of all cases. Mutations in PS-1 tend to produce AD with an earlier age of onset (mean onset 45 years) and a shorter, more rapidly progressive course (mean duration 6–7 years) than the disease caused by mutations in PS-2 (mean onset 53 years; duration 11 years). Although some carriers of PS-2 mutations have had onset of dementia after the age of 70, mutations in the presenilins rarely lead to late-age-of-onset AD. Clinical genetic testing for these uncommon mutations is available but likely to be revealing only in early-age-of-onset FAD and should be performed in association with formal genetic counseling.

The Apo ε gene on chromosome 19 is involved in the pathogenesis of AD. The protein, apolipoprotein E, participates in cholesterol transport, and the gene has three alleles: ε2, ε3, and ε4. The Apo ε4 allele confers increased risk of AD in the general population, including sporadic and late-age-of-onset familial forms. Approximately 24–30% of the nondemented white population has at least one ε4 allele (12–15% allele frequency), and about 2% are ε4/ε4 homozygotes. Among patients with AD, 40–65% have at least one ε4 allele, a highly significant elevation compared with controls. Conversely, many AD patients have no ε4 allele, and ε4 carriers may never develop AD. Therefore, ε4 is neither necessary nor sufficient to cause AD. Nevertheless, the Apo ε4 allele represents the most important genetic risk factor for sporadic AD and acts as a dose-dependent disease modifier, with the earliest age of onset associated with the ε4 homozygosity. Precise mechanisms through which Apo ε4 confers AD risk or hastens onset remain unclear, but ε4 leads to less efficient amyloid clearance and to the production of toxic fragments from cleavage of the molecule. Apo ε can be identified in neuritic plaques and may also be involved in neurofibrillary tangle formation, because it binds to tau protein. Apo ε4 decreases neurite outgrowth in dorsal root ganglion neuronal cultures, perhaps indicating a deleterious role in the brain's response to injury. Some evidence suggests that the ε2 allele may reduce AD risk. Use of Apo ε testing in AD diagnosis remains controversial. It is not indicated as a predictive test in normal persons because its precise predictive value is unclear, and many individuals with the ε4 allele never develop dementia. Many cognitively normal ε4 heterozygotes and homozygotes show decreased cerebral cortical metabolic function with PET, suggesting presymptomatic abnormalities due to AD or an inherited vulnerability of the AD-targeted network. In demented persons who meet clinical criteria for AD, finding an ε4 allele increases the reliability of diagnosis; however, the absence of an ε4 allele cannot be considered evidence against AD. Furthermore, all patients with dementia, including those with an ε4 allele, require a search for reversible causes of their cognitive impairment. Nevertheless, Apo ε4 remains the single most important biologic marker associated with AD risk, and studies of ε4's functional role and diagnostic utility are progressing rapidly. The ε4 allele is not associated with risk for FTD, DLB, or CJD, although some evidence suggests that ε4 may exacerbate the phenotype of non-AD degenerative disorders, head trauma, and other brain injuries. Additional genes are also likely to be involved in AD, especially as minor risk alleles for sporadic forms of the disease. Genome-wide association studies have implicated the clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM), and complement component (3b/4b) receptor 1 (CR1) genes. CLU may play a role in synapse turnover, PICALM participates in clathrin-mediated endocytosis, and CR1 may be involved in amyloid clearance through the complement pathway. TREM2 is a gene involved with inflammation that increases the likelihood of dementia. Homozygous mutation carriers develop a frontal dementia with bone cysts (Nasu-Hakola disease), whereas heterozygotes are predisposed to the development of AD.

TREATMENT Alzheimer's Disease

The management of AD is challenging and gratifying despite the absence of a cure or a robust pharmacologic treatment. The primary focus is on long-term amelioration of associated behavioral and neurologic problems, as well as providing caregiver support.

Building rapport with the patient, family members, and other caregivers is essential to successful management. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Family members should emphasize activities that are pleasant while curtailing those that increase stress on the patient. Kitchens, bathrooms,

www.ketabpezeshki.com (021) 66485457 - 66485438

stairways, and bedrooms need to be made safe, and eventually patients will need to stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver "burnout" is common, often resulting in nursing home placement of the patient or new health problems for the caregiver. Respite breaks for the caregiver help to maintain a successful long-term therapeutic milieu. Use of adult day care centers can be helpful. Local and national support groups, such as the Alzheimer's Association and the Family Caregiver Alliance, are valuable resources. Internet access to these resources has become available to clinicians and families in recent years.

Donepezil (target dose, 10 mg daily), rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily), galantamine (target dose 24 mg daily, extended-release), and memantine (target dose, 10 mg twice daily) are approved by the Food and Drug Administration (FDA) for the treatment of AD. Due to hepatotoxicity, tacrine is no longer used. Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of the cholinesterases, primarily acetylcholinesterase, with a resulting increase in cerebral acetylcholine levels. Memantine appears to act by blocking overexcited N-methyl-d-aspartate (NMDA) glutamate receptors. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors and memantine in moderate to severe AD have shown them to be associated with improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years. The average patient on an anticholinesterase inhibitor maintains his or her mini-mental state examination (MMSE) score for close to a year, whereas a placebo-treated patient declines 2–3 points over the same time period. Memantine, used in conjunction with cholinesterase inhibitors or by itself, slows cognitive deterioration and decreases caregiver burden for patients with moderate to severe AD but is not approved for mild AD. Each of these compounds has only modest efficacy for AD. Cholinesterase inhibitors are relatively easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with unpleasant or vivid dreams, bradycardia (usually benign), and muscle cramps.

In a prospective observational study, the use of estrogen replacement therapy appeared to protect—by about 50%—against development of AD in women. This study seemed to confirm the results of two earlier case-controlled studies. Sadly, a prospective placebo-controlled study of a combined estrogen-progesterone therapy for asymptomatic postmenopausal women increased, rather than decreased, the prevalence of dementia. This study markedly dampened enthusiasm for hormonal treatments to prevent dementia. Additionally, no benefit has been found in the treatment of AD with estrogen alone.

A controlled trial of an extract of Ginkgo biloba found modest improvement in cognitive function in subjects with AD and vascular dementia. Unfortunately, a comprehensive 6-year multicenter prevention study using ginkgo found no slowing of progression to dementia in the treated group.

Vaccination against $A\beta_{42}$ has proved highly efficacious in mouse models of AD, helping clear brain amyloid and preventing further amyloid accumulation. In human trials, this approach led to life-threatening complications, including meningoencephalitis, in a minority of patients. Another experimental approach to AD treatment has been the use of β and γ secretase inhibitors that diminish the production of $A\beta_{42}$, but the first two placebo-controlled trials of γ secretase inhibitors, tarenflurbil and semagacestat, were negative, and semagacestat may have accelerated cognitive decline compared to placebo. Passive immunization with monoclonal antibodies against $A\beta_{42}$ has been tried in mild to moderate AD. These studies were negative, leading some to suggest that the patients treated were too advanced to respond to amyloid-lowering therapies. Therefore, new trials have started in asymptomatic individuals with mild AD, in asymptomatic autosomal dominant forms of AD, and in cognitively normal elderly who are amyloid positive with PET. Medications that modify tau phosphorylation and aggregation, including tau antibodies, are beginning to be studied as possible treatments for both AD and non-AD tau-related disorders including FTD and progressive supranuclear palsy.

Several retrospective studies suggest that nonsteroidal anti-inflammatory agents and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) may have a protective effect on dementia if used prior to the onset of disease but do not influence clinically symptomatic AD. Finally, there is now a strong interest in the relationship between diabetes and AD, and insulin-regulating studies are being conducted.

Mild to moderate depression is common in the early stages of AD and may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects (for example, escitalopram, target dose 5–10 mg daily). Seizures can be treated with levetiracetam unless the patient had a different regimen that was effective prior to the onset of AD. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The newer generation of atypical antipsychotics, such as risperidone, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. The few controlled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications, including an increased risk of death. All antipsychotics carry a black box FDA warning and should be used with caution in the demented elderly; however, careful, daily, nonpharmacologic behavior management

www.ketabpezeshki.com (021) 66485457 - 66485438

is often not available, rendering medications necessary for some patients. Finally, medications with strong anticholinergic effects should be vigilantly avoided, including prescription and over-the-counter sleep aids (e.g., diphenhydramine) or incontinence therapies (e.g., oxybutynin).

VASCULAR DEMENTIA

Dementia associated with cerebrovascular disease can be divided into two general categories: multi-infarct dementia and diffuse white matter disease (also called leukoaraiosis, subcortical arteriosclerotic leukoencephalopathy, or Binswanger's disease). Cerebrovascular disease appears to be a more common cause of dementia in Asia than in Europe and North America, perhaps due to the increased prevalence of intracranial atherosclerosis. Individuals who have had strokes may develop chronic cognitive deficits, commonly called multi-infarct dementia. The strokes may be large or small (sometimes lacunar) and usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex. Patients typically report previous discrete episodes of sudden neurologic deterioration. Many patients with multi-infarct dementia have a history of hypertension, diabetes, coronary artery disease, or other manifestations of widespread atherosclerosis. Physical examination may show focal neurologic deficits such as hemiparesis, a unilateral Babinski sign, a visual field defect, or pseudobulbar palsy. Recurrent strokes result in a stepwise disease progression. Neuroimaging reveals multiple areas of infarction. Thus, the history and neuroimaging findings differentiate this condition from AD; however, both AD and multiple infarctions are common and sometimes co-occur. With normal aging, there is also an accumulation of amyloid in cerebral blood vessels, leading to a condition called cerebral amyloid angiopathy (without dementia), which predisposes older persons to lobar hemorrhage and brain microhemorrhages. AD patients appear to be at increased risk for amyloid angiopathy, and this association may explain some of the observed links between AD and stroke.

Some individuals with dementia are discovered on MRI to have bilateral T2 signal hyperintensities in the subcortical white matter, termed *diffuse* white matter disease, often occurring in association with lacunar infarctions (see Fig. 35-2). The dementia may be insidious in onset and progress slowly, features that distinguish it from multi-infarct dementia, but other patients show a stepwise deterioration more typical of multi-infarct dementia. Early symptoms include mild confusion, apathy, anxiety, psychosis, and memory, spatial, or executive deficits. Marked difficulties in judgment and orientation and dependence on others for daily activities develop later. Euphoria, elation, depression, or aggressive behaviors are common as the disease progresses. Pyramidal and cerebellar signs may be present, and a gait disorder is seen in at least half of these patients. With advanced disease, urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability) are frequent. Seizures and myoclonic jerks appear in a minority of patients. Often, this disorder results from chronic ischemia due to occlusive disease of small, penetrating cerebral arteries and arterioles (microangiopathy). Any disease-causing stenosis of small cerebral vessels may be the critical underlying factor, although hypertension is the major cause. The term Binswanger's disease should be used with caution, because it does not clearly identify a single entity.

Other rare causes of white matter disease also present with dementia, such as adult metachromatic leukodystrophy (arylsulfatase A deficiency) and progressive multifocal leukoencephalopathy **(Chap. 46)**. A dominantly inherited form of white matter disease is known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), discussed later in "Other Causes of Dementia."

Mitochondrial disorders can present with stroke-like episodes and can selectively injure basal ganglia or cortex. Many such patients show other findings suggestive of a neurologic or systemic disorder such as ophthalmoplegia, retinal degeneration, deafness, myopathy, neuropathy, or diabetes. Diagnosis is difficult, but serum or (especially) CSF levels of lactate and pyruvate may be abnormal, and biopsy of affected tissue, preferably muscle, may be diagnostic.

Treatment of vascular dementia must be focused on preventing new ischemic injury by stabilizing or removing the underlying causes, such as hypertension, diabetes, smoking, or lack of exercise. Recovery of lost cognitive function is not likely, although fluctuations with periods of improvement are common.

FRONTOTEMPORAL LOBAR DEGENERATION SPECTRUM

Frontotemporal dementia (FTD) refers to a group of clinical syndromes united by underlying frontotemporal lobar degeneration (FTLD) pathology. FTD most often begins in the fifth to seventh decades and is nearly as prevalent as AD in this age group. Early studies suggested that FTD may be more common in men than women, although more recent reports cast doubt on this finding. Although a family history of dementia is common, autosomal dominant inheritance is seen in only 10–20% of all FTD cases.

www.ketabpezeshki.com (021) 66485457 - 66485438

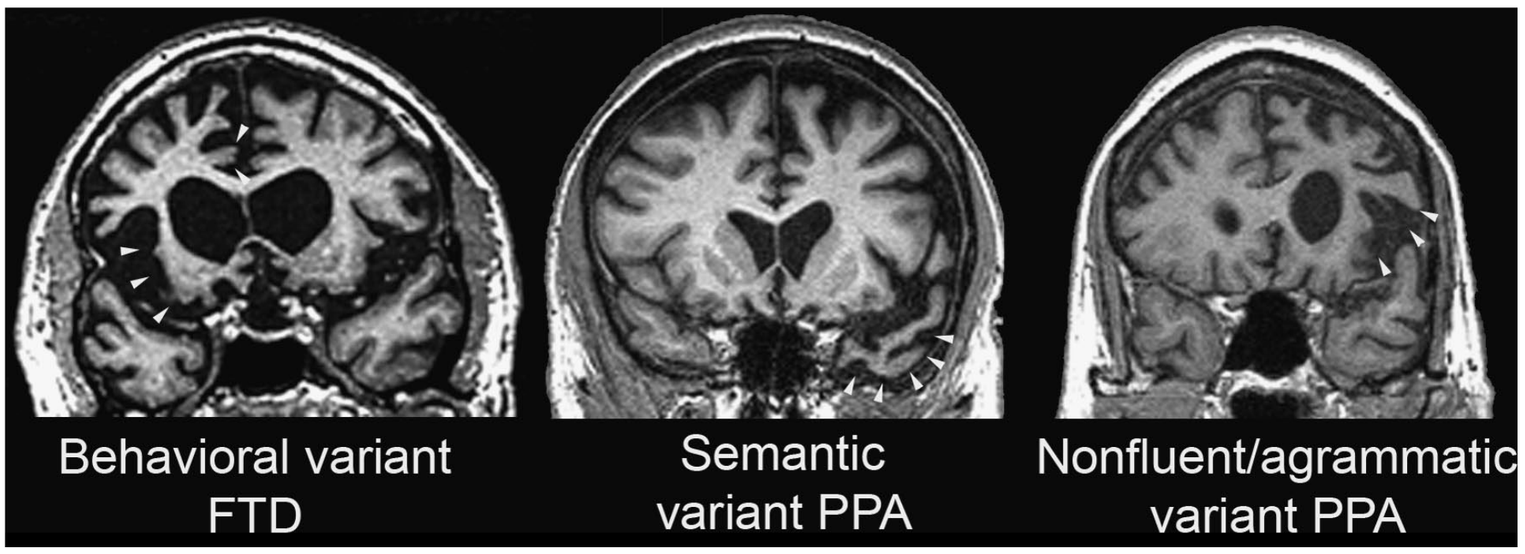


FIGURE 35-3
Three major frontotemporal dementia (FTD) clinical syndromes. Coronal magnetic resonance imaging sections from representative patients with behavioral variant FTD (left), semantic dementia (center), and progressive nonfuent aphasia (right). Areas of early and severe atrophy in each syndrome are highlighted (white arrowheads). The behavioral variant features anterior cingulate and frontoinsular atrophy, spreading to orbital and dorsolateral prefrontal cortex. Semantic variant primary progressive aphasia (PPA) shows prominent temporopolar atrophy, more often on the left. Nonfuent/agrammatic variant PPA is associated with dominant frontal opercular and dorsal insula degeneration.

T e clinical heterogeneity seen in familial and sporadic FTD is remarkable. T ree core clinical syndromes have been described **(Fig. 35-3)**. In the behavioral variant (bvFTD), the most common FTD syndrome, social and emotional systems dysfunction manifests as apathy, disinhibition, compulsivity, loss of empathy, and overeating, often but not always accompanied by deficits in executive control. Two forms of primary progressive aphasia (PPA), the semantic and nonfluent/agrammatic variants, are commonly due to FTLD and included under the FTD umbrella. In the semantic variant, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, whereas patients with the nonfluent/agrammatic variant develop profound inability to produce words, often with prominent motor speech impairment. Any of these three clinical syndromes, but most often bvFTD, may be accompanied by motor neuron disease (MND), in which case the term FTD-MND is applied. In addition, the corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSP-S) can be considered part of the FTLD clinical spectrum. Furthermore, patients may evolve from any of the major syndromes described above to have prominent features of another syndrome.

Findings at the bedside are dictated by the anatomic localization of the disorder. Right hemisphere-predominant or symmetric anterior cingulate/medial prefrontal, orbital, and anterior insular degeneration predicts bvFTD. Patients with nonfluent/agrammatic PPA show left (dominant) frontal opercular and precentral gyrus degeneration, whereas left anterior temporal atrophy presents with semantic variant PPA. Visuoconstructive ability, arithmetic calculations, and navigation may remain normal late into any FTD syndrome. Many patients with nonfluent aphasia or bvFTD later develop PSP-S, as disease spreads into diencephalic and brainstem structures, or CBS-like features, as disease moves into dorsal and lateral perirolandic cortices.

T e most common autosomal dominantly inherited mutations causing FTD involve the C9ORF72 (chromosome 9), GRN (chromosome 17), and MAP*T* (chromosome 17) genes. Hexanucleotide (GGGGCC) expansions in the noncoding portion of C9ORF72 are the most recently identified and represent the most common genetic cause of familial or sporadic FTD (usually presenting as bvFTD with or without MND) and amyotrophic lateral sclerosis (ALS). T e expansion is associated with reduced C9ORF72 mRNA expression, nuclear mRNA foci containing transcribed portions of the expansion and other mRNAs, neuronal cytoplasmic inclusions containing dipeptide repeat proteins translated from the repeat mRNA, and transactive response DNA-binding protein of 43 kDa (TDP-43) neuronal cytoplasmic and glial inclusions. T e pathogenic significance of these various features is a topic of vigorous investigation. MAP*T* mutations lead to a change in the alternate splicing of tau or cause loss of function in the tau molecule, thereby altering microtubule binding. With GRN, mutations in the coding sequence of the gene encoding progranulin protein result in mRNA degradation due to nonsense-mediated decay, providing a rare example of an autosomal dominant mutation that leads to haploinsufficiency and leads to a ~50% reduction in circulating progranulin protein levels. Intriguingly, a patient with GRN mutations on both chromosomes was recently reported to develop neuronal ceroid lipofuscinosis, focusing investigators on the

www.ketabpezeshki.com (021) 66485457 - 66485438

lysosome as a site of molecular dysfunction in GRN-related FTD. Progranulin is a growth factor that binds to tumor necrosis factor (TNF) receptors and participates in tissue repair and tumor growth. How progranulin mutations lead to FTD remains unknown, but the most likely mechanisms include lysosomal dysfunction and enhanced neuroinflammation. Both MAP*T* and GRN mutations are associated with parkinsonian features, whereas ALS is rare. Infrequently, mutations in the valosin-containing protein (VCP, chromosome 9) and charged multivesicular body protein 2b (CHMP2b, chromosome 3) genes also lead to autosomal dominant familial FTD. Mutations in the *T*ARDBP (encoding TDP-43) and FUS (encoding fused in sarcoma [FUS]) genes (see below) cause familial ALS, sometimes in association with an FTD syndrome, although a few patients presenting with FTD alone have been reported.

T e gross pathologic hallmark of FTLD is a focal atrophy of frontal, insular, and/or temporal cortex, which can be visualized with neuroimaging studies (Fig. 35-3) and is often profound at autopsy. Despite the appearance of advanced disease, however, imaging studies suggest that atrophy often begins focally in one hemisphere before spreading to anatomically interconnected regions, including basal ganglia. Loss of cortical serotonergic innervation is seen in many patients. In contrast to AD, the cholinergic system is relatively spared in FTD, which accounts for the poor efficacy of acetylcholinesterase inhibitors in this group.

Although early studies suggested that 15–30% of patients with FTD showed underlying AD at autopsy, progressive refinement in clinical diagnosis has improved pathologic prediction accuracy, and most patients diagnosed with FTD at a dementia clinic with expertise in FTD will show underlying FTLD pathology. Microscopic findings seen across all patients with FTLD include gliosis, microvacuolation, and neuronal loss, but the disease is subtyped according to the protein composition of neuronal and glial inclusions, which contain either tau or TDP-43 in ~90% of patients, with the remaining ~10% showing inclusions containing FUS **(Fig. 35-4)**.

T e toxicity and spreading capacity of tau aggregates underlies the pathogenesis of many familial cases and is emerging as a key factor in sporadic tauopathies, although loss of tau microtubule stabilizing function may also play a role. TDP-43 and FUS, in contrast, are RNA/DNA binding proteins whose roles in neuronal function are still being actively investigated, but one key role may be the chaperoning of mRNAs to the distal neuron for activity-dependent translation within dendritic spines. Because these proteins also form intracellular aggregates and produce similar anatomic progression, protein toxicity and spreading may also factor heavily in the pathogenesis of these FTLD-TDP and FTLD-FUS.

Increasingly, misfolded proteins in neurodegenerative disease are being recognized as having "prion-like" properties in that they can template the misfolding of their natively folded protein counterparts, a process that creates exponential amplification of protein misfolding within a cell and may promote transcellular and even transsynaptic protein propagation between cells. T is hypothesis could provide a unifying explanation for the stereotypical patterns of disease spread observed in each syndrome **(Chap. 30)**.

Although the term Pick's disease was once used to describe a progressive degenerative disorder characterized by selective involvement of the anterior frontal and temporal neocortex and pathologically by intraneuronal cytoplasmic inclusions (Pick bodies), it is now used only in reference to a specific FTLD-tau histopathologic entity. Classical Pick bodies are argyrophilic, staining positively with the Bielschowsky silver method (but not with the Gallyas method) and also with immunostaining for hyperphosphorylated tau. Recognition of the three FTLD major molecular classes has allowed delineation of distinct FTLD subtypes within each class. T ese subtypes, based on the morphology and distribution of the neuronal and glial inclusions **(Fig. 35-5)**, account for the vast majority of patients, and some subtypes show strong clinical or genetic associations (Fig. 35-4). Despite this progress, available data do not allow reliable prediction of the underlying FTLD subtype, or even the major molecular class, based on clinical features alone. Molecular PET imaging with ligands chosen to bind misfolded tau protein shows great promise and is already being applied to the study of patients with AD and FTD. Because FTLD-tau and FTLD-TDP account for 90% of FTLD patients, the ability to detect pathologic tau protein deposition in vivo will greatly improve prediction accuracy, especially when amyloid PET imaging is negative.

T e burden on caregivers of patients with FTD is extremely high, especially when the illness disrupts core emotional and personality functions of the loved one. Treatment is symptomatic, and there are currently no therapies known to slow progression or improve symptoms. Many of the behaviors that may accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with antidepressants, especially SSRIs. T e co-association with motor disorders such as parkinsonism necessitates the careful use of antipsychotics, which can exacerbate this problem.

Progressive supranuclear palsy syndrome (PSP-S; also known as Steele-Richardson-Olszewski syndrome) is a degenerative disorder that involves the brainstem, basal ganglia, limbic structures, and selected areas of cortex. Clinically, PSP-S begins with falls and executive or subtle personality changes (such as mental rigidity, impulsivity, or apathy). Shortly thereafter, a progressive oculomotor syndrome ensues that begins with square

www.ketabpezeshki.com (021) 66485457 - 66485438

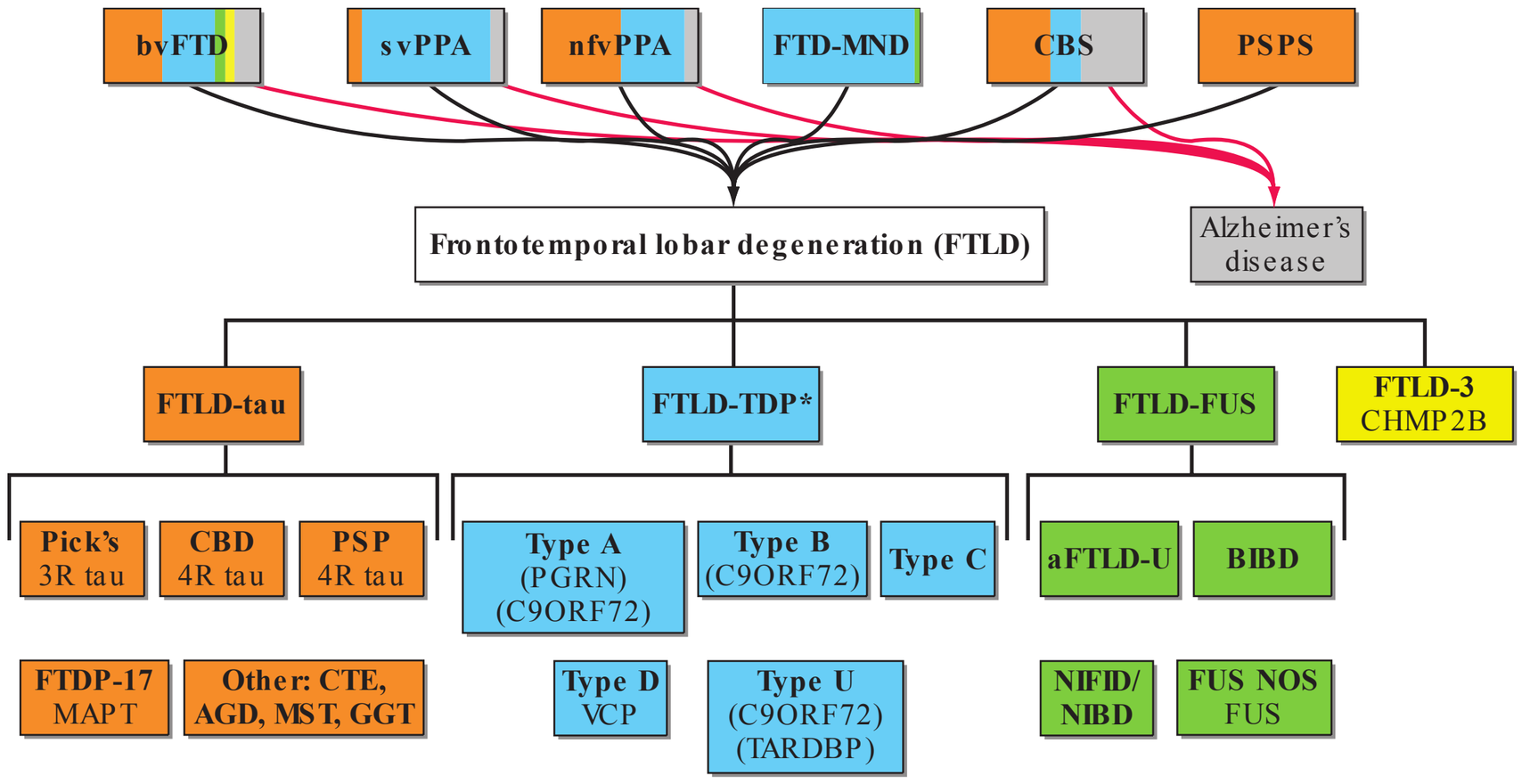


FIGURE 35-4

Frontotemporal dementia syndromes are united by underlying frontotemporal lobar degeneration pathology, which can be divided according to the presence of tau, TPD-43, or FUS-containing inclusions in neurons and glia. Correlations between clinical syndromes and major molecular classes are shown with colored shading. Despite improvements in clinical syndromic diagnosis, a small percentage of patients with some frontotemporal dementia syndromes will show Alzheimer's disease neuropathology at autopsy (gray shading). aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; FTD-MND, frontotemporal dementia with motor neuron disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; FUS, fused in sarcoma; GGT, globular glial tauopathy; MST, multisystem tauopathy; nfvPPA, nonfluent/agrammatic variant primary progressive aphasia; NIBD, neurofilament inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; PSP, progressive supranuclear palsy; PSPS, progressive supranuclear palsy syndrome; svPPA, semantic variant primary progressive aphasia; Type U, unclassifiable type.

wave jerks, followed by slowed saccades (vertical worse than horizontal) before resulting in progressive supranuclear ophthalmoparesis. Dysarthria, dysphagia, and symmetric axial rigidity can be prominent features that emerge at any point in the illness. A stif , unstable posture with hyperextension of the neck and a slow, jerky, toppling gait are characteristic. Frequent unexplained and sometimes spectacular falls are common secondary to a combination of axial rigidity, inability to look down, and poor judgment. Even once patients have severely limited voluntary eye movements, they retain oculocephalic reflexes (demonstrated using a vertical doll's head maneuver); thus, the oculomotor disorder is supranuclear. T e dementia overlaps with bvFTD, featuring apathy, frontal-executive dysfunction, poor judgment, slowed thought processes, impaired verbal fluency, and difficulty with sequential actions and with shifting from one task to another. T ese features are common at presentation and often precede the motor syndrome. Some patients with a pathologic diagnosis of PSP begin with a nonfluent aphasia or motor speech disorder and progress to classical PSP-S. Response to l-dopa is limited or absent; no other treatments exist. Death occurs within 5–10 years of onset. Like Pick's disease, increasingly the term PSP is used to refer to a specific histopathologic entity within the FTLD-tau class. In PSP, accumulation of hyperphosphorylated 4-repeat tau is seen within neurons and glia. Neuronal inclusions often take the form of NFTs, which may be large, spherical ("globose"), and coarse in brainstem, cerebellar dentate, and diencephalic neurons. Tau deposition is most prominent in subcortical structures (including the subthalamic nucleus, globus pallidus, substantia nigra, locus coeruleus, periaqueductal gray, tectum, oculomotor nuclei, and dentate nucleus of cerebellum). Neocortical NFTs, like those in AD, often take on a more flame-shaped morphology, but on electron microscopy, PSP tangles can be shown to consist of straight tubules rather than the paired helical filaments found in AD. Furthermore, PSP is associated with prominent tau-positive glial pathologies, such as tufted astrocytes (Fig. 35-5), thorny astrocytes, and coiled oligodendroglial inclusions ("coiled bodies"). Most patients with PSP-S show PSP at autopsy, although small numbers will show another tauopathy (corticobasal degeneration [CBD] or Pick's disease; Fig. 35-4).

In addition to its overlap with FTD and CBS (see below), PSP is often confused with idiopathic

www.ketabpezeshki.com (021) 66485457 - 66485438

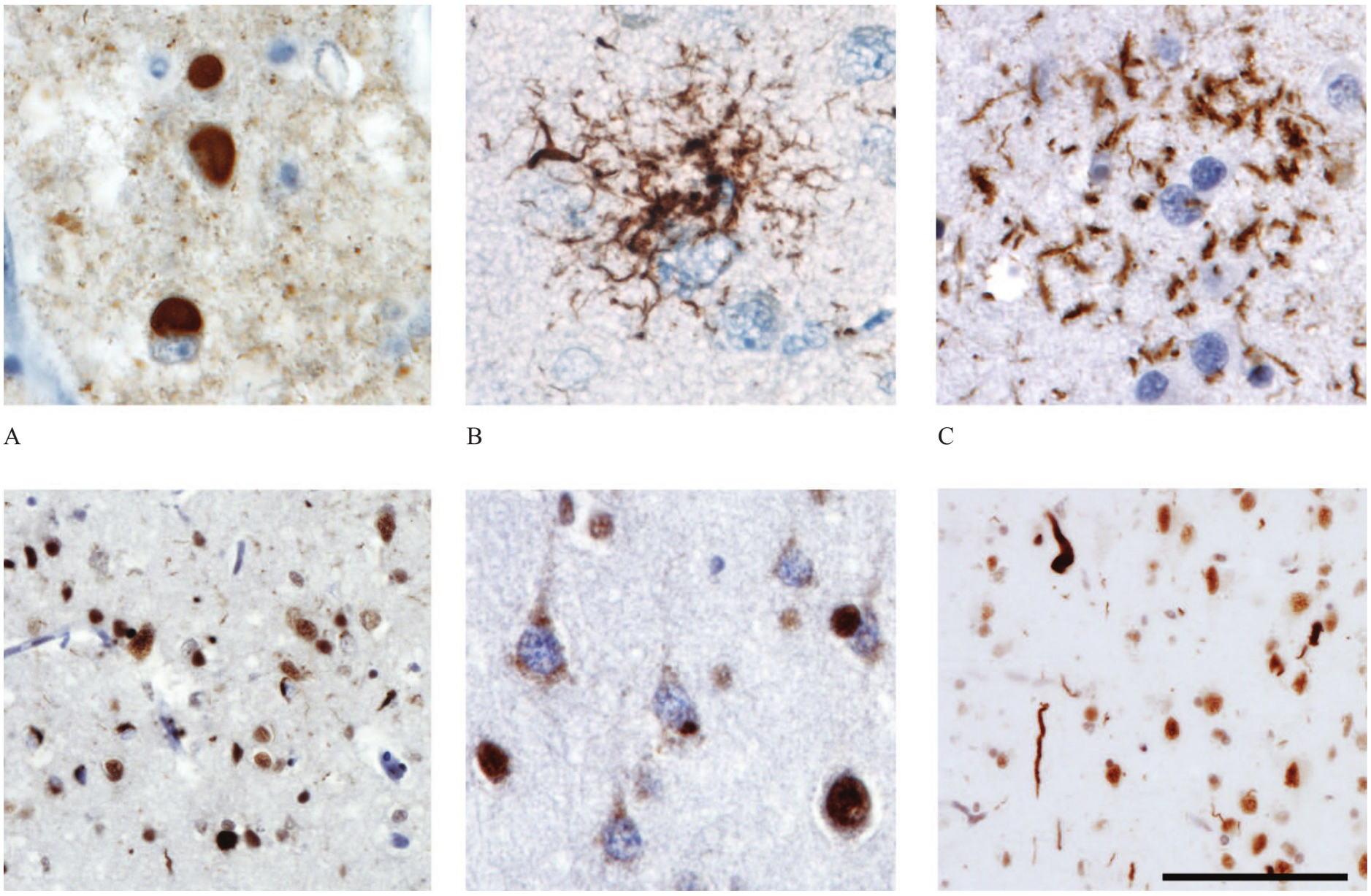


FIGURE 35-5
Neuropathology in frontotemporal lobar degeneration (FTLD). FTLD-tau (A–C) and FTLD-TDP (D–F) account for over 90% of patients with FTLD, and immunohistochemistry reveals characteristic lesions in each of the major histopathologic subtypes within each class: (A) Pick bodies in Pick's disease; (B) a tufted astrocyte in progressive supranuclear palsy; (C) an astrocytic plaque in corticobasal degeneration; (D) small compact or crescentic neuronal cytoplasmic inclusions and short, then neuropil threads in FTLD-TDP, type A; (E) diffuse/granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP, type B; and (F) long, tortuous dystrophic neurites in FTLD-TDP, type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalizes to the cytoplasm and forms inclusions in FTLD-TDP. Immunostains are 3-repeat tau (A), phospho-tau (B and C), and TDP-43 (D–F). Sections are counterstained with hematoxylin. Scale bar applies to all panels and represents 50 μm in A, B, C, and E and 100 μm in D and F.

Parkinson's disease (PD). Although elderly patients with PD may have restricted upgaze, they do not develop downgaze paresis or other abnormalities of voluntary eye movements typical of PSP. Dementia occurs in ~20% of patients with PD, often due to the emergence of a full-blown DLB-like syndrome. Furthermore, the behavioral syndromes seen with DLB dif er from PSP (see below). Dementia in PD becomes more likely with increasing age, increasing severity of extrapyramidal signs, long disease duration, and the presence of depression. Patients with PD who develop dementia also show cortical atrophy on brain imaging. Neuropathologically, there may be AD-related changes in the cortex, LBD-related α-synuclein inclusions in both the limbic system and cortex, or no specific microscopic changes other than gliosis and neuronal loss. **PD is discussed in detail in Chap. 36.**

Corticobasal syndrome (CBS) is a slowly progressive dementia-movement disorder associated with severe atrophy in perirolandic cortex and basal ganglia (substantia nigra and striatopallidum). Patients typically present with asymmetric onset of rigidity, dystonia, myoclonus, and apraxia of one limb, at times associated with alien limb phenomena in which the limb exhibits unintended motor actions such as grasping, groping, drifting, or undoing. Eventually CBS becomes bilateral and leads to dysarthria, slow gait, action tremor, and typically a frontal-predominant dementia. Whereas CBS refers to the clinical syndrome, CBD refers to a specific histopathologic FTLD-tau entity (Fig. 35-4). Although CBS was once thought to be pathognomonic for CBD, increasingly it has been recognize that CBS can be due to CBD, PSP, FTLD-TDP, or even AD. In CBD, the microscopic features include ballooned, achromatic, tau-positive neurons; astrocytic plaques (Fig. 35-5); and other dystrophic glial tau pathomorphologies that overlap with those seen in PSP. Most specifically, CBD features a severe tauopathy burden in

www.ketabpezeshki.com (021) 66485457 - 66485438

the subcortical white matter, consisting of threads and oligodendroglial coiled bodies. As shown in Fig. 35-4, patients with bvFTD, nonfluent/agrammatic PPA, and PSP-S may also show CBD at autopsy, emphasizing the importance of distinguishing clinical and pathologic constructs and terminology. Treatment of CBS remains symptomatic; no disease-modifying therapies are available.

PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

The parkinsonian dementia syndromes are under increasing study, with many cases unified by Lewy body and Lewy neurite pathology that ascends from the low brainstem up through the substantia nigra, limbic system, and cortex. The DLB clinical syndrome is characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often rapid eye movement (REM) sleep behavior disorder (RBD). Dementia can precede or follow the appearance of parkinsonism. Hence, one pathway occurs in patients with long-standing PD without cognitive impairment, who slowly develop a dementia that is associated with visual hallucinations and fluctuating alertness. When this occurs after an established diagnosis of PD, many use the term Parkinson's disease dementia (PDD). In others, the dementia and neuropsychiatric syndrome precede or co-emerge with the parkinsonism, and this constellation is referred to as DLB. Both PDD and DLB may be accompanied or preceded by symptoms referable to brainstem pathology below the substantia nigra including constipation, orthostatic lightheadedness, or RBD, and many researchers conceptualize these disorders as points on a spectrum of α-synuclein pathology.

Patients with PDD and DLB are highly sensitive to metabolic perturbations, and in some patients, the first manifestation of illness is a delirium, often precipitated by an infection, new medicine, or other systemic disturbance. A hallucinatory delirium induced by l-dopa, prescribed for parkinsonian symptoms attributed to PD, may likewise provide the initial clue to a PDD or DLB diagnosis. Conversely, patients with mild cognitive deficits and hallucinations may receive typical or atypical antipsychotic medications, which induce profound parkinsonism at low doses due to a subclinical DLB-related nigral dopaminergic neuron loss. Even without an underlying precipitant, fluctuations can be marked in DLB, with episodic confusion or even stupor admixed with lucid intervals. Despite the fluctuating pattern, however, the core clinical features persist, unlike delirium, which resolves following correction of the inciting factor. Cognitively, DLB features relative preservation of memory but more severe visuospatial and executive deficits than seen in patients with early AD.

The key neuropathologic feature in DLB is the presence of Lewy bodies and Lewy neurites throughout specific brainstem nuclei, substantia nigra, amygdala, cingulate gyrus, and, ultimately, the neocortex. Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid–Schif (PAS) and ubiquitin but are now identified with antibodies to the presynaptic protein, α-synuclein. Lewy bodies are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material and contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and α-synuclein. Lewy bodies are typically found in the substantia nigra of patients with idiopathic PD, where they can be readily seen with hematoxylin-and-eosin staining. A profound cholinergic deficit, owing to basal forebrain and pedunculopontine nucleus involvement, is present in many patients with DLB and may be a factor responsible for the fluctuations, inattention, and visual hallucinations.

Due to the frequent comorbidity with AD and the cholinergic deficit in DLB, cholinesterase inhibitors often provide significant benefit, reducing hallucinosis, stabilizing delusional symptoms, and even helping with RBD in some patients. Exercise programs maximize motor function and protect against fall-related injury. Antidepressants are often necessary. Atypical antipsychotics may be required for psychosis but can worsen extrapyramidal syndromes, even at low doses, and increase risk of death. Patients with DLB are extremely sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved by concomitant use of a cholinesterase inhibitor.

OTHER CAUSES OF DEMENTIA

Prion diseases such as Creutz*f*eldt-Jakob disease (CJD) are rare neurodegenerative conditions (prevalence ~1 per million) that produce dementia. CJD is a rapidly progressive disorder associated with dementia, focal cortical signs, rigidity, and myoclonus, causing death <1 year after first symptoms appear. The rapidity of progression seen with CJD is uncommon in AD so that the distinction between the two disorders is usually straightforward. CBD and DLB, more rapid degenerative dementias with prominent movement abnormalities, are more likely to be mistaken for CJD. The differential diagnosis for CJD includes other rapidly progressive dementing conditions such as viral or bacterial encephalitides, Hashimoto's encephalopathy, central nervous system (CNS) vasculitis, lymphoma, or paraneoplastic/autoimmune syndromes. The markedly abnormal periodic complexes on EEG and

www.ketabpezeshki.com (021) 66485457 - 66485438

cortical ribboning and basal ganglia hyperintensities on fluid-attenuate inversion recovery MRI are diagnostic features of CJD, although rarely, prolonged focal or generalized seizures can produce a similar imaging appearance. **Prion diseases are discussed in detail in Chap. 40.**

Huntington's disease (HD) **(Chap. 36)** is an autosomal dominant degenerative brain disorder. HD clinical hallmarks include chorea, behavioral disturbance, and executive impairment. Symptoms typically begin in the fourth or fifth decade, but there is a wide range, from childhood to >70 years. Memory is frequently not impaired until late in the disease, but attention, judgment, self-awareness, and executive functions are often deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are common. Delusions and obsessive-compulsive behavior may occur. Disease duration is variable but typically lasts approximately 15 years.

Normal-pressure hydrocephalus (NPH) is a relatively uncommon but treatable syndrome. T e clinical, physiologic, and neuroimaging characteristics of NPH must be carefully distinguished from those of other dementias associated with gait impairment. Historically, many patients treated for NPH have suf ered from other dementias, particularly AD, vascular dementia, DLB, and PSP. For NPH, the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate, with an emphasis on executive impairment), and urinary urgency or incontinence. Neuroimaging reveals enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy, although the sylvian fissures may appear propped open (so-called "boxcarring"), which can be mistaken for perisylvian atrophy. T is syndrome is a communicating hydrocephalus with a patent aqueduct of Sylvius (see Fig. 35-3), in contrast to aqueductal stenosis, in which the aqueduct is small. Lumbar puncture opening pressure falls in the high-normal range, and the CSF protein, glucose, and cell counts are normal. NPH may be caused by obstruction to normal CSF flow over the cerebral convexities and delayed resorption into the venous system. T e indolent nature of the process results in enlarged lateral ventricles with relatively little increase in CSF pressure. Presumed edema, stretching, and distortion of subfrontal white matter tracts may lead to clinical symptoms, but the precise underlying pathophysiology remains unclear. Some patients provide a history of conditions that produce meningeal scarring (blocking CSF resorption) such as previous meningitis, subarachnoid hemorrhage, or head trauma. Others with long-standing but asymptomatic congenital hydrocephalus may have adult-onset deterioration in gait or memory that is confused with NPH. In contrast to AD, the patient with NPH complains of an early and prominent gait disturbance without cortical atrophy on CT or MRI.

Numerous attempts to improve NPH diagnosis with various special studies and predict the success of ventricular shunting have been undertaken. T ese tests include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various ef orts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. A transient improvement in gait or cognition may follow lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding has also not proved to be consistently predictive of postshunt improvement. Perhaps the most reliable strategy is a period of close inpatient evaluation before, during, and after lumbar CSF drainage. Occasionally, when a patient with AD presents with gait impairment (at times due to comorbid subfrontal vascular injury) and absent or only mild cortical atrophy on CT or MRI, distinguishing NPH from AD can be challenging. Hippocampal atrophy on MRI favors AD, whereas a characteristic "magnetic" gait with external hip rotation, low foot clearance, and short strides, along with prominent truncal sway or instability, favors NPH. T e diagnosis of NPH should be avoided when hydrocephalus is not detected on imaging studies, even if the symptoms otherwise fit. T irty to fifty percent of patients identified by careful diagnosis as having NPH will improve with ventricular shunting. Gait may improve more than cognition, but many reported failures to improve cognitively may have resulted from comorbid AD. Short-lasting improvement is common. Patients should be carefully selected for shunting, because subdural hematoma, infection, and shunt failure are known complications and can be a cause for early nursing home placement in an elderly patient with previously mild dementia.

Intracranial hypotension, sometimes called sagging brain syndrome, is a disorder caused by low CSF pressure, leading to downward pressure on the subcortical structures and disruption of cerebral function. It presents in a variable manner with headache, often exacerbated by coughing or a Valsalva maneuver or by moving from lying to standing. Other common symptoms include dizziness, vomiting, disruption of sleep-wake cycles, and sometimes a progressive bvFTD-like syndrome. Although sometimes idiopathic, this syndrome can be caused by CSF leaks secondary to lumbar puncture, head trauma, or spinal cord arachnoid cysts. Treatment consists of finding and patching CSF leaks.

Dementia can accompany chronic alcoholism **(Chap. 63)** and may result from associated malnutrition, especially of B vitamins, particularly thiamine. Other poorly defined aspects of chronic alcoholism may, however, also produce cerebral damage. A rare idiopathic syndrome of dementia and seizures with degeneration of the corpus callosum has been reported primarily in male Italian red wine drinkers (Marchiafava-Bignami disease).

www.ketabpezeshki.com (021) 66485457 - 66485438

Thiamine (vitamin B_1) deficiency causes Wernicke's encephalopathy **(Chap. 33)**. The clinical presentation features a malnourished patient (frequently but not necessarily alcoholic) with confusion, ataxia, and diplopia resulting from inflammation and necrosis of periventricular midline structures, including dorsomedial thalamus, mammillary bodies, midline cerebellum, periaqueductal gray matter, and trochlear and abducens nuclei. Damage to the dorsomedial thalamus correlates most closely with the memory loss. Prompt administration of parenteral thiamine (100 mg intravenously for 3 days followed by daily oral dosage) may reverse the disease if given in the first days of symptom onset. Prolonged untreated thiamine deficiency can result in an irreversible and profound amnestic syndrome (Korsakoff's syndrome) or even death.

In Korsakoff's syndrome, the patient is unable to recall new information despite normal immediate memory, attention span, and level of consciousness. Memory for new events is seriously impaired, whereas knowledge acquired prior to the illness remains relatively intact. Patients are easily confused, disoriented, and cannot store information for more than a few minutes. Superficially, they may be conversant, engaging, and able to perform simple tasks and follow immediate commands. Confabulation is common, although not always present. There is no specific treatment because the previous thiamine deficiency has produced irreversible damage to the medial thalamic nuclei and mammillary bodies. Mammillary body atrophy may be visible on MRI in the chronic phase **(see Fig. 33-6)**.

Vitamin B_{12} deficiency, as can occur in pernicious anemia, causes a megaloblastic anemia and may also damage the nervous system **(Chap. 43)**. Neurologically, it most commonly produces a spinal cord syndrome (myelopathy) affecting the posterior columns (loss of vibration and position sense) and corticospinal tracts (hyperactive tendon reflexes with Babinski signs); it also damages peripheral nerves (neuropathy), resulting in sensory loss with depressed tendon reflexes. Damage to myelinated axons may also cause dementia. The mechanism of neurologic damage is unclear but may be related to a deficiency of S-adenosyl methionine (required for methylation of myelin phospholipids) due to reduced methionine synthase activity or accumulation of methylmalonate, homocysteine, and propionate, providing abnormal substrates for fatty acid synthesis in myelin. Use of histamine blockers or metformin, vegan diets, autoimmunity against gastric parietal cells, and various causes of malabsorption are the typical causes for vitamin B_{12} deficiency. The neurologic sequelae of vitamin B_{12} deficiency may occur in the absence of hematologic manifestations, making it critical to avoid using the complete blood count (CBC) and blood smear as a substitute for measuring B_{12} blood levels. Treatment with parenteral vitamin B_{12} (1000 μg intramuscularly daily for a week, weekly for a month, and monthly for life for pernicious anemia) stops progression of the disease if instituted promptly, but complete reversal of advanced nervous system damage will not occur.

Deficiency of nicotinic acid (pellagra) is associated with skin rash over sun-exposed areas, glossitis, and angular stomatitis. Severe dietary deficiency of nicotinic acid along with other B vitamins such as pyridoxine may result in spastic paraparesis, peripheral neuropathy, fatigue, irritability, and dementia. This syndrome has been seen in prisoners of war and in concentration camps but should be considered in any malnourished individual. Low serum folate levels appear to be a rough index of malnutrition, but isolated folate deficiency has not been proved as a specific cause of dementia.

CNS infections usually cause delirium and other acute neurologic syndromes. However, some chronic CNS infections, particularly those associated with chronic meningitis **(Chap. 47)**, may produce a dementing illness. The possibility of chronic infectious meningitis should be suspected in patients presenting with a dementia or behavioral syndrome, who also have headache, meningismus, cranial neuropathy, and/or radiculopathy. Between 20 and 30% of patients in the advanced stages of HIV infection become demented **(Chap. 48)**. Cardinal features include psychomotor retardation, apathy, and impaired memory. This syndrome may result from secondary opportunistic infections but can also be caused by direct infection of CNS neurons with HIV. Neurosyphilis was a common cause of dementia in the preantibiotic era; it is now uncommon but can still be encountered in patients with multiple sex partners, particularly among patients with HIV. Characteristic CSF changes consist of pleocytosis, increased protein, and a positive Venereal Disease Research Laboratory (VDRL) test.

Primary and metastatic neoplasms of the CNS **(Chap. 49)** usually produce focal neurologic findings and seizures rather than dementia, but if tumor growth begins in the frontal or temporal lobes, the initial manifestations may be memory loss or behavioral changes. A paraneoplastic syndrome of dementia associated with occult carcinoma (often small-cell lung cancer) is termed limbic encephalitis. In this syndrome, confusion, agitation, seizures, poor memory, emotional changes, and frank dementia may occur. Paraneoplastic encephalitis associated with NMDA receptor antibodies presents as a progressive psychiatric disorder with memory loss and seizures; affected patients are often young women with ovarian teratoma **(Chap. 50)**.

A nonconvulsive seizure disorder **(Chap. 31)** may underlie a syndrome of confusion, clouding of

www.ketabpezeshki.com (021) 66485457 - 66485438

consciousness, and garbled speech. Often, psychiatric disease is suspected, but an EEG demonstrates the epileptic nature of the illness. If recurrent or persistent, the condition may be termed complex partial status epilepticus. T e cognitive disturbance often responds to anticonvulsant therapy. T e etiology may be previous small strokes or head trauma; some cases are idiopathic.

It is important to recognize systemic diseases that indirectly af ect the brain and produce chronic confusion or dementia. Such conditions include hypothyroidism; vasculitis; and hepatic, renal, or pulmonary disease. Hepatic encephalopathy may begin with irritability and confusion and slowly progress to agitation, lethargy, and coma.

Isolated vasculitis *of* the CNS (CNS granulomatous angiitis) **(Chap. 32)** occasionally causes a chronic encephalopathy associated with confusion, disorientation, and clouding of consciousness. Headache is common, and strokes and cranial neuropathies may occur. Brain imaging studies may be normal or nonspecifically abnormal. CSF analysis reveals a mild pleocytosis or protein elevation. Cerebral angiography can show multifocal stenoses involving medium-caliber vessels, but some patients have only small-vessel disease that is not revealed on angiography. T e angiographic appearance is not specific and may be mimicked by atherosclerosis, infection, or other causes of vascular disease. Brain or meningeal biopsy demonstrates endothelial cell proliferation and mononuclear infiltrates within blood vessel walls. T e prognosis is often poor, although the disorder may remit spontaneously. Some patients respond to glucocorticoids or chemotherapy.

Chronic metal exposure represents a rare cause of dementia. T e key to diagnosis is to elicit a history of exposure at work or home. Chronic lead poisoning from inadequately fire-glazed pottery has been reported. Fatigue, depression, and confusion may be associated with episodic abdominal pain and peripheral neuropathy. Gray lead lines appear in the gums, usually accompanied by an anemia with basophilic stippling of red blood cells. T e clinical presentation can resemble that of acute intermittent porphyria, including elevated levels of urine porphyrins as a result of the inhibition of δ-aminolevulinic acid dehydrase. T e treatment is chelation therapy with agents such as ethylenediamine tetraacetic acid (EDTA). Chronic mercury poisoning produces dementia, peripheral neuropathy, ataxia, and tremulousness that may progress to a cerebellar intention tremor or choreoathetosis. T e confusion and memory loss of chronic arsenic intoxication is also associated with nausea, weight loss, peripheral neuropathy, pigmentation and scaling of the skin, and transverse white lines of the fingernails (Mees' lines). Treatment is chelation therapy with dimercaprol (BAL). Aluminum poisoning is rare but was documented with the dialysis dementia syndrome, in which water used during renal dialysis was contaminated with excessive amounts of aluminum. T is poisoning resulted in a progressive encephalopathy associated with confusion, nonfluent aphasia, memory loss, agitation, and, later, lethargy and stupor. Speech arrest and myoclonic jerks were common and associated with severe and generalized EEG changes. T e condition has been eliminated by the use of deionized water for dialysis.

Recurrent head trauma in professional athletes may lead to a dementia previously referred to as "punch-drunk" syndrome or dementia pugilistica but now known as chronic traumatic encephalopathy (CTE) to signify its relevance to contact sport athletes other than boxers. T e symptoms can be progressive, beginning late in an athlete's career or, more often, after retirement. Early in the course, a personality change associated with social instability and sometimes paranoia and delusions occurs. Later, memory loss progresses to full-blown dementia, often associated with parkinsonian signs and ataxia or intention tremor. At autopsy, the cerebral cortex shows changes tau-immunoreactive NFTs that are more prominent than amyloid plaques (which are usually dif use or absent rather than neuritic). NFTs and tau-positive reactive astrocytes are often clustered in the depths of cortical sulci, and TDP-43 inclusions have also been reported, highlighting the overlap with the FTLD spectrum. Loss of neurons in the substantia nigra is a variable feature.

Chronic subdural hematoma **(Chap. 44)** is also occasionally associated with dementia, often in the context of underlying cortical atrophy from conditions such as AD or HD.

*T*ransient global amnesia (TGA) is characterized by the sudden onset of a severe episodic memory deficit, usually occurring in persons over the age of 50 years. Often the amnesia occurs in the setting of an emotional stimulus or physical exertion. During the attack, the individual is alert and communicative, general cognition seems intact, and there are no other neurologic signs or symptoms. T e patient may seem confused and repeatedly ask about his or her location in place and time. T e ability to form new memories returns after a period of hours, and the individual returns to normal with no recall for the period of the attack. Frequently no cause is determined, but cerebrovascular disease, epilepsy (7% in one study), migraine, or cardiac arrhythmias have all been implicated. Approximately one-quarter of patients experience recurrent attacks. Rare instances of permanent memory loss have been reported in patients with TGA-like spells, usually representing ischemic infarction of the hippocampus or dorsomedial thalamic nucleus bilaterally. Seizure activity due to AD should always be suspected in this syndrome.

www.ketabpezeshki.com (021) 66485457 - 66485438

T e ALS/parkinsonian/dementia complex *of* Guam is a rare degenerative disease that has occurred in the Chamorro natives on the island of Guam. Individuals may have any combination of parkinsonian features, dementia, and MND. T e most characteristic pathologic features are the presence of NFTs in degenerating neurons of the cortex and substantia nigra and loss of motor neurons in the spinal cord, although recent reanalysis has shown that some patients with this illness also show coexisting TDP-43 pathology. Epidemiologic evidence supports a possible environmental cause, such as exposure to a neurotoxin or an infectious agent with a long latency period. One interesting but unproven candidate neurotoxin occurs in the seed of the false palm tree, which Guamanians traditionally used to make flour. T e ALS syndrome is no longer present in Guam, but a dementing illness with rigidity continues to be seen.

Rarely, adult-onset leukodystrophies, lysosomal storage diseases, and other genetic disorders can present as a dementia in middle to late life. Metachromatic leukodystrophy (MLD) causes a progressive psychiatric or dementia syndrome associated with extensive, confluent frontal white matter abnormality. MLD is diagnosed by measuring arylsulfatase A enzyme activity in white blood cells. Adult-onset presentations of adrenoleukodystrophy have been reported in female carriers, and these patients often feature spinal cord and posterior white matter involvement. Adrenoleukodystrophy is diagnosed with measurement of plasma very-long-chain fatty acids. CADASIL is another genetic syndrome associated with white matter disease, often frontally and temporally predominant. Diagnosis is made with skin biopsy, which shows osmophilic granules in arterioles, or, increasingly, through genetic testing for mutations in Notch 3. T e neuronal ceroid lipofuscinoses are a genetically heterogeneous group of disorders associated with myoclonus, seizures, vision loss, and progressive dementia. Diagnosis is made by finding eosinophilic curvilinear inclusions within white blood cells or neuronal tissue.

Psychogenic amnesia for personally important memories can be seen. Whether this results from deliberate avoidance of unpleasant memories, outright malingering, or unconscious repression remains unknown and probably depends on the patient. Event-specific amnesia is more likely to occur after violent crimes such as homicide of a close relative or friend or sexual abuse. It may develop in association with severe drug or alcohol intoxication and sometimes with schizophrenia. More prolonged psychogenic amnesia occurs in fugue states that also commonly follow severe emotional stress. T e patient with a fugue state suf ers from a sudden loss of personal identity and may be found wandering far from home. In contrast to neurologic amnesia, *f*ugue states are associated with amnesia *f*or personal identity and events closely associated with the personal past. At the same time, memory for other recent events and the ability to learn and use new information are preserved. T e episodes usually last hours or days and occasionally weeks or months while the patient takes on a new identity. On recovery, there is a residual amnesia gap for the period of the fugue. Very rarely does selective loss of autobiographic information reflect a focal injury to the brain areas involved with these functions.

Psychiatric diseases may mimic dementia. Severely depressed or anxious individuals may appear demented, a phenomenon sometimes called pseudodementia. Memory and language are usually intact when carefully tested, and a significant memory disturbance usually suggests an underlying dementia, even if the patient is depressed. Patients in this condition may feel confused and unable to accomplish routine tasks. Vegetative symptoms, such as insomnia, lack of energy, poor appetite, and concern with bowel function, are common. Onset is often more abrupt, and the psychosocial milieu may suggest prominent reasons for depression. Such patients respond to treatment of the underlying psychiatric illness. Schizophrenia is usually not difficult to distinguish from dementia, but occasionally the distinction can be problematic. Schizophrenia generally has a much earlier age of onset (second and third decades) than most dementing illnesses and is associated with intact memory. T e delusions and hallucinations of schizophrenia are usually more complex, bizarre, and threatening than those of dementia. Some chronic schizophrenics develop an unexplained progressive dementia late in life that is not related to AD. Conversely, FTD, HD, vascular dementia, DLB, AD, or leukoencephalopathy can begin with schizophrenia-like features, leading to the misdiagnosis of a psychiatric condition. Later age of onset, significant deficits on cognitive testing, or the presence of abnormal neuroimaging suggest a degenerative condition. Memory loss may also be part of a conversion disorder. In this situation, patients commonly complain bitterly of memory loss, but careful cognitive testing either does not confirm the deficits or demonstrates inconsistent or unusual patterns of cognitive problems. T e patient's behavior and "wrong" answers to questions often indicate that he or she understands the question and knows the correct answer.

Clouding of cognition by chronic drug or medication use, often prescribed by physicians, is an important cause of dementia. Sedatives, tranquilizers, and analgesics used to treat insomnia, pain, anxiety, or agitation may cause confusion, memory loss, and lethargy, especially in the elderly. Discontinuation of the of ending medication often improves mentation.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 36

PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

C. Warren Olanow ■ Anthony H.V. Schapira ■ Jose A. Obeso

PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second commonest neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. It is noteworthy that James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients. It is estimated that approximately 1 million persons in the United States, 1 million in Western Europe, and 5 million worldwide suffer from this disorder. PD affects men and women of all races, all occupations, and all countries. T e mean age of onset is about 60 years. T e frequency of PD increases with aging, but cases can be seen in patients in their 20s and even younger. Based on the aging of the population and projected demographics, it is estimated that the prevalence of the disease will dramatically increase in the next several decades.

Clinically, PD is characterized by rest tremor, rigidity, bradykinesia (slowing), and gait impairment, known as the "cardinal features" of the disease. Additional features can include freezing of gait, postural instability, speech difficulty, autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia **(Table 36-1)**.

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intracytoplasmic proteinaceous inclusions known as Lewy bodies that primarily contain the protein alpha synuclein **(Fig. 36-1)**. While interest has primarily focused on the dopamine system, neuronal degeneration with inclusion body formation can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. T is "nondopaminergic" pathology is likely responsible for the development of nondopaminergic clinical features listed in Table 36-1 characterized by their lack of satisfactory response to dopaminergic replacement therapy. T ere is evidence that Lewy body pathology first begins in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower brainstem, and then spreads in a predictable and sequential manner to affect the upper brainstem and cerebral hemispheres (Braak staging). T ese studies suggest that degeneration of dopamine neurons develops in a mid-stage of the disease. Indeed, epidemiologic studies suggest that clinical symptoms reflecting this nondopaminergic degeneration, such as constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, and cardiac denervation, can precede the onset of the classic motor features of PD.

DIFFERENTIAL DIAGNOSIS

Parkinsonism is a generic term that is used to define a syndrome manifest as bradykinesia with rigidity and/or tremor. It has a differential diagnosis **(Table 36-2)** that reflects damage to different components of the basal ganglia. T e basal ganglia are comprised of a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GPe), globus pallidus pars interna (GPi), and the SNc **(Fig. 36-2)**. Among the different forms of parkinsonism, PD is the most common (approximately

www.ketabpezeshki.com (021) 66485457 - 66485438

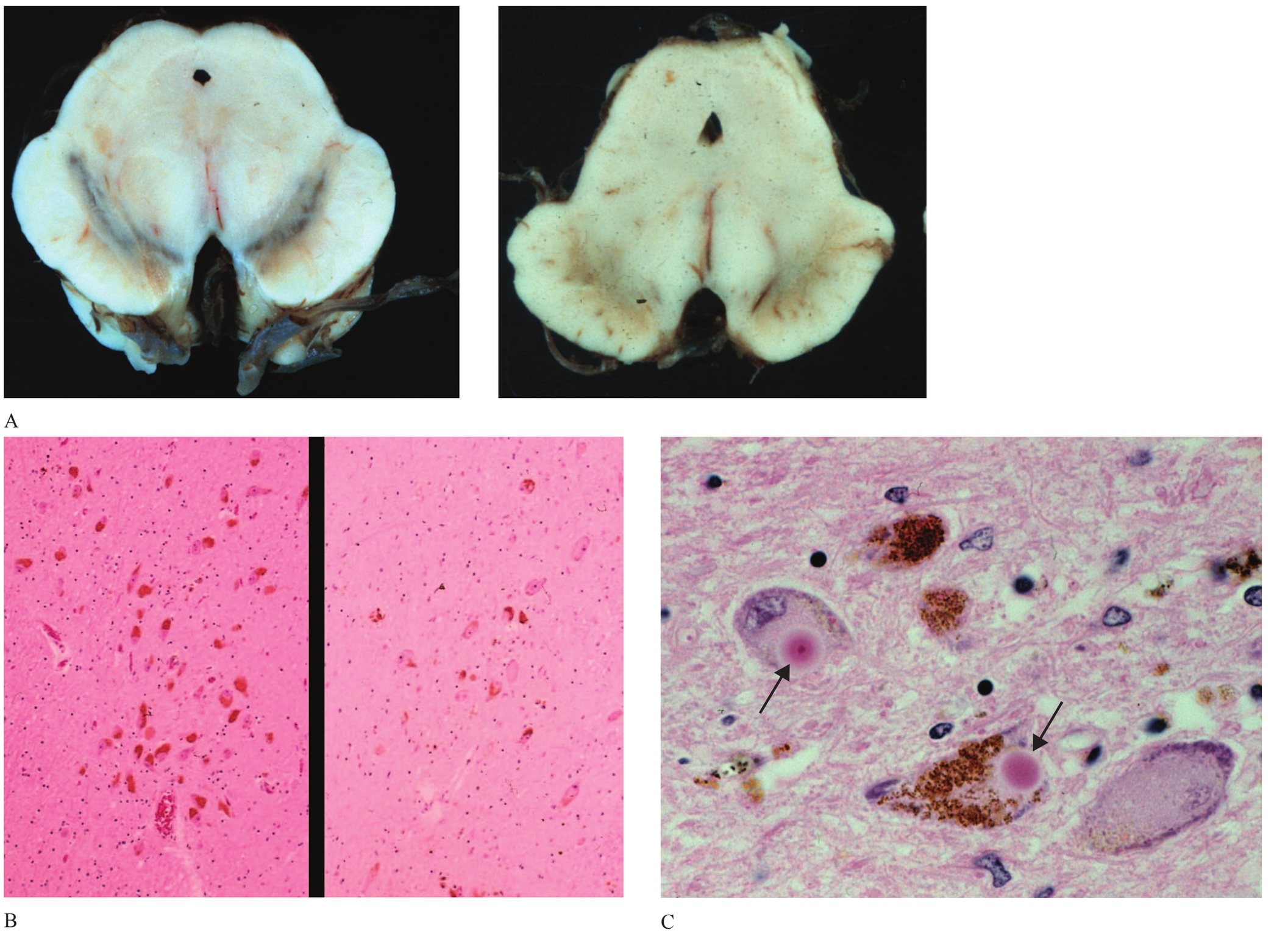
TABLE 36-1

CLINICAL FEATURES OF PARKINSON'S DISEASE

CARDINAL MOTOR FEATURES	OTHER MOTOR FEATURES	NONMOTOR FEATURES
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blinking	Mood disorders (e.g., depression)
Gait disturbance/postural instability	Soft voice (hypophonia)	Sleep disturbances (e.g., RBD)
	Dysphagia	Autonomic disturbances
	Freezing	Orthostatic hypotension
		Gastrointestinal disturbances
		Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment (MCI/dementia)

Abbreviations:; MCI, mild cognitive impairment; RBD, rapid eye movement behavior disorder.

75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, postmortem studies found a 24% error rate when diagnosis was based on these criteria. Clinicopathologic correlation studies subsequently determined that parkinsonism associated with rest tremor, asymmetry, and a good response to levodopa was more likely to predict the correct pathologic diagnosis. With these revised criteria (known as the U.K. Brain Bank Criteria), a



A

B

C

FIGURE 36-1

Pathologic specimens from a patient with Parkinson's disease **(**PD**)** compared to a normal control demonstrating (A) reduction of pigment in SNc in PD (right) versus control (left), (B) reduced numbers of cells in SNc in PD (right) compared to control (left), and (C) Lewy bodies (arrows) within melanized dopamine neurons in PD. SNc, substantia nigra pars compacta.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 36-2

DIFFERENTIAL DIAGNOSIS OF PARKINSONISM			
Parkinson's Disease Genetic Sporadic Dementia with Lewy bodies	Atypical Parkinsonism Multiple-system atrophy (MSA) Cerebellar type (MSA-c) Parkinson type (MSA-p) Progressive supranuclear palsy Corticobasal ganglionic degeneration Frontotemporal dementia	Secondary Parkinsonism Drug-induced Tumor Infection Vascular Normal-pressure hydrocephalus Trauma Liver failure Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Other Neurodegenerative Disorders Wilson's disease Huntington's disease Neurodegeneration with brain iron accumulation SCA 3 (spinocerebellar ataxia) Fragile X–associated ataxia-tremor-parkinsonism Prion disease Dystonia-parkinsonism (DYT3) Alzheimer's disease with parkinsonism

Abbreviation: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

clinical diagnosis of PD is confirmed pathologically in as many as 99% of cases. A more complete definition of PD is now needed to incorporate the fact that there is widespread pathology beyond the dopaminergic system, nondopamine and nonmotor clinical features, and a premotor stage of the disease.

Imaging of the brain dopamine system in PD with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) shows reduced uptake of striatal dopaminergic markers, particularly in the posterior putamen with relative sparing of the caudate nucleus **(Fig. 36-3)**, reflecting the degeneration of nigrostriatal dopamine neurons. Imaging can be useful in patients where there is diagnostic uncertainty (e.g., dystonic tremor, essential tremor) or in research studies, but is rarely necessary in routine practice because the diagnosis can usually be established on clinical criteria alone. T is may change in the future when there is a disease-modifying therapy and it is important to make the diagnosis as early as possible. Genetic testing is not routinely used at present, but can be helpful for identifying at-risk individuals in a research setting. Mutations of the LRRK2 gene (see below) have attracted particular interest because they are the commonest cause of familial PD and are responsible for approximately 1% of typical sporadic cases of the disease. Mutations in LRRK2 are a particularly common cause of PD in Ashkenazi Jews and North African Berber Arabs. T e penetrance of the most common LRRK2 mutation ranges from 28 to 74% and is strongly correlated to the age of the carrier, with 50% affected by age 60 years. Mutations in the parkin gene should be considered in patients with onset prior to 40 years of age.

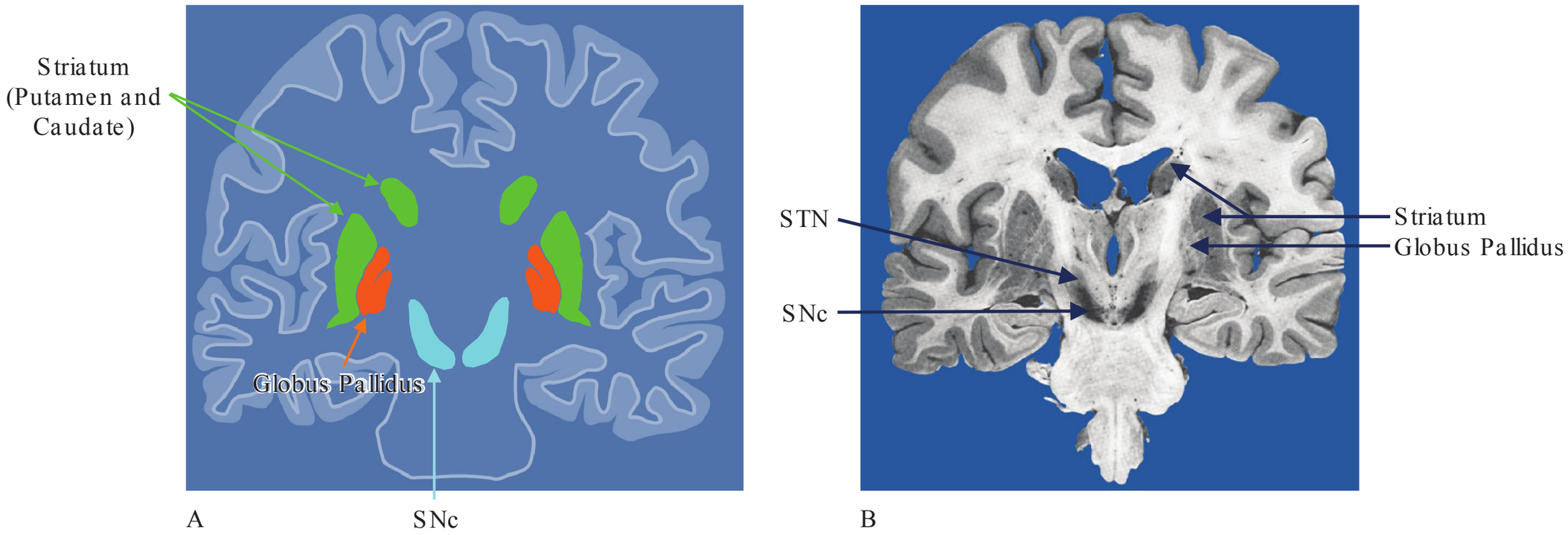


FIGURE 36-2

Basal ganglia nuclei. Schematic (A) and postmortem (B) coronal sections illustrating the various components of the basal ganglia. SNc, substantia nigra pars compacta; STN, subthalamic nucleus.

www.ketabpezeshki.com (021) 66485457 - 66485438

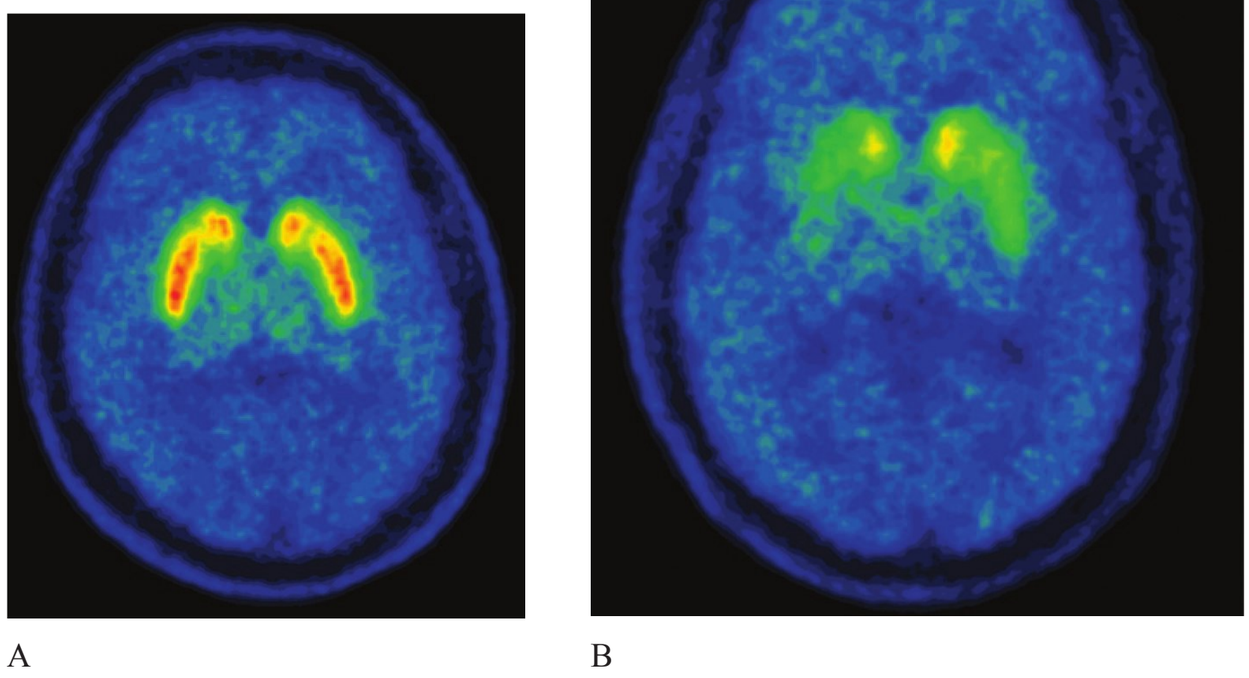


FIGURE 36-3
[^{11}C]Dihydrotetrabenazine positron emission tomography (a marker of VMAT2) in healthy control (A) and Parkinson's disease (B) patient. Note the reduced striatal uptake of tracer, which is most pronounced in the posterior putamen and tends to be asymmetric. (Courtesy of Dr. Jon Stoessl.)

Atypical and secondary parkinsonism

Atypical parkinsonism refers to a group of neurodegenerative conditions that usually are associated with more widespread neurodegeneration than is found in PD (often involvement of striatum and/or globus pallidus as well as the SNc). As a group, they present with parkinsonism (rigidity and bradykinesia) but have a slightly different clinical picture than PD, reflecting differences in the underlying pathology. In these conditions, parkinsonism is typically characterized by early speech and gait impairment, absence of rest tremor, no motor asymmetry, poor or no response to levodopa, and an aggressive clinical course. In the early stages, they may show some modest benefit from levodopa and be difficult to distinguish from PD. Pathologically, neurodegeneration typically involves degeneration of the SNc but occurs without Lewy bodies (see below for individual conditions). Neuroimaging of the dopamine system is usually not helpful, because dopamine depletion can be seen in both PD and atypical parkinsonism. By contrast, metabolic imaging of the basal ganglia/thalamus network (using 2-F-deoxiglucose PET) may be helpful, showing a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

Multiple-system atrophy (MSA) manifests as a combination of parkinsonian, cerebellar, and autonomic features and can be divided into a predominant parkinsonian (MSA-p) or cerebellar (MSA-c) form. Clinically, MSA is suspected when a patient presents with atypical parkinsonism in conjunction with cerebellar signs and/or early and prominent autonomic dysfunction, usually orthostatic hypotension **(Chap. 41)**. Pathologically, MSA is characterized by degeneration of the SNc, striatum, cerebellum, and inferior olivary nuclei coupled with characteristic glial cytoplasmic inclusions (GCIs) that stain for α-synuclein. Magnetic resonance imaging (MRI) can show pathologic iron accumulation in the striatum on T2-weighted scans, high signal change in the region of the external surface of the putamen (putaminal rim) in MSA-p, or cerebellar and brainstem atrophy (the pontine "hot cross buns" sign (Fig. 41-2) in MSA-c. Mutations in the CoQ2 gene encoding parahydroxybenzoate-polyprenyl transferase, an enzyme involved in the biosynthesis of coenzyme Q10 (CoQ10), a cofactor of the mitochondrial respiratory chain, have been identified in familial and sporadic forms of MSA.

Progressive supranuclear palsy (PSP) is a form of atypical parkinsonism that is characterized by slow ocular saccades, eyelid apraxia, and restricted eye movements with particular impairment of downward gaze. Patients frequently experience hyperextension of the neck with early gait disturbance and falls. In later stages, speech and swallowing difficulty and cognitive impairment become evident. MRI may reveal a characteristic atrophy of the midbrain with relative preservation of the pons, the "hummingbird sign" on midsagittal images. Pathologically, PSP is characterized by degeneration of the SNc, striatum, subthalamic nucleus, midline thalamic nuclei, and pallidum along with neurofibrillary tangles and inclusions that stain for the tau protein.

Corticobasal ganglionic degeneration is less common and is usually manifest by asymmetric dystonic contractions and clumsiness of one hand coupled with

www.ketabpezeshki.com (021) 66485457 - 66485438

cortical sensory disturbances manifest as apraxia, agnosia, focal limb myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of it). Dementia may occur at any stage of the disease. Both cortical and basal ganglia features are required to make this diagnosis. MRI frequently shows asymmetric cortical atrophy. Pathologic findings include achromatic neuronal degeneration with tau deposits. Because other disorders such as PSP can present with a similar clinical picture, the term corticobasal ganglia syndrome should be used until a precise diagnosis can be confirmed pathologically.

Secondary parkinsonism can occur as a result of drugs, stroke, tumor, infection, or exposure to toxins such as carbon monoxide or manganese. Dopamine-blocking agents such as the neuroleptics are the commonest cause of secondary parkinsonism. T ese drugs are most widely used in psychiatry, but physicians should be aware that drugs such as metoclopramide and chlorpromazine, which are primarily used to treat gastrointestinal problems, are also neuroleptic agents and common causes of secondary parkinsonism (as well as acute and tardive dyskinesias; see below). Other drugs that can cause secondary parkinsonism include tetrabenazine, calcium channel blockers (flunarizine, cinnarizine), amiodarone, and lithium.

Finally, parkinsonism can be seen as a feature of other degenerative disorders such as Wilson's disease, Huntington's disease (especially the juvenile form known as the Westphal variant), dopa-responsive dystonia, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)–associated neurodegeneration (formerly known as Hallervorden-Spatz disease).

Some features that suggest parkinsonism might be due to a condition other than PD are shown in **Table 36-3**.

TABLE 36-3

FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Exam	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired down gaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

ETIOLOGY AND PATHOGENESIS

Most PD cases occur sporadically (~85–90%) and are of unknown cause. Twin studies suggest that environmental factors likely play an important role in patients older than 50 years, with genetic factors being more important in younger patients. Epidemiologic studies also suggest increased risk with exposure to pesticides, rural living, and drinking well water and reduced risk with cigarette smoking and caffeine. However, no environmental factor has yet been proven to cause typical PD. T e environmental hypothesis received support with the demonstration in the 1980s that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a byproduct of the illicit manufacture of a heroin-like drug, caused a PD-like syndrome in addicts in northern California. MPTP is transported to the central nervous system, where it is oxidized to form MPP^+, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons. However, MPTP or MPTP-like compounds have not been linked to sporadic PD.

About 10–15% of cases are familial in origin, and multiple specific mutations and gene associations have been identified **(Table 36-4)**. Genetic factors have also been linked to sporadic cases, with several typical PD cases found to carry the LRRK2 mutation, and genome-wide association studies (GWAS) implicating alpha synuclein, tau, and HLA as risk factors. It has been proposed that most cases of PD may be due to a "double hit" involving an interaction between a gene mutation that induces susceptibility coupled with exposure to a toxic environmental factor that may induce epigenetic or somatic DNA alterations. In this scenario, both

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 36-4

GENETIC CAUSES OF PARKINSON'S DISEASE

NAME	CHROMOSOME	LOCUS	GENE	INHERITANCE
Park 1	Chr 4	q21-23	α-Synuclein	AD
Park 2	Chr 6	q25-27	Parkin	AR
Park 3	Chr 2	p13	Unknown	AD
Park 4	Chr 4	q21-23	α-Synuclein	AD
Park 5	Chr 4	p14	UCHL-1	AD
Park 6	Chr 1	p35-36	PINK-1	AR
Park 7	Chr 1	p36	DJ-1	AR
Park 8	Chr 12	p11-q13	LRRK2	AR/Sp
Park 9	Chr 1	p36	ATP13A2	AR
Park 10	Chr 1	p32	Unknown	Sp
Park 11	Chr 2	q36-37	GIGYF2	AD
Park 12	Chr X	q21-25	Unknown	Sp
Park 13	Chr 2	p13	Omi/HtrA2	AD
Park 14	Chr 22	q13	PLA2G6	AR
Park 15	Chr 22	q12-13	FBX07	AR
Park 16	Chr 1	q32	Unknown	Sp

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; Chr, chromosome; Sp, sporadic.

factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease.

Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, mitochondrial dysfunction, and proteolytic stress. Recent studies have demonstrated that with aging dopamine neurons switch from sodium to calcium pacing through calcium channels, potentially making these high-energy neurons vulnerable to calcium-mediated neurotoxicity. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or "suicidal" process. Each of these mechanisms offers a potential target for neuroprotective drugs. However, it is not clear which of these factors is primary, if the mechanism is the same in each individual case, if they act by way of a network such that a cocktail of agents might be required to provide neuroprotection, or if the findings to date merely represent epiphenomena unrelated to the true cause of cell death that remains undiscovered **(Fig. 36-4)**.

Gene mutations may not cause all cases of PD, but may be helpful in pointing to specific pathogenic pathways and mechanisms that are central to a neurodegenerative process that might be relevant to all forms of the disease. To date, most interest has focused on pathways implicated by mutations in α-synuclein, LRRK2, and PINK1/Parkin.

Most interest has focused on α-synuclein. Mutations in α-synuclein cause rare familial forms of PD, and α-synuclein constitutes the major component of Lewy bodies in patients with sporadic PD (Fig. 36-1). Furthermore, duplication or triplication of the wild-type α-synuclein can also cause a form of PD, indicating that increased production of the normal protein alone can cause the disease. More recently, Lewy pathology was discovered to have developed in healthy embryonic dopamine neurons that had been implanted into the striatum of PD patients, suggesting that the abnormal protein had transferred from affected cells to healthy unaffected dopamine neurons. Based on these findings, it has been proposed that α-synuclein is a prion and PD is a prion disorder. Here it is proposed that, like the prion protein PrP^{C}, α-synuclein can misfold to form β-rich sheets, generate toxic oligomers and aggregates, polymerize to form amyloid plaques (i.e., Lewy bodies), cause neurodegeneration, and spread to involve unaffected neurons. Indeed, injection of α-synuclein fibrils into the striatum promotes the development of Lewy pathology in host neurons, neurodegeneration, behavioral abnormalities, and the spread of α-synuclein pathology to anatomically connected sites. Further support for this hypothesis comes from the demonstration that inoculation of α-synuclein derived from human Lewy bodies induces widespread Lewy pathology in mice and primates. Collectively, this evidence supports the possibility that neuroprotective therapies for PD might be developed based on inhibiting accumulation or accelerating removal of α-synuclein aggregates.

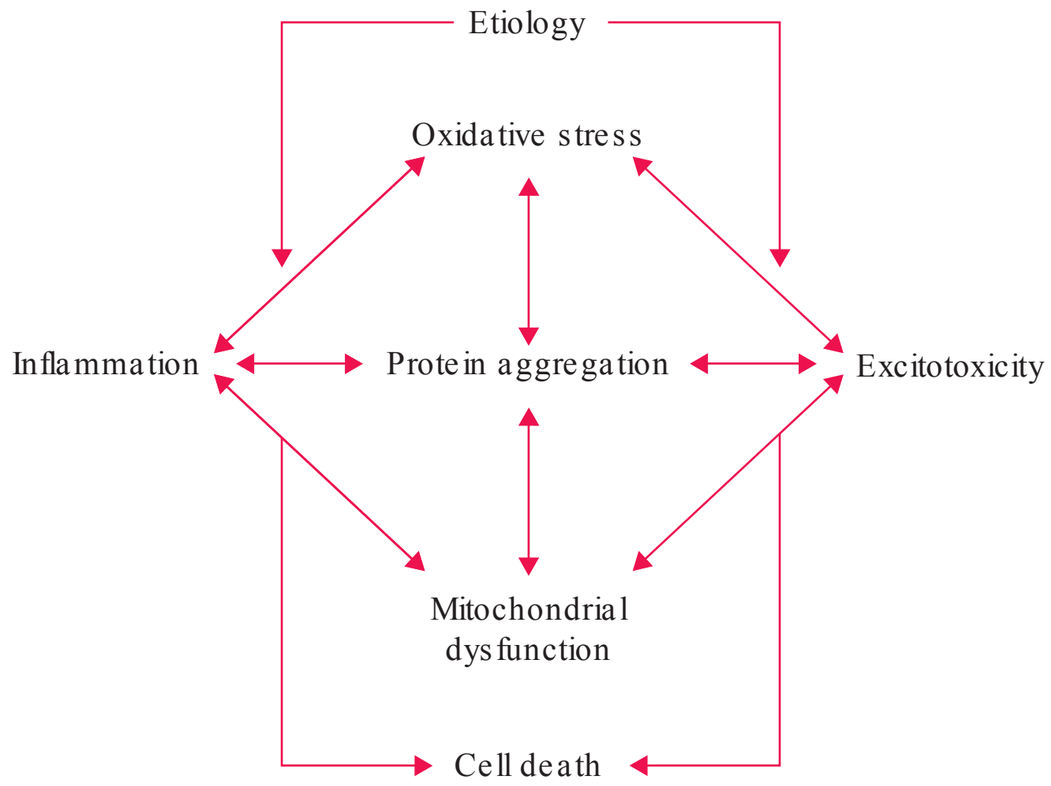


FIGURE 36-4

Schematic representation of how pathogenetic factors implicated in Parkinson's disease interact in a network manner, ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. (Adapted from CW Olanow: Movement Disorders 22:S-335, 2007.)

www.ketabpezeshki.com (021) 66485457 - 66485438

Mutations in the glucocerebrosidase (GBA) gene associated with Gaucher's disease numerically represent the most important risk factor for the development of PD. While the responsible mechanism is not precisely known, it is noteworthy that GBA mutations are associated with altered autophagy and lysosomal function and could impair the clearance of α-synuclein.

Six different LRRK2 mutations have been linked to PD, with Gly2019Ser being the most common. The mechanism responsible for cell death with this mutation is not known but is thought to involve changes in kinase activity with altered phosphorylation of target proteins (including autophosphorylation) and possibly lysosomal dysfunction. Kinase inhibitors can block toxicity associated with LRRK2 mutations in laboratory models, and there has been much interest in developing drugs directed at this target. However, kinase inhibitors are likely to be toxic, the physiologic role of LRRK2 is not known, and the large majority of PD patients do not carry a LRRK2 mutation.

Mutations in PINK1 and parkin have implicated mitochondrial dysfunction as a possible cause of PD. Recent studies suggest a role for parkin and PINK1 proteins in the turnover and clearance of damaged mitochondria (mitophagy), and mutations in parkin and PINK1 cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of parkin. This is a particularly attractive target because postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons.

Thus, evidence is accumulating that genetics plays an important role in both familial and "sporadic" forms of PD. It is anticipated that better understanding of the pathways responsible for cell death caused by these mutations will permit the development of more relevant animal models of PD and targets for the development of neuroprotective drugs.

PATHOPHYSIOLOGY OF PD

The classic model of the organization of the basal ganglia in the normal and PD states is provided in **Fig. 36-5**. With respect to motor function, a series of neuronal circuits or loops link the basal ganglia nuclei with corresponding cortical motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on the activity of the output pathway. The output of the basal ganglia provides inhibitory (GABAergic) tone to thalamic and brainstem neurons that in turn connect to motor systems in the cerebral cortex and spinal cord that control motor function. Physiologically, decreased neuronal activity in the GPi/SNr is associated with movement facilitation and vice versa. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network. The basal ganglia and similar cortical loops are now thought to also play an important role in regulating normal behavioral, emotional, and cognitive functions.

In PD, dopamine denervation with loss of dopaminergic tone leads to increased firing of neurons in the STN and GPi, excessive inhibition of the thalamus, reduced activation of cortical motor systems, and the development of parkinsonian features (Fig. 36-5). The current role of surgery in the treatment of PD is based on this model, which predicted that lesions or high-frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features.

TREATMENT Parkinson's Disease

LEVODOPA Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by Carlsson demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients and suggested the potential benefit of dopaminergic replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, a precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting due to activation of dopamine receptors in the area postrema that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet), whereas in many other countries, it is combined with benserazide (Madopar). Levodopa is also available in controlled-release formulations as well as in combination with a catechol-O-methyltransferase (COMT) inhibitor (see below). Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Almost all PD patients experience improvement, and failure to respond to an adequate trial should cause the diagnosis to be questioned.

There are, however, important limitations of levodopa therapy. Acute dopaminergic side effects include nausea,

www.ketabpezeshki.com (021) 66485457 - 66485438

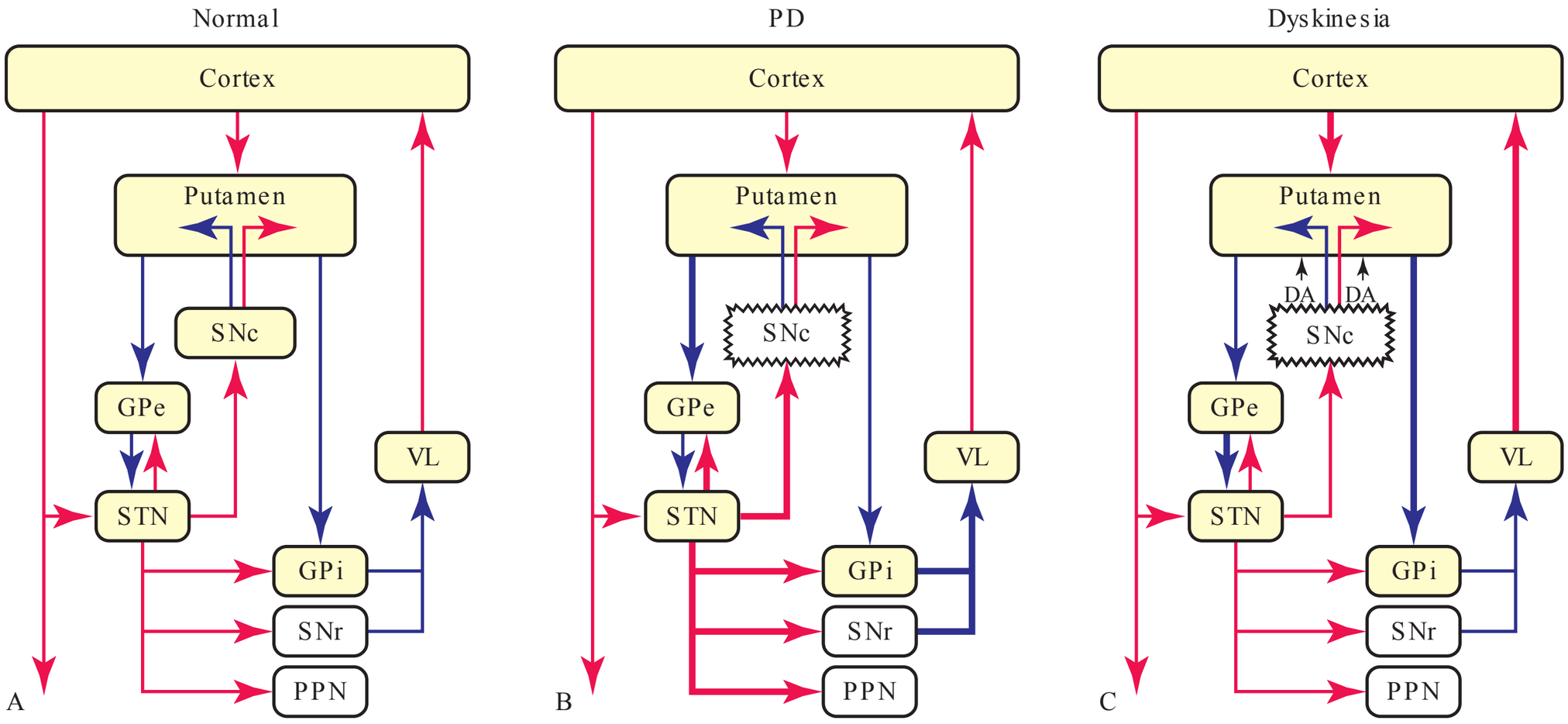


FIGURE 36-5

Basal ganglia organization. Classic model of the organization of the basal ganglia in the normal (A), Parkinson's disease (PD) (B), and levodopa-induced dyskinesia (C) state. Inhibitory connections are shown as blue arrows and excitatory connections as red arrows. The striatum is the major input region and receives its major input from the cortex. The GPi and SNr are the major output regions, and they project to the thalamocortical and brainstem motor regions. The striatum and GPi/SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPi and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions, resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct because lesions of the GPi ameliorate rather than increase dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia. DBS, deep brain stimulation; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventrolateral thalamus. (Derived from JA Obeso et al: Trends Neurosci 23:S8, 2000.)

vomiting, and orthostatic hypotension. T ese are usually transient and can generally be avoided by gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa) or a peripheral dopamine-blocking agent such as domperidone (not available in the United States). More important are motor complications (see below) that develop in the majority of patients treated long-term with levodopa. In addition, the disease continues to progress, and features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge with disease progression that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falling and dementia) are the primary source of disability and the main reason for nursing home placement for patients with advanced PD

Levodopa-induced motor complications consist of fluctuations in motor response ("on" episodes when the drug is working and "off" episodes when parkinsonian features return) and involuntary movements known as dyskinesias **(Fig. 36-6)**. When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60–90 min). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. T is loss of benefit is known as the wearing-of ef ect. In more severe cases, patients may experience a delay in turning on (delayed-on) or no response at all to a given dose (no-on). Dyskinesias tend to occur at the time of levodopa peak plasma concentration and maximal clinical benefit (peak-dose dyskinesia). T ey are usually choreiform in nature but can manifest as dystonic movements, myoclonus, or other movement disorders. T ey are not troublesome when mild, but can be disabling when severe, and can limit the ability to fully use levodopa to control PD features. In more advanced states, patients may cycle between "on" periods complicated by disabling dyskinesias and "off" periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may also experience "diphasic dyskinesias," which occur as the levodopa dose begins to take effect and again as it wears off. T ese dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities and are frequently associated with parkinsonism in other body regions. T ey can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia.

www.ketabpezeshki.com (021) 66485457 - 66485438

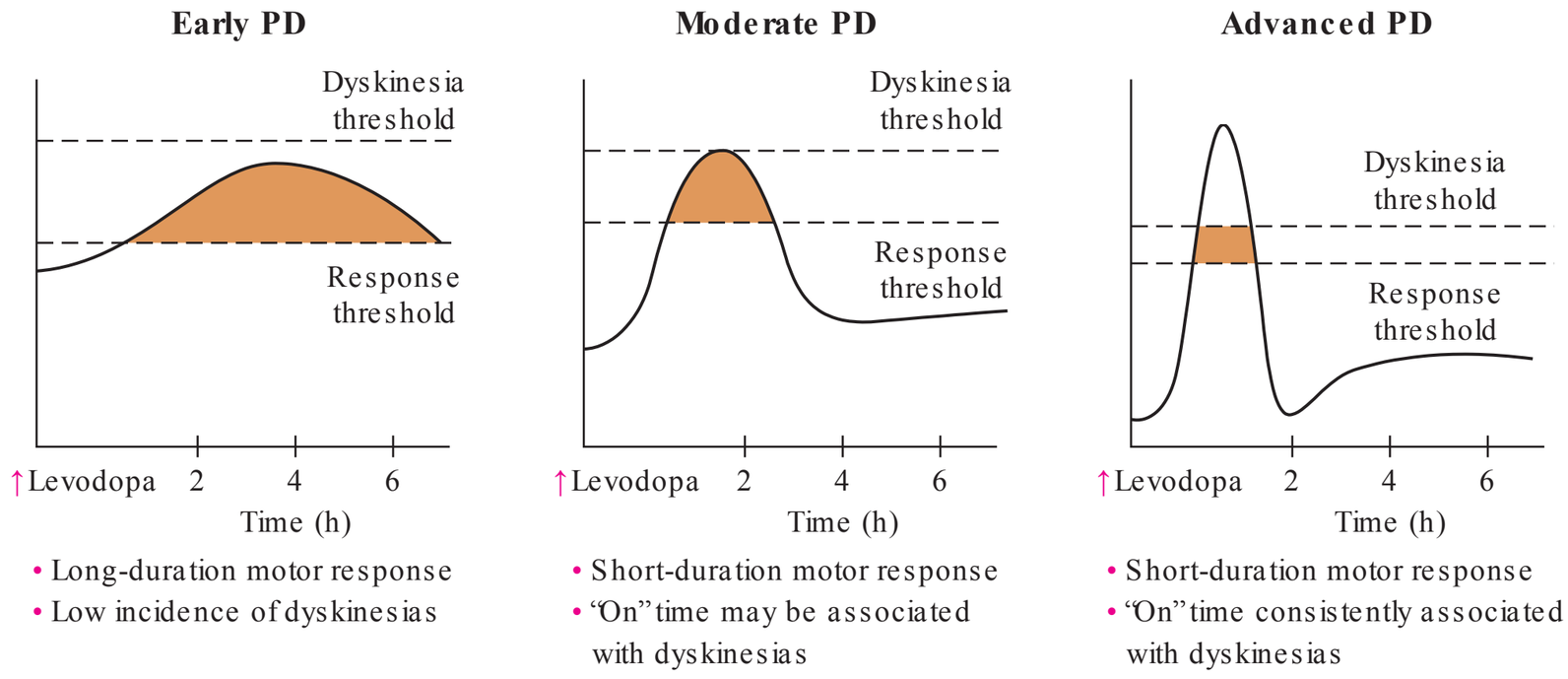


FIGURE 36-6
Changes in motor response associated with chronic levodopa treatment. Levodopa-induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating "on" time. PD, Parkinson's disease.

The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in females, younger individuals with more severe disease, and with the use of higher doses (mg/kg) of levodopa. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD, but has proved less valuable for understanding levodopa-induced dyskinesias (Fig. 36-5). The model predicts that dopamine replacement might excessively inhibit the pallidal output system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the development of dyskinesia. However, lesions of the pallidum that completely destroy its output are associated with amelioration rather than induction of dyskinesia as suggested by the classic model. It is now thought that dyskinesia results from levodopa-induced alterations in the GPi neuronal firing pattern (pauses, bursts, synchrony, etc.) and oscillatory activity, and not simply the firing frequency alone. This is in turn leads to the transmission of misinformation from pallidum to thalamus/cortex, resulting in dyskinesia. Surgical lesions or high-frequency stimulation might ameliorate dyskinesia by interfering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems.

Current information suggests that altered neuronal firing patterns and motor complications relate to nonphysiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In PD, dopamine neurons degenerate and striatal dopamine is dependent on the peripheral availability of levodopa. Intermittent doses of short-acting levodopa result in fluctuating plasma levels because of variability in transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug. This is variability results in exposure of dopamine receptors to pathologically high and low concentrations of dopamine. It has been hypothesized that more continuous delivery of levodopa might prevent the development of motor complications. Indeed, a recent controlled study demonstrated that continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) is associated with significant improvement in "off" time and in "on" time without dyskinesia in advanced PD patients compared with optimized standard oral levodopa.

Behavioral alterations can also be encountered in levodopa-treated patients. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. PD patients taking high doses of levodopa can develop purposeless, stereotyped behaviors such as the meaningless assembly and disassembly or collection and sorting of objects. This is known as punding, a term taken from the Swedish description of the meaningless behaviors seen in chronic amphetamine users. Hypersexuality and other impulse-control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

DOPAMINE AGONISTS Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolism to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) and were associated with ergot-related side effects, including cardiac valvular damage. They have largely been replaced by a second generation of nonergot dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce "off" time in fluctuating patients. Subsequently, it was shown that dopamine agonists, possibly because they are relatively long-acting, are less prone than levodopa to induce dyskinesia. For this reason, many physicians initiate therapy with a dopamine agonist, although supplemental levodopa is eventually required in virtually all patients. Both ropinirole and

www.ketabpezeshki.com (021) 66485457 - 66485438

pramipexole are available as orally administered immediate (tid) and extended-release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch. Apomorphine is a dopamine agonist with efficacy comparable to levodopa, but it must be administered parenterally and has a very short half-life and duration of activity (45 min). It is generally administered by injection as a rescue agent for the treatment of severe "off" episodes. Apomorphine can also be administered by continuous subcutaneous infusion and has been demonstrated to reduce both "off" time and dyskinesia in advanced patients. However, this approach has not been approved in the United States.

Dopamine agonist use is associated with a variety of side effects. Acute side effects are primarily dopaminergic and include nausea, vomiting, and orthostatic hypotension. As with levodopa, these can usually be avoided by slow titration. Side effects associated with chronic use include hallucinations and cognitive impairment. Sedation with sudden unintended episodes of falling asleep while driving a motor vehicle have been reported. Patients should be informed about this potential problem and should not drive when tired. Dopamine agonists can also be associated with impulse-control disorders, including pathologic gambling, hypersexuality, and compulsive eating and shopping. T e precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are dose-related and can be avoided or minimized with lower doses. Injections of apomorphine and patch delivery of rotigotine can be complicated by development of skin lesions at sites of administration.

MAO-B INHIBITORS Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B enzyme. Clinically, MAO-B inhibitors provide antiparkinsonian benefits when used as monotherapy in early disease and reduced "off" time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. T ey may increase dyskinesia in levodopa-treated patients, but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut, leading to a potentially fatal hypertensive reaction known as a "cheese effect" because it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A and are not associated with a cheese effect with doses typically used in clinical practice. T ere are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented experimentally by coadministration of an MAO-B inhibitor that blocks its conversion to the toxic pyridinium ion MPP^+. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides antiapoptotic effects in laboratory models. T e DATATOP study showed that selegiline significantly delayed the time until the emergence of disability, necessitating the introduction of levodopa, in untreated PD patients. However, it could not be determined whether this was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that merely masked ongoing neurodegeneration. More recently, the ADAGIO study demonstrated that early treatment with rasagiline 1 mg/d, but not 2 mg/d, provided benefits that could not be achieved when treatment with the same drug was initiated at a later time point, consistent with a disease-modifying effect; however, the long-term significance of these findings is uncertain.

COMT INHIBITORS When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by COMT. Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces "off" time and prolongs "on" time in fluctuating patients while enhancing motor scores. Two COMT inhibitors have been approved, tolcapone and entacapone. T ere is also a combination tablet of levodopa, carbidopa, and entacapone (Stalevo).

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20–30%. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5–10% of individuals. Cases of fatal hepatic toxicity have been reported with tolcapone, and periodic monitoring of liver function is required. T is problem has not been encountered with entacapone. Discoloration of urine can be seen with both COMT inhibitors due to accumulation of a metabolite, but it is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half-life could provide more continuous levodopa delivery if administered at frequent intervals and reduce the risk of motor complications. While this result has been demonstrated in a preclinical MPTP model, and continuous infusion reduces both "off" time and dyskinesia in advanced PD patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study. T is may have been because the combination was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be in patients who experience motor fluctuations.

www.ketabpezeshki.com (021) 66485457 - 66485438

OTHER MEDICAL THERAPIES Centrally acting anticholinergic drugs such as trihexyphenidyl and benztropine were used historically for the treatment of PD, but they lost favor with the introduction of dopaminergic agents. Their major clinical effect is on tremor, although it is not certain that this benefit is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients with severe tremor. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.

Amantadine also has historical importance. Originally introduced as an antiviral agent, it was appreciated to also have antiparkinsonian effects that are now thought to be due to N-methyl-d-aspartate (NMDA) receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features, although benefits may be relatively transient. Cognitive impairment is a major concern. Other side effects include livido reticularis and weight gain. Amantadine should always be discontinued gradually because patients can experience withdrawal-like symptoms.

Several new classes of drug are currently being investigated in an attempt to enhance antiparkinsonian effects, reduce off time, and treat or prevent dyskinesia. These include adenosine A_{2A} antagonists, nicotinic agonists, glutamate antagonists, and 5-HT_{1A} agonists.

A list of the major drugs and available dosage strengths is provided in **Table 36-5**.

NEUROPROTECTION Despite the many therapeutic agents available for the treatment of PD, patients continue to experience disease progression with intolerable disability. A neuroprotective therapy that slows or stops disease progression remains the major unmet therapeutic need in PD. As noted above, trials of certain drugs (e.g., selegiline and rasagiline) have provided positive results consistent with a disease-modifying effect. However, it is not possible to determine if the positive results were due to neuroprotection with slowing of disease progression or confounding symptomatic effects that mask ongoing progression. CoQ10, a mitochondrial bioenhancer and antioxidant, attracted attention with a positive preliminary trial, but this was not replicated in larger double-blind studies.

SURGICAL TREATMENT Surgical treatments for PD have been used for more than a century. Lesions placed in the motor cortex improved tremor but were associated with motor deficits, and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the ventral intermediate (VIM) nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. In the 1990s, it was shown that lesions placed in the posteroventral portion of the GPi (motor territory) improved rigidity and bradykinesia as well as tremor. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal for patients with bilateral disease, because bilateral lesions are associated with side effects such as dysphagia, dysarthria, and impaired cognition, and has largely been replaced by deep brain stimulation (DBS). Unilateral lesions of the STN are associated with a larger antiparkinsonian benefit and reduced levodopa requirement, but there is a concern about the risk of hemiballismus, and this procedure is not commonly performed.

Most surgical procedures for PD performed today use DBS. Here, an electrode is placed into the target area and connected to a stimulator inserted SC over the chest wall. DBS simulates the effects of a lesion without necessitating making a brain lesion. The precise mechanism whereby DBS works is not fully resolved but may act by disrupting the abnormal signal associated with PD and motor complications. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. In cases with intolerable side effects, stimulation can be stopped and the system removed. The procedure does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety.

DBS for PD primarily targets the STN or the GPi. It provides dramatic results, particularly with respect to reducing "off" time and dyskinesias, but does not improve or prevent the development of features that fail to respond to levodopa such as freezing, falling, and dementia. The procedure is thus primarily indicated for patients who suffer disability resulting from severe tremor, or levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation. In such patients, DBS has been shown to improve quality of life in comparison to best medical therapy. Side effects can be seen with respect to the surgical procedure (hemorrhage, infarction, infection), the DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation itself (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. Although not all PD patients are candidates, the procedure is profoundly beneficial for many. Studies of DBS in early PD patients show benefits in comparison to medical therapy, but this must be weighed against the cost of the procedure and the risk of side effects. Long-term studies demonstrate continued benefits with respect to the classical motor features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to be a source of disability. Studies continue to evaluate the optimal way to use DBS (low- vs high-frequency stimulation, closed systems, etc.). Comparison of DBS to other therapies aimed at improving motor function without causing dyskinesia, such as Duodopa and apomorphine infusions,

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 36-5

DRUGS COMMONLY USED FOR TREATMENT OF PARKINSON'S DISEASE[a]

AGENT	AVAILABLE DOSAGES	TYPICAL DOSING
Levodopa[a]		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/d 2–4 times/d
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250	
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC		2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	1.0 mg QAM

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.
Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.
Abbreviations: COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

remains to be performed. Studies are examining additional DBS targets that might benefit gait dysfunction, depression, and cognitive impairment in PD patients.

EXPERIMENTAL THERAPIES FOR PD T ere has been considerable scientific and public interest in a number of novel interventions that are being investigated as possible treatments for PD. T ese include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, and trophic factors. Transplant strategies are based on the concept of implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, re-innervate the striatum in an organotypic manner, and restore motor function in PD models. However, two double-blind studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Additionally, graf ing of fetal nigral cells is associated with a previously unrecognized form of dyskinesia that persists af er lowering or even stopping levodopa. T is has been postulated to be related to unregulated release of dopamine from serotonin neurons. In addition, there is evidence that af er many years, transplanted healthy embryonic dopamine neurons from unrelated donors develop PD pathology and become dysfunctional, suggesting transfer of α-synuclein from affected to unaffected neurons in a prion-like manner (see discussion above). Perhaps most importantly, it is not clear how replacing dopamine cells alone will improve nondopaminergic features such as falling and dementia, which are the major sources of disability for patients with advanced disease. T ese same concerns apply to dopamine neurons derived from stem cells, which have not yet been properly tested in PD patients and bear the additional concern of tumors and unanticipated side effects. T e short-term future for this technology as a treatment for PD, at least in its current state, is therefore not promising, and there is no scientific basis to warrant routine treatment with stem cells as is being marketed in some countries.

Trophic factors are a series of proteins that enhance neuronal growth and restore function to damaged neurons. T ere are several different trophic factors that have been demonstrated to

www.ketabpezeshki.com (021) 66485457 - 66485438

have beneficial effects on dopamine neurons in laboratory studies. Glial-derived neurotrophic factor (GDNF) and neurturin have attracted particular attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to show benefits compared to placebo in PD patients, possibly because of inadequate delivery of the trophic molecule throughout the target region.

Gene delivery offers the potential of providing widespread delivery throughout a target region and long-term expression of a therapeutic protein with a single procedure. Gene therapy involves placing the DNA of a therapeutic protein into a viral vector that can then be delivered to specific target regions. T e DNA of the therapeutic protein is then incorporated into the genome of the host cells and released on a continual basis. T e AAV2 virus has been most of en used as the viral vector because it does not promote an inflammatory response, is not incorporated into the host genome, and is associated with long-lasting transgene expression. Clinical trials of AAV2 delivery of the trophic factor neurturin showed promising results in open label trials but failed in double-blind trials, possibly because axonal damage in PD prevented retrograde transport of the protein to dopamine neurons in the SNc where it is required to induce upregulation of repair genes required for the trophic response. However, a subsequent double-blind trial of AAV2-neurturin delivered into both the putamen and SNc also failed.

Gene delivery is also being explored as a means of delivering aromatic amino acid decarboxylase with or without tyrosine hydroxylase to the striatum to facilitate dopamine production and glutamic acid decarboxylase to the STN to inhibit overactive neuronal firing. None of these procedures has been established to be effective in PD patients. Furthermore, although gene delivery technology has great potential, this approach also carries the risk of unanticipated side effects, and current approaches directed at the nigrostriatal system do not address the nondopaminergic features of the illness.

MANAGEMENT OF THE NONMOTOR AND NONDOPAMINERGIC FEATURES OF PD

Although PD management has primarily focused on the dopaminergic features of the disease, management of the nondopaminergic features should not be ignored. Some nonmotor features, although not thought to reflect dopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example, problems such as anxiety, panic attacks, depression, sweating, sensory problems, freezing, and constipation all tend to be worse during "off" periods and may improve with better dopaminergic control. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiagnosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression. Serotonin syndromes have been a theoretical concern with the combined use of SSRIs and MAO-B inhibitors but are rarely encountered. Anxiety can be treated with short-acting benzodiazepines.

Psychosis can be a problem for some PD patients. In contrast to AD, hallucinations are typically visual, formed, and nonthreatening. Importantly, they can limit the use of dopaminergic agents to obtain satisfactory motor control. Psychosis in PD of en responds to low doses of atypical neuroleptics and permits higher doses of levodopa to be tolerated. Clozapine is the most effective drug, but it can be associated with agranulocytosis, and regular monitoring is required. For this reason, many physicians start with quetiapine even though it has not been established to be effective in placebo- controlled trials. Hallucinations in PD patients are of en a harbinger of a developing dementia.

Dementia in PD (PDD) is common, ultimately affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to AD, primarily affects executive functions and attention, with relative sparing of language, memory, and calculations. When dementia precedes, or develops within 1 year af er, the onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; **Chap. 35**). T ese patients are particularly prone to have hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies distributed throughout the cerebral cortex (especially the hippocampus and amygdala) and is of en also associated with AD pathology. It is likely that DLB and PDD represent a PD spectrum rather than separate disease entities. Mild cognitive impairment (MCI) frequently precedes the onset of dementia and is a more reliable index of impending dementia in PD than in the general population. Dopaminergic drugs can worsen cognitive function in demented patients and should be stopped or reduced to try and provide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually, patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful antiparkinsonian effects and does not worsen mental function. Anticholinesterase agents such as rivastigmine and donepezil reduce the rate of deterioration of measures of cognitive function and can improve attention, but do not typically improve cognitive function in any meaningful way.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium natriuresis. Low doses of fludrocortisone (Florinef) or midodrine provide control for most cases. Vasopressin, erythropoietin, and the norepinephrine precursor 3-0-methylDOPS can be used in more severe or refractory cases. If orthostatic hypotension is prominent in early disease, MSA should be considered. Sexual dysfunction can be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude prostate problems. Anticholinergic agents, such as oxybutynin (Ditropan), may be helpful. Constipation can be a very important problem for PD patients. Mild laxatives or enemas can be useful, but physicians should first ensure that patients are drinking adequate amounts of fluid and consuming a diet

www.ketabpezeshki.com (021) 66485457 - 66485438

rich in bulk with green leafy vegetables and bran. Agents that promote gastrointestinal (GI) motility can also be helpful.

Sleep disturbances are common in PD patients, with many experiencing fragmented sleep with excess daytime sleepiness. Restless leg syndrome, sleep apnea, and other sleep disorders should be treated as appropriate. REM behavior disorder (RBD) is a syndrome comprised of violent movements and vocalizations during REM sleep, possibly representing acting out of dreams due to a failure of the normal inhibition of motor movements that typically accompanies REM sleep. Many PD patients have a history of antecedent RBD preceding the onset of the classic motor features of PD, and most cases of RBD go on to develop an α-synucleinopathy (PD or MSA). Low doses of clonazepam (0.5–1 mg at bedtime) are usually effective in controlling this problem. Consultation with a sleep specialist and polysomnography may be necessary to identify and optimally treat sleep problems.

NONPHARMACOLOGIC THERAPY Gait dysfunction with falling is an important cause of disability in PD. Dopaminergic therapies can help patients whose gait is worse in "off" time, but there are currently no specific therapies available. Canes and walkers may become necessary to increase stability and reduce the risk of falling.

Freezing, where patients suddenly become stuck in place for seconds to minutes as if their feet were glued to the ground, is a major cause of falling. Freezing may occur during "on" or "off" periods. Freezing during "off" periods may respond to dopaminergic therapies, but there are no specific treatments for "on" period freezing. Some patients will respond to sensory cues such as marching in place, singing a song, or stepping over an imaginary line.

Exercise, with a full range of active and passive movements, has been shown to maintain and even improve function for PD patients, and active and passive exercises with full range of motion reduce the risk of arthritis and frozen joints. Some laboratory studies suggest the possibility that exercise might also have neuroprotective effects, but this has not been confirmed in PD. Exercise is generally recommended for all PD patients. It is less clear that physical therapy or specific exercises such as tai chi are required. It is important for patients to maintain social and intellectual activities to the extent possible. Education, assistance with financial planning, social services, and attention to home safety are important elements of the overall care plan. Information is available through numerous PD foundations and on the web, but should be reviewed with physicians to ensure accuracy. The needs of the caregiver should not be neglected. Caring for a person with PD involves a substantial work effort and there is an increased incidence of depression among caregivers. Support groups for patients and caregivers may be useful.

CURRENT MANAGEMENT OF PD The management of PD should be tailored to the needs of the individual patient, and there is no single treatment approach that is universally accepted and applicable to all individuals. Clearly, if an agent could be demonstrated to have disease-modifying effects, it should be initiated at the time of diagnosis. Indeed, constipation, RBD, and anosmia may represent premotor features of PD and could permit the initiation of a disease-modifying therapy prior to the onset of the classical motor features of the disease. However, no therapy has yet been proved to be disease modifying. For now, physicians must use their judgment in deciding whether or not to introduce rasagiline (see above) or other drugs for their possible disease-modifying effects.

The next important issue to address is when to initiate symptomatic therapy. Several studies now suggest that it may be best to start therapy at the time of diagnosis (or soon after) in order to preserve beneficial compensatory mechanisms and possibly provide functional benefits even in the early stage of the disease. Levodopa remains the most effective symptomatic therapy for PD, and some recommend starting it immediately using low doses (≤400 mg/d), but others prefer to delay levodopa treatment, particularly in younger patients, in order to reduce the risk of inducing motor complications. An alternate approach is to begin with an MAO-B inhibitor and/or a dopamine agonist, and reserve levodopa for later stages when these drugs can no longer provide satisfactory control. In making this decision, the age, degree of disability, and side effect profile of the drug must all be considered. In patients with more severe disability, the elderly, those with cognitive impairment, or those in whom the diagnosis is uncertain, most physicians would initiate therapy with levodopa. Regardless of initial choice, it is important not to deny patients levodopa when they cannot be adequately controlled with alternative medications.

If motor complications develop, patients can initially be treated by manipulating the frequency and dose of levodopa or by combining lower doses of levodopa with a dopamine agonist, a COMT inhibitor, or an MAO-B inhibitor. Amantadine is the only drug that has been demonstrated to treat dyskinesia without worsening parkinsonism, but benefits may be short-lasting, and there are important side effects related to cognitive function. In advanced cases, it may be necessary to consider a surgical therapy such as DBS if the patient is a suitable candidate, but as described above, these procedures have their own set of complications. Continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) appears to offer similar benefits to DBS, but also requires a surgical intervention with potentially serious complications. Continuous infusion of apomorphine is another treatment option and does not require surgery but is associated with potentially troublesome skin nodules. Comparative studies of these approaches in more advanced patients are awaited. There are ongoing efforts aimed at developing a long-acting oral or transdermal formulation of levodopa that mirrors the pharmacokinetic properties of a levodopa infusion. Such a formulation might provide all of the benefits of levodopa without motor complications and avoid the need for polypharmacy and surgical intervention.

A decision tree that considers the various treatment options and decision points for the management of PD is provided in **Fig. 36-7**.

www.ketabpezeshki.com (021) 66485457 - 66485438

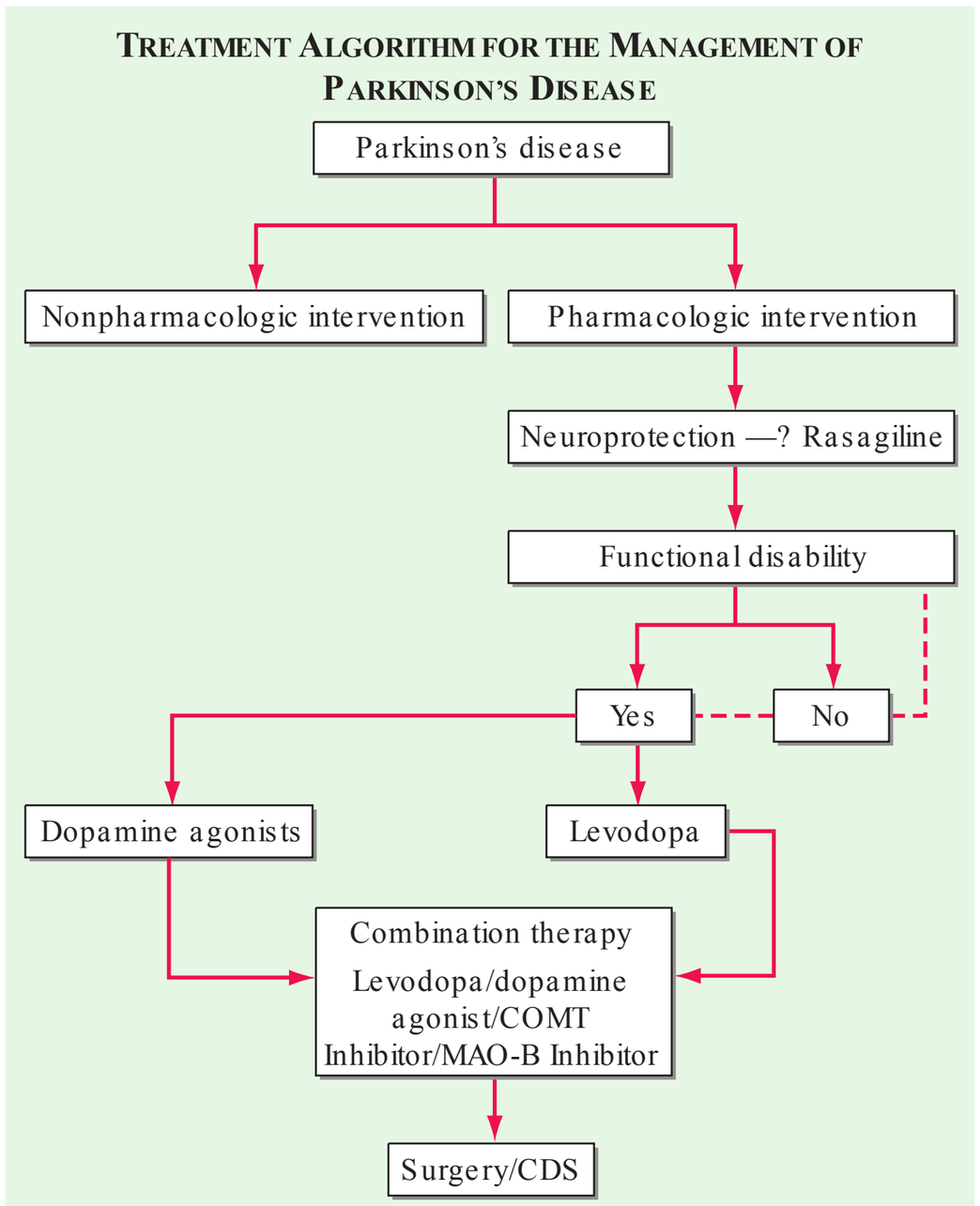


FIGURE 36-7

Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: No drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonists ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: Many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected patients because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger patients with functionally significant disability to reduce the risk of motor complications; and levodopa for patients with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: Motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: Interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (Adapted from CW Olanow et al: Neurology 72:S1, 2009.)

HYPERKINETIC MOVEMENT DISORDERS

Hyperkinetic movement disorders are characterized by involuntary movements unaccompanied by weakness and occurring in isolation or in combination **(Table 36-6)**. The major hyperkinetic movement disorders and the diseases with which they are associated are considered in this section.

TREMOR

CLINICAL FEATURES

Tremor consists of alternating contractions of agonist and antagonist muscles in an oscillating, rhythmic manner. It can be most prominent at rest (rest tremor), on assuming a posture (postural tremor), or on actively reaching for a target (kinetic tremor). Tremor is also

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 36-6

HYPERKINETIC MOVEMENT DISORDERS	
Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions
Dystonia	Involuntary, patterned, sustained or repeated muscle contractions often associated with twisting movements and abnormal posture
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands (this represents a form of dystonia with increased mobility)
Chorea	Rapid, semi-purposeful, graceful, dance-like nonpatterned involuntary movements involving distal or proximal muscle groups. When the movements are of large amplitude and predominant proximal distribution, the term ballism is used.
Myoclonus	Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped muscle contractions that can often be suppressed for a short time. These can be simple and involve a single muscle group or complex and affect a range of motor activities.

assessed based on distribution, frequency, and related neurologic dysfunction.

PD is characterized by a resting tremor, essential tremor (ET) by a postural tremor (trying to sustain a posture), and cerebellar disease by an intention or kinetic tremor (on reaching to touch a target). Normal individuals can have a physiologic tremor that typically manifests as a mild, high-frequency (10–12 Hz), postural or action tremor that is usually of no clinical consequence and often is only appreciated with an accelerometer. An enhanced physiologic tremor (EPT) can be seen in up to 10% of the population, often in association with anxiety, fatigue, a metabolic disturbance (e.g., hyperthyroidism, electrolyte abnormalities), drugs (e.g., valproate, lithium), or toxins (e.g., alcohol). Treatment is initially directed to the control of any underlying disorder and, if necessary, can often be improved with a beta blocker.

ESSENTIAL TREMOR

ET is the commonest movement disorder, affecting approximately 5–10 million persons in the United States. It can present in childhood but dramatically increases in prevalence over the age of 70 years. ET is characterized by a high-frequency tremor (6–10 Hz) that predominantly affects the upper extremities. The tremor is most often manifest as a postural or action (kinetic) tremor and, in severe cases, can interfere with functions such as eating and drinking. It is typically bilateral and symmetric but may begin on one side and remain asymmetric. Patients with severe ET can have an intention tremor with overshoot and slowness of movement. Tremor involves the head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10%, and lower limbs in ~10%. The tremor is characteristically improved by alcohol and worsened by stress. Subtle impairment of coordination or tandem walking may be present, and disturbances of hearing, cognition, personality, mood, and olfaction have also been described, but usually the neurologic examination is normal aside from tremor. The major differential is a dystonic tremor (see below) or PD. PD can usually be differentiated from ET based on the presence of bradykinesia, rigidity, micrographia, and other parkinsonian features. However, the examiner should be aware that PD patients may have a postural tremor and ET patients may develop a rest tremor. These typically begin after a latency of a few seconds (emergent tremor). The examiner must take care to differentiate the effect of tremor on measurement of tone in ET from the cogwheel rigidity found in PD.

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology and pathophysiology of ET are not known. Approximately 50% of cases have a positive family history with an autosomal dominant pattern of inheritance. Linkage studies have detected loci at chromosomes 3q13 (ETM-1), 2p22-25 (ETM-2), and 6p23 (ETM-3), but no causative genes have been identified to date. GWAS demonstrated an association with the LINGO1 gene, which is involved in oligodendrocyte differentiation and myelination, particularly in patients with young-onset ET. Recently, a nonsense mutation in the fused in sarcoma (FUS) gene was implicated as a cause of ET in a multigenerational family from Canada; this finding is of particular interest because different mutations in FUS are a known cause of familial amyotrophic lateral sclerosis **(Chap. 39)**. It is likely that there are many other undiscovered genes for ET. The cerebellum and inferior olives have been implicated as possible sites of a "tremor pacemaker" based on the presence of cerebellar signs and increased metabolic activity and blood flow in these regions in some patients. Some pathologic studies have described cerebellar pathology with a loss of Purkinje cells and axonal torpedoes, but these findings are controversial and the precise pathologic correlate of ET remains to be defined.

TREATMENT

Many cases are mild and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily

www.ketabpezeshki.com (021) 66485457 - 66485438

living. T is is more likely to occur as the patient ages and is of en associated with a reduction in tremor frequency. Beta blockers and primidone are the standard drug therapies for ET and help in about 50% of cases. Propranolol (20–120 mg daily, given in divided doses) is usually effective at relatively low doses, but higher doses may be effective in some patients. T e drug is contraindicated in patients with bradycardia or asthma. Hand tremor tends to be most improved, while head tremor is of en refractory. Primidone can be helpful but should be started at low doses (12.5 mg) and gradually increased (125–250 mg tid) to avoid sedation. Benefits have also been reported with gabapentin and topiramate. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with secondary muscle weakness. Surgical therapies targeting the VIM nucleus of the thalamus can be very effective for severe and drug-resistant cases.

DYSTONIA

CLINICAL FEATURES

Dystonia is a disorder characterized by sustained (>100 ms) or repetitive involuntary muscle contractions frequently associated with twisting and abnormal postures. Dystonia can range from minor contractions in an individual muscle group to severe and disabling involvement of multiple muscle groups. T e frequency is estimated to be 300,000 cases in the United States but is likely to be much higher because many cases are not recognized. Dystonia is of en brought out by voluntary movements (action dystonia) and can extend to involve muscle groups and body regions not required for a given action (overflow). It can be aggravated by stress and fatigue and attenuated by relaxation and sensory tricks such as touching the affected body part (geste antagoniste). Dystonia can be classified according to age of onset (childhood vs adult), distribution (focal, multifocal, segmental, or generalized), or etiology (primary or secondary).

PRIMARY DYSTONIAS

At least 16 gene mutations are associated with dystonia and classified as DYT1–DYT16. Idiopathic torsion dystonia (DYT1) or Oppenheim's dystonia is predominantly a childhood-onset form of dystonia with an autosomal dominant pattern of inheritance that primarily affects Ashkenazi Jewish families. T e majority of patients have an age of onset younger than 26 years (mean 14 years). In young-onset patients, dystonia typically begins in the foot or the arm and in 60–70% progresses to involve other limbs as well as the head and neck. In severe cases, patients can suffer disabling postural deformities that compromise mobility. Severity can vary within family members, with some affected relatives having severe disability and others a mild dystonia that may not even be appreciated. Most childhood-onset cases are linked to a mutation in the DYT1 gene located on chromosome 9q34, resulting in a trinucleotide GAG deletion with loss of one of a pair of glutamic acid residues in the protein torsin A. DYT1 mutations are found in 90% of Ashkenazi Jewish patients with DYT1 dystonia and probably relate to a founder effect that occurred about 350 years ago. T ere is variable penetrance, with only about 30% of gene carriers expressing a clinical phenotype. Why some gene carriers express dystonia and others do not is not known. T e function of torsin A is unknown, but it is a member of the AAA^+ (ATPase) family that resembles heat-shock proteins and may be related to protein processing and transport. T e precise pathology responsible for DYT1 dystonia is not known.

Dopa-responsive dystonia (DRD) or the Segawa variant (DYT5) is a dominantly inherited form of childhood-onset dystonia caused by a mutation in the gene that encodes GTP cyclohydrolase-I, the rate-limiting enzyme for the synthesis of tetrahydrobiopterin. T is mutation leads to a defect in the biochemical synthesis of tyrosine hydroxylase, the rate-limiting enzyme in the formation of dopamine. DRD typically presents in early childhood (1–12 years) and is characterized by foot dystonia that interferes with walking. Patients of en experience diurnal fluctuations, with worsening of gait as the day progresses and improvement with sleep. DRD is typified by an excellent and sustained response to small doses of levodopa. Some patients may present with parkinsonian features, but can be differentiated from juvenile PD by normal striatal dopamine imaging and the absence of levodopa-induced dyskinesias. DRD may occasionally be confused with cerebral palsy because patients appear to have spasticity, increased reflexes, and Babinski responses (which likely reflect a dystonic contraction rather than an upper motor neuron lesion). Any patient suspected of having a childhood-onset dystonia should receive a trial of levodopa to exclude this treatable condition.

Mutations in the THAP1 gene (DYT6) on chromosome 8p21q22 have been identified in Amish families and are the cause of as many as 25% of cases of non-DYT1 young-onset primary torsion dystonia. T ese patients are more likely to have dystonia beginning in the brachial and cervical muscles, which later can become generalized and associated with speech impairment. Myoclonic dystonia (DYT11) results from a mutation in the epsilon-sarcoglycan gene on chromosome 7q21. It typically manifests as a combination of dystonia and myoclonic jerks, frequently accompanied by psychiatric disturbances.

www.ketabpezeshki.com (021) 66485457 - 66485438

FOCAL DYSTONIAS

T ese are the most common forms of dystonia. T ey typically present in the fourth to sixth decades and affect women more than men. T e major types are as follows: (1) Blepharospasm—dystonic contractions of the eyelids with increased blinking that can interfere with reading, watching television, and driving. T is can sometimes be so severe as to cause functional blindness. (2) Oromandibular dystonia (OMD)—contractions of muscles of the lower face, lips, tongue, and jaw (opening or closing). Meige's syndrome is a combination of OMD and blepharospasm that predominantly affects women older than age 60 years. (3) Spasmodic dysphonia—dystonic contractions of the vocal cords during phonation, causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly, the abductors are affected, leading to speech with a breathy or whispering quality. (4) Cervical dystonia—dystonic contractions of neck muscles causing the head to deviate to one side (torticollis), in a forward direction (anterocollis), or in a backward direction (retrocollis). Muscle contractions can be painful and associated with a secondary cervical radiculopathy. (5) Limb dystonias—these can be present in either arms or legs and are often brought out by task-specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp), or putting (the yips). Focal dystonias can extend to involve other body regions (about 30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic in origin. T eir cause is not known, but genetic factors, autoimmunity, and trauma have been suggested. Focal dystonias are often associated with a high-frequency tremor that resembles ET. Dystonic tremor can usually be distinguished from ET because it tends to occur in conjunction with the dystonic contraction and disappears when the dystonia is relieved.

SECONDARY DYSTONIAS

T ese develop as a consequence of drugs or other neurologic disorders. Drug-induced dystonia is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients and may be acute or chronic (see below). Secondary dystonia can also be observed following discrete lesions in the striatum and occasionally in the pallidum, thalamus, cortex, and brainstem due to infarction, anoxia, metabolic disorders, trauma, tumor, infection, or toxins such as manganese or carbon monoxide. In these cases, dystonia often assumes a segmental distribution, but it can be generalized when lesions are bilateral or widespread. More rarely, dystonia can develop following peripheral nerve injury and be associated with features of complex regional pain syndrome **(Chap. 41)**. A psychogenic origin is responsible for some cases of dystonia presenting with fixed, immobile dystonic postures (see below).

DYSTONIA PLUS SYNDROMES

Dystonia may occur as a part of another neurodegenerative conditions such as Huntington's disease, PD, Wilson's disease, corticobasilar ganglionic degeneration, PSP, the Lubag form of dystonia-parkinsonism (DYT3), and mitochondrial encephalopathies. In contrast to the primary dystonias, dystonia is usually not the dominant neurologic feature in these conditions.

PATHOPHYSIOLOGY OF DYSTONIA

T e pathophysiologic basis of dystonia is not completely known. T e phenomenon is characterized by co-contracting synchronous bursts of agonist and antagonist muscle groups with recruitment of muscle groups that are not required for a given movement (overflow). Dystonia is characterized by derangement of the basic physiological principle of action-selection, leading to abnormal recruitment of inappropriate muscles for a given action with inadequate inhibition of this undesired motor activity. Physiologically, loss of inhibition is observed at multiple levels of the motor system (e.g., cortex, brainstem, spinal cord) accompanied by increased cortical excitability and reorganization. Attention has focused on the basal ganglia as the site of origin of at least some types of dystonia because there are alterations in blood flow and metabolism in these structures. Further, lesions of the GPi can induce dystonia, and surgical ablation or DBS of the globus pallidus can ameliorate dystonia. T e dopamine system has also been implicated, because dopaminergic therapies can both induce and treat some forms of dystonia. Interestingly, no specific pathology has been consistently identified in primary dystonia.

TREATMENT Dystonia

Treatment of dystonia is for the most part symptomatic except in rare cases where correction of a primary underlying condition is possible. Wilson's disease should be ruled out in young patients with dystonia. Levodopa should be tried in all cases of childhood-onset dystonia to rule out DRD. High-dose anticholinergics (e.g., trihexyphenidyl 20–120 mg/d) may be beneficial in children, but adults can rarely tolerate high doses because of side effects related to cognitive impairment with hallucinations. Oral baclofen (20–120 mg) may also be helpful, but benefits, if present, are usually modest, and side effects of sedation, weakness, and memory loss

www.ketabpezeshki.com (021) 66485457 - 66485438

can be problematic. Intrathecal infusion of baclofen is more likely to be useful, particularly for leg and trunk dystonia, but benefits are frequently not sustained, and complications can be serious and include infection, seizures, and coma. Tetrabenazine (the usual starting dose is 12.5 mg/d and the average treating dose is 25–75 mg/d) is another consideration, but use may be limited by sedation and the development of parkinsonism. Neuroleptics can improve as well as induce dystonia, but they are typically not recommended because of their potential to induce parkinsonism and other movement disorders, including tardive dystonia. Clonazepam and diazepam are rarely effective.

Botulinum toxin has become the preferred treatment for patients with focal dystonia, particularly where involvement is limited to small muscle groups such as in blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction, leading to reduced dystonic muscle contractions, but excessive weakness may ensue and can be troublesome particularly if it involves neck and swallowing muscles. Two serotypes of botulinum toxin are available (A and B). Both are effective, and it is not clear that there are advantages of one over the other. No systemic side effects are encountered with the doses typically used, but benefits are transient, and repeat injections are required at 2- to 5-month intervals. Some patients fail to respond af er having experienced an initial benefit. T is has been attributed to antibody formation, but improper muscle selection, injection technique, and inadequate dose should be excluded.

Surgical therapy is an alternative for patients with severe dystonia who are not responsive to other treatments. Peripheral procedures such as rhizotomy and myotomy were used in the past to treat cervical dystonia, but are now rarely used. DBS of the pallidum can provide dramatic benefits for patients with primary DYT1 dystonia. T is represents a major therapeutic advance because previously there was no consistently effective therapy, especially for these patients who had severe disability. Benefits tend to be obtained with a lower frequency of stimulation and of en occur af er a relatively long latency (weeks) in comparison to PD. Better results are typically obtained in younger patients with shorter disease duration. Recent studies suggest that DBS may also be valuable for patients with focal and secondary dystonias, although results are less consistent. Supportive treatments such as physical therapy and education are important and should be a part of the treatment regimen.

Physicians should be aware of dystonic storm, a rare but potentially fatal condition that can occur in response to a stress situation such as surgery in patients with preexisting dystonia. It consists of the acute onset of generalized and persistent dystonic contractions that can involve the vocal cords or laryngeal muscles, leading to airway obstruction. Patients may experience rhabdomyolysis with renal failure and should be managed in an intensive care unit with airway protection if required. Treatment can be instituted with one or a combination of anticholinergics, diphenhydramine, baclofen, benzodiazepines, and dopaminergic agents. Spasms may be difficult to control, and anesthesia with muscle paralysis may be required. Most, if not all, cases of dystonic storm are due to a secondary cause.

CHOREAS

HUNTINGTON'S DISEASE (HD)

HD is a progressive, fatal, highly penetrant autosomal dominant disorder characterized by motor, behavioral, oculomotor, and cognitive dysfunction. T e disease is named for George Huntington, a family physician who described cases on Long Island, New York, in the nineteenth century. Onset is typically between the ages of 25 and 45 years (range, 3–70 years) with a prevalence of 2–8 cases per 100,000 and an average age at death of 60 years. It is prevalent in Europe, North and South America, and Australia but is rare in African blacks and Asians. HD is characterized by rapid, nonpatterned, semipurposeful, involuntary choreiform movements, and for this reason was formerly referred to as Huntington's chorea. In the early stages, the chorea tends to be focal or segmental, but progresses over time to involve multiple body regions. Dysarthria, gait disturbance, oculomotor abnormalities, behavioral disturbance, and cognitive impairment with dementia are also common features. With advancing disease, there tends to be a reduction in chorea and the emergence of dystonia, rigidity, bradykinesia, and myoclonus. Functional decline is of en predicted by progressive weight loss despite adequate calorie intake. In younger patients (~10% of cases), HD can present as an akinetic-rigid or parkinsonian syndrome (Westphal variant). HD patients eventually develop behavioral and cognitive disturbances, and the majority progress to dementia. Depression with suicidal tendencies, aggressive behavior, and psychosis can be prominent features. HD patients may also develop non-insulin-dependent diabetes mellitus and neuroendocrine abnormalities (e.g., hypothalamic dysfunction). A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history, but genetic testing provides the ultimate confirmation of the diagnosis. T e disease predominantly affects the striatum. Progressive atrophy of the heads of the caudate nuclei, which form the lateral margins of the lateral ventricles, can be visualized by MRI **(Fig. 36-8)**, but the putamen can be equally or even more severely affected. More diffuse cortical atrophy is seen in the middle and late stages of the disease. Supportive studies include reduced metabolic activity in the caudate nucleus and putamen. Genetic testing can be used to confirm the diagnosis and to detect at-risk individuals in the family, but must be performed with caution and

www.ketabpezeshki.com (021) 66485457 - 66485438

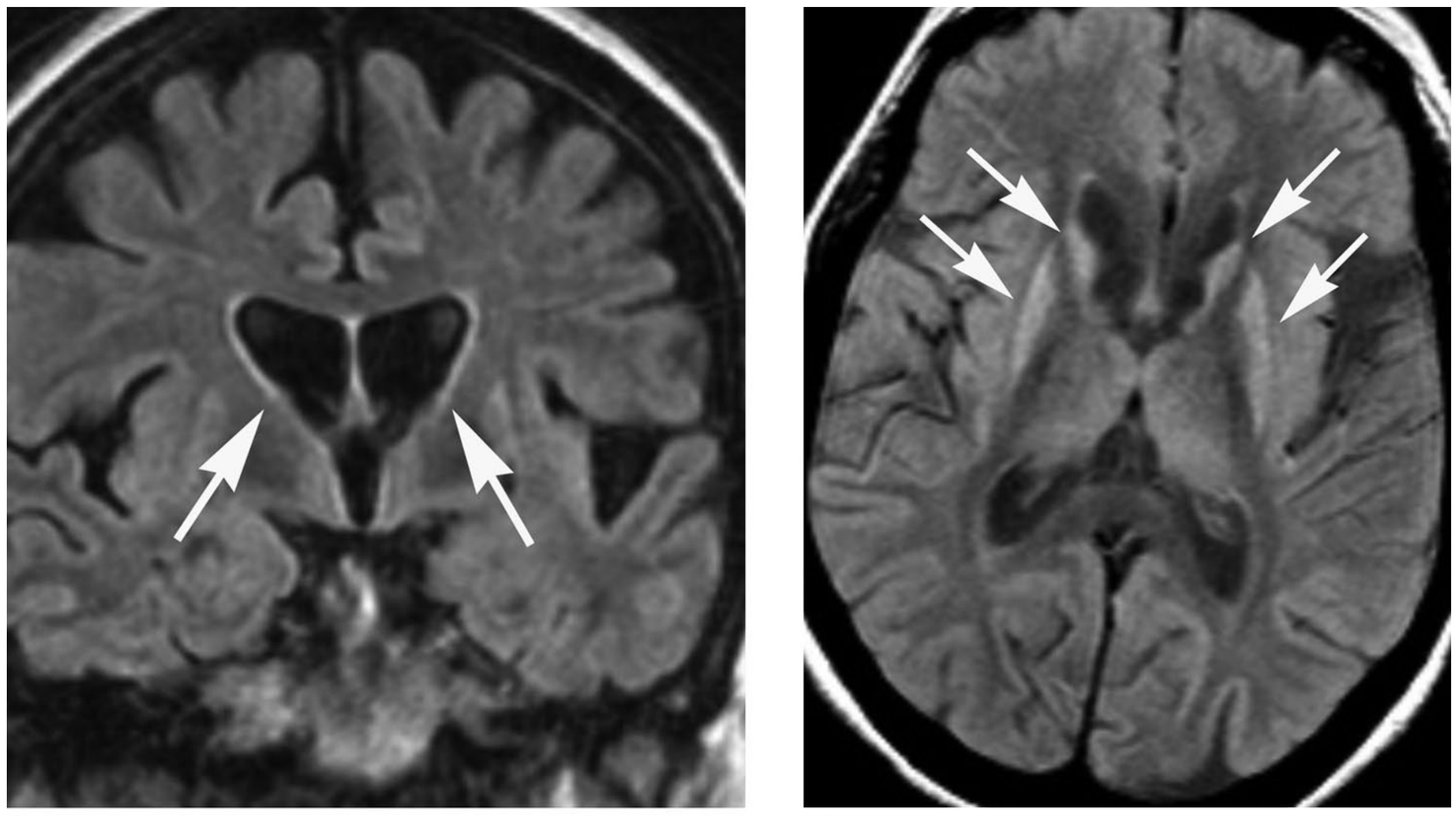


FIGURE 36-8
Huntington's disease. A. Coronal fuid attenuated inversion recovery (FLAIR) magnetic resonance imaging shows enlargement of the lateral ventricles ref ecting typical atrophy (arrows). B. Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (arrows).

in conjunction with trained counselors, because positive results can worsen depression and generate suicidal reactions. T e neuropathology of HD consists of prominent neuronal loss and gliosis in the caudate nucleus and putamen; similar changes are also widespread in the cerebral cortex. Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in the nuclei of affected neurons.

In anticipation of developing neuroprotective therapies, there has been an intensive effort to define the premanifest stage of HD. Subtle motor impairment, cognitive alterations, and imaging changes can be detected in at-risk individuals who later go on to develop the manifest form of the disease. Defining the rate of progression of these features is paramount for future studies of putative disease-modifying therapies.

ETIOLOGY

HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the huntingtin gene located on the short arm of chromosome 4. T e larger the number of repeats, the earlier the disease is manifest. Intermediate forms of the disease with 36–39 repeats are described in some patients, typically with less severe clinical involvement. Acceleration of the process tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. T e gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the central nervous system (CNS) but whose function is not known. Models of HD with striatal pathology can be induced by excitotoxic agents such as kainic acid and 3-nitropoprionic acid, which promote calcium entry into the cell and cytotoxicity. Mitochondrial dysfunction has been demonstrated in the striatum and skeletal muscle of symptomatic and presymptomatic individuals. Fragments of the mutant huntingtin protein can be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulation of proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins.

TREATMENT Huntington's Disease

Although the gene for HD was identified more than two decades ago, there is still no disease-modifying therapy for this disorder. Current treatment involves a multidisciplinary approach, with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine-blocking agents may control the choreatic movements. Tetrabenazine (a presynaptic dopamine depleting agent) has been approved for the treatment of chorea in the United States, but can cause secondary parkinsonism. Neuroleptics are generally not recommended because of their potential to induce other more troubling movement disorders and because HD chorea tends to be self-limited and is usually not disabling. Depression and anxiety can be greater problems, and patients should be treated with appropriate antidepressant and antianxiety drugs and monitored for mania and suicidal ideations. Psychosis

www.ketabpezeshki.com (021) 66485457 - 66485438

can be treated with atypical anti-psychotics such as clozapine (50–600 mg/d), quetiapine (50–600 mg/d), and risperidone (2–8 mg/d). T ere is no adequate treatment for the cognitive or motor decline. A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in HD. Drugs that enhance mitochondrial function and increase the clearance of defective mitochondria are being tested as possible disease-modifying therapies. Antiglutamate agents, dopamine stabilizers, caspase inhibitors, neurotrophic factors, and transplantation of fetal striatal cells are areas of active research, but none has as yet been demonstrated to have a beneficial effect in HD. T e potential to use transcriptional blockade of the mutant huntingtin gene with small interfering RNAs (siRNAs) is an exciting area currently being explored.

HUNTINGTON'S DISEASE–LIKE DISORDERS

A group of rare inherited conditions that can mimic HD, designated HD-like (HDL) disorders, have also been identified. HDL-1, -2, and -4 are autosomal dominant conditions that typically present in adulthood. HDL-1 is due to expansion of an octapeptide repeat in PRNP, the gene encoding the prion protein **(Chap. 40)**. T us HDL-1 is properly considered a prion disease. Patients exhibit onset of personality change in the third or fourth decade, followed by chorea, rigidity, myoclonus, ataxia, and epilepsy. HDL-2 manifests in the third or fourth decade with a variety of movement disorders, including chorea, dystonia, or parkinsonism and dementia. Most patients are of African descent. Acanthocytosis can sometimes be seen in these patients, and this condition must be distinguished from neuroacanthocytosis. HDL-2 is caused by an abnormally expanded CTG/CAG trinucleotide repeat expansion in the junctophilin-3 (JPH3) gene. T e pathology of HDL-2 consists of intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats. HDL-4, the most common condition in this group, is caused by expansion of trinucleotide repeats in TBP, the gene that encodes the TATA box binding protein involved in regulating transcription; this condition is identical to spinocerebellar ataxia (SCA) 17 **(Chap. 38)**, and most patients present primarily with ataxia rather than chorea. Mutations of the C9Or*f* gene associated with amyotrophic lateral sclerosis have also been reported in some individuals with an HDL phenotype.

OTHER CHOREAS

Chorea can be seen in a number of additional disorders. Sydenham's chorea (originally called St. Vitus's dance) is more common in females and is typically seen in childhood (5–15 years). It of en develops in association with prior exposure to group A streptococcal infection and is thought to be autoimmune in nature. It is characterized by the acute onset of choreiform movements and behavioral disturbances. With the reduction in the incidence of rheumatic fever, the incidence of Sydenham's chorea has fallen, but it can still be seen in developing countries. T e chorea generally responds to dopamine-blocking agents, valproic acid, and carbamazepine, but is self-limited, and treatment is generally restricted to those with severe chorea. Chorea may recur in later life, particularly in association with pregnancy (chorea gravidarum) or treatment with sex hormones. Several reports have documented cases of chorea associated with NMDA receptor antibody–positive encephalitis following herpes simplex virus encephalitis.

Chorea-acanthocytosis (neuroacanthocytosis) is a progressive and typically fatal autosomal recessive disorder that is characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). T e chorea can be severe and associated with self-mutilating behavior, dystonia, tics, seizures, and a polyneuropathy. Mutations in the VPS13A gene encoding chorein have been described. A phenotypically similar X-linked form of the disorder has been described in older individuals who have reactivity with Kell blood group antigens (McLeod syndrome). A benign hereditary chorea of childhood (BHC1) due to mutations in the gene for thyroid transcription factor 1 and a late-onset benign senile chorea (BHC2) have also been described. It is important to ensure that patients with these types of choreas do not have HD.

Chorea may also occur in association with vascular diseases, hypo- and hyperglycemia, and a variety of infections and degenerative disorders. Systemic lupus erythematosus is the most common systemic disorder that causes chorea, which can last for days to years. Chorea can also be seen with hyperthyroidism, autoimmune disorders including Sjögren's syndrome, infectious disorders including HIV disease, metabolic alterations, and polycythemia rubra vera; following open-heart surgery in the pediatric population; and in association with many medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, and lithium). Chorea is commonly seen in association with chronic levodopa treatment (discussed in the section on PD above). Chorea can also be seen in paraneoplastic syndromes associated with anti-CRMP-5 or anti-Hu antibodies **(Chap. 50)**.

HEMIBALLISMUS

Hemiballismus is a violent form of chorea comprised of wild, flinging, large-amplitude movements on one side of the body. Proximal limb muscles tend to be predominantly affected. T ese movements may affect just

www.ketabpezeshki.com (021) 66485457 - 66485438

one limb (monoballism) or, more exceptionally, both upper or lower limbs (paraballism). The movements may be so severe as to cause exhaustion, dehydration, local injury, and, in extreme cases, death. Fortunately, dopamine-blocking drugs can be very helpful, and importantly, hemiballismus is usually self-limiting and tends to resolve spontaneously after weeks or months. The most common cause is a partial lesion (infarct or hemorrhage) in the STN, but cases can also be seen with lesions in the putamen, thalamus, and parietal cortex. In extreme cases, pallidotomy can be very effective. Interestingly, surgically induced lesions and DBS of the STN in PD patients are usually not associated with hemiballismus.

TICS

A tic is a brief, rapid, recurrent, and seemingly purposeless stereotyped motor contraction. Motor tics can be simple, with movement only affecting an individual muscle group (e.g., blinking, twitching of the nose, jerking of the neck), or complex, with coordinated involvement of multiple muscle groups (e.g., jumping, sniffing, head banging, and echopraxia [mimicking movements]). Phonic (or vocal) tics can also be simple (e.g., grunting) or complex (e.g., echolalia [repeating other people's words], palilalia [repeating one's own words], and coprolalia [expression of obscene words]). Patients may also experience sensory tics, composed of unpleasant focal sensations in the face, head, or neck. These can be mild and of little clinical consequence or severe and disabling to the patient.

TOURETTE'S SYNDROME (TS)

TS is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette. It predominantly affects males, and the prevalence is estimated to be 0.03–1.6%, but it is likely that many mild cases do not come to medical attention. TS is characterized by multiple motor tics often accompanied by vocalizations (phonic tics). Patients characteristically can voluntarily suppress tics for short periods of time, but then experience an irresistible urge to express them. Tics vary in intensity and may be absent for days or weeks only to recur, occasionally in a different pattern. Tics tend to present between ages 2 and 15 years (mean 7 years) and often lessen or even disappear in adulthood. Associated behavioral disturbances include anxiety, depression, attention deficit hyperactivity disorder, and obsessive-compulsive disorder. Patients may experience personality disorders, self-destructive behaviors, difficulties in school, and impaired interpersonal relationships. Tics may present in adulthood and can also be seen in association with a variety of other disorders, including PD, HD, trauma, dystonia, drugs (e.g., levodopa, neuroleptics), and toxins.

Etiology and pathophysiology

TS is thought to be a genetic disorder, but no specific gene mutation has been identified. Current evidence supports a complex inheritance pattern, with one or more major genes, multiple loci, low penetrance, and environmental influences. The risk of a family with one affected child having a second is about 25%. The pathophysiology of TS is not known, but alterations in dopamine neurotransmission, opioids, and second-messenger systems have been proposed. Some cases of TS may be the consequence of an autoimmune response to β-hemolytic streptococcal infection (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection [PANDAS]); however, this entity remains controversial.

TREATMENT Tourette's Syndrome

Patients with mild disease often only require education and counseling (for themselves and family members). Drug treatment is indicated when the tics are disabling and interfere with quality of life. Therapy is individualized, and there is no singular treatment regimen that has been properly evaluated in double-blind trials. Some physicians use the α-agonist clonidine, starting at low doses and gradually increasing the dose and frequency until satisfactory control is achieved. Guanfacine (0.5–2 mg/d) is an α-agonist that is preferred by some because it only requires once-a-day dosing. Other physicians prefer to use neuroleptics. Atypical neuroleptics are usually used initially (risperidone, olanzapine, ziprasidone) because they are thought to be associated with a reduced risk of tardive dyskinesia. If they are not effective, low doses of classical neuroleptics such as haloperidol, fluphenazine, pimozide, or tiapride can be tried because the risk of tardive dyskinesia in young people is relatively low. Botulinum toxin injections can be effective in controlling focal tics that involve small muscle groups. Behavioral features, and particularly anxiety and compulsions, can be a disabling feature of TS and should be treated. The potential value of DBS targeting the anterior portion of the internal capsule, the GPi, or the thalamus is currently being explored.

MYOCLONUS

Myoclonus is a brief, rapid (<100 ms), shock-like, jerky movement consisting of single or repetitive muscle discharges. Myoclonic jerks can be focal, multifocal, segmental, or generalized and can occur spontaneously,

www.ketabpezeshki.com (021) 66485457 - 66485438

in association with voluntary movement (action myoclonus) or in response to an external stimulus (reflex or startle myoclonus). Negative myoclonus consists of a brief loss of muscle activity (e.g., asterixis in hepatic failure). Myoclonic jerks can be severe and interfere with normal movement or benign and of no clinical consequence as is commonly observed in normal people when waking up or falling asleep (hypnogogic jerks).

Myoclonic jerks differ from tics in that they are not typically repetitive, can interfere with normal voluntary movement, and are not suppressible. T ey can arise in association with abnormal neuronal discharges in cortical, subcortical, brainstem, or spinal cord regions and can be associated with lesions in each of these regions, particularly in association with hypoxemia (especially following cardiac arrest), encephalopathy, and neurodegeneration. Reversible myoclonus can be seen with metabolic disturbances (renal failure, electrolyte imbalance, hypocalcemia), toxins, and many medications. Essential myoclonus is a relatively benign familial condition characterized by multifocal, very brief, lightning-like movements that are frequently alcohol sensitive. A mutation in the epsilon-sarcoglycan gene has been associated with a variety of myoclonus seen in association with dystonia (myoclonic dystonia).

TREATMENT Myoclonus

Treatment primarily consists of managing the underlying condition or removing an offending agent. Pharmacologic therapy involves one or a combination of GABAergic agents such as valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d) and may be associated with striking clinical improvement in chronic cases (e.g., postanoxic myoclonus, progressive myoclonic epilepsy). T e serotonin precursor 5-hydroxitriptophan (plus carbidopa) may be useful in some cases of postanoxic myoclonus.

DRUG-INDUCED MOVEMENT DISORDERS

T is important group of movement disorders is primarily associated with drugs that block dopamine receptors (neuroleptics) or central dopaminergic transmission. T ese drugs are widely used in psychiatry, but it is important to appreciate that drugs used in the treatment of nausea or vomiting (e.g., prochlorperazine [Compazine]) or gastroesophageal disorders (e.g., metoclopramide) are neuroleptic agents. Hyperkinetic movement disorders secondary to neuroleptic drugs can be divided into those that present acutely, subacutely, or af er prolonged exposure (tardive syndromes). Dopamine-blocking drugs can also be associated with a reversible parkinsonian syndrome for which anticholinergics are of en concomitantly prescribed, but there is concern that this may increase the risk of developing a tardive syndrome.

ACUTE

Dystonia is the most common acute hyperkinetic drug reaction. It is typically generalized in children and focal in adults (e.g., blepharospasm, torticollis, or oromandibular dystonia). T e reaction can develop within minutes of exposure and can be successfully treated in most cases with parenteral administration of anticholinergics (benztropine or diphenhydramine), benzodiazepines (lorazepam, clonazepam, or diazepam), or dopamine agonists. T e abrupt onset of severe spasms may occasionally be confused with a seizure; however, there is no loss of consciousness, automatisms, or postictal features typical of epilepsy. T e acute onset of chorea, stereotypic behavior, and tics may also be seen, particularly following exposure to CNS stimulants such as methylphenidate, cocaine, or amphetamines.

SUBACUTE

Akathisia is the commonest reaction in this category. It consists of motor restlessness with a need to move that is alleviated by movement. T erapy consists of removing the offending agent. When this is not possible, symptoms may be ameliorated with benzodiazepines, anticholinergics, beta blockers, or dopamine agonists.

TARDIVE SYNDROMES

T ese disorders develop months to years af er initiation of neuroleptic treatment. Tardive dyskinesia (TD) is most common and typically presents with choreiform movements involving the mouth, lips, and tongue. In severe cases, the trunk, limbs, and respiratory muscles may also be affected. In approximately one-third of patients, TD remits within 3 months of stopping the drug, and most patients gradually improve over the course of several years. Abnormal movements may also develop or worsen af er stopping the offending agent. T e movements are of en mild and more upsetting to the family than to the patient, but they can be severe and disabling, particularly in the context of an underlying psychiatric disorder. Atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are thought to be associated with a lower risk of TD in comparison to traditional

www.ketabpezeshki.com (021) 66485457 - 66485438

antipsychotics, although this remains to be established in controlled studies. Younger patients have a lower risk of developing neuroleptic-induced TD, whereas the elderly, females, and those with underlying organic cerebral dysfunction have been reported to be at greater risk. Chronic use is associated with increased risk, and specifically, the U.S. Food and Drug Administration has warned that use of metoclopramide for more than 12 weeks increases the risk of TD. Because TD can be permanent and resistant to treatment, antipsychotics should be used judiciously, atypical neuroleptics should be the preferred agent when possible, and the need for continued use should be regularly monitored.

Treatment primarily consists of stopping the offending agent. If the patient is receiving a traditional antipsychotic and withdrawal is not possible, replacement with an atypical antipsychotic should be tried. Abrupt cessation of a neuroleptic should be avoided because acute withdrawal can induce worsening. TD can persist af er withdrawal of antipsychotics and can be difficult to treat. Benefits may occasionally be achieved with valproic acid, anticholinergics, or botulinum toxin injections. In refractory cases, catecholamine depleters such as tetrabenazine may be helpful, but this drug can be associated with dose-dependent sedation and orthostatic hypotension and may induce parkinsonism as a side effect. Other approaches include baclofen (40–80 mg/d), clonazepam (1–8 mg/d), or valproic acid (750–3000 mg/d). In some cases, the abnormal movement is refractory to therapy.

Chronic neuroleptic exposure can also be associated with tardive dystonia, with preferential involvement of axial muscles and characteristic rocking movements of the trunk and pelvis. Tardive dystonia can be more troublesome than tardive dyskinesia and frequently persists despite stopping medication. Valproic acid, anticholinergics, and botulinum toxin may occasionally be beneficial, but patients are frequently refractory to medical therapy. Tardive akathisia, tardive Tourette's, and tardive tremor syndromes are rare but may also occur af er chronic neuroleptic exposure.

Neuroleptic medications can also be associated with a neuroleptic malignant syndrome (NMS). NMS is characterized by the acute or subacute onset of muscle rigidity, elevated temperature, altered mental status, hyperthermia, tachycardia, labile blood pressure, renal failure, and markedly elevated creatine kinase levels. Symptoms typically evolve within days or weeks af er initiating the drug. NMS can also be precipitated by the abrupt withdrawal of dopaminergic medications in PD patients. Treatment involves immediate cessation of the offending antipsychotic drug and the introduction of a dopaminergic agent (e.g., a dopamine agonist or levodopa), dantrolene, or a benzodiazepine. Treatment may need to be undertaken in an intensive care setting and include supportive measures such as control of body temperature (antipyretics and cooling blankets), hydration, electrolyte replacement, and control of renal function and blood pressure.

Drugs that have serotonin-like activity (tryptophan, MDMA or "ecstasy," meperidine) or that block serotonin reuptake can induce a rare, but potentially fatal, serotonin syndrome that is characterized by confusion, hyperthermia, tachycardia, and coma as well as rigidity, ataxia, and tremor. Myoclonus is of en a prominent feature, in contrast to NMS, which it resembles. Patients can be managed with propranolol, diazepam, diphenhydramine, chlorpromazine, or cyproheptadine as well as supportive measures.

A variety of drugs can also be associated with parkinsonism (see above) and hyperkinetic movement disorders. Some examples include phenytoin (chorea, dystonia, tremor, myoclonus), carbamazepine (tics and dystonia), tricyclic antidepressants (dyskinesias, tremor, myoclonus), fluoxetine (myoclonus, chorea, dystonia), oral contraceptives (dyskinesia), β-adrenergics (tremor), buspirone (akathisia, dyskinesias, myoclonus), and digoxin, cimetidine, diazoxide, lithium, methadone, and fentanyl (dyskinesias).

PAROXYSMAL DYSKINESIAS

Paroxysmal dyskinesias are a group of rare disorders characterized by episodic, brief involuntary movements that can manifest as various types of hyperkinetic movements, including chorea, dystonia, tremor, and myoclonus. T ere are two main categories: (1) paroxysmal kinesigenic dyskinesia, where the involuntary movements are triggered by sudden movement, and (2) paroxysmal nonkinesigenic dyskinesias, where the attacks are not induced by movement. T ere are rare cases of exercise-induced dyskinesia, where attacks are induced by prolonged exercise.

Paroxysmal kinesigenic dyskinesia (PKD) is characterized by brief, self-limited attacks induced by movement onset such as running but also occasionally by unexpected sound or photic stimulation. Attacks may affect one side of the body, last seconds to minutes at a time, and recur several times a day. T ey usually manifest as dystonic posturing of a limb but may also become generalized. PKD is most commonly familial with an autosomal dominant pattern of inheritance but may also occur secondary to various brain disorders such as multiple sclerosis or hyperglycemia. PKD is more frequent in males (4:1), and the onset is typically in the first or second decade of life. About 70% report sensory symptoms such as tingling or numbness of the affected limb preceding the attack by a few milliseconds. T e evolution is relatively benign, and there is a trend toward

www.ketabpezeshki.com (021) 66485457 - 66485438

resolution of the attacks over time. The cause is not known, but a mutation in the proline-rich transmembrane protein 2 (PRRT2) gene that may be involved in neurotransmitter release has now been identified. Treatment with low-dose anticonvulsant therapy such as carbamazepine or phenytoin is advised when the attacks are frequent and interfere with daily life activities and is effective in about 80% of patients. Some clinical features of PKD (abrupt and short-lasting attacks preceded by an "aura") and its favorable response to anticonvulsant drugs have led to speculation that it is epileptic in origin, but this has not been established.

Paroxysmal nonkinesigenic dyskinesia (PNKD) involves attacks of generalized dyskinesias precipitated by alcohol, caffeine, stress, or fatigue. In comparison to PKD, the episodes have a relatively longer duration (minutes to hours) and are less frequent (one to three per day). PNKD is inherited as autosomal dominant with incomplete penetrance pattern in some 80% of cases. A missense mutation in the myofibrillogenesis regulator (MR-1) gene has been identified in several families. Recognition of the condition and elimination of the underlying precipitating factors, where possible, are the first priority. Tetrabenazine, neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treatment may not be required if the condition is mild and self-limited. Most patients with PNKD do not benefit from anticonvulsant drugs, but some may respond to clonazepam or other benzodiazepines.

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a neurologic disorder that affects approximately 10% of the adult population (it is rare in Asians) and can cause significant morbidity in some. It was first described in the seventeenth century by an English physician (Thomas Willis), but has only recently been recognized as being a bona fide movement disorder. The four core symptoms required for diagnosis are as follows: an urge to move the legs, usually caused or accompanied by an unpleasant sensation in the legs; symptoms that begin or worsen with rest; partial or complete relief by movement; and worsening during the evening or night.

Symptoms most commonly begin in the legs, but can spread to or even begin in the upper limbs. The unpleasant sensation is often described as a creepy-crawly feeling, paresthesia, or burning. In about 80% of patients, RLS is associated with periodic leg movements (PLMs) during sleep and occasionally while awake. These involuntary movements are usually brief, lasting no more than a few seconds, and recur every 5–90 s. The restlessness and PLMs are a major cause of sleep disturbance in patients, leading to poor-quality sleep and daytime sleepiness.

RLS is a heterogeneous condition. Primary RLS is genetic, and several loci have been found with an autosomal dominant pattern of inheritance, although penetrance may be variable. The mean age of onset in genetic forms is 27 years, although pediatric cases are recognized. The severity of symptoms is variable. Secondary RLS may be associated with pregnancy or a range of underlying disorders, including anemia, ferritin deficiency, renal failure, and peripheral neuropathy. The pathogenesis probably involves disordered dopamine function, which may be peripheral or central, in association with an abnormality of iron metabolism. Diagnosis is made on clinical grounds but can be supported by polysomnography and the demonstration of PLMs. The neurologic examination is normal. Secondary RLS should be excluded, and ferritin levels, glucose, and renal function should be measured.

Most RLS sufferers have mild symptoms that do not require specific treatment. General measures to improve sleep hygiene and quality should be attempted first. If symptoms remain intrusive, low doses of dopamine agonists, e.g., pramipexole (0.25–0.5 mg) or ropinirole (1–2 mg), are given 1–2 h before bedtime. Levodopa can be effective but is frequently associated with augmentation (spread and worsening of restlessness and its appearance earlier in the day) or rebound (reappearance sometimes with worsening of symptoms at a time compatible with the drug's short half-life). Other drugs that can be effective include anticonvulsants, analgesics, and opiates. Management of secondary RLS should be directed to correcting the underlying disorder; for example, iron replacement for anemia. Iron infusion may also be helpful for severe primary RLS but requires expert supervision.

DISORDERS THAT MAY PRESENT WITH A COMBINATION OF PARKINSONISM AND HYPERKINETIC MOVEMENTS

WILSON'S DISEASE

Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism that may manifest with neurologic, psychiatric, and liver disorders, alone or in combination. It is caused by mutations in the gene encoding a P-type ATPase. The disease was first comprehensively described by the English neurologist Kinnier Wilson at the beginning of the twentieth century, although at around the same time the German physicians Kayser and Fleischer separately noted the

www.ketabpezeshki.com (021) 66485457 - 66485438

characteristic association of corneal pigmentation with hepatic and neurologic features. WD has a worldwide prevalence of approximately 1 in 30,000, with a gene carrier frequency of 1 in 90. About half of WD patients (especially younger patients) manifest with liver abnormalities. T e remainder present with neurologic disease (with or without underlying liver abnormalities), and a small proportion have hematologic or psychiatric problems at disease onset.

Neurologic onset usually manifests in the second decade with tremor and rigidity. T e tremor is usually in the upper limbs, bilateral, and asymmetric. Tremor can be on intention or occasionally resting and, in advanced disease, can take on a wing-beating characteristic. Other features include parkinsonism with bradykinesia, dystonia (particularly facial grimacing), dysarthria, and dysphagia. More than half of those with neurologic features have a history of psychiatric disturbances, including depression, mood swings, and overt psychosis. Kayser-Fleischer (KF) rings are seen in 80% of those with hepatic presentations and virtually all with neurologic features. KF rings represent the deposition of copper in Descemet's membrane around the cornea. T ey consist of a characteristic grayish rim or circle at the limbus of the cornea and are best detected by slit-lamp examination. Neuropathologic examination is characterized by neurodegeneration and astrogliosis in the basal ganglia, particularly in the striatum.

WD should always be considered in the differential diagnosis of a movement disorder in the first decades of life. Low levels of blood copper and ceruloplasmin and high levels of urinary copper may be present, but normal levels do not exclude the diagnosis. A computed tomography (CT) scan usually reveals generalized brain atrophy in established cases, and ~50% have signal hypointensity in the caudate head, putamen, globus pallidum, substantia nigra, and red nucleus on T2-weighted MRI. However, correlation of imaging changes with clinical features is not good. It is very rare for WD patients with neurologic features not to have KF rings, and therefore when the diagnosis is considered, examination by slit-lamp is essential. Liver biopsy with demonstration of high copper levels remains the gold standard for the diagnosis.

In the absence of treatment, the course is progressive and leads to severe neurologic dysfunction and early death. Treatment is directed at reducing tissue copper levels and maintenance therapy to prevent reaccumulation. T ere is no clear consensus on treatment, and all patients should be managed in a unit with expertise in WD. Penicillamine is frequently used to increase copper excretion, but it may lead to a worsening of symptoms in the initial stages of therapy. Side effects are common and can to some degree be attenuated by coadministration of pyridoxine. Tetrathiomolybdate blocks the absorption of copper and can be used instead of penicillamine. Trientine and zinc are useful drugs for maintenance therapy. Effective treatment can reverse the neurologic features in most patients, particularly when started early. Some patients stabilize, and a few may still progress, especially those with hepatocerebral disease. KF rings tend to decrease af er 3–6 months and disappear by 2 years. Adherence to maintenance therapy is a major challenge in long-term care.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation (NBIA) represents a group of inherited disorders characterized by iron accumulation in the basal ganglia. Clinically, they can manifest as a progressive neurologic disorder manifesting a variety of features including parkinsonism, dystonia, neuropsychiatric abnormalities, and retinal degeneration. Cognitive disorders and cerebellar dysfunction may also be seen. Presentation is usually in childhood, but adult cases have been described. Multiple genes have been identified to date. Pantothenate kinase–associated neurodegeneration (PKAN) formerly known as Hallervorden-Spatz disease and caused by a mutation in the PANK2 gene is the most common form of NBIA, accounting for about 50% of cases. Onset is usually in early childhood and is manifest as a combination of dystonia, parkinsonism, and spasticity. MRI shows a characteristic low signal abnormality in the center of the globus pallidus on T2-weighted scans known as the "eye of the tiger" sign caused by iron accumulation. Numerous other gene mutations have been described associated with iron accumulation including mutations in PLA2G6, C19or*f*12, FA2H, ATP13A2, WDR45, FTL, CP, and DCAF17. One must be cautious, however, not to assume that all cases with iron accumulation in the basal ganglia represent an NBIA, because iron accumulation in specific basal ganglia regions is normal, and excess iron accumulation may occur in the basal ganglia region as a consequence of neurodegeneration of multiple causes unrelated to a defect in iron metabolism.

OTHER DISORDERS

Acanthocytosis, some hereditary spinocerebellar atrophies and spastic parapareses, and HD can also present with parkinsonian features associated with involuntary movements. Diagnosis in these cases is best established with genetic testing.

www.ketabpezeshki.com (021) 66485457 - 66485438

PSYCHOGENIC DISORDERS

Virtually all movement disorders including tremor, tics, dystonia, myoclonus, chorea, ballism, and parkinsonism can be psychogenic in origin. Tremor affecting the upper limbs is the most common psychogenic movement disorder. Psychogenic movements can result from a somatoform or conversion disorder, malingering (e.g., seeking financial gain), or a factitious disorder (e.g., seeking psychological gain). Psychogenic movement disorders are common (estimated to be 2–3% of patients seen in a movement disorder clinic), more frequent in women, disabling for the patient and family, and expensive for society (estimated $20 billion annually). Clinical features suggesting a psychogenic movement disorder include an acute onset and a pattern of abnormal movement that is inconsistent with a known movement disorder. Diagnosis is based on the nonorganic quality of the movement, the absence of findings of an organic disease process, and positive features that specifically point to a psychogenic illness such as variability and distractibility. For example, the magnitude of a psychogenic tremor is increased with attention and diminishes or even disappears when the patient is distracted by being asked to perform a different task or is unaware that he or she is being observed. Other positive features suggesting a psychogenic problem include a tremor frequency that is variable or that entrains with the frequency of a designated movement in the contralateral limb, and a positive response to placebo medication. Associated features can include nonanatomic sensory findings, give-way weakness, astasia-abasia (an odd, gyrating gait; **Chap. 16**), and multiple somatic complaints with no underlying pathology (somatoform disorder). Comorbid psychiatric problems such as anxiety, depression, and emotional trauma may be present but are not necessary for the diagnosis of a psychogenic movement disorder to be made. Psychogenic movement disorders can occur as an isolated entity or in association with an underlying organic problem. T e diagnosis can of en be made based on clinical features alone, and unnecessary tests or medications can be avoided. Underlying psychiatric problems may be present and should be identified and treated, but many patients with psychogenic movement disorders have no obvious psychiatric pathology. Psychotherapy and hypnosis may be of value for patients with conversion reaction, and cognitive behavioral therapy may be helpful for patients with somatoform disorders. Patients with hypochondriasis, factitious disorders, and malingering have a poor prognosis.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 37

ATAXIC DISORDERS

Roger N. Rosenberg

APPROACH TO THE PATIENT: Ataxic Disorders

Symptoms and signs of ataxia consist of gait impairment, unclear ("scanning") speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement. These result from the involvement of the cerebellum and its afferent and efferent pathways, including the spinocerebellar pathways, and the frontopontocerebellar pathway originating in the rostral frontal lobe. True cerebellar ataxia must be distinguished from ataxia associated with vestibular nerve or labyrinthine disease, as the latter results in a disorder of gait associated with a significant degree of dizziness, light-headedness, or the perception of movement **(Chap. 12)**. True cerebellar ataxia is devoid of these vertiginous complaints and is clearly an unsteady gait due to imbalance. Sensory disturbances can also on occasion simulate the imbalance of cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is removed (Romberg sign). Rarely, weakness of proximal leg muscles mimics cerebellar disease. In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms help to narrow the diagnostic possibilities **(Table 37-1)**. A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a genetic, metabolic, immune, or toxic etiology. Conversely, focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion.

SYMMETRIC ATAXIA Progressive and symmetric ataxia can be classified with respect to onset as acute (over hours or days), subacute (weeks or months), or chronic (months to years). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as fluorouracil and paclitaxel. Patients with a postinfectious syndrome (especially after varicella) may develop gait ataxia and mild dysarthria, both of which are reversible **(Chap. 45)**. Rare infectious causes of acquired ataxia include poliovirus, coxsackievirus, echovirus, Epstein-Barr virus, toxoplasmosis, Legionella, and Lyme disease.

The subacute development of ataxia of gait over weeks to months (degeneration of the cerebellar vermis) may be due to the combined effects of alcoholism and malnutrition, particularly with deficiencies of vitamins B_1 and B_{12}. Hyponatremia has also been associated with ataxia. Paraneoplastic cerebellar ataxia is associated with a number of different tumors (and autoantibodies) such as breast and ovarian cancers (anti-Yo), small-cell lung cancer (anti-PQ-type voltage-gated calcium channel), and Hodgkin's disease (anti-Tr) **(Chap. 50)**. Another paraneoplastic syndrome associated with myoclonus and opsoclonus occurs with breast (anti-Ri) and lung cancers and neuroblastoma. Elevated serum anti-glutamic acid decarboxylase (GAD) antibodies have been associated with a progressive ataxic syndrome affecting speech and gait. For all of these paraneoplastic ataxias, the neurologic syndrome may be the presenting symptom of the cancer. Another immune-mediated progressive ataxia is associated with antigliadin (and antiendomysium) antibodies and the human leukocyte antigen (HLA) DQB1*0201 haplotype; in some affected patients, biopsy of the small intestine reveals villus atrophy consistent with gluten-sensitive enteropathy. Finally, subacute progressive ataxia may be caused by a prion disorder, especially when an infectious etiology, such as transmission from contaminated human growth hormone, is responsible **(Chap. 40)**.

Chronic symmetric gait ataxia suggests an inherited ataxia (discussed below), a metabolic disorder, or a chronic infection. Hypothyroidism must always be

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 37-1

ETIOLOGY OF CEREBELLAR ATAXIA

SYMMETRIC AND PROGRESSIVE SIGNS			FOCAL AND IPSILATERAL CEREBELLAR SIGNS		
ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)	ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen)	Intoxication: mercury, solvents, gasoline, glue; cytotoxic chemotherapeutic, hemotherapeutic drugs	Paraneoplastic syndrome Antigliadin antibody syndrome Hypothyroidism	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent)	Stable gliosis secondaryto vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months)
Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfectionsyndrome	Alcoholic-nutritional (vitamin B_1 and B_{12} deficiency) Lyme disease	Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone		AIDS-related multifocal leukoencephalopathy (positive HIVtest and CD4+ cell count for AIDS)	Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)

Abbreviations: CSF, cerebrospinal fuid; CT, computed tomography; MRI, magnetic resonance imaging.

considered as a readily treatable and reversible form of gait ataxia. Infectious diseases that can present with ataxia are meningovascular syphilis and tabes dorsalis due to degeneration of the posterior columns and spinocerebellar pathways in the spinal cord.

FOCAL ATAXIA Acute focal ataxia commonly results from cerebrovascular disease, usually ischemic infarction or cerebellar hemorrhage. T ese lesions typically produce cerebellar symptoms ipsilateral to the injured cerebellum and may be associated with an impaired level of consciousness due to brainstem compression and increased intracranial pressure; ipsilateral pontine signs, including sixth and seventh nerve palsies, may be present. Focal and worsening signs of acute ataxia should also prompt consideration of a posterior fossa subdural hematoma, bacterial abscess, or primary or metastatic cerebellar tumor. Computed tomography (CT) or magnetic resonance imaging (MRI) studies will reveal clinically significant processes of this type. Many of these lesions represent true neurologic emergencies, as sudden herniation, either rostrally through the tentorium or caudal herniation of cerebellar tonsils through the foramen magnum, can occur and is usually devastating. Acute surgical decompression may be required **(Chap. 33)**. Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS may present with an acute or subacute focal cerebellar syndrome. Chronic etiologies of progressive ataxia include multiple sclerosis **(Chap. 45)** and congenital lesions such as a Chiari malformation **(Chap. 43)** or a congenital cyst of the posterior fossa (Dandy-Walker syndrome).

THE INHERITED ATAXIAS

T ese may show autosomal dominant, autosomal recessive, or maternal (mitochondrial) modes of inheritance. A genomic classification **(Chap. 38)** has now largely superseded previous ones based on clinical expression alone.

Although the clinical manifestations and neuropathologic findings of cerebellar disease dominate the clinical picture, there may also be characteristic changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves. In large families with dominantly inherited ataxias, many gradations are observed from purely cerebellar manifestations to mixed cerebellar and brainstem disorders, cerebellar and basal ganglia syndromes, and spinal cord or peripheral nerve disease. Rarely, dementia is present as well. T e clinical picture may be homogeneous within a family with dominantly inherited ataxia, but sometimes most af ected family members show one characteristic syndrome, while one or several members have an entirely dif erent phenotype.

AUTOSOMAL DOMINANT ATAXIAS

T e autosomal spinocerebellar ataxias (SCAs) include SCA types 1 through 36, dentatorubropallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 to 7 **(Chap. 38)**. SCA1, SCA2, SCA3 (Machado-Joseph disease [MJD]), SCA6, SCA7, and SCA17 are caused by

www.ketabpezeshki.com (021) 66485457 - 66485438

CAG triplet repeat expansions in different genes. SCA8 is due to an untranslated CTG repeat expansion, SCA12 is linked to an untranslated CAG repeat, and SCA10 is caused by an untranslated pentanucleotide repeat. T e clinical phenotypes of these SCAs overlap. T e genotype has become the gold standard for diagnosis and classification. CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed ataxins, that produce a toxic gain of function with autosomal dominant inheritance. Although the phenotype is variable for any given disease gene, a pattern of neuronal loss with gliosis is produced that is relatively unique for each ataxia. Immunohistochemical and biochemical studies have shown cytoplasmic (SCA2), neuronal (SCA1, MJD, SCA7), and nucleolar (SCA7) accumulation of the specific mutant polyglutamine-containing ataxin proteins. Expanded polyglutamine ataxins with more than ~40 glutamines are potentially toxic to neurons for a variety of reasons including: high levels of gene expression for the mutant polyglutamine ataxin in affected neurons; conformational change of the aggregated protein to a β-pleated structure; abnormal transport of the ataxin into the nucleus (SCA1, MJD, SCA7); binding to other polyglutamine proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions; altering the efficiency of the ubiquitin-proteasome system of protein turnover; and inducing neuronal apoptosis. An earlier age of onset (anticipation) and more aggressive disease in subsequent generations are due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. T e most common disorders are discussed below.

SCA1

SCA1 was previously referred to as olivopontocerebellar atrophy, but genomic data have shown that that entity represents several different genotypes with overlapping clinical features.

Symptoms and signs

SCA1 is characterized by the development in early or middle adult life of progressive cerebellar ataxia of the trunk and limbs, impairment of equilibrium and gait, slowness of voluntary movements, scanning speech, nystagmoid eye movements, and oscillatory tremor of the head and trunk. Dysarthria, dysphagia, and oculomotor and facial palsies may also occur. Extrapyramidal symptoms include rigidity, an immobile face, and parkinsonian tremor. T e reflexes are usually normal, but knee and ankle jerks may be lost, and extensor plantar responses may occur. Dementia may be noted but is usually mild. Impairment of sphincter function

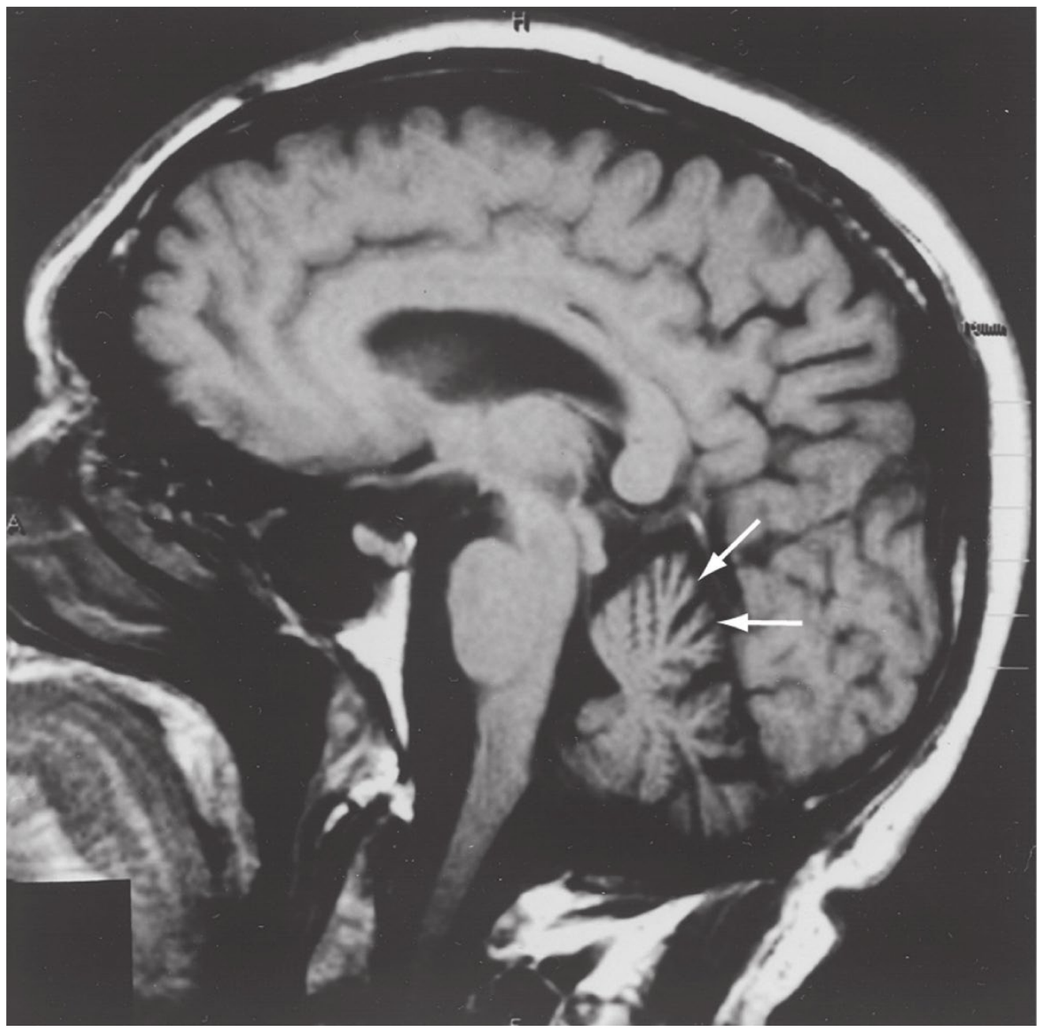


FIGURE 37-1
Sagittal magnetic resonance imaging (MRI) of the brain of a 60-year-old man with gait ataxia and dysarthria due to spinocerebellar ataxia type 1 (SCA1), illustrating cerebellar atrophy (arrows). (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.)

is common, with urinary and sometimes fecal incontinence. Cerebellar and brainstem atrophy are evident on MRI **(Fig. 37-1)**.

Marked shrinkage of the ventral half of the pons, disappearance of the olivary eminence on the ventral surface of the medulla, and atrophy of the cerebellum are evident on gross postmortem inspection of the brain. Variable loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, demyelination of the middle cerebellar peduncle and the cerebellar hemispheres, and severe loss of cells in the pontine nuclei and olives are found on histologic examination. Degenerative changes in the striatum, especially the putamen, and loss of the pigmented cells of the substantia nigra may be found in cases with extrapyramidal features. More widespread degeneration in the central nervous system (CNS), including involvement of the posterior columns and the spinocerebellar fibers, is of en present.

GENETIC CONSIDERATIONS

SCA1 encodes a gene product, called ataxin-1, which is a novel protein of unknown function. T e mutant allele has 40 CAG repeats located within the coding region, whereas alleles from unaffected

www.ketabpezeshki.com (021) 66485457 - 66485438

individuals have ≤36 repeats. A few patients with 38–40 CAG repeats have been described. T ere is a direct correlation between a larger number of repeats and a younger age of onset for SCA1. Juvenile patients have higher numbers of repeats, and anticipation is present in subsequent generations. Transgenic mice carrying SCA1 developed ataxia and Purkinje cell pathology. Nuclear localization, but not aggregation, of ataxin-1 appears to be required for cell death initiated by the mutant protein.

SCA2

Symptoms and signs

Another clinical phenotype, SCA2, has been described in patients from Cuba and India. Cuban patients probably are descendants of a common ancestor, and the population may be the largest homogeneous group of patients with ataxia yet described. T e age of onset ranges from 2–65 years, and there is considerable clinical variability within families. Although neuropathologic and clinical findings are compatible with a diagnosis of SCA1, including slow saccadic eye movements, ataxia, dysarthria, parkinsonian rigidity, optic disc pallor, mild spasticity, and retinal degeneration, SCA2 is a unique form of cerebellar degenerative disease.

GENETIC CONSIDERATIONS

T e gene in SCA2 families also contains CAG repeat expansions coding for a polyglutamine-containing protein, ataxin-2. Normal alleles contain 15–32 repeats; mutant alleles have 35–77 repeats.

MACHADO-JOSEPH DISEASE/SCA3

MJD was first described among the Portuguese and their descendants in New England and California. Subsequently, MJD has been found in families from Portugal, Australia, Brazil, Canada, China, England, France, India, Israel, Italy, Japan, Spain, Taiwan, and the United States. In most populations, it is the most common autosomal dominant ataxia.

Symptoms and signs

MJD has been classified into three clinical types. In type I MJD (amyotrophic lateral sclerosis-parkinsonism-dystonia type), neurologic deficits appear in the first two decades and involve weakness and spasticity of extremities, especially the legs, often with dystonia of the face, neck, trunk, and extremities. Patellar and ankle clonus are common, as are extensor plantar responses. T e gait is slow and stiff, with a slightly broadened base and lurching from side to side; this gait results from spasticity, not true ataxia. T ere is no truncal titubation. Pharyngeal weakness and spasticity cause difficulty with speech and swallowing. Of note is the prominence of horizontal and vertical nystagmus, loss of fast saccadic eye movements, hypermetric and hypometric saccades, and impairment of upward vertical gaze. Facial fasciculations, facial myokymia, lingual fasciculations without atrophy, ophthalmoparesis, and ocular prominence are common early manifestations.

In type II MJD (ataxic type), true cerebellar deficits of dysarthria and gait and extremity ataxia begin in the second to fourth decades along with corticospinal and extrapyramidal deficits of spasticity, rigidity, and dystonia. Type II is the most common form of MJD. Ophthalmoparesis, upward vertical gaze deficits, and facial and lingual fasciculations are also present. Type II MJD can be distinguished from the clinically similar disorders SCA1 and SCA2.

Type III MJD (ataxic-amyotrophic type) presents in the fifth to the seventh decades with a pancerebellar disorder that includes dysarthria and gait and extremity ataxia. Distal sensory loss involving pain, touch, vibration, and position senses and distal atrophy are prominent, indicating the presence of peripheral neuropathy. T e deep tendon ref exes are depressed to absent, and there are no corticospinal or extrapyramidal findings.

T e mean age of onset of symptoms in MJD is 25 years. Neurologic deficits invariably progress and lead to death from debilitation within 15 years of onset, especially in patients with types I and II disease. Usually, patients retain full intellectual function.

T e major pathologic findings are variable loss of neurons and glial replacement in the corpus striatum and severe loss of neurons in the pars compacta of the substantia nigra. A moderate loss of neurons occurs in the dentate nucleus of the cerebellum and in the red nucleus. Purkinje cell loss and granule cell loss occur in the cerebellar cortex. Cell loss also occurs in the dentate nucleus and in the cranial nerve motor nuclei. Sparing of the inferior olives distinguishes MJD from other dominantly inherited ataxias.

GENETIC CONSIDERATIONS

T e gene for MJD maps to 14q24.3-q32. Unstable CAG repeat expansions are present in the MJD gene coding for a polyglutamine-containing protein named ataxin-3, or MJD-ataxin. An earlier age of onset is associated with longer repeats. Alleles from normal individuals have between 12 and 37 CAG repeats, whereas MJD alleles have 60–84 CAG repeats. Polyglutamine-containing aggregates of ataxin-3 (MJD-ataxin) have

www.ketabpezeshki.com (021) 66485457 - 66485438

been described in neuronal nuclei undergoing degeneration. MJD-ataxin codes for a ubiquitin protease, which is inactive due to expanded polyglutamines. Proteosome function is impaired, resulting in altered clearance of proteins and cerebellar neuronal loss.

SCA6

Genomic screening for CAG repeats in other families with autosomal dominant ataxia and vibratory and proprioceptive sensory loss have yielded another locus. Of interest is that different mutations in the same gene for the α_{1A} voltage-dependent calcium channel subunit (CACNLIA4; also referred to as the CACNA1A gene) at 19p13 result in different clinical disorders. CAG repeat expansions (21–27 in patients; 4–16 triplets in normal individuals) result in late-onset progressive ataxia with cerebellar degeneration. Missense mutations in this gene result in familial hemiplegic migraine. Nonsense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or EA. Some patients with familial hemiplegic migraine develop progressive ataxia and also have cerebellar atrophy.

SCA7

T is disorder is distinguished from all other SCAs by the presence of retinal pigmentary degeneration. T e visual abnormalities first appear as blue-yellow color blindness and proceed to frank visual loss with macular degeneration. In almost all other respects, SCA7 resembles several other SCAs in which ataxia is accompanied by various noncerebellar findings, including ophthalmoparesis and extensor plantar responses. T e genetic defect is an expanded CAG repeat in the SCA7 gene at 3p14-p21.1. T e expanded repeat size in SCA7 is highly variable. Consistent with this, the severity of clinical findings varies from essentially asymptomatic to mild late-onset symptoms to severe, aggressive disease in childhood with rapid progression. Marked anticipation has been recorded, especially with paternal transmission. T e disease protein, ataxin-7, forms aggregates in nuclei of affected neurons, as has also been described for SCA1 and SCA3/MJD.

SCA8

T is form of ataxia is caused by a CTG repeat expansion in an untranslated region of a gene on chromosome 13q21. T ere is marked maternal bias in transmission, perhaps reflecting contractions of the repeat during spermatogenesis. T e mutation is not fully penetrant. Symptoms include slowly progressive dysarthria and gait ataxia beginning at ~40 years of age with a range between 20 and 65 years. Other features include nystagmus, leg spasticity, and reduced vibratory sensation. Severely affected individuals are nonambulatory by the fourth to sixth decades. MRI shows cerebellar atrophy. T e mechanism of disease may involve a dominant "toxic" effect occurring at the RNA level, as occurs in myotonic dystrophy.

DENTATORUBROPALLIDOLUYSIAN ATROPHY

DRPLA has a variable presentation that may include progressive ataxia, choreoathetosis, dystonia, seizures, myoclonus, and dementia. DRPLA is due to unstable CAG triplet repeats in the open reading frame of a gene named atrophin located on chromosome 12p12-ter. Larger expansions are found in patients with earlier onset. T e number of repeats is 49 in patients with DRPLA and ≤26 in normal individuals. Anticipation occurs in successive generations, with earlier onset of disease in association with an increasing CAG repeat number in children who inherit the disease from their father. One well-characterized family in North Carolina has a phenotypic variant known as the Haw River syndrome, now recognized to be due to the DRPLA mutation.

EPISODIC ATAXIA

EA types 1 and 2 are two rare dominantly inherited disorders that have been mapped to chromosomes 12p (a potassium channel gene) for type 1 and 19p for type 2. Patients with EA-1 have brief episodes of ataxia with myokymia and nystagmus that last only minutes. Startle, sudden change in posture, and exercise can induce episodes. Acetazolamide or anticonvulsants may be therapeutic. Patients with EA-2 have episodes of ataxia with nystagmus that can last for hours or days. Stress, exercise, or excessive fatigue may be precipitants. Acetazolamide may be therapeutic and can reverse the relative intracellular alkalosis detected by magnetic resonance spectroscopy. Stop codon, nonsense mutations causing EA-2 have been found in the CACNA1A gene, encoding the α_{1A} voltage-dependent calcium channel subunit (see "SCA6," above).

AUTOSOMAL RECESSIVE ATAXIAS

Friedreich's ataxia

T is is the most common form of inherited ataxia, comprising one-half of all hereditary ataxias. It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome; the two forms are clinically indistinguishable.

www.ketabpezeshki.com (021) 66485457 - 66485438

Symptoms and signs

Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones. Dysarthria occasionally is the presenting symptom; rarely, progressive scoliosis, foot deformity, nystagmus, or cardiopathy is the initial sign.

The neurologic examination reveals nystagmus, loss of fast saccadic eye movements, truncal titubation, dysarthria, dysmetria, and ataxia of trunk and limb movements. Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs. The median age of death is 35 years. Women have a significantly better prognosis than men.

Cardiac involvement occurs in 90% of patients. Cardiomegaly, symmetric hypertrophy, murmurs, and conduction defects are reported. Moderate mental retardation or psychiatric syndromes are present in a small percentage of patients. A high incidence of diabetes mellitus (20%) is found and is associated with insulin resistance and pancreatic β-cell dysfunction. Musculoskeletal deformities are common and include pes cavus, pes equinovarus, and scoliosis. MRI of the spinal cord shows atrophy **(Fig. 37-2)**.

FIGURE 37-2

Sagittal magnetic resonance imaging (MRI) of the brain and spinal cord of a patient with Friedreich's ataxia, demonstrating spinal cord atrophy. (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.)

The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves. Slight atrophy of the cerebellum and cerebral gyri may occur. Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns. Degeneration of the glossopharyngeal, vagus, hypoglossal, and deep cerebellar nuclei is described. The cerebral cortex is histologically normal except for loss of Betz cells in the precentral gyri. The peripheral nerves are extensively involved, with a loss of large myelinated fibers. Cardiac pathology consists of myocytic hypertrophy and fibrosis, focal vascular fibromuscular dysplasia with subintimal or medial deposition of periodic acid-Schiff (PAS)-positive material, myocytopathy with unusual pleomorphic nuclei, and focal degeneration of nerves and cardiac ganglia.

GENETIC CONSIDERATIONS

The classic form of Friedreich's ataxia has been mapped to 9q13-q21.1, and the mutant gene, frataxin, contains expanded GAA triplet repeats in the first intron. There is homozygosity for expanded GAA repeats in >95% of patients. Normal persons have 7–22 GAA repeats, and patients have 200–900 GAA repeats. A more varied clinical syndrome has been described in compound heterozygotes who have one copy of the GAA expansion and the other copy a point mutation in the frataxin gene. When the point mutation is located in the region of the gene that encodes the amino-terminal half of frataxin, the phenotype is milder, often consisting of a spastic gait, retained or exaggerated reflexes, no dysarthria, and mild or absent ataxia.

Patients with Friedreich's ataxia have undetectable or extremely low levels of frataxin mRNA, as compared with carriers and unrelated individuals; thus, disease appears to be caused by a loss of expression of the frataxin protein. Frataxin is a mitochondrial protein involved in iron homeostasis. Mitochondrial iron accumulation due to loss of the iron transporter coded by the mutant frataxin gene results in oxidized intramitochondrial iron. Excess oxidized iron results in turn in the oxidation of cellular components and irreversible cell injury.

Two forms of hereditary ataxia associated with abnormalities in the interactions of vitamin E (α-tocopherol) with very-low-density lipoprotein (VLDL) have been delineated. These are abetalipoproteinemia (Bassen-Kornzweig syndrome) and ataxia with vitamin E deficiency (AVED). Abetalipoproteinemia is caused by mutations in the gene coding for the larger subunit of the microsomal triglyceride transfer protein (MTP). Defects in MTP result in impairment of formation and secretion of VLDL in liver. This is

www.ketabpezeshki.com (021) 66485457 - 66485438

defect results in a deficiency of delivery of vitamin E to tissues, including the central and peripheral nervous system, as VLDL is the transport molecule for vitamin E and other fat-soluble substitutes. AVED is due to mutations in the gene for α-tocopherol transfer protein (α-TTP). T ese patients have an impaired ability to bind vitamin E into the VLDL produced and secreted by the liver, resulting in a deficiency of vitamin E in peripheral tissues. Hence, either absence of VLDL (abetalipoproteinemia) or impaired binding of vitamin E to VLDL (AVED) causes an ataxic syndrome. Once again, a genotype classification has proved to be essential in sorting out the various forms of the Friedreich's disease syndrome, which may be clinically indistinguishable.

Ataxia telangiectasia

Symptoms and signs

Patients with ataxia telangiectasia (AT) present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. T e neurologic manifestations correspond to those in Friedreich's disease, which should be included in the differential diagnosis. Truncal and limb ataxia, dysarthria, extensor plantar responses, myoclonic jerks, areflexia, and distal sensory deficits may develop. T ere is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic and reticuloendothelial system in patients with AT. T ymic hypoplasia with cellular and humoral (IgA and IgG2) immunodeficiencies, premature aging, and endocrine disorders such as type 1 diabetes mellitus are described. T ere is an increased incidence of lymphomas, Hodgkin's disease, acute T cell leukemias, and breast cancer.

T e most striking neuropathologic changes include loss of Purkinje, granule, and basket cells in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei. T e inferior olives of the medulla may also have neuronal loss. T ere is a loss of anterior horn neurons in the spinal cord and of dorsal root ganglion cells associated with posterior column spinal cord demyelination. A poorly developed or absent thymus gland is the most consistent defect of the lymphoid system.

GENETIC CONSIDERATIONS

T e gene for AT (the ATM gene) encodes a protein that is similar to several yeast and mammalian phosphatidylinositol-3′-kinases involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Defective DNA repair in AT fibroblasts exposed to ultraviolet light has been demonstrated. T e discovery of ATM permits early diagnosis and identification of heterozygotes who are at risk for cancer (e.g., breast cancer).

MITOCHONDRIAL ATAXIAS

Spinocerebellar syndromes have been identified with mutations in mitochondrial DNA (mtDNA). T irty pathogenic mtDNA point mutations and 60 different types of mtDNA deletions are known, several of which cause or are associated with ataxia **(Chap. 56)**.

TREATMENT Ataxic Disorders

T e most important goal in management of patients with ataxia is to identify treatable disease entities. Mass lesions must be recognized promptly and treated appropriately. Paraneoplastic disorders can of en be identified by the clinical patterns of disease that they produce, measurement of specific autoantibodies, and uncovering the primary cancer; these disorders are of en refractory to therapy, but some patients improve following removal of the tumor or immunotherapy **(Chap. 50)**. Ataxia with antigliadin antibodies and gluten-sensitive enteropathy may improve with a gluten-free diet. Malabsorption syndromes leading to vitamin E deficiency may lead to ataxia. T e vitamin E deficiency form of Friedreich's ataxia must be considered, and serum vitamin E levels measured. Vitamin E therapy is indicated for these rare patients. Vitamin B_1 and B_{12} levels in serum should be measured, and the vitamins administered to patients having deficient levels. Hypothyroidism is easily treated. T e cerebrospinal fluid should be tested for a syphilitic infection in patients with progressive ataxia and other features of tabes dorsalis. Similarly, antibody titers for Lyme disease and Legionella should be measured and appropriate antibiotic therapy should be instituted in antibody-positive patients. Aminoacidopathies, leukodystrophies, urea-cycle abnormalities, and mitochondrial encephalomyopathies may produce ataxia, and some dietary or metabolic therapies are available for these disorders. T e deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in patients with ataxia of any cause.

T ere is no proven therapy for any of the autosomal dominant ataxias (SCA1 to SCA36). T ere is preliminary evidence that idebenone, a free-radical scavenger, can improve myocardial hypertrophy in patients with classic Friedreich's ataxia; there is no current evidence, however, that it improves neurologic function. A small preliminary study in a mixed population of patients with different inherited ataxias raised the possibility that the glutamate antagonist riluzole may offer modest benefit. Iron chelators and antioxidant drugs are potentially harmful in Friedreich's patients because they may increase heart muscle injury. Acetazolamide can reduce the duration of symptoms of episodic ataxia. At present, identification of an at-risk person's genotype, together with appropriate family and genetic counseling, can reduce the incidence of these cerebellar syndromes in future generations.

www.ketabpezeshki.com (021) 66485457 - 66485438

GENETIC DIAGNOSTIC LABORATORIES

1. Baylor College of Medicine; Houston, Texas, 1-713-798-6522
   http://www.bcm.edu/genetics/index.cfm?pmid=21387
2. GeneDx
   http://www.genedx.com
3. Transgenomic, 1-877-274-9432
   http://www.transgenomic.com/labs/neurology

GLOBAL FEATURES

Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial forms of inheritance are present on a worldwide basis. Machado-Joseph disease (SCA3) (autosomal dominant) and Friedreich's ataxia (autosomal recessive) are the most common types in most populations. Genetic markers are now commercially available to precisely identify the genetic mutation for correct diagnosis and also for family planning. Early detection of asymptomatic preclinical disease can reduce or eliminate the inherited form of ataxia in some families on a global, worldwide basis.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 38

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS

Roger N. Rosenberg

Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial forms of inheritance are present on a worldwide basis. Machado-Joseph disease (SCA3) (autosomal dominant) and Friedreich's ataxia (autosomal recessive) are the most common types in most populations. Mutation markers are now commercially available to identify carriers at risk in their families, which allows for precise identification of the genetic mutation for correct diagnosis and also for family planning. Identification of positive mutation carriers with family planning has allowed for early detection of asymptomatic preclinical disease to reduce or eliminate the inherited form of ataxia in specific families on a global, worldwide basis.

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA)

NAME	LOCUS	PHENOTYPE
SCA1 (autosomal dominant type 1)	6p22-p23 with CAG repeats (exonic); leucine-rich acidic nuclear protein (LANP), region-specific interaction protein Ataxin-1	Ataxia with ophthalmoparesis, pyramidal and extrapyramidal findings; genetic testing is available; 6% of all autosomal dominant (AD) cerebellar ataxia
SCA2 (autosomal dominant type 2)	12q23-q24.1 with CAG repeats (exonic) Ataxin-2	Ataxia with slow saccades and minimal pyramidal and extrapyramidal findings; genetic testing available; 13% of all AD cerebellar ataxia
Machado-Joseph disease/SCA3 (autosomal dominant type 3)	14q24.3-q32 with CAG repeats (exonic); codes for ubiquitin protease (inactive with polyglutamine expansion); altered turnover of cellular proteins due to proteosome dysfunction MJD–ataxin-3	Ataxia with ophthalmoparesis and variable pyramidal, extrapyramidal, and amyotrophic signs; dementia (mild); 23% of all AD cerebellar ataxia; genetic testing available
SCA4 (autosomal dominant type 4)	16q22.1-ter; pleckstrin homology domain-containing protein, family G, member 4 (PLEKHG4; puratrophin-1: Purkinje cell atrophy associated protein-1, including spectrin repeat and the guanine-nucleotide exchange factor, GEF for Rho GTPases)	Ataxia with normal eye movements, sensory axonal neuropathy, and pyramidal signs; genetic testing available
SCA5 (autosomal dominant type 5)	11p12-q12; β-III spectrin mutations; (SPTBN2); stabilizes glutamate transporter EAAT4; descendants of President Abraham Lincoln	Ataxia and dysarthria; genetic testing available
SCA6 (autosomal dominant type 6)	19p13.2 with CAG repeats in α_{1A}-voltage–dependent calcium channel gene (exonic); CACNA1A protein, P/Q type calcium channel subunit	Ataxia and dysarthria, nystagmus, mild proprioceptive sensory loss; genetic testing available

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA) (CONTINUED)

NAME	LOCUS	PHENOTYPE
SCA7 (autosomal dominant type 7)	3p14.1-p21.1 with CAG repeats (exonic); ataxin-7; subunit of GCN5, histone acetyltransferase-containing complexes; ataxin-7 binding protein; Cbl-associated protein (CAP; SH3D5)	Ophthalmoparesis, visual loss, ataxia, dysarthria, extensor plantar response, pigmentary retinal degeneration; genetic testing available
SCA8 (autosomal dominant type 8)	13q21 with CTG repeats; noncoding; 3‘ untranslated region of transcribed RNA; KLHL1AS	Gait ataxia, dysarthria, nystagmus, leg spasticity, and reduced vibratory sensation; genetic testing available
SCA10 (autosomal dominant type 10)	22q13; pentanucleotide repeat ATTCT repeat; noncoding, intron 9	Gait ataxia, dysarthria, nystagmus; partial complex and generalized motor seizures; polyneuropathy; genetic testing available
SCA11 (autosomal dominant type 11)	15q14-q21.3 by linkage	Slowly progressive gait and extremity ataxia, dysarthria, vertical nystagmus, hyperreflexia
SCA12 (autosomal dominant type 12)	5q31-q33 by linkage; CAG repeat; protein phosphatase 2A, regulatory subunit B, (PPP2R2B); protein PP2A, serine/threonine phosphatase	Tremor, decreased movement, increased reflexes, dystonia, ataxia, dysautonomia, dementia, dysarthria; genetic testing available
SCA13 (autosomal dominant type 13)	19q13.3-q14.4; potassium channel voltage-gated; KCNC3	Ataxia, legs > arms; dysarthria, horizontal nystagmus; delayed motor development; mental developmental delay; tendon reflexes increased; MRI: cerebellar and pontine atrophy; genetic testing available
SCA14 (autosomal dominant type 14)	19q-13.4; protein kinase Cγ (PRKCG), missense mutations including in-frame deletion and a splice site mutation among others; serine/threonine kinase	Gait ataxia; leg > arm ataxia; dysarthria; pure ataxia with later onset; myoclonus; tremor of head and extremities; increased deep tendon reflexes at ankles; occasional dystonia and sensory neuropathy; genetic testing available
SCA15 (autosomal dominant type 15)	3p24.2-3pter; inositol 1,4,5- triphosphate receptor type 1 (ITPRI)	Gait and extremity ataxia, dysarthria; nystagmus; MRI: superior vermis atrophy; sparing of hemispheres and tonsils
SCA16 (autosomal dominant type 16)	8q22.1-24.1	Pure cerebellar ataxia and head tremor, gait ataxia, and dysarthria; horizontal gaze–evoked nystagmus; MRI: cerebellar atrophy; no brainstem changes
SCA17 (autosomal dominant type 17)	6q27; CAG expansion in the TATA-binding protein (TBP) gene	Gait ataxia, dementia, parkinsonism, dystonia, chorea, seizures; hyperreflexia; dysarthria and dysphagia; MRI shows cerebral and cerebellar atrophy; genetic testing available
SCA18 (autosomal dominant type 18)	7q22-q32	Ataxia; motor/sensory neuropathy; head tremor; dysarthria; extensor plantar responses in some patients; sensory axonal neuropathy; EMG denervation; MRI: cerebellar atrophy
SCA19 (autosomal dominant type 19)	1p21-q21; KCND3; missense mutations; T352P; M373I; S390N; allelic with SCA22; overlaps with the locus of SCA22	Ataxia, tremor, cognitive impairment, myoclonus; MRI: atrophy of cerebellum
SCA20 (autosomal dominant)	11p13-q11; 260 kb duplication	Dysarthria; gait ataxia; ocular gaze–evoked saccades; palatal tremor; dentate calcification on CT; MRI: cerebral atrophy
SCA21 (autosomal dominant)	7p21.3-p15.1	Ataxia, dysarthria, extrapyramidal features of akinesia, rigidity, tremor, cognitive defect; reduced deep tendon reflexes; MRI: cerebellar atrophy, normal basal ganglia and brainstem
SCA22 (autosomal dominant)	1p21-q23; deletion (in frame); V338E; G345V; T377M; allelic with SCA19; KCND3; Kv4.3 channels	Pure cerebellar ataxia; dysarthria; dysphagia; nystagmus; MRI: cerebellar atrophy

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA) (CONTINUED)

NAME	LOCUS	PHENOTYPE
SCA23 (autosomal dominant)	20p13-12.3; prodynorphin (PDYN protein); missense R138S; L211S; R212W; R215C	Gait ataxia; dysarthria; extremity ataxia; ocular nystagmus, dysmetria; leg vibration loss; extensor plantar responses; MRI: cerebellar atrophy
SCA25 (autosomal dominant)	2p15-p21	Ataxia, nystagmus; vibratory loss in the feet; pain loss in some; abdominal pain; nausea and vomiting may be prominent; absent ankle reflexes; sensory nerve action potentials are absent; MRI: cerebellar atrophy, normal brainstem
SCA26 (autosomal dominant)	19p13.3	Gait ataxia; extremity ataxia; dysarthria; nystagmus; MRI: cerebellar atrophy
SCA27 (autosomal dominant)	13q34; fibroblast growth factor 14 protein; mutation F145S; produces reduced protein stability	Tremor in extremities and head and orofacial dyskinesia; ataxia of arms > legs, gait ataxia; dysarthria; nystagmus; psychiatric symptoms; cognitive defect; MRI: cerebellar atrophy; genetic testing available
SCA28 (autosomal dominant)	18p11.22-q11.2; ATPase family gene 3- like 2 (AFG3L2 protein) mutations: N432T; S674L; E691K; A694E; R702Q	Extremity and gait ataxia; dysarthria; nystagmus; ophthalmoparesis; leg hyperreflexia and extensor plantar responses; MRI: cerebellar atrophy
SCA30 (autosomal dominant)	4q34.3-q35.1; candidate gene ODZ3	Candidate gene ODZ3; gait ataxia, dysarthria, saccades; nystagmus, brisk tendon reflexes in legs; MRI: cerebellar atrophy
SCA31 (autosomal dominant)	16q22.1; associated with NEDD4 (BEAN)	Pentanucleotide $(TGGAA)_n$ repeat insertions; previously called SCA4; gait ataxia; limb dysmetria; MRI: cerebellar atrophy
SCA32 (autosomal dominant)	7q32-q33	Ataxia, azoospermia, mental retardation; absent germ cells on testicular biopsy
SCA35 (autosomal dominant)	20p13;TGM6 protein; transglutaminase 6	Ataxia; ocular dysmetria; upper motor neuron signs; extensor plantars; onset fifth decade
SCA36 (autosomal dominant)	20p13; large intronic expansion of GGCCTG (1500–2500); also phe265leu mutation; RNA gain of function; microRNA; MIR 1292 suppression	Ataxia; onset fifth to sixth decades; motor neuron disorder; grouped atrophy (muscle biopsy) fasciculations; increased reflexes; flexor plantars
Prion disease (autosomal dominant)	20p13;pro102leu; ala 117 val mutations; proteinase k resistant form PrP27-30 accumulates in brain; eponym: Gerstmann-Straüssler-Scheinker disease Glu200Lys mutation; increased octapeptide repeats; eponym: Creutzfeldt-Jakob disease	Ataxia; dementia third to seventh decades Ataxia; dementia; rigidity
Multiple hamartoma syndrome (autosomal dominant)	10q23.31; phosphatase and tensin homolog (PTEN); Cowden's; Lhermitte-Duclos syndrome	Skin hamartomas; ataxia; mental retardation; increased intracranial pressure; epilepsy
Cerebellar ataxia, deafness, and narcolepsy (autosomal dominant)	19p13.2; exon 21; missense ala570val; val606phe mutations	Ataxia; deafness; narcolepsy cataplexy; REM sleep disorder
Cerebellar ataxia (nonprogressive) mental retardation (autosomal dominant)	1p36.31-p36.23	Ataxia, mental retardation
Familial dementia with amyloid angiopathy and spastic ataxia (autosomal dominant)	13q14.2; integral membrane protein 2B (ITM2B)	Ataxia; dementia; amyloid angiopathy
Dentatorubropalli-doluysian atrophy (autosomal dominant)	12p13.31 with CAG repeats (exonic) Atrophin 1	Ataxia, choreoathetosis, dystonia, seizures, myoclonus, dementia; genetic testing available

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA) (CONTINUED)

NAME	LOCUS	PHENOTYPE
Friedreich's ataxia (autosomal recessive)	9q13-q21.1 with intronic GAA repeats, in intron at end of exon 1 Frataxin defective; abnormal regulation of mitochondrial iron metabolism; iron accumulates in mitochondria in yeast mutants	Ataxia, areflexia, extensor plantar responses, position sense deficits, cardiomyopathy, diabetes mellitus, scoliosis, foot deformities; optic atrophy; late-onset form, as late as 50 years with preserved deep tendon reflexes, slower progression, reduced skeletal deformities, associated with an intermediate number of GAA repeats and missense mutations in one allele of frataxin; genetic testing available
Vitamin E deficiency syndrome (autosomal recessive)	8q13.1-q13.3 (α-TTP deficiency)	Same as phenotype that maps to 9q but associated with vitamin E deficiency; genetic testing available
Sensory ataxic neuropathy and ophthalmoparesis (SANDO) with dysarthria (autosomal recessive)	15q25; mutations in DNA polymerase-gamma (POLG) gene that leads to mtDNA deletions	Young adult–onset ataxia, sensory neuropathy, ophthalmoparesis, hearing loss, gastric symptoms; a variant of progressive external ophthalmoplegia; MRI: cerebellar and thalamic abnormalities; mildly increased lactate and creatine kinase
Von Hippel-Lindau syndrome (autosomal dominant)	3p26-p25	Cerebellar hemangioblastoma; pheochromocytoma
Baltic myoclonus (Unverricht-Lundborg) (recessive)	21q22.3; cystatin B; extra repeats of 12–base pair tandem repeats	Myoclonus epilepsy; late-onset ataxia; responds to valproic acid, clonazepam; phenobarbital
Marinesco-Sjögren syndrome (recessive)	5q31; SIL1 protein, nucleotide exchange factor for the heat-shock protein 70 (HSP70); chaperone HSPA5; homozygous 4-nucleotide duplication in exon 6; also compound heterozygote	Ataxia, dysarthria; nystagmus; retarded motor and mental maturation; rhabdomyolysis after viral illness; weakness; hypotonia; areflexia; cataracts in childhood; short stature; kyphoscoliosis; contractures; hypogonadism
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	Chromosome 13q12; SACS gene; loss of sacsin peptide activity	Childhood onset of ataxia, spasticity, dysarthria, distal muscle wasting, foot deformity, retinal striations, mitral valve prolapse
Kearns-Sayre syndrome (sporadic)	mtDNA deletion and duplication mutations	Ptosis, ophthalmoplegia, pigmentary retinal degeneration, cardiomyopathy, diabetes mellitus, deafness, heart block, increased CSF protein, ataxia
Myoclonic epilepsy and ragged red fiber syndrome (MERRF) (maternal inheritance)	Mutation in mtDNA of the $tRNA^{lys}$ at 8344; also mutation at 8356	Myoclonic epilepsy, ragged red fiber myopathy, ataxia
Mitochondrial encephalopathy, lactic acidosis, and stroke syndrome (MELAS) (maternal inheritance)	$tRNA^{leu}$ mutation at 3243; also at 3271 and 3252	Headache, stroke, lactic acidosis, ataxia
Neuropathy; ataxia; retinitis pigmentosa (NARP)	ATPase6 (Complex 5); mtDNA point mutation at 8993	Neuropathy; ataxia; retinitis pigmentosa; dementia; seizures
Episodic ataxia, type 1 (EA-1) (autosomal dominant)	12p13; potassium voltage-gated channel gene, KCNA1; Phe249Leu mutation; variable syndrome	Episodic ataxia for minutes; provoked by startle or exercise; with facial and hand myokymia; cerebellar signs are not progressive; choreoathetotic movements; responds to phenytoin; genetic testing available

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA) (CONTINUED)

NAME	LOCUS	PHENOTYPE
Episodic ataxia, type 2 (EA-2) (autosomal dominant)	19p-13 (CACNA1A) (allelic with SCA6) (α_{1A}-voltage–dependent calcium channel subunit); point mutations or small deletions; allelic with SCA6 and familial hemiplegic migraine	Episodic ataxia for days; provoked by stress, fatigue; with down-gaze nystagmus; vertigo; vomiting; headache; cerebellar atrophy results; progressive cerebellar signs; responds to acetazolamide; genetic testing available
Episodic ataxia, type 3 (autosomal dominant)	1q42	Episodic ataxia; 1 min to over 6 h; induced by movement; vertigo and tinnitus; headache; responds to acetazolamide
Episodic ataxia, type 4 (autosomal dominant)	Not mapped	Episodic ataxia; vertigo; diplopia; ocular slow pursuit defect; no response to acetazolamide
Episodic ataxia, type 5 (autosomal dominant)	2q22-q23; CACNB4β4 protein	Episodic ataxia; hours to weeks; seizures
Episodic ataxia type 6 with seizures, migraine, and alternating hemiplegia (autosomal dominant)	SLC1A3; 5p13; EAAT1 protein; missense mutations; glial glutamate transporter (GLAST); 1047 C to G; proline to arginine	Ataxia, duration 2–4 days; episodic hypotonia; delayed motor milestones; seizures; migraine; alternating hemiplegia; mild truncal ataxia; coma; febrile illness as a trigger; MRI: cerebellar atrophy
Episodic ataxia, type 7 (autosomal dominant)	19q13	Episodic ataxia; vertigo, weakness; less than 24 h
Episodic ataxia with paroxysmal choreoathetosis and spasticity (dystonia-9) (DYT9; CSE) (autosomal dominant)	1p	Ataxia; involuntary movements; dystonia; headache; spastic paraplegia; responds on occasion to acetazolamide
Fragile X tremor/ataxia syndrome (FXTAS) X-linked dominant	Xq27.3; CGG premutation expansion in FMR1 gene; expansions of 55–200 repeats in 5'UTR of the FMR-1 mRNA; presumed dominant toxic RNA effect	Late-onset ataxia with tremor, cognitive impairment, occasional parkinsonism; males typically affected, although affected females also reported; syndrome is of high concern if affected male has grandson with mental retardation (fragile X syndrome); MRI shows increased T2 signal in middle cerebellar peduncles, cerebellar atrophy, and occasional widespread brain atrophy; genetic testing available
Ataxia telangiectasia (autosomal recessive)	11q22-23; ATM gene for regulation of cell cycle; mitogenic signal transduction and meiotic recombination; elevated serum alpha-fetoprotein level; immunoglobulin deficiency	Telangiectasia, ataxia, dysarthria, pulmonary infections, neoplasms of lymphatic system; IgA and IgG deficiencies; diabetes mellitus, breast cancer; genetic testing available; chorea; dystonia
Early-onset cerebellar ataxia with retained deep tendon reflexes (autosomal recessive)	13q11-12	Ataxia; neuropathy; preserved deep tendon reflexes; impaired cognitive and visuospatial functions; MRI, cerebellar atrophy
Ataxia with oculomotor apraxia (AOA1) (autosomal recessive)	9p21; protein is member of histidine triad superfamily, role in DNA repair; elevation of serum LDL cholesterol and low serum albumin level; APTX, aprataxin	Ataxia; dysarthria; limb dysmetria; dystonia; oculomotor apraxia; optic atrophy; motor neuropathy; late sensory loss (vibration); genetic testing available
Ataxia with oculomotor apraxia 2 (AOA2) (autosomal recessive)	9q34; senataxin protein, involved in RNA maturation and termination; helicase superfamily 1; elevated serum alpha-fetoprotein level; SETX, senataxin	Gait ataxia; choreoathetosis; dystonia; oculomotor apraxia; neuropathy, vibration loss, position sense loss, and mild light touch loss; absent leg deep tendon reflexes; extensor plantar response; genetic testing available

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 38-1

CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA) (CONTINUED)

NAME	LOCUS	PHENOTYPE
Cerebellar ataxia with muscle coenzyme Q10 deficiency (autosomal recessive)	9p13	Ataxia; hypotonia; seizures; mental retardation; increased deep tendon reflexes; extensor plantar responses; coenzyme Q10 levels reduced with about 25% of patients with a block in transfer of electrons to complex 3; may respond to coenzyme 10
Refsum's disease (autosomal recessive)	10pter; elevated serum phytanic acid level; phytanoyl-COH hydroxylase and PEX7	Retinitis pigmentosa; ataxia; sensorineural deafness; demyelinating neuropathy
Cerebrotendinous xanthomatosis (autosomal recessive)	2p33; elevated cholesterol level; CYP27; sterol 27 hydroxylase	Spastic ataxia; mental retardation; dementia; tendon xanthomas; diarrhea; cataracts
Joubert's syndrome (autosomal recessive)	9q34.3	Ataxia; ptosis; mental retardation; oculomotor apraxia; nystagmus; retinopathy; rhythmic tongue protrusion; episodic hyperpnea or apnea; dimples at wrists and elbows; telecanthus; micrognathia
Sideroblastic anemia and spinocerebellar ataxia (X-linked recessive)	Xq13; ATP-binding cassette 7 (ABCB7; ABC7) transporter; mitochondrial inner membrane; iron homeostasis; export from matrix to the intermembrane space	Ataxia; elevated free erythrocyte protoporphyrin levels; ring sideroblasts in bone marrow; heterozygous females may have mild anemia but not ataxia
Infantile-onset spinocerebellar ataxia of Nikali et al (autosomal recessive)	10q23.3-q24.1; twinkle protein (gene); homozygous for Tyr508Cys missense mutations	Infantile ataxia, sensory neuropathy; athetosis, hearing deficit, reduced deep tendon reflexes; ophthalmoplegia, optic atrophy; seizures; primary hypogonadism in females
Hypoceruloplasminemia with ataxia and dysarthria (autosomal recessive)	Ceruloplasmin gene; 3q23-q25 (trp 858 ter)	Gait ataxia and dysarthria; hyperreflexia; cerebellar atrophy by MRI; iron deposition in cerebellum, basal ganglia, thalamus, and liver; onset in the fourth decade
Spinocerebellar ataxia with neuropathy (SCAN1) (autosomal recessive)	Tyrosyl-DNA phosphodiesterase-1 (TDP-1) 14q31-q32	Onset in second decade; gait ataxia, dysarthria, seizures, cerebellar vermis atrophy on MRI, dysmetria
Cerebellar ataxia type 1 (autosomal recessive)	6p25 SCAR8; SYNE1; spectrin repeats-nuclear envelope 1	Pure ataxia
Cerebellar ataxia type 2 (autosomal recessive)	1q42;ADCK3 (CABC1); aarf-domain containing kinase 3; elevation of serum lactate and decreased coenzyme Q10 level	Ataxia; mental retardation; myoclonus; epilepsy; exercise intolerance; stroke or transient ischemic-like episodes
Niemann-Pick type C disease	18q11; NPCI; NPCH1 and 2; skin biopsy (filipin staining)	Ataxia; vertical supranuclear ophthalmoplegia; splenomegaly; dystonia; impaired cognition

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyogram; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; REM, rapid eye movement; UTR, untranslated region.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 39

AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES

Robert H. Brown, Jr.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the most common form of progressive motor neuron disease. It is a prime example of a neurodegenerative disease and is arguably the most devastating of the neurodegenerative disorders.

PATHOLOGY

The pathologic hallmark of motor neuron degenerative disorders is death of lower motor neurons (consisting of anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles) and upper, or corticospinal, motor neurons (originating in layer five of the motor cortex and descending via the pyramidal tract to synapse with lower motor neurons, either directly or indirectly via interneurons) **(Chap. 14)**. Although at its onset ALS may involve selective loss of function of only upper or lower motor neurons, it ultimately causes progressive loss of both categories of motor neurons. Indeed, in the absence of clear involvement of both motor neuron types, the diagnosis of ALS is questionable. In a subset of cases, ALS arises concurrently with frontotemporal dementia **(Chap. 35)**; in these instances, there is degeneration of frontotemporal cortical neurons and corresponding cortical atrophy.

Other motor neuron diseases involve only particular subsets of motor neurons **(Tables 39-1 and 39-2)**. Thus, in bulbar palsy and spinal muscular atrophy (SMA; also called progressive muscular atrophy), the lower motor neurons of brainstem and spinal cord, respectively, are most severely involved. By contrast, pseudobulbar palsy, primary lateral sclerosis (PLS), and familial spastic paraplegia (FSP) affect only upper motor neurons innervating the brainstem and spinal cord.

In each of these diseases, the affected motor neurons undergo shrinkage, often with accumulation of the pigmented lipid (lipofuscin) that normally develops in these cells with advancing age. In ALS, the motor neuron cytoskeleton is typically affected early in the illness. Focal enlargements are frequent in proximal motor axons; ultrastructurally, these "spheroids" are composed of accumulations of neurofilaments and other proteins. Commonly in both sporadic and familial ALS, the affected neurons demonstrate ubiquitin-positive aggregates, typically associated with the protein TDP43 (see below). Also seen is proliferation of astroglia and microglia, the inevitable accompaniment of all degenerative processes in the central nervous system (CNS).

The death of the peripheral motor neurons in the brainstem and spinal cord leads to denervation and consequent atrophy of the corresponding muscle fibers. Histochemical and electrophysiologic evidence indicates that in the early phases of the illness denervated muscle can be reinnervated by sprouting of nearby distal motor nerve terminals, although reinnervation in this disease is considerably less extensive than in most other disorders affecting motor neurons (e.g., poliomyelitis, peripheral neuropathy). As denervation progresses, muscle atrophy is readily recognized in muscle biopsies and on clinical examination. This is the basis for the term amyotrophy. The loss of cortical motor neurons results in thinning of the corticospinal tracts that travel via the internal capsule **(Fig. 39-1)** and brainstem to the lateral and anterior white matter columns of the spinal cord. The loss of fibers in the lateral columns and resulting fibrillary gliosis impart a particular firmness (lateral sclerosis). A remarkable feature of the disease is the selectivity of neuronal cell death. By light microscopy, the entire sensory apparatus, the regulatory mechanisms for the control and coordination of movement, remains intact. Except in

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 39-1

ETIOLOGY OF MOTOR NEURON DISORDERS

DIAGNOSTIC CATEGORY	INVESTIGATION
Structural lesions Parasagittal or foramen magnum tumors Cervical spondylosis Chiari malformation of syrinx Spinal cord arteriovenous malformation	MRI scan of head (including foramen magnum and cervical spine)
Infections Bacterial—tetanus, Lyme Viral—poliomyelitis, herpes zoster Retroviral—myelopathy	CSF exam, culture Lyme titer Anti-viral antibody HTLV-1 titers
Intoxications, physical agents Toxins—lead, aluminum, others Drugs—strychnine, phenytoin Electric short, x-irradiation	24-h urine for heavy metals Serum lead level
Immunologic mechanisms Plasma cell dyscrasias Autoimmune polyradiculopathy Motor neuropathy with conduction block Paraneoplastic Paracarcinomatous	Complete blood count[a] Sedimentation rate[a] Total protein[a] Anti-GM1 antibodies[a] Anti-Hu antibody MRI scan, bone marrow biopsy
Metabolic Hypoglycemia Hyperparathyroidism Hyperthyroidism Deficiency of folate, vitamin B_{12}, vitamin E Malabsorption Deficiency of copper, zinc Mitochondrial dysfunction	Fasting blood sugar[a] Routine chemistries including calcium[a] PTH Thyroid function[a] Vitamin B_{12}, vitamin E, folate[a] Serum zinc, copper[a] 24-h stool fat, carotene, prothrombin time Fasting lactate, pyruvate, ammonia Consider mtDNA
Hyperlipidemia	Lipid electrophoresis
Hyperglycinuria	Urine and serum amino acids CSF amino acids
Hereditary disorders Superoxide dismutase TDP43 FUS/TLS Androgen receptor defect (Kennedy's disease) Hexosaminidase deficiency Infantile a-glucosidase deficiency (Pompe's disease)	WBC DNA for mutational analysis

[a]Should be obtained in all cases.

Abbreviations: CSF, cerebrospinal fluid; FUS/TLS, fused in sarcoma/translocated in liposarcoma; HTLV-1, human T-cell lymphotropic virus; MRI, magnetic resonance imaging; PTH, parathyroid; WBC, white blood cell.

cases of frontotemporal dementia, the components of the brain required for cognitive processing are also preserved. However, immunostaining indicates that neurons bearing ubiquitin, a marker for degeneration, are also detected in nonmotor systems. Moreover, studies of glucose metabolism in the illness also indicate that there is neuronal dysfunction outside of the motor system. Within the motor system, there is some selectivity of involvement. Thus, motor neurons required for ocular motility remain unaffected, as do the parasympathetic neurons in the sacral spinal cord (the nucleus of Onufrowicz, or Onuf) that innervate the sphincters of the bowel and bladder.

CLINICAL MANIFESTATIONS

The manifestations of ALS are somewhat variable depending on whether corticospinal neurons or lower motor neurons in the brainstem and spinal cord are more prominently involved. With lower motor neuron

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 39-2

SPORADIC MOTOR NEURON DISEASES	
Chronic	**Entity**
Upper and lower motor neuron	Amyotrophic lateral sclerosis
Predominantly upper motor neuron	Primary lateral sclerosis
Predominantly lower motor neuron	Multifocal motor neuropathy with conduction block Motor neuropathy with paraproteinemia or cancer Motor predominant peripheral neuropathies
Other	
Associated with other neurodegenerative disorders	
Secondary motor neuron disorders (see Table 39-1)	
Acute	
Poliomyelitis Herpes zoster Coxsackie virus West Nile virus	

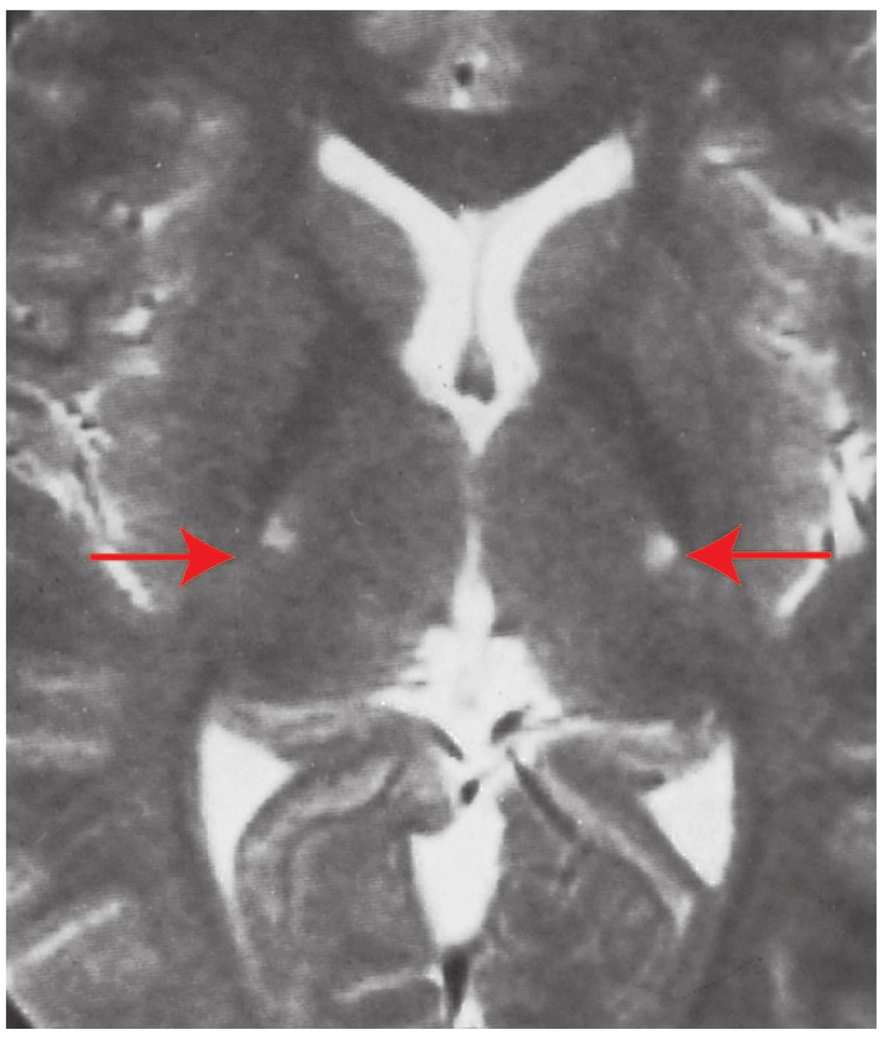


FIGURE 39-1
Amyotrophic lateral sclerosis. Axial T2-weighted magnetic resonance imaging (MRI) scan through the lateral ventricles of the brain reveals abnormal high signal intensity within the corticospinal tracts (arrows). This MRI feature represents an increase in water content in myelin tracts undergoing Wallerian degeneration secondary to cortical motor neuronal loss. This finding is commonly present in ALS, but can also be seen in AIDS-related encephalopathy, infarction, or other disease processes that produce corticospinal neuronal loss in a symmetric fashion.

dysfunction and early denervation, typically the first evidence of the disease is insidiously developing asymmetric weakness, usually first evident distally in one of the limbs. A detailed history often discloses recent development of cramping with volitional movements, typically in the early hours of the morning (e.g., while stretching in bed). Weakness caused by denervation is associated with progressive wasting and atrophy of muscles and, particularly early in the illness, spontaneous twitching of motor units, or fasciculations. In the hands, a preponderance of extensor over flexor weakness is common. When the initial denervation involves bulbar rather than limb muscles, the problem at onset is difficulty with chewing, swallowing, and movements of the face and tongue. Early involvement of the muscles of respiration may lead to death before the disease is far advanced elsewhere. With prominent corticospinal involvement, there is hyperactivity of the muscle-stretch reflexes (tendon jerks) and, often, spastic resistance to passive movements of the affected limbs. Patients with significant reflex hyperactivity complain of muscle stiffness often out of proportion to weakness. Degeneration of the corticobulbar projections innervating the brainstem results in dysarthria and exaggeration of the motor expressions of emotion. The latter leads to involuntary excess in weeping or laughing (pseudobulbar affect).

Virtually any muscle group may be the first to show signs of disease, but, as time passes, more and more muscles become involved until ultimately the disorder takes on a symmetric distribution in all regions. It is characteristic of ALS that, regardless of whether the initial disease involves upper or lower motor neurons, both will eventually be implicated. Even in the late stages of the illness, sensory, bowel and bladder, and cognitive functions are preserved. Even when there is severe brainstem disease, ocular motility is spared until the very late stages of the illness. As noted, in some cases (particularly those that are familial), ALS develops concurrently with frontotemporal dementia, characterized by early behavioral abnormalities with prominent behavioral features indicative of frontal lobe dysfunction.

A committee of the World Federation of Neurology has established diagnostic guidelines for ALS. Essential for the diagnosis is simultaneous upper and lower motor neuron involvement with progressive weakness and the exclusion of all alternative diagnoses. The disorder is ranked as "definite" ALS when three or four of the following are involved: bulbar, cervical, thoracic, and lumbosacral motor neurons. When two sites are involved, the diagnosis is "probable," and when only one site is implicated, the diagnosis is "possible." An exception is made for those who have progressive upper and lower motor neuron signs at only one site and a mutation in the gene encoding superoxide dismutase (SOD1; see below).

www.ketabpezeshki.com (021) 66485457 - 66485438

EPIDEMIOLOGY

T e illness is relentlessly progressive, leading to death from respiratory paralysis; the median survival is from 3–5 years. T ere are very rare reports of stabilization or even regression of ALS. In most societies, there is an incidence of 1–3 per 100,000 and a prevalence of 3–5 per 100,000. It is striking that about 1 in 1000 adult deaths in North America and Western Europe (and probably elsewhere) are due to ALS; this finding predicts that some 300,000 individuals now alive in the United States will die of ALS. Several endemic foci of higher prevalence exist in the western Pacific (e.g., in specific regions of Guam or Papua New Guinea). In the United States and Europe, males are somewhat more frequently affected than females. Epidemiologic studies have incriminated risk factors for this disease including exposure to pesticides and insecticides, smoking, and, in one report, service in the military. Although ALS is overwhelmingly a sporadic disorder, some 5–10% of cases are inherited as an autosomal dominant trait.

FAMILIAL ALS

Several forms of selective motor neuron disease are inheritable **(Table 39-3)**. Familial ALS (FALS) involves both corticospinal and lower motor neurons. Apart from its inheritance as an autosomal dominant trait, it is clinically indistinguishable from sporadic ALS. Genetic studies have identified mutations in multiple genes, including those encoding the protein C9orf 72 (open reading frame 72 on chromosome 9), cytosolic enzyme SOD1 (superoxide dismutase), the RNA binding proteins TDP43 (encoded by the TAR DNA binding protein gene), and FUS/TLS (fused in sarcoma/translocated in liposarcoma), as the most common causes of FALS. Mutations in C9orf72 account for ~45–50% of FALS and perhaps 4–5% of sporadic ALS cases. Mutations in SOD1 explain another 20% of cases of FALS, whereas TDP43 and FUS/TLS each represent about 5% of familial cases. It has recently been reported that ~1–2% of cases are caused by mutations in genes encoding the proteins optineuron and profilin-1 as well.

Rare mutations in other genes are also clearly implicated in ALS-like diseases. T us, a familial, dominantly inherited motor disorder that in some individuals closely mimics the ALS phenotype arises from mutations in a gene that encodes a vesicle-binding protein. A predominantly lower motor neuron disease with early hoarseness due to laryngeal dysfunction has been ascribed to mutations in the gene encoding the cellular accessory motor protein dynactin. Mutations in senataxin, a helicase, cause an early adult-onset, slowly evolving ALS variant. Kennedy's syndrome is an X-linked, adult-onset disorder that may mimic ALS, as described below.

Genetic analyses are also beginning to illuminate the pathogenesis of some childhood-onset motor neuron diseases. For example, a slowly disabling degenerative, predominantly upper motor neuron disease that starts in the first decade is caused by mutations in a gene that expresses a novel signaling molecule with properties of a guanine-exchange factor, termed alsin.

DIFFERENTIAL DIAGNOSIS

Because ALS is currently untreatable, it is imperative that potentially remediable causes of motor neuron dysfunction be excluded (Table 39-1). T is is particularly true in cases that are atypical by virtue of (1) restriction to either upper or lower motor neurons, (2) involvement of neurons other than motor neurons, and (3) evidence of motor neuronal conduction block on electrophysiologic testing. Compression of the cervical spinal cord or cervicomedullary junction from tumors in the cervical regions or at the foramen magnum or from cervical spondylosis with osteophytes projecting into the vertebral canal can produce weakness, wasting, and fasciculations in the upper limbs and spasticity in the legs, closely resembling ALS. T e absence of cranial nerve involvement may be helpful in differentiation, although some foramen magnum lesions may compress the twelfth cranial (hypoglossal) nerve, with resulting paralysis of the tongue. Absence of pain or of sensory changes, normal bowel and bladder function, normal roentgenographic studies of the spine, and normal cerebrospinal f uid (CSF) all favor ALS. Where doubt exists, magnetic resonance imaging (MRI) scans and contrast myelography should be performed to visualize the cervical spinal cord.

Another important entity in the differential diagnosis of ALS is multifocal motor neuropathy with conduction block (MMCB), discussed below. A diffuse, lower motor axonal neuropathy mimicking ALS sometimes evolves in association with hematopoietic disorders such as lymphoma or multiple myeloma. In this clinical setting, the presence of an M-component in serum should prompt consideration of a bone marrow biopsy. Lyme disease may also cause an axonal, lower motor neuropathy, although typically with intense proximal limb pain and a CSF pleocytosis.

Other treatable disorders that occasionally mimic ALS are chronic lead poisoning and thyrotoxicosis. T ese disorders may be suggested by the patient's social or occupational history or by unusual clinical features. When the family history is positive, disorders involving the genes encoding C9orf72, cytosolic SOD1, TDP43, FUS/TLS, and adult hexosaminidase A or α-glucosidase deficiency must be excluded. T ese are readily identified by appropriate laboratory tests. Benign fasciculations are occasionally a source of

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 39-3

GENETIC MOTOR NEURON DISEASES

DISEASE	LOCUS	GENE	INHERITANCE	USUAL ONSET	GENE FUNCTION	UNUSUAL FEATURES
I. Upper and Lower Motor Neurons (Familial ALS)						
ALS1	21q	Superoxide dismutase	AD	Adult	Protein antioxidant	
ALS2	2q	Alsin	AR	Juvenile	GEF signaling	Severe corticobulbar, corticospinal features
ALS4	9q	Senataxin	AD	Late juvenile	DNA helicase	Late childhood onset
ALS6	16p	FUS/TLS	AD	Adult	DNA, RNA binding	
ALS8	20q	Vesicle associated protein B	AD	Adult	Vesicular trafficking	
ALS9	14q	Angiogenin	AD	Adult	RNAse, angiogenesis	
ALS10	1q	TDP43	AD	Adult	DNA, RNA binding	
ALS12	10p	Optineurin	AD/AR	Adult	Attenuates NF-κB	
ALS13	12q	Ataxin-2	AD	Adult	Cytotoxic expanded CAG repeat	
ALS14	9p	Valosin-containing protein	AD	Adult	ATPase	
ALS18	17p	Profilin-1	AD	Adult	Involved in actin polymerization	
ALS19	2q	ErbB4	AD	Adult	Signaling molecule	
ALS20	12q	HNRNPA1	AD	Adult	Heteronuclear RNA binding protein	
ALS21	5q	MTR3	AD	Adult	Nuclear matrix protein	Early vocal/bulbar involvement
ALS	2p	Dynactin	AD	Adult	Axonal transport	
ALS	17q	Paraoxonases 1-3	AD	Adult	Detoxify intoxicants	
ALS	mtDNA	Cytochrome c oxidase		Adult	ATP generation	
ALS	mtDNA	tRNA-isoleucine		Adult	ATP generation	
II. Lower Motor Neurons						
Spinal muscular atrophies	5q	Survival motor neuron	AR	Infancy	RNA metabolism	
GM2-gangliosidosis						
1. Sandhof 's disease	5q	Hexosaminidase B	AR	Childhood	Ganglioside recycling	

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 39-3

GENETIC MOTOR NEURON DISEASES (CONTINUED)

DISEASE	LOCUS	GENE	INHERITANCE	USUAL ONSET	GENE FUNCTION	UNUSUAL FEATURES
2. AB variant	5q	GM2-activator protein	AR	Childhood	Ganglioside recycling	
3. Adult Tay-Sachs disease	15q	Hexosaminidase A	AR	Childhood	Ganglioside recycling	
X-linked spinobulbar muscular atrophy	Xq	Androgen receptor	XR	Adult	Nuclear signaling	
III. Upper Motor Neuron (Selected FSPs)						
SPG3A	14q	Atlastin	AD	Childhood	GTPase—vesicle recycling	
SPG4	2p	Spastin	AD	Early adulthood	ATPase family—microtubule associate	Some sensory loss
SPG6	15q	NIPA1	AD	Early adulthood	Membrane transporter or receptor	Deleted in Prader-Willi, Angelman's
SPG8	8q	Strumpellin	AD	Early adulthood	Ubiquitous, spectrin-like	
SPG10	12q	Kinesin heavy chain KIF5A	AD	Second–third decade	Motor-associated protein	± Peripheral neuropathy, retardation
SPG12	19q	Reticulon 2	AD	Childhood	ER protein, interacts with spastin	
SPG13	2q	Heat shock protein 60	AD	Early adulthood	Chaperone protein	
SPG17	11q	Silver (BSCL2)	AD	Variable	Membrane protein in ER	Amyotrophy hands, feet
SPG31	2p	REEP1	AD	Early	Mitochondrial protein	Rarely, amyotrophy
SPG33	10q	ZFYVE27	AD	Adult	Interacts with spastin	Pes equinus
SPG42	3q	Acetyl-CoA-transporter	AD	Variable	Solute carrier	
SPG72	5q	REEP2	AD	Childhood	ER protein	
SPG5	8q	Cytochrome P450	AR	Variable	Degrades endogenous substances	Sensory loss
SPG7	16q	Paraplegin	AR	Variable	Mitochondrial protein	Rarely, optic atrophy, ataxia
SPG11	15q	Spatacsin	AR	Childhood	Cytosolic, ? membrane-associated	Some sensory loss, thin corpus callosum
SPG15	14q	Spastizin	AR	Childhood	Zinc finger protein	Some amyotrophy, some CNS features
SPG20	13q	Spartin	AR	Childhood	Endosomal trafficking protein	

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 39-3

GENETIC MOTOR NEURON DISEASES (CONTINUED)

DISEASE	LOCUS	GENE	INHERITANCE	USUAL ONSET	GENE FUNCTION	UNUSUAL FEATURES
SPG21	15q	Maspardin	AR	Childhood	Endosomal trafficking protein	
SPG35	16q	Fatty acid 2 hydrolase	AR	Childhood	Membrane protein	Multiple CNS features
SPG39	19p	Neuropathy target esterase	AR	Early childhood	Esterase	
SPG44	1q	Connexin 47	AR	Childhood	Gap junction protein	Possible mild CNS features
SPG46	9p	β-Glucosidase 2	AR	Childhood	Glycoside hydrolase	Thin corpus callosum, mental retardation
SPG2	Xq	Proteolipid protein	XR	Early childhood	Myelin protein	Sometimes multiple CNS features
SPG1	Xq	L1-CAM	XR	Infancy	Cell adhesion molecule	
SPG22	Xq	SLC16A2	XR	Infancy	Monocarboxylic acid transporter	
	Xq	Adrenoleukodystrophy	XR	Early adulthood	ATP binding transporter protein	Possible adrenal insufficiency, CNS inflammation
IV. ALS-Plus Syndromes						
ALS with frontotemporal dementia, Parkinson's disease	9p	C9orf72				
Amyotrophy with behavioral disorders	17q	Tau protein				
Parkinsonism						

Abbreviation: ALS, amyotrophic lateral sclerosis; BSCL2, Bernadelli-Seip congenital lipodystrophy 2B; AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; FSP, familial spastic paraplegia; FUS/TLS, fused in sarcoma/translocated in liposarcoma; TDP43, Tar DNA binding protein 43 kd; XR, X-linked recessive.

concern because on inspection they resemble the fasciculations that accompany motor neuron degeneration. The absence of weakness, atrophy, or denervation phenomena on electrophysiologic examination usually excludes ALS or other serious neurologic disease. Patients who have recovered from poliomyelitis may experience a delayed deterioration of motor neurons that presents clinically with progressive weakness, atrophy, and fasciculations. Its cause is unknown, but it is thought to reflect sublethal prior injury to motor neurons by poliovirus.

Rarely, ALS develops concurrently with features indicative of more widespread neurodegeneration. Thus, one infrequently encounters otherwise typical ALS patients with a parkinsonian movement disorder or frontotemporal dementia, particularly in instances of C9orf72 mutations, which strongly suggests that the simultaneous occurrence of two disorders is a direct consequence of the gene mutation. As another example, prominent amyotrophy has been described as a dominantly inherited disorder in individuals with bizarre behavior and a movement disorder suggestive of parkinsonism; many such cases have now been ascribed to mutations that alter the expression of tau protein in brain **(Chap. 35)**. In other cases, ALS develops simultaneously with a striking frontotemporal dementia. An

www.ketabpezeshki.com (021) 66485457 - 66485438

ALS-like disorder has also been described in some individuals with chronic traumatic encephalopathy, associated with deposition of TDP43 and neurofibrillary tangles in motor neurons.

PATHOGENESIS

T e cause of sporadic ALS is not well defined. Several mechanisms that impair motor neuron viability have been elucidated in mice and rats induced to develop motor neuron disease by SOD1 transgenes with ALS-associated mutations. One may loosely group the genetic causes of ALS into three categories. In one group, the primarily problem is inherent instability of the mutant proteins, with subsequent perturbations in protein degradation (SOD1, ubiquilin-1 and -2, p62). In the second, most rapidly growing category, the causative mutant genes perturb RNA processing, transport, and metabolism (C9orf73, TDP43, FUS). In the case of C9orf72, the molecular pathology is an expansion of an intronic hexanucleotide repeat (-GGGGCC-) beyond an upper normal of 30 repeats to hundreds or more repeats. As observed in other intronic repeat disorders such as myotonic dystrophy **(Chap. 56)** and spinocerebellar atrophy type 8 **(Chap. 37)**, data suggest that the expanded intronic repeats generate expanded RNA repeats that form intranuclear foci and confer toxicity by sequestering transcription factors or by undergoing noncanonical protein translation across all possible reading frames of the expanded RNA tracts. TDP43 and FUS are multifunctional proteins that bind RNA and DNA and shuttle between the nucleus and the cytoplasm, playing multiple roles in the control of cell proliferation, DNA repair and transcription, and gene translation, both in the cytoplasm and locally in dendritic spines in response to electrical activity. How mutations in FUS/TLS provoke motor neuron cell death is not clear, although this may represent loss of function of FUS/TLS in the nucleus or an acquired, toxic function of the mutant proteins in the cytosol. In the third group of ALS genes, the primary problem is defective axonal cytoskeleton and transport (dynactin, profilin-1). It is striking that variants in other genes (e.g., EphA4) inf uence survival in ALS but not ALS susceptibility. Beyond the upstream, primary defects, it is also evident that the ultimate neuronal cell death process is complex involving multiple cellular processes that accelerate cell death. T ese include but are not limited to excitotoxicity, impairment of axonal transport, oxidative stress, activation of endoplasmic reticulum stress and the unfolded protein response, and mitochondrial dysfunction.

Multiple recent studies have convincingly demonstrated that nonneuronal cells importantly inf uence the disease course, at least in ALS transgenic mice. A striking additional finding in neurodegenerative disorders is that miscreant proteins arising from gene defects in familial forms of these diseases are often implicated in sporadic forms of the same disorder. For example, germline mutations in the genes encoding β-amyloid and α-synuclein cause familial forms of Alzheimer's and Parkinson's diseases, and posttranslational, noninherited abnormalities in these proteins are also central to sporadic Alzheimer's and Parkinson's diseases. Analogously, recent reports propose that nonheritable, posttranslational modifications in SOD1 are pathogenic in sporadic ALS.

TREATMENT Amyotrophic Lateral Sclerosis

No treatment arrests the underlying pathologic process in ALS. T e drug riluzole (100 mg/d) was approved for ALS because it produces a modest lengthening of survival. In one trial, the survival rate at 18 months with riluzole was similar to placebo at 15 months. T e mechanism of this effect is not known with certainty; riluzole may reduce excitotoxicity by diminishing glutamate release. Riluzole is generally well tolerated; nausea, dizziness, weight loss, and elevated liver enzymes occur occasionally. Pathophysiologic studies of mutant SOD1–related ALS in mice have disclosed diverse targets for therapy; consequently, multiple therapies are presently in clinical trials for ALS including experimental trials of small molecules, mesenchymal stem cells, and immunosuppression. Interventions such as antisense oligonucleotides (ASO) that diminish expression of mutant SOD1 protein prolong survival in transgenic ALS mice and rats and are also nearing trial now for SOD1-mediated ALS.

In the absence of a primary therapy for ALS, a variety of rehabilitative aids may substantially assist ALS patients. Footdrop splints facilitate ambulation by obviating the need for excessive hip f exion and by preventing tripping on a f oppy foot. Finger extension splints can potentiate grip. Respiratory support may be life-sustaining. For patients electing against long-term ventilation by tracheostomy, positive-pressure ventilation by mouth or nose provides transient (several weeks) relief from hypercarbia and hypoxia. Also extremely beneficial for some patients is a respiratory device (Cough Assist Device) that produces an artificial cough. T is is highly effective in clearing airways and preventing aspiration pneumonia. When bulbar disease prevents normal chewing and swallowing, gastrostomy is uniformly helpful, restoring normal nutrition and hydration. Fortunately, an increasing variety of speech synthesizers are now available to augment speech when there is advanced bulbar palsy. T ese facilitate oral communication and may be effective for telephone use.

In contrast to ALS, several of the disorders (Tables 39-1 and 39-3) that bear some clinical resemblance to ALS are treatable. For this reason, a careful search for causes of secondary motor neuron disease is warranted.

www.ketabpezeshki.com (021) 66485457 - 66485438

OTHER MOTOR NEURON DISEASES

SELECTED LOWER MOTOR NEURON DISORDERS

In these motor neuron diseases, the peripheral motor neurons are affected without evidence of involvement of the corticospinal motor system (Tables 39-1, 39-2, and 39-3).

X-linked spinobulbar muscular atrophy (Kennedy's disease)

T is is an X-linked lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in mid-adult life and is conjoined with androgen insensitivity manifested by gynecomastia and reduced fertility. In addition to gynecomastia, which may be subtle, two findings distinguishing this disorder from ALS are the absence of signs of pyramidal tract disease (spasticity) and the presence of a subtle sensory neuropathy in some patients. T e underlying molecular defect is an expanded trinucleotide repeat (-CAG-) in the first exon of the androgen receptor gene on the X chromosome. DNA testing is available. An inverse correlation appears to exist between the number of -CAG- repeats and the age of onset of the disease.

Adult Tay-Sachs disease

Several reports have described adult-onset, predominantly lower motor neuropathies arising from deficiency of the enzyme β-hexosaminidase (hex A). T ese tend to be distinguishable from ALS because they are very slowly progressive; dysarthria and radiographically evident cerebellar atrophy may be prominent. In rare cases, spasticity may also be present, although it is generally absent.

Spinal muscular atrophy

T e SMAs are a family of selective lower motor neuron diseases of early onset. Despite some phenotypic variability (largely in age of onset), the defect in the majority of families with SMA maps to a locus on chromosome 5 encoding a putative motor neuron survival protein (SMN, for survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clinical forms exist.

Infantile SMA (SMA I, Werdnig-Hoffmann disease) has the earliest onset and most rapidly fatal course. In some instances it is apparent even before birth, as indicated by decreased fetal movements late in the third trimester. T ough alert, afflicted infants are weak and floppy (hypotonic) and lack muscle stretch reflexes. Death generally ensues within the first year of life. Chronic childhood SMA (SMA II) begins later in childhood and evolves with a more slowly progressive course. Juvenile SMA (SMA III, Kugelberg-Welander disease) manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder, weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes. T ere is no primary therapy for SMA, although remarkable recent experimental data indicate that it may be possible to deliver the missing SMN gene to motor neurons using intravenously or intrathecally delivered adeno-associated viruses (e.g., AAV9) immediately af er birth.

Multifocal motor neuropathy with conduction block

In this disorder lower motor neuron function is regionally and chronically disrupted by remarkably focal blocks in conduction. Many cases have elevated serum titers of mono- and polyclonal antibodies to ganglioside GM1; it is hypothesized that the antibodies produce selective, focal, paranodal demyelination of motor neurons. MMCB is not typically associated with corticospinal signs. In contrast with ALS, MMCB may respond dramatically to therapy such as IV immunoglobulin or chemotherapy; thus, it is imperative that MMCB be excluded when considering a diagnosis of ALS.

Other forms of lower motor neuron disease

In individual families, other syndromes characterized by selective lower motor neuron dysfunction in an SMA-like pattern have been described. T ere are rare X-linked and autosomal dominant forms of apparent SMA. T ere is an ALS variant of juvenile onset, the Fazio-Londe syndrome, that involves mainly the musculature innervated by the brainstem. A component of lower motor neuron dysfunction is also found in degenerative disorders such as Machado-Joseph disease and the related olivopontocerebellar degenerations **(Chap. 37)**.

SELECTED DISORDERS OF THE UPPER MOTOR NEURON

Primary lateral sclerosis

T is exceedingly rare disorder arises sporadically in adults in mid to late life. Clinically PLS is characterized by progressive spastic weakness of the limbs, preceded or followed by spastic dysarthria and dysphagia,

www.ketabpezeshki.com (021) 66485457 - 66485438

indicating combined involvement of the corticospinal and corticobulbar tracts. Fasciculations, amyotrophy, and sensory changes are absent; neither electromyography nor muscle biopsy shows denervation. On neuropathologic examination, there is selective loss of the large pyramidal cells in the precentral gyrus and degeneration of the corticospinal and corticobulbar projections. The peripheral motor neurons and other neuronal systems are spared. The course of PLS is variable; although long-term survival is documented, the course may be as aggressive as in ALS, with ~3-year survival from onset to death. Early in its course, PLS raises the question of multiple sclerosis or other demyelinating diseases such as adrenoleukodystrophy as diagnostic considerations **(Chap. 45)**. A myelopathy suggestive of PLS is infrequently seen with infection with the retrovirus human T cell lymphotropic virus 1 (HTLV-1) **(Chap. 43)**. The clinical course and laboratory testing will distinguish these possibilities.

Familial spastic paraplegia

In its pure form, FSP is usually transmitted as an autosomal trait; most adult-onset cases are dominantly inherited. Symptoms usually begin in the third or fourth decade, presenting as progressive spastic weakness beginning in the distal lower extremities; however, there are variants with onset so early that the differential diagnosis includes cerebral palsy. FSP typically has a long survival, presumably because respiratory function is spared. Late in the illness, there may be urinary urgency and incontinence and sometimes fecal incontinence; sexual function tends to be preserved.

In pure forms of FSP, the spastic leg weakness is often accompanied by posterior column (vibration and position) abnormalities and disturbance of bowel and bladder function. Some family members may have spasticity without clinical symptoms.

By contrast, particularly when recessively inherited, FSP may have complex or complicated forms in which altered corticospinal and dorsal column function is accompanied by significant involvement of other regions of the nervous system, including amyotrophy, mental retardation, optic atrophy, and sensory neuropathy.

Neuropathologically, in FSP, there is degeneration of the corticospinal tracts, which appear nearly normal in the brainstem but show increasing atrophy at more caudal levels in the spinal cord; in effect, the pathologic picture is of a dying-back or distal axonopathy of long neuronal fibers within the CNS.

Defects at numerous loci underlie both dominantly and recessively inherited forms of FSP (Table 39-3). More than 30 FSP genes have now been identified. The gene most commonly implicated in dominantly inherited FSP is spastin, which encodes a microtubule interacting protein. The most common childhood-onset dominant form arises from mutations in the atlastin gene. A kinesin heavy-chain protein implicated in microtubule motor function was found to be defective in a family with dominantly inherited FSP of variable-onset age.

An infantile-onset form of X-linked, recessive FSP arises from mutations in the gene for myelin proteolipid protein. This is an example of rather striking allelic variation, as most other mutations in the same gene cause not FSP but Pelizaeus-Merzbacher disease, a widespread disorder of CNS myelin. Another recessive variant is caused by defects in the paraplegin gene. Paraplegin has homology to metalloproteases that are important in mitochondrial function in yeast.

WEBSITES

Several websites provide valuable information on ALS including those offered by the Muscular Dystrophy Association (www.mdausa.org), the Amyotrophic Lateral Sclerosis Association (www.alsa.org), and the World Federation of Neurology and the Neuromuscular Unit at Washington University in St. Louis (www.neuro.wustl.edu).

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 40

PRION DISEASES

Stanley B. Prusiner ■ Bruce L. Miller

Prions are proteins that adopt an alternative conformation, which becomes self-propagating. Some prions cause degeneration of the central nervous system (CNS). Once relegated to causing a group of rare disorders of the CNS such as Creutzfeldt-Jakob disease (CJD), prions—as mounting evidence shows—also appear to play a key role in more common illnesses such as Alzheimer's disease (AD) and Parkinson's disease (PD). While CJD is caused by the accumulation of PrP^{Sc}, increasing data argue that Aβ prions cause AD, α-synuclein prions cause PD, and tau prions cause the frontotemporal dementias (FTDs). In this chapter, we confine our discussion to CJD, which typically presents with a rapidly progressive dementia as well as motor abnormalities. T e illness is relentlessly progressive and generally causes death within 9 months of onset. Most CJD patients are between 50 and 75 years of age; however, patients as young as 17 and as old as 83 have been recorded.

CJD is one malady in a group of disorders caused by prions composed of the prion protein (PrP). PrP prions reproduce by binding to the normal, cellular isoform of the prion protein (PrP^{C}) and stimulating conversion of PrP^{C} into the disease-causing isoform PrP^{Sc}. PrP^{C} is rich in α-helix and has little β-structure, whereas PrP^{Sc} has less α-helix and a high amount of β-structure **(Fig. 40-1)**. T is α-to-β structural transition in PrP is the fundamental event underlying this group of prion diseases **(Table 40-1)**.

Four new concepts have emerged from studies of prions: (1) Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may be manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. (3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^{C}. (4) Distinct strains of prions exhibit different biologic properties, which are epigenetically inherited. In other words, PrP^{Sc} can exist in a variety of different conformations, many of which seem to specify particular disease phenotypes.

How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^{C} during prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited.

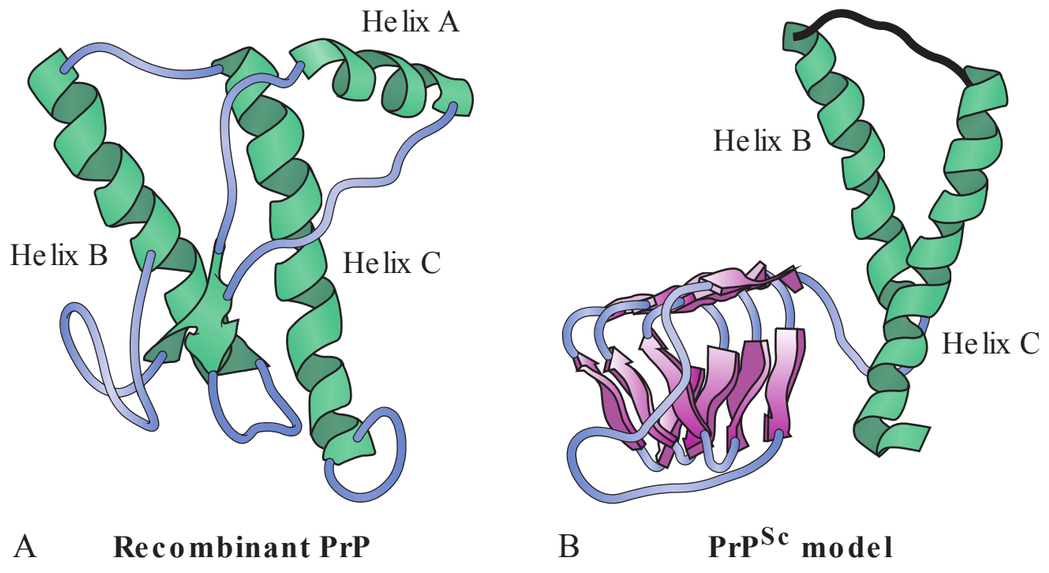


FIGURE 40-1

Structures of prion proteins. A. NMR structure of Syrian hamster recombinant (rec) PrP(90–231). Presumably, the structure of the α-helical form of recPrP(90–231) resembles that of PrP^{C}. recPrP(90–231) is viewed from the interface where PrP^{Sc} is thought to bind to PrP^{C}. Shown are: α-helices A (residues 144–157), B (172–193), and C (200–227). Flat ribbons depict β-strands S1 (129–131) and S2 (161–163). B. Structural model of PrP^{Sc}. The 90–160 region has been modeled onto a β-helical architecture while the COOH terminal helices B and C are preserved as in PrP^{C}.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 40-1

GLOSSARY OF PRION TERMINOLOGY	
Prion	Proteinaceous infectious particle that lacks nucleic acid. Prions are composed entirely of alternatively folded proteins that undergo self-propagation. Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable. PrP prions cause scrapie in sheep and goats, mad cow disease, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-causing isoform of the prion protein. This protein is the only identifable macromolecule in purifed preparations of scrapie prions.
PrP^{C}	Cellular isoform of the prion protein. PrP^{C} is the precursor of PrP^{Sc}.
PrP 27-30	A fragment of PrP^{Sc}, generated by truncation of the NH_2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP^{Sc}. Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

SPECTRUM OF PRION DISEASES

T e sporadic form of CJD is the most common prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human PrP prion disease, whereas inherited prion diseases account for 10–15% of all cases **(Table 40-2)**. Familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI) are all dominantly inherited prion diseases that are caused by mutations in the PrP gene.

Although infectious PrP prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of prions is an important biologic feature. Kuru of the Fore people of New Guinea is thought to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. With the cessation of ritualistic cannibalism in the late 1950s, kuru has nearly disappeared, with the exception of a few recent patients exhibiting incubation periods of >40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. Variant CJD (vCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). Although occasional cases of iatrogenic CJD still occur, this form of CJD is currently on the decline due to public health measures aimed at preventing the spread of PrP prions.

Six diseases of animals are caused by prions (Table 40-2). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. T e BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. T e origin of chronic wasting disease (CWD), a prion disease endemic in deer and elk in regions of North America, is uncertain. In contrast to other prion diseases, CWD is highly communicable. Feces from asymptomatic, infected cervids contain prions that are likely to be responsible for the spread of CWD.

EPIDEMIOLOGY

CJD is found throughout the world. T e incidence of sCJD is approximately one case per million population, and thus it accounts for approximately 1 in every 10,000 deaths. Because sCJD is an age-dependent neurodegenerative disease, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand. Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies, although speculation about this potential route of inoculation continues. Of particular interest are deer hunters who develop CJD, because up to 90% of culled deer in some game herds have been shown to harbor CWD prions. Whether prion disease in deer or elk has passed to cows, sheep, or directly to humans remains unknown. Studies with rodents demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

PATHOGENESIS

T e human prion diseases were initially classified as neurodegenerative disorders of unknown etiology on the basis of pathologic changes being confined to the CNS. With the transmission of kuru and CJD to apes, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Even though the familial nature of a subset of CJD cases was well

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 40-2

THE PrP PRION DISEASES

DISEASE	HOST	MECHANISM OF PATHOGENESIS
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germline mutations in PRNP
GSS	Humans	Germline mutations in PRNP
FFI	Humans	Germline mutation in PRNP (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
Animal		
Scrapie	Sheep, goats	Infection in genetically susceptible sheep
BSE	Cattle	Infection with prion-contaminated MBM
TME	Mink	Infection with prions from sheep or cattle
CWD	Mule deer, elk	Unknown
FSE	Cats	Infection with prion-contaminated beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CWD, chronic wasting disease; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; iCJD, iatrogenic Creutzfeldt-Jakob disease; MBM, meat and bone meal; sCJD, sporadic Creutzfeldt-Jakob disease; sFI, sporadic fatal insomnia; TME, transmissible mink encephalopathy; vCJD, variant Creutzfeldt-Jakob disease.

described, the significance of this observation became more obscure with the transmission of CJD to animals. Eventually the meaning of heritable CJD became clear with the discovery of mutations in the PRNP gene of these patients. The prion concept explains how a disease can manifest as a heritable as well as an infectious illness. Moreover, the hallmark of all prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of PrP.

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated PRNP and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; PrP^{C} is completely hydrolyzed under the same conditions **(Fig. 40-2)**. In the presence of detergent, PrP 27-30 polymerizes into amyloid. Prion rods formed by limited proteolysis and detergent extraction are indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

Prion strains

Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable. The existence of prion strains raised the question of how heritable biologic information can be enciphered in

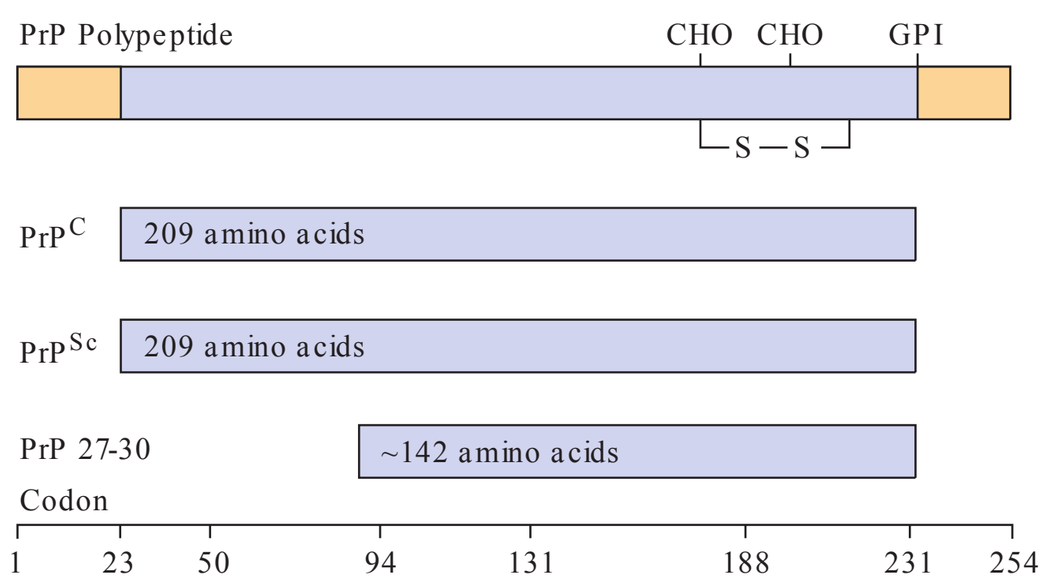


FIGURE 40-2

Prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH_2 and COOH termini, both PrP^{C} and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH_2 terminus of PrP^{Sc} is truncated to form PrP 27–30 composed of ~142 amino acids. GPI, glycosylphosphatidyl inositol anchor attachment site; S—S, disulfide bond; CHO, N-linked sugars.

www.ketabpezeshki.com (021) 66485457 - 66485438

a molecule other than nucleic acid. Various strains of prions have been defined by incubation times and the distribution of neuronal vacuolation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize prion strains.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene. In FFI, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 19 kDa, whereas in fCJD and most sporadic prion diseases, it is 21 kDa **(Table 40-3)**. T is difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH_2 termini of the two human PrP^{Sc} molecules, ref ecting different tertiary structures. T ese distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of patients with FFI transmitted disease into mice expressing a chimeric human-mouse PrP transgene and induced formation of the 19-kDa PrP^{Sc}, whereas brain extracts from fCJD and sCJD patients produced the 21-kDa PrP^{Sc} in mice expressing the same transgene. On second passage, these differences were maintained, demonstrating that chimeric PrP^{Sc} can exist in two different conformations based on the sizes of the protease-resistant fragments, even though the amino acid sequence of PrP^{Sc} is invariant.

T is analysis was extended when patients with sporadic fatal insomnia (sFI) were identified. Although they did not carry a PRNP gene mutation, the patients demonstrated a clinical and pathologic phenotype that was indistinguishable from that of patients with FFI. Furthermore, 19-kDa PrP^{Sc} was found in their brains, and on passage of prion disease to mice expressing a chimeric human-mouse PrP transgene, 19-kDa PrP^{Sc} was also found. T ese findings indicate that the disease phenotype is dictated by the conformation of PrP^{Sc} and not the amino acid sequence. PrP^{Sc} acts as a template for the conversion of PrP^{C} into nascent PrP^{Sc}. On the passage of prions into mice expressing a chimeric hamster-mouse PrP transgene, a change in the conformation of PrP^{Sc} was accompanied by the emergence of a new strain of prions.

Many new strains of prions were generated using recombinant (rec) PrP produced in bacteria; recPrP was polymerized into amyloid fibrils and inoculated into transgenic mice expressing high levels of wild-type mouse PrP^{C}; approximately 500 days later, the mice died of prion disease. T e incubation times of the "synthetic prions" in mice were dependent on the conditions used for polymerization of the amyloid fibrils. Highly stable amyloids gave rise to stable prions with long incubation times; low-stability amyloids led to prions with short incubation times. Amyloids of intermediate stability gave rise to prions with intermediate stabilities and intermediate incubation times. Such findings are consistent with earlier studies showing that the incubation times of synthetic and naturally occurring prions are directly proportional to the stability of the prion.

Species barrier

Studies on the role of the primary and tertiary structures of PrP in the transmission of prion disease have given new insights into the pathogenesis of these maladies. T e amino acid sequence of PrP encodes the species of the prion, and the prion derives its PrP^{Sc} sequence from the last mammal in which it was passaged. While the primary structure of PrP is likely to

TABLE 40-3

DISTINCT PRION STRAINS GENERATED IN HUMANS WITH INHERITED PRION DISEASES AND TRANSMITTED TO TRANSGENIC MICE[a]

INOCULUM	HOST SPECIES	HOST PrP GENOTYPE	INCUBATION TIME [DAYS ± SEM] (n/n_0)	PRP^{SC} (kDa)
None	Human	FFI(D178N, M129)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

[a]Tg(MHu2M) mice express a chimeric mouse-human PrP gene.

Notes: Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to transgenic mice.

Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; SEM, standard error of the mean.

www.ketabpezeshki.com (021) 66485457 - 66485438

be the most important or even sole determinant of the tertiary structure of PrP^{C}, PrP^{Sc} seems to function as a template in determining the tertiary structure of nascent PrP^{Sc} molecules as they are formed from PrP^{C}. In turn, prion diversity appears to be enciphered in the conformation of PrP^{Sc}, and thus prion strains seem to represent different conformers of PrP^{Sc}.

In general, transmission of PrP prion disease from one species to another is inefficient, in that not all intracerebrally inoculated animals develop disease, and those that fall ill do so only after long incubation times that can approach the natural life span of the animal. T is "species barrier" to transmission is correlated with the degree of similarity between the amino acid sequences of PrP^{C} in the inoculated host and of PrP^{Sc} in the prion inoculum. T e importance of sequence similarity between the host and donor PrP argues that PrP^{C} directly interacts with PrP^{Sc} in the prion conversion process.

SPORADIC AND INHERITED PrP PRION DISEASES

Several different scenarios might explain the initiation of sporadic prion disease: (1) A somatic mutation may be the cause and thus follow a path similar to that for germline mutations in inherited disease. In this situation, the mutant PrP^{Sc} must be capable of targeting wild-type PrP^{C}, a process known to be possible for some mutations but less likely for others. (2) T e activation energy barrier separating wild-type PrP^{C} from PrP^{Sc} could be crossed on rare occasions when viewed in the context of a population. Most individuals would be spared, while presentations in the elderly with an incidence of ~1 per million would be seen. (3) PrP^{Sc} may be present at low levels in some normal cells, where it performs some important, as yet unknown, function. T e level of PrP^{Sc} in such cells is hypothesized to be sufficiently low as to be not detected by routine bioassay. In some altered metabolic states, the cellular mechanisms for clearing PrP^{Sc} might become compromised, and the rate of PrP^{Sc} formation would then begin to exceed the capacity of the cell to clear it. T e third possible mechanism is attractive because it suggests PrP^{Sc} is not simply a misfolded protein, as proposed for the first and second mechanisms, but that it is an alternatively folded molecule with a function. Moreover, the multitude of conformational states that PrP^{Sc} can adopt, as described above, raises the possibility that PrP^{Sc} or another prion-like protein might function in a process like short-term memory where information storage occurs in the absence of new protein synthesis.

More than 40 different mutations resulting in nonconservative substitutions in the human PRNP gene have been found to segregate with inherited human prion diseases. Missense mutations and expansions in the octapeptide repeat region of the gene are responsible for familial forms of prion disease. Five different mutations of the PRNP gene have been linked genetically to heritable prion disease.

Although phenotypes may vary dramatically within families, specific phenotypes tend to be observed with certain mutations. A clinical phenotype indistinguishable from typical sCJD is usually seen with substitutions at codons 180, 183, 200, 208, 210, and 232. Substitutions at codons 102, 105, 117, 198, and 217 are associated with the GSS variant of prion disease. T e normal human PrP sequence contains five repeats of an eight-amino-acid sequence. Insertions from two to nine extra octarepeats frequently cause variable phenotypes ranging from a condition indistinguishable from sCJD to a slowly progressive dementing illness of many years in duration to an early-age-of-onset disorder that is similar to AD. A mutation at codon 178 resulting in substitution of asparagine for aspartic acid produces FFI if a methionine is encoded at the polymorphic residue 129 on the same allele. Typical CJD is seen if the D178N mutation occurs with a valine encoded at position 129 of the same allele.

HUMAN PRNP GENE POLYMORPHISMS

Polymorphisms infuence the susceptibility to sporadic, inherited, and infectious forms of prion disease. T e methionine/valine polymorphism at position 129 not only modulates the age of onset of some inherited prion diseases but can also determine the clinical phenotype. T e finding that homozygosity at codon 129 predisposes to sCJD supports a model of prion production that favors PrP interactions between homologous proteins.

Substitution of the basic residue lysine at position 218 in mouse PrP produced dominant-negative inhibition of prion replication in transgenic mice. T is same lysine at position 219 in human PrP has been found in 12% of the Japanese population, and this group appears to be resistant to prion disease. Dominant-negative inhibition of prion replication was also found with substitution of the basic residue arginine at position 171; sheep with arginine were resistant to scrapie prions but were susceptible to BSE prions that were inoculated intracerebrally.

INFECTIOUS PrP PRION DISEASES

IATROGENIC CJD

Accidental transmission of CJD to humans appears to have occurred with corneal transplantation, contaminated electroencephalogram (EEG) electrode implantation, and surgical procedures. Corneas from

www.ketabpezeshki.com (021) 66485457 - 66485438

donors with unsuspected CJD have been transplanted to apparently healthy recipients who developed CJD after variable incubation periods. T e same improperly decontaminated EEG electrodes that caused CJD in two young patients with intractable epilepsy caused CJD in a chimpanzee 18 months after their experimental implantation.

Surgical procedures may have resulted in accidental inoculation of patients with prions, presumably because some instrument or apparatus in the operating theater became contaminated when a CJD patient underwent surgery. Although the epidemiology of these studies is highly suggestive, no proof for such episodes exists.

Dura mater grafts

More than 160 cases of CJD after implantation of dura mater grafts have been recorded. All of the grafts appear to have been acquired from a single manufacturer whose preparative procedures were inadequate to inactivate human prions. One case of CJD occurred after repair of an eardrum perforation with a pericardium graft.

Human growth hormone and pituitary gonadotropin therapy

T e transmission of CJD prions from contaminated human growth hormone (hGH) preparations derived from human pituitaries has been responsible for fatal cerebellar disorders with dementia in >180 patients ranging in age from 10 to 41 years. T ese patients received injections of hGH every 2–4 days for 4–12 years. If it is thought that these patients developed CJD from injections of prion-contaminated hGH preparations, the possible incubation periods range from 4 to 30 years. Only recombinant hGH is now used therapeutically so that possible contamination with prions is no longer an issue. Four cases of CJD have occurred in women receiving human pituitary gonadotropin.

VARIANT CJD

T e restricted geographic occurrence and chronology of vCJD raised the possibility that BSE prions had been transmitted to humans through the consumption of tainted beef. More than 190 cases of vCJD have occurred, with >90% of these in Britain. vCJD has also been reported in people either living in or originating from France, Ireland, Italy, Netherlands, Portugal, Spain, Saudi Arabia, United States, Canada, and Japan.

T e steady decline in the number of vCJD cases over the past decade argues that there will not be a prion disease epidemic in Europe, similar to those seen for BSE and kuru. What is certain is that prion-tainted meat should be prevented from entering the human food supply.

T e most compelling evidence that vCJD is caused by BSE prions was obtained from experiments in mice expressing the bovine PrP transgene. Both BSE and vCJD prions were efficiently transmitted to these transgenic mice and with similar incubation periods. In contrast to sCJD prions, vCJD prions did not transmit disease efficiently to mice expressing a chimeric human-mouse PrP transgene. Earlier studies with nontransgenic mice suggested that vCJD and BSE might be derived from the same source because both inocula transmitted disease with similar but very long incubation periods.

Attempts to determine the origin of BSE and vCJD prions have relied on passaging studies in mice, some of which are described above, as well as studies of the conformation and glycosylation of PrP^{Sc}. One scenario suggests that a particular conformation of bovine PrP^{Sc} was selected for heat resistance during the rendering process and was then reselected multiple times as cattle infected by ingesting prion-contaminated meat and bone meal (MBM) were slaughtered and their offal rendered into more MBM. Variant CJD cases have virtually disappeared with protection of the beef supply in Europe.

NEUROPATHOLOGY

Frequently the brains of patients with CJD have no recognizable abnormalities on gross examination. Patients who survive for several years have variable degrees of cerebral atrophy.

On light microscopy, the pathologic hallmarks of CJD are spongiform degeneration and astrocytic gliosis. T e lack of an inf ammatory response in CJD and other prion diseases is an important pathologic feature of these degenerative disorders. Spongiform degeneration is characterized by many 1- to 5-µm vacuoles in the neuropil between nerve cell bodies. Generally the spongiform changes occur in the cerebral cortex, putamen, caudate nucleus, thalamus, and molecular layer of the cerebellum. Astrocytic gliosis is a constant but nonspecific feature of prion diseases. Widespread proliferation of fibrous astrocytes is found throughout the gray matter of brains infected with CJD prions. Astrocytic processes filled with glial filaments form extensive networks.

Amyloid plaques have been found in ~10% of CJD cases. Purified CJD prions from humans and animals exhibit the ultrastructural and histochemical characteristics of amyloid when treated with detergents during limited proteolysis. In first passage from some human Japanese CJD cases, amyloid plaques have been found in mouse brains. T ese plaques stain with antibodies raised against PrP.

T e amyloid plaques of GSS disease are morphologically distinct from those seen in kuru or scrapie. GSS plaques consist of a central dense core of

www.ketabpezeshki.com (021) 66485457 - 66485438

amyloid surrounded by smaller globules of amyloid. Ultrastructurally, they consist of a radiating fibrillar network of amyloid fibrils, with scant or no neuritic degeneration. T e plaques can be distributed throughout the brain but are most frequently found in the cerebellum. T ey are often located adjacent to blood vessels. Congophilic angiopathy has been noted in some cases of GSS disease.

In vCJD, a characteristic feature is the presence of "f orid plaques." T ese are composed of a central core of PrP amyloid, surrounded by vacuoles in a pattern suggesting petals on a f ower.

CLINICAL FEATURES

Nonspecific prodromal symptoms occur in approximately a third of patients with CJD and may include fatigue, sleep disturbance, weight loss, headache, anxiety, vertigo, malaise, and ill-defined pain. Most patients with CJD present with deficits in higher cortical function. Similarly, psychiatric symptoms, such as depression, psychosis, and visual hallucinations, are often the defining features of the illness. T ese deficits almost always progress over weeks or months to a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function. A few patients present with either visual impairment or cerebellar gait and coordination deficits. Frequently the cerebellar deficits are rapidly followed by progressive dementia. Visual problems often begin with blurred vision and diminished acuity, rapidly followed by dementia.

Other symptoms and signs include extrapyramidal dysfunction manifested as rigidity, masklike facies, or (less commonly) choreoathetoid movements; pyramidal signs (usually mild); seizures (usually major motor) and, less commonly, hypoesthesia; supranuclear gaze palsy; optic atrophy; and vegetative signs such as changes in weight, temperature, sweating, or menstruation.

Myoclonus

Most patients (~90%) with CJD exhibit myoclonus that appears at various times throughout the illness. Unlike other involuntary movements, myoclonus persists during sleep. Startle myoclonus elicited by loud sounds or bright lights is frequent. It is important to stress that myoclonus is neither specific nor confined to CJD and tends to occur later in the course of CJD. Dementia with myoclonus can also be due to AD **(Chap. 35)**, dementia with Lewy bodies **(Chap. 35)**, corticobasal degeneration **(Chap. 35)** cryptococcal encephalitis, or the myoclonic epilepsy disorder Unverricht-Lundborg disease **(Chap. 31)**.

Clinical course

In documented cases of accidental transmission of CJD to humans, an incubation period of 1.5–2 years preceded the development of clinical disease. In other cases, incubation periods of up to 40 years have been suggested. Most patients with CJD live 6–12 months after the onset of clinical signs and symptoms, whereas some live for up to 5 years.

DIAGNOSIS

T e constellation of dementia, myoclonus, and periodic electrical bursts in an afebrile 60-year-old patient generally indicates CJD. Clinical abnormalities in CJD are confined to the CNS. Fever, elevated sedimentation rate, leukocytosis in blood, or a pleocytosis in cerebrospinal f uid (CSF) should alert the physician to another etiology to explain the patient's CNS dysfunction, although there are rare cases of CJD in which mild CSF pleocytosis is observed.

Variations in the typical course appear in inherited and transmitted forms of the disease. fCJD has an earlier mean age of onset than sCJD. In GSS disease, ataxia is usually a prominent and presenting feature, with dementia occurring late in the disease course. GSS disease presents earlier than CJD (mean age 43 years) and is typically more slowly progressive than CJD; death usually occurs within 5 years of onset. FFI is characterized by insomnia and dysautonomia; dementia occurs only in the terminal phase of the illness. Rare sporadic cases have been identified. vCJD has an unusual clinical course, with a prominent psychiatric prodrome that may include visual hallucinations and early ataxia, whereas frank dementia is usually a late sign of vCJD.

DIFFERENTIAL DIAGNOSIS

Many conditions mimic CJD. Dementia with Lewy bodies **(Chap. 35)** is the most common disorder to be mistaken for CJD. It can present in a subacute fashion with delirium, myoclonus, and extrapyramidal features. Other neurodegenerative disorders **(Chap. 35)** to consider include AD, FTD, corticobasal degeneration, progressive supranuclear palsy, ceroid lipofuscinosis, and myoclonic epilepsy with Lafora bodies **(Chap. 31)**. T e absence of abnormalities on diffusion-weighted and f uid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) will almost always distinguish these dementing conditions from CJD.

Hashimoto's encephalopathy, which presents as a subacute progressive encephalopathy with myoclonus and periodic triphasic complexes on the EEG, should be excluded in every case of suspected CJD. It is diagnosed by the finding of high titers of antithyroglobulin

www.ketabpezeshki.com (021) 66485457 - 66485438

or antithyroid peroxidase (antimicrosomal) antibodies in the blood and improves with glucocorticoid therapy. Unlike CJD, fluctuations in severity typically occur in Hashimoto's encephalopathy.

Intracranial vasculitides may produce nearly all of the symptoms and signs associated with CJD, sometimes without systemic abnormalities. Myoclonus is exceptional with cerebral vasculitis, but focal seizures may confuse the picture. Prominent headache, absence of myoclonus, stepwise change in deficits, abnormal CSF, and focal white matter changes on MRI or angiographic abnormalities all favor vasculitis.

Paraneoplastic conditions **(Chap. 50)**, particularly limbic encephalitis and cortical encephalitis, can also mimic CJD. In many of these patients, dementia appears prior to the diagnosis of a tumor, and in some, no tumor is ever found. Detection of the paraneoplastic antibodies is often the only way to distinguish these cases from CJD.

Other diseases that can simulate CJD include neurosyphilis, AIDS dementia complex **(Chap. 48)**, progressive multifocal leukoencephalopathy **(Chap. 46)**, subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis **(Chap. 46)**, diffuse intracranial tumor (gliomatosis cerebri; **Chap. 49**), anoxic encephalopathy, dialysis dementia, uremia, hepatic encephalopathy, voltage-gated potassium channel (VGkC) autoimmune encephalopathy, and lithium or bismuth intoxication.

LABORATORY TESTS

The only specific diagnostic tests for CJD and other human prion diseases measure PrP^{Sc}. The most widely used method involves limited proteolysis that generates PrP 27-30, which is detected by immunoassay after denaturation. The conformation-dependent immunoassay (CDI) is based on immunoreactive epitopes that are exposed in PrP^{C} but buried in PrP^{Sc}. In humans, the diagnosis of CJD can be established by brain biopsy if PrP^{Sc} is detected. If no attempt is made to measure PrP^{Sc}, but the constellation of pathologic changes frequently found in CJD is seen in a brain biopsy, then the diagnosis is reasonably secure (see "Neuropathology," above). The high sensitivity and specificity of cortical ribboning and basal ganglia hyperintensity on FLAIR and diffusion-weighted MRI for the diagnosis of CJD have greatly diminished the need for brain biopsy in patients with suspected CJD. Because PrP^{Sc} is not uniformly distributed throughout the CNS, the apparent absence of PrP^{Sc} in a limited sample such as a biopsy does not rule out prion disease. At autopsy, sufficient brain samples should be taken for both PrP^{Sc} immunoassay, preferably by CDI, and immunohistochemistry of tissue sections.

To establish the diagnosis of either sCJD or familial prion disease, sequencing the PRNP gene must be performed. Finding the wild-type PRNP gene sequence permits the diagnosis of sCJD if there is no history to suggest infection from an exogenous source of prions. The identification of a mutation in the PRNP gene sequence that encodes a nonconservative amino acid substitution argues for familial prion disease.

CT may be normal or show cortical atrophy. MRI is valuable for distinguishing sCJD from most other conditions. On FLAIR sequences and diffusion-weighted imaging, ~90% of patients show increased intensity in the basal ganglia and cortical ribboning **(Fig. 40-3)**. This pattern is not seen with other neurodegenerative disorders but has been seen infrequently with viral encephalitis, paraneoplastic syndromes, or seizures. When the typical MRI pattern is present, in the proper clinical setting, diagnosis is facilitated. However, some cases of sCJD do not show this typical pattern, and other early diagnostic approaches are still needed.

CSF is nearly always normal but may show protein elevation and, rarely, mild pleocytosis. Although the stress protein 14-3-3 is elevated in the CSF of some patients with CJD, similar elevations of 14-3-3 are found in patients with other disorders; thus this elevation is not specific. Similarly, elevations of CSF neuron-specific enolase and tau occur in CJD but lack specificity for diagnosis.

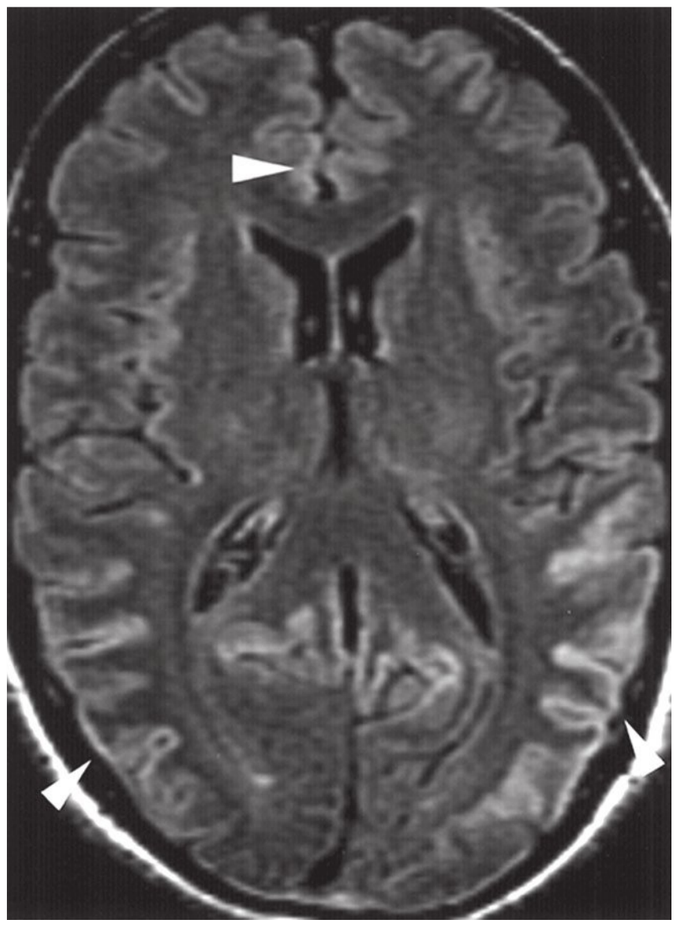


FIGURE 40-3
T2-weighted (fluid-attenuated inversion recovery) magnetic resonance imaging showing hyperintensity in the cortex in a patient with sporadic CJD. This so-called "cortical ribboning" along with increased intensity in the basal ganglia on T2- or diffusion-weighted imaging can aid in the diagnosis of Creutzfeldt-Jakob disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

The EEG is often useful in the diagnosis of CJD, although only approximately 60% of individuals show the typical pattern. During the early phase of CJD, the EEG is usually normal or shows only scattered theta activity. In most advanced cases, repetitive, high-voltage, triphasic, and polyphasic sharp discharges are seen, but in many cases their presence is transient. The presence of these stereotyped periodic bursts of <200 ms in duration, occurring every 1–2 s, makes the diagnosis of CJD very likely. These discharges are frequently but not always symmetric; there may be a one-sided predominance in amplitude. As CJD progresses, normal background rhythms become fragmentary and slower.

CARE OF CJD PATIENTS

Although CJD should not be considered either contagious or communicable, it is transmissible. The risk of accidental inoculation by aerosols is very small; nonetheless, procedures producing aerosols should be performed in certified biosafety cabinets. Biosafety level 2 practices, containment equipment, and facilities are recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. The primary problem in caring for patients with CJD is the inadvertent infection of health care workers by needle and stab wounds. Electroencephalographic and electromyographic needles should not be reused after studies on patients with CJD have been performed.

There is no reason for pathologists or other morgue employees to resist performing autopsies on patients whose clinical diagnosis was CJD. Standard microbiologic practices outlined here, along with specific recommendations for decontamination, seem to be adequate precautions for the care of patients with CJD and the handling of infected specimens.

DECONTAMINATION OF CJD PRIONS

Prions are extremely resistant to common inactivation procedures, and there is some disagreement about the optimal conditions for sterilization. Some investigators recommend treating CJD-contaminated materials once with 1 N NaOH at room temperature, but we believe this procedure may be inadequate for sterilization. Autoclaving at 134°C for 5 h or treatment with 2 N NaOH for several hours is recommended for sterilization of prions. The term sterilization implies complete destruction of prions; any residual infectivity can be hazardous. Recent studies show that sCJD prions bound to stainless steel surfaces are resistant to inactivation by autoclaving at 134°C for 2 h; exposure of bound prions to an acidic detergent solution prior to autoclaving rendered prions susceptible to inactivation.

PREVENTION AND THERAPEUTICS

There is no known effective therapy for preventing or treating CJD. The finding that phenothiazines and acridines inhibit PrP^{Sc} formation in cultured cells led to clinical studies of quinacrine in CJD patients. Unfortunately, quinacrine failed to slow the rate of cognitive decline in CJD, possibly because therapeutic concentrations in the brain were not achieved. Although inhibition of the P-glycoprotein (Pgp) transport system resulted in substantially increased quinacrine levels in the brains of mice, the prion incubation times were not extended by treatment with the drug. Whether such an approach can be used to treat CJD remains to be established.

Like the acridines, anti-PrP antibodies have been shown to eliminate PrP^{Sc} from cultured cells. Additionally, such antibodies in mice, either administered by injection or produced from a transgene, have been shown to prevent prion disease when prions are introduced by a peripheral route, such as intraperitoneal inoculation. Unfortunately, the antibodies were ineffective in mice inoculated intracerebrally with prions. Several drugs, including pentosan polysulfate as well as porphyrin and phenylhydrazine derivatives, delay the onset of disease in animals inoculated intracerebrally with prions if the drugs are given intracerebrally beginning soon after inoculation.

DIFFERENT PRIONS CAUSING OTHER NEURODEGENERATIVE DISEASES

There is a rapidly expanding body of literature demonstrating that in addition to PrP, other proteins including amyloid beta (Aβ), tau, α-synuclein, and huntingtin can all becomes prions **(Chap. 30)**. Experimental studies have shown that transgenic mice expressing mutant amyloid precursor protein (APP) develop amyloid plaques containing fibrils composed of the Aβ peptide approximately a year after inoculation with synthetic Aβ peptides polymerized into amyloid fibrils or extracts prepared from the brains of patients with AD. Mutant tau aggregates in transgenic mice and cultured cells can trigger the aggregation of tau into fibrils that resemble those found in neurofibrillary tangles and Pick bodies. Such tangles have been found in AD, FTDs, Pick's disease, and some cases of posttraumatic brain injury, all of which are likely to be caused by the prion isoforms of Aβ and/or tau.

In patients with advanced PD who received grafts of fetal substantia nigral neurons, Lewy bodies containing β-sheet–rich α-synuclein were identified in grafted cells approximately 10 years after transplantation, arguing for the axonal transport of misfolded α-synuclein crossing into grafted neurons, where it initiated aggregation

www.ketabpezeshki.com (021) 66485457 - 66485438

of nascent α-synuclein into fibrils that coalesced into Lewy bodies. T ese findings combined with studies of multiple system atrophy (MSA) argue that the synucleinopathies are caused by prions. Brain homogenates from MSA patients injected into transgenic mice transmitted lethal neurodegeneration in approximately 3 months; moreover, recombinant synuclein injected into wild-type mice initiated the deposition of synuclein fibrils.

In summary, a wealth of evidence continues to accumulate arguing that proteins causing AD, PD, FTDs, ALS, and even HD acquire alternative conformations that become self-propagating. Each of these neurodegenerative diseases is caused by a different protein that undergoes a conformational transformation to become a prion. Prions explain many of the features that the neurodegenerative diseases have in common: (1) incidence increases with age, (2) steady progression over years, (3) spread from one region of the CNS to another, (4) protein deposits consisting of amyloid fibrils, and (5) late onset of inherited forms of the neurodegenerative diseases. Notably, amyloid plaques containing PrP^{Sc} are a nonobligatory feature of PrP prion disease in humans and animals. Furthermore, amyloid plaques in AD do not correlate with the level of dementia; however, the level of soluble (oligomeric) Aβ peptide does correlate with memory loss and other intellectual deficits.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 41

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Phillip A. Low ■ John W. Engstrom

The autonomic nervous system (ANS) innervates the entire neuraxis and influences all organ systems. It regulates blood pressure (BP), heart rate, sleep, and bladder and bowel function. It operates automatically; its full importance becomes recognized only when ANS function is compromised, resulting in dysautonomia. **Hypothalamic disorders that cause disturbances in homeostasis are discussed in Chap. 23.**

ANATOMIC ORGANIZATION

The activity of the ANS is regulated by central neurons responsive to diverse afferent inputs. After central integration of afferent information, autonomic outflow is adjusted to permit the functioning of the major organ systems in accordance with the needs of the whole organism. Connections between the cerebral cortex and the autonomic centers in the brainstem coordinate autonomic outflow with higher mental functions.

The preganglionic neurons of the parasympathetic nervous system leave the central nervous system (CNS) in the third, seventh, ninth, and tenth cranial nerves as well as the second and third sacral nerves, while the preganglionic neurons of the sympathetic nervous system exit the spinal cord between the first thoracic and the second lumbar segments **(Fig. 41-1)**. These are thinly myelinated. The postganglionic neurons, located in ganglia outside the CNS, give rise to the postganglionic unmyelinated autonomic nerves that innervate organs and tissues throughout the body. Responses to sympathetic and parasympathetic stimulation are frequently antagonistic **(Table 41-1)**, reflecting highly coordinated interactions within the CNS; the resultant changes in parasympathetic and sympathetic activity provide more precise control of autonomic responses than could be achieved by the modulation of a single system.

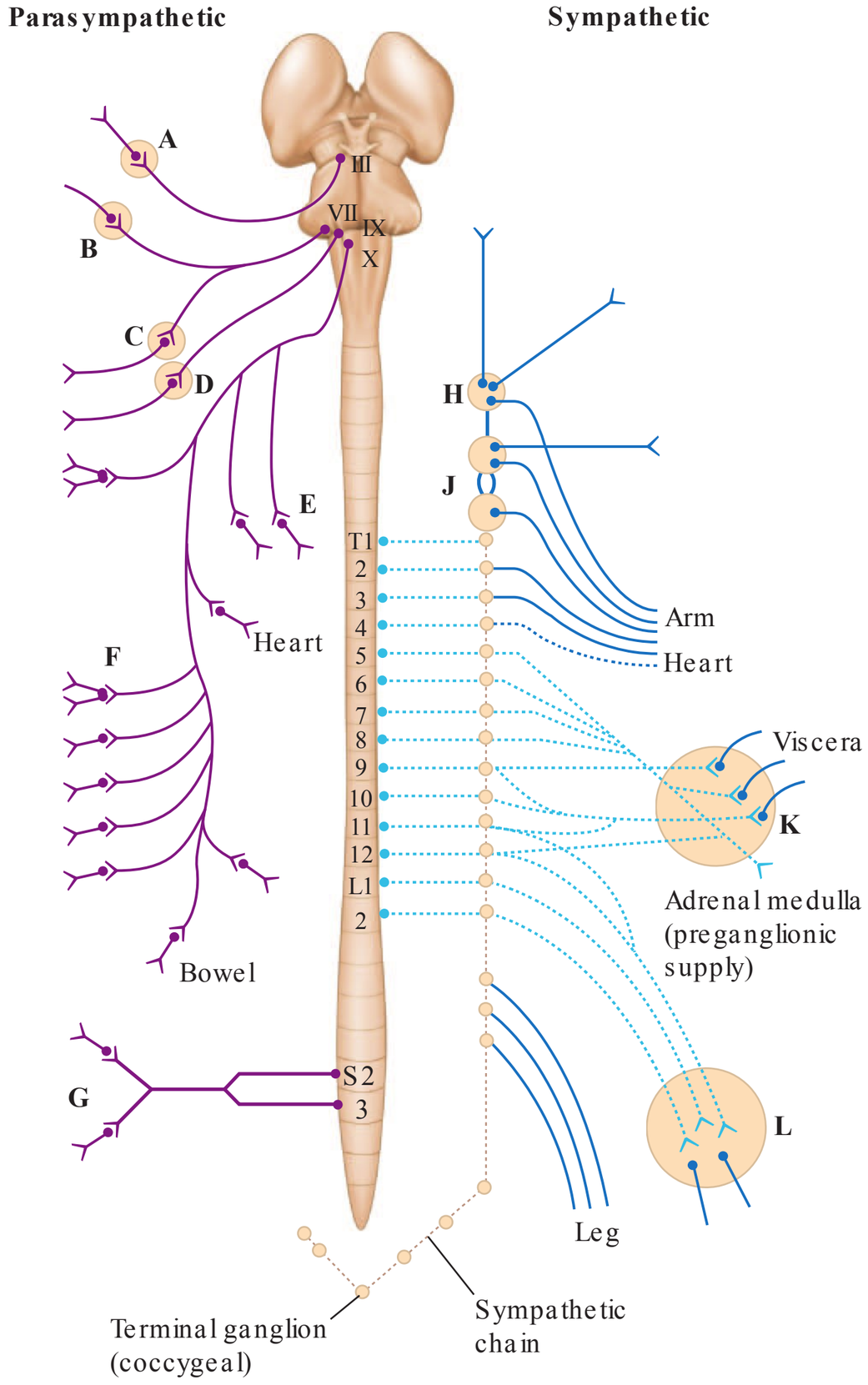
Acetylcholine (ACh) is the preganglionic neurotransmitter for both divisions of the ANS as well as the postganglionic neurotransmitter of the parasympathetic neurons; the preganglionic receptors are nicotinic, and the postganglionic are muscarinic in type. Norepinephrine (NE) is the neurotransmitter of the postganglionic sympathetic neurons, except for cholinergic neurons innervating the eccrine sweat glands.

CLINICAL EVALUATION

CLASSIFICATION

Disorders of the ANS may result from pathology of either the CNS or the peripheral nervous system (PNS) **(Table 41-2)**. Signs and symptoms may result from interruption of the afferent limb, CNS processing centers, or efferent limb of reflex arcs controlling autonomic responses. For example, a lesion of the medulla produced by a posterior fossa tumor can impair BP responses to postural changes and result in orthostatic hypotension (OH). OH can also be caused by lesions of the spinal cord or peripheral vasomotor nerve fibers (e.g., diabetic autonomic neuropathy). Lesions of the efferent limb cause the most consistent and severe OH. The site of reflex interruption is usually established by the clinical context in which the dysautonomia arises, combined with judicious use of ANS testing and neuroimaging studies. The presence or absence of CNS signs, association with sensory or motor polyneuropathy, medical illnesses, medication use, and family history are often important considerations. Some syndromes do not fit easily into any classification scheme.

www.ketabpezeshki.com (021) 66485457 - 66485438



Parasympathetic system
from cranial nerves III, VII, IX, X and from sacral nerves 2 and 3

A Ciliary ganglion
B Sphenopalatine (pterygopalatine) ganglion
C Submandibular ganglion
D Otic ganglion
E Vagal ganglion cells in the heart wall
F Vagal ganglion cells in bowel wall
G Pelvic ganglia

Sympathetic system
from T1-L2
Preganglionic fibers
Postganglionic fibers

H Superior cervical ganglion
J Middle cervical ganglion and inferior cervical (stellate) ganglion including T1 ganglion
K Coeliac and other abdominal ganglia
L Lower abdominal sympathetic ganglia

FIGURE 41-1
Schematic representation of the autonomic nervous system. (From M Moskowitz: Clin Endocrinol Metab 6:77, 1977.)

TABLE 41-1

FUNCTIONAL CONSEQUENCES OF NORMAL ANS ACTIVATION

	SYMPATHETIC	PARASYMPATHETIC
Heart rate	Increased	Decreased
Blood pressure	Increased	Mildly decreased
Bladder	Increased sphincter tone	Voiding (decreased tone)
Bowel motility	Decreased motility	Increased
Lung	Bronchodilation	Bronchoconstriction
Sweat glands	Sweating	—
Pupils	Dilation	Constriction
Adrenal glands	Catecholamine release	—
Sexual function	Ejaculation, orgasm	Erection
Lacrimal glands	—	Tearing
Parotid glands	—	Salivation

SYMPTOMS OF AUTONOMIC DYSFUNCTION

Clinical manifestations can result from loss of function, overactivity, or dysregulation of autonomic circuits. Disorders of autonomic function should be considered in patients with unexplained OH, syncope, sleep dysfunction, altered sweating (hyperhidrosis or hypohidrosis), impotence, constipation or other gastrointestinal symptoms (bloating, nausea, vomiting of old food, diarrhea), or bladder disorders (urinary frequency, hesitancy, or incontinence). Symptoms may be widespread or regional in distribution. An autonomic history focuses on systemic functions (BP, heart rate, sleep, fever, sweating) and involvement of individual organ systems (pupils, bowel, bladder, sexual function). T e autonomic symptom profile is a self-report questionnaire that can be used for formal assessment. It is also important to recognize the modulating effects of age. For example, OH typically produces lightheadedness in the young, whereas cognitive slowing is more common in the elderly. Specific symptoms of orthostatic intolerance are diverse **(Table 41-3)**. Autonomic symptoms may vary dramatically, reflecting the dynamic nature of autonomic control over homeostatic function. For example, OH might be manifest only in the early morning, following a meal, with exercise, or with raised ambient temperature, depending on the regional vascular bed affected by the dysautonomia.

Early symptoms may be overlooked. Impotence, although not specific for autonomic failure, often heralds autonomic failure in men and may precede other symptoms by years. A decrease in the frequency of spontaneous early morning erections may occur months before loss of nocturnal penile tumescence and development of total impotence. Bladder dysfunction may appear early in men and women, particularly in those with a CNS etiology. Cold feet may indicate increased peripheral vasomotor constriction. Brain and

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 41-2 CLASSIFICATION OF CLINICAL AUTONOMIC DISORDERS

I. Autonomic disorders with brain involvement
  A. Associated with multisystem degeneration
    1. Multisystem degeneration: autonomic failure clinically prominent
      a. Multiple system atrophy (MSA)
      b. Parkinson's disease with autonomic failure
      c. Diffuse Lewy body disease (some cases)
    2. Multisystem degeneration: autonomic failure clinically not usually prominent
      a. Parkinson's disease
      b. Other extrapyramidal disorders (inherited spinocerebellar atrophies, progressive supranuclear palsy, corticobasal degeneration, Machado-Joseph disease, fragile X syndrome [FXTAS])
  B. Unassociated with multisystem degeneration (focal CNS disorders)
  1. Disorders mainly due to cerebral cortex involvement
    a. Frontal cortex lesions causing urinary/bowel incontinence
    b. Focal seizures (temporal lobe or anterior cingulate)
    c. Cerebral infarction of the insula
  2. Disorders of the limbic and paralimbic circuits
    a. Shapiro's syndrome (agenesis of corpus callosum, hyperhidrosis, hypothermia)
    b. Autonomic seizures
    c. Limbic encephalitis
  3. Disorders of the hypothalamus
    a. Thiamine deficiency (Wernicke-Korsakoff syndrome)
    b. Diencephalic syndrome
    c. Neuroleptic malignant syndrome
    d. Serotonin syndrome
    e. Fatal familial insomnia
    f. Antidiuretic hormone (ADH) syndromes (diabetes insipidus, inappropriate ADH secretion)
    g. Disturbances of temperature regulation (hyperthermia, hypothermia)
    h. Disturbances of sexual function
    i. Disturbances of appetite
    j. Disturbances of BP/HR and gastric function
    k. Horner's syndrome
  4. Disorders of the brainstem and cerebellum
    a. Posterior fossa tumors
    b. Syringobulbia and Arnold-Chiari malformation
    c. Disorders of BP control (hypertension, hypotension)
    d. Cardiac arrhythmias
    e. Central sleep apnea
    f. Baroreflex failure
    g. Horner's syndrome
    h. Vertebrobasilar and lateral medullary (Wallenberg's) syndromes
    i. Brainstem encephalitis
II. Autonomic disorders with spinal cord involvement
  A. Traumatic quadriplegia
  B. Syringomyelia
  C. Subacute combined degeneration
  D. Multiple sclerosis and neuromyelitis optica
  E. Amyotrophic lateral sclerosis
  F. Tetanus
  G. Stiff-person syndrome
  H. Spinal cord tumors
III. Autonomic neuropathies
  A. Acute/subacute autonomic neuropathies
    1. Subacute autoimmune autonomic ganglionopathy (AAG)
      a. Subacute paraneoplastic autonomic neuropathy
      b. Guillain-Barré syndrome
      c. Botulism
      d. Porphyria
      e. Drug induced autonomic neuropathies-stimulants, drug withdrawal, vasoconstrictor, vasodilators, beta-receptor antagonists, beta-agonists
      f. Toxin-induced autonomic neuropathies
      g. Subacute cholinergic neuropathy
  B. Chronic peripheral autonomic neuropathies
    1. Distal small fiber neuropathy
    2. Combined sympathetic and parasympathetic failure
      a. Amyloid
      b. Diabetic autonomic neuropathy
      c. Autoimmune autonomic ganglionopathy (paraneoplastic and idiopathic)
      d. Sensory neuronopathy with autonomic failure
      e. Familial dysautonomia (Riley-Day syndrome)
      f. Diabetic, uremic, or nutritional deficiency
      g. Dysautonomia of old age
    3. Disorders of reduced orthostatic intolerance: reflex syncope, POTS, associated with prolonged bed rest, associated with space flight, chronic fatigue

Abbreviations: BP, blood pressure; CNS, central nervous system; HR, heart rate; POTS, postural orthostatic tachycardia syndrome.

spinal cord disease above the level of the lumbar spine results first in urinary frequency and small bladder volumes and eventually in incontinence (upper motor neuron or spastic bladder). By contrast, PNS disease of autonomic nerve fibers results in large bladder volumes, urinary frequency, and overflow incontinence (lower motor neuron flaccid bladder). Measurement of bladder volume (postvoid residual) is a useful bedside test for distinguishing between upper and lower motor neuron bladder dysfunction in the early stages of dysautonomia. Gastrointestinal autonomic dysfunction typically presents as severe constipation. Diarrhea may develop (typically in diabetes mellitus) due to rapid transit of contents or uncoordinated small-bowel motor activity, or on an osmotic basis from bacterial overgrowth associated with small-bowel stasis. Impaired glandular secretory function may cause difficulty with food intake due to decreased salivation or eye irritation due to decreased lacrimation. Occasionally, temperature elevation and vasodilation can result from anhidrosis because sweating is normally important for heat dissipation **(Chap. 23)**. Lack of sweating after a hot bath, during exercise, or on a hot day can suggest sudomotor failure.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 41-3

SYMPTOMS OF ORTHOSTATIC INTOLERANCE	
Lightheadedness (dizziness)	88%
Weakness or tiredness	72%
Cognitive dif culty (thinking/concentrating)	47%
Blurred vision	47%
Tremulousness	38%
Vertigo	37%
Pallor	31%
Anxiety	29%
Palpitations	26%
Clammy feeling	19%
Nausea	18%

Source: PA Low et al: Mayo Clin Proc 70:617, 1995.

OH (also called orthostatic or postural hypotension) is perhaps the most disabling feature of autonomic dysfunction. T e prevalence of OH is relatively high, especially when OH associated with aging and diabetes mellitus is included **(Table 41-4)**. OH can cause a variety of symptoms, including dimming or loss of vision, lightheadedness, diaphoresis, diminished hearing, pallor, and weakness. Syncope results when the drop in BP impairs cerebral perfusion. Other manifestations of impaired baroreflexes are supine hypertension, a heart rate that is fixed regardless of posture, postprandial hypotension, and an excessively high nocturnal BP. Many patients with OH have a preceding diagnosis of hypertension or have concomitant supine hypertension, reflecting the great importance of baroreflexes in maintaining postural and supine normotension. T e appearance of OH in patients receiving antihypertensive treatment may indicate overtreatment or the onset of an autonomic disorder. T e most common causes of OH are not neurologic in origin; these must be distinguished from the neurogenic causes **(Table 41-5)**. **Neurocardiogenic and cardiac causes of syncope are considered in Chap. 11.**

APPROACH TO THE PATIENT: Orthostatic Hypotension and Other ANS Disorders

T e first step in the evaluation of symptomatic OH is the exclusion of treatable causes. T e history should include a review of medications that may affect the ANS **(Table 41-6)**. T e main classes of drugs that may cause OH are diuretics, antihypertensives, antidepressants, ethanol, narcotics, insulin, dopamine agonists, barbiturates, and calcium channel-blocking agents. However, the precipitation of OH by medications may also be the first sign of an underlying autonomic disorder. T e history may reveal an underlying cause for symptoms (e.g., diabetes, Parkinson's disease) or specific underlying mechanisms (e.g., cardiac pump failure, reduced intravascular volume). T e relationship of symptoms to meals (splanchnic pooling), standing on awakening in the morning (intravascular volume depletion), ambient warming (vasodilatation), or exercise (muscle arteriolar vasodilatation) should be sought. Standing time to first symptom and to presyncope **(Chap. 11)** should be followed for management.

Physical examination includes measurement of supine and standing pulse and BP. OH is defined as a sustained drop in systolic (≥20 mmHg) or diastolic (≥10 mmHg) BP af er 2–3 min of standing.

TABLE 41-4

PREVALENCE OF ORTHOSTATIC HYPOTENSION IN DIFFERENT DISORDERS	
DISORDER	PREVALENCE
Aging	14–20%
Diabetic neuropathy	10%
Other autonomic neuropathies	10–50 per 100,000
Multiple system atrophy	5–15 per 100,000
Pure autonomic failure	10–30 per 100,000

TABLE 41-5

NONNEUROGENIC CAUSES OF ORTHOSTATIC HYPOTENSION	
Cardiac pump failure	**Venous pooling**
Myocardial infarction	Alcohol
Myocarditis	Postprandial dilation of splanchnic vessel beds
Constrictive pericarditis	Vigorous exercise with dilation of skeletal vessel beds
Aortic stenosis	Heat: hot environment, hot showers and baths, fever
Tachyarrhythmias	Prolonged recumbency or standing
Bradyarrhythmias	Sepsis
Salt-losing nephropathy	**Medications**
Adrenal insuf ciency	Antihypertensives
Diabetes insipidus	Diuretics
Venous obstruction	Vasodilators: nitrates, hydralazine
Reduced intravascular volume	Alpha- and beta-blocking agents
Straining or heavy lifting, urination, defecation	Central nervous system sedatives: barbiturates, opiates
Dehydration	Tricyclic antidepressants
Diarrhea, emesis	Phenothiazines
Hemorrhage	
Burns	
Metabolic	
Adrenocortical insuf ciency	
Hypoaldosteronism	
Pheochromocytoma	
Severe potassium depletion	

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 41-6

SOME DRUGS THAT AFFECT AUTONOMIC FUNCTION

SYMPTOM	DRUG CLASS	SPECIFIC EXAMPLES
Impotence	Opioids	Tylenol #3
	Anabolic steroids	—
	Some antiarrhythmics	Prazosin
	Some antihypertensives	Clonidine
	Some diuretics	Benazepril
	Some SSRIs	Venlafaxine
Urinary retention	Opioids	Fentanyl
	Decongestants	Brompheniramine
		Diphenhydramine
Diaphoresis	Some antihypertensives	Amlodipine
	Some SSRIs	Citalopram
	Opioids	Morphine
Hypotension	Tricyclics	Amitriptyline
	Beta blockers	Propranolol
	Diuretics	HCTZ
	CCBs	Verapamil

Abbreviations: CCBs, calcium channel blockers; HCTZ, hydrochlorothiazide; SSRIs, selective serotonin reuptake inhibitors.

In nonneurogenic causes of OH (such as hypovolemia), the BP drop is accompanied by a compensatory increase in heart rate of >15 beats/min. A clue that the patient has neurogenic OH is the aggravation or precipitation of OH by autonomic stressors (a meal, hot bath, or exercise). Neurologic examination should include mental status (neurodegenerative disorders), cranial nerves (impaired downgaze with progressive supranuclear palsy; abnormal pupils with Horner's or Adie's syndrome), motor tone (Parkinson's disease and parkinsonism), and sensation (polyneuropathies). In patients without a clear diagnosis initially, follow-up evaluations every few months or whenever symptoms worsen may reveal the underlying cause.

Disorders of autonomic function should be considered in patients with symptoms of altered sweating (hyperhidrosis or hypohidrosis), gastroparesis (bloating, nausea, vomiting of old food), impotence, constipation, or bladder disturbances (urinary frequency, hesitancy, or incontinence).

AUTONOMIC TESTING Autonomic function tests are helpful to document abnormalities when findings on history and examination are inconclusive; to detect subclinical involvement; or to follow the course of an autonomic disorder.

Heart rate variation with deep breathing T is tests the parasympathetic component of cardiovascular reflexes via the vagus nerve. Results are influenced by multiple factors including the subject's position (recumbent, sitting, or standing), rate and depth of respiration (6 breaths per minute and a forced vital capacity [FVC] >1.5 L are optimal), age, medications, weight, and degree of hypocapnia. Interpretation of results requires comparison of test data with results from age-matched controls collected under identical test conditions. For example, the lower limit of normal heart rate variation with deep breathing in persons <20 years is >15–20 beats/min, but for persons over age 60 it is 5–8 beats/min. Heart rate variation with deep breathing (respiratory sinus arrhythmia) is abolished by the muscarinic ACh receptor antagonist atropine but is unaffected by sympathetic postganglionic blockade (e.g., propranolol).

Valsalva response T is response **(Table 41-7)** assesses the integrity of the baroreflex control of heart rate (parasympathetic) and BP (adrenergic). Under normal conditions, increases in BP at the carotid bulb trigger a reduction in heart rate (increased vagal tone), and decreases in BP trigger an increase in heart rate (reduced vagal tone). T e Valsalva response is tested in the supine position. T e subject exhales against a closed glottis (or into a manometer maintaining a constant expiratory pressure of 40 mmHg) for 15 s while measuring changes in heart rate and beat-to-beat BP. T ere are four phases of the BP and heart rate response to the Valsalva maneuver. Phases I and III are mechanical and related to changes in intrathoracic and intraabdominal pressure. In early phase II, reduced venous return results in a fall in stroke volume and BP, counteracted by a combination of reflex tachycardia and increased total peripheral resistance. Increased total peripheral resistance arrests the BP drop ~5–8 s af er the onset of the maneuver. Late phase II begins with a progressive rise in BP toward or above baseline. Venous return and cardiac output return to normal in phase IV. Persistent peripheral arteriolar vasoconstriction and increased cardiac adrenergic tone result in a temporary BP overshoot and phase IV bradycardia (mediated by the baroreceptor reflex).

Autonomic function during the Valsalva maneuver can be measured using beat-to-beat BP or heart rate changes. T e Valsalva ratio is defined as the maximum phase II tachycardia divided by the minimum phase IV bradycardia **(Table 41-8)**. T e ratio reflects the integrity of the entire baroreceptor reflex arc and of sympathetic efferents to blood vessels.

Sudomotor function Sweating is induced by release of ACh from sympathetic postganglionic fibers. T e quantitative sudomotor axon reflex test (QSART) is a measure of regional autonomic function mediated by ACh-induced sweating. A reduced or absent response indicates a lesion of the postganglionic sudomotor axon. For example, sweating may be reduced in the feet as a result of distal

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 41-7

NORMAL BLOOD PRESSURE AND HEART RATE CHANGES DURING THE VALSALVA MANEUVER

PHASE	MANEUVER	BLOOD PRESSURE	HEART RATE	COMMENTS
I	Forced expiration against a partially closed glottis	Rises; aortic compression from raised intrathoracic pressure	Decreases	Mechanical
II early	Continued expiration	Falls; decreased venous return to the heart	Increases (reflex tachycardia)	Reduced vagal tone
II late	Continued expiration	Rises; reflex increase in peripheral vascular resistance	Increases at slower rate	Requires intact efferent sympathetic response
III	End of expiration	Falls; increased capacitance of pulmonary bed	Increases further	Mechanical
IV	Recovery	Rises; persistent vasoconstriction and increased cardiac output	Compensatory bradycardia	Requires intact efferent sympathetic response

polyneuropathy (e.g., diabetes). The thermoregulatory sweat test (TST) is a qualitative measure of regional sweat production in response to an elevation of body temperature under controlled conditions. An indicator powder placed on the anterior surface of the body changes color with sweat production during temperature elevation. The pattern of color change is a measure of regional sweat secretion. A postganglionic lesion is present if both QSART and TST show absent sweating. In a preganglionic lesion, the QSART is normal but TST shows anhidrosis.

TABLE 41-8

NEURAL PATHWAYS UNDERLYING SOME STANDARDIZED AUTONOMIC TESTS

TEST EVALUATED	PROCEDURE	AUTONOMIC FUNCTION
HRDB	6 deep breaths/min	Cardiovagal function
Valsalva ratio	Expiratory pressure, 40 mmHg for 10–15 s	Cardiovagal function
QSART	Axon-reflex test 4 limb sites	Postganglionic sudomotor function
BP_{BB} to VM	BP_{BB} response to VM	Adrenergic function: baroreflex adrenergic control of vagal and vasomotor function
HUT	BP_{BB} and heart rate response to HUT	Adrenergic and cardiovagal responses to HUT

Abbreviations: BP_{BB}, beat-to-beat blood pressure; HRDB, heart rate response to deep breathing; HUT, head-up tilt; QSART, quantitative sudomotor axon reflex test; VM, Valsalva maneuver.

Orthostatic BP recordings Beat-to-beat BP measurements determined in supine, 70° tilt, and tilt-back positions are useful to quantitate orthostatic failure of BP control. Allow a 20-min period of rest in the supine position before assessing changes in BP during tilting. The BP change combined with heart rate monitoring is useful for the evaluation of patients with suspected OH or unexplained syncope.

Tilt table testing for syncope The great majority of patients with syncope do not have autonomic failure. Tilt table testing can be used to make the diagnosis of vasovagal syncope with sensitivity, specificity, and reproducibility. A standardized protocol is used that specifies the tilt apparatus, angle and duration of tilt, and procedure for provocation of vasodilation (e.g., sublingual or spray nitroglycerin). A positive nitroglycerin-stimulated test predicts recurrence of syncope. Recommendations for the performance of tilt studies for syncope have been incorporated in consensus guidelines.

SPECIFIC SYNDROMES OF ANS DYSFUNCTION

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) is an entity that comprises autonomic failure (OH or a neurogenic bladder) and either parkinsonism (MSA-p) or a cerebellar syndrome (MSA-c) **(Chap. 36)**. MSA-p is the more common form; the parkinsonism is atypical in that it is usually unassociated with significant tremor or a response to levodopa. Symptomatic OH within 1 year of onset of parkinsonism predicts eventual development

www.ketabpezeshki.com (021) 66485457 - 66485438

of MSA-p in 75% of patients. There is a very high frequency of impotence in men. Although autonomic abnormalities are common in advanced Parkinson's disease **(Chap. 36)**, the severity and distribution of autonomic failure are more severe and generalized in MSA. Brain magnetic resonance imaging (MRI) is a useful diagnostic adjunct: in MSA-p, iron deposition in the striatum may be evident as T2 hypointensity, and in MSA-c, cerebellar atrophy is present with a characteristic T2 hyperintense signal ("hot cross buns sign") in the pons **(Fig. 41-2)**. Cardiac postganglionic adrenergic innervation, measured by uptake of fluorodopamine on positron emission tomography, is markedly impaired in the dysautonomia of Parkinson's disease (PD) but is usually normal in MSA. Neuropathologic changes include neuronal loss and gliosis in many CNS regions, including the brainstem, cerebellum, striatum, and intermediolateral cell column of the thoracolumbar spinal cord.

MSA is uncommon, with a prevalence estimated at 2–5 per 100,000 individuals. Onset is typically in the mid-fifties, men are slightly more often affected than women, and most cases are sporadic. The diagnosis should be considered in adults over the age of 30 years who present with OH or urinary incontinence and either parkinsonism that is poorly responsive to dopamine replacement or a cerebellar syndrome. MSA generally progresses relentlessly to death 7–10 years after onset, but survival beyond 15 years has been reported. Factors that predict a worse prognosis include rapid progression of disability, bladder dysfunction, female gender, the MSA-p subtype, and an older age at onset. Attempts to slow the progression of MSA have thus far been unsuccessful, including trials of lithium, growth hormone, riluzole, rasagiline, minocycline, and a recent trail of rifampicin.

Management is symptomatic for neurogenic OH (see below), sleep disorders including laryngeal stridor, and gastrointestinal (GI) and urinary dysfunction. GI management includes frequent small meals, soft diet, stool softeners, and bulk agents. Gastroparesis is difficult to treat; metoclopramide stimulates gastric emptying but worsens parkinsonism by blocking central dopamine receptors. The peripheral dopamine (D_2 and D_3) receptor antagonist domperidone has been used patients with various GI conditions in many countries and is now available in the United States through the U.S. Food and Drug Administration's (FDA) Expanded Access to Investigational Drugs program.

Autonomic dysfunction is also a common feature in dementia with Lewy bodies **(Chap. 35)**; the severity is usually less than that found in MSA or PD. In multiple sclerosis (MS; **Chap. 45**), autonomic complications reflect the CNS location of MS involvement and generally worsen with disease duration and disability.

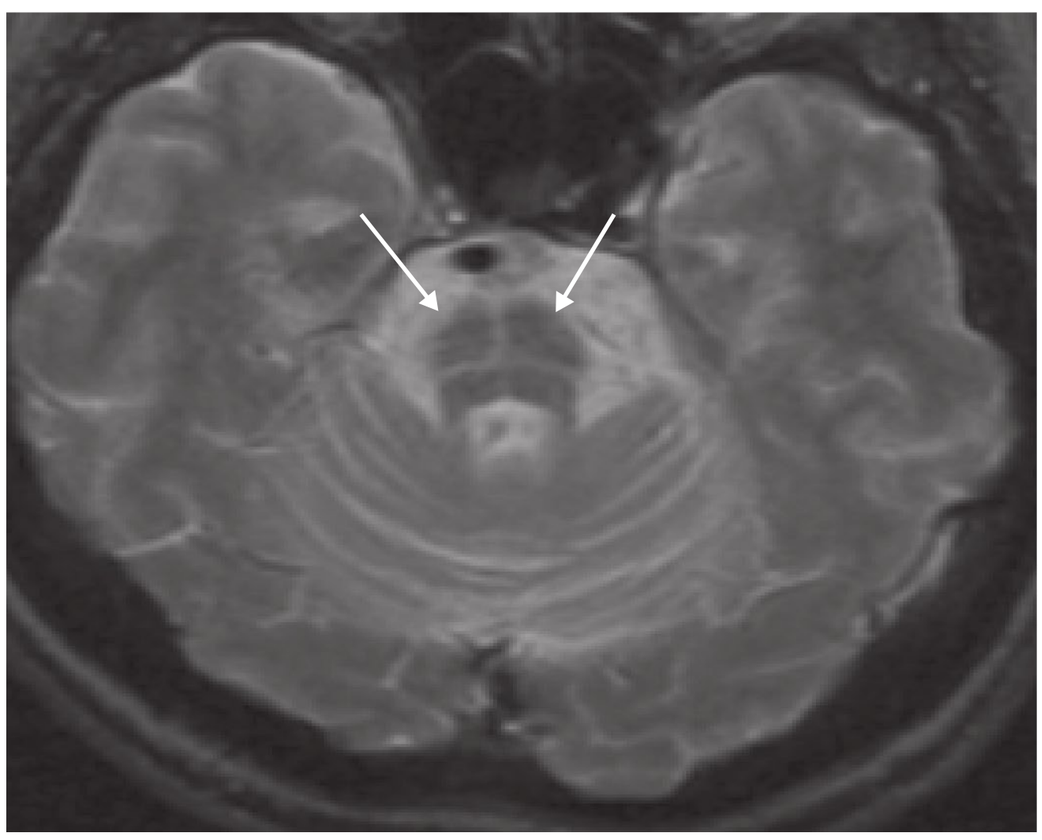


FIGURE 41-2
Multiple system atrophy, cerebellar type (MSA-c). Axial T2-weighted magnetic resonance image at the level of the pons shows a characteristic hyperintense signal, the "hot cross buns" sign. This appearance can also be seen in some spinocerebellar atrophies, as well as other neurodegenerative conditions affecting the brainstem.

SPINAL CORD

Spinal cord lesions from any cause may result in focal autonomic deficits or autonomic hyperreflexia (e.g., spinal cord transection or hemisection) affecting bowel, bladder, sexual, temperature-regulation, or cardiovascular functions. Quadriparetic patients exhibit both supine hypertension and OH after upward tilting. Autonomic dysreflexia describes a dramatic increase in BP in patients with traumatic spinal cord lesions above the T6 level, often in response to stimulation of the bladder, skin, or muscles. A distended or obstructed bladder, suprapubic palpation, catheter insertion, and urinary infection are common triggers. Associated symptoms can include facial flushing, headache, hypertension, or piloerection. Potential complications include intracranial vasospasm or hemorrhage, cardiac arrhythmia, and death. Awareness of the syndrome, identifying the trigger, and careful monitoring of BP during procedures in patients with acute or chronic spinal cord injury are essential. In patients with supine hypertension, BP can be lowered by tilting the head upward or sitting the patient up. Vasodilator drugs may be used to treat acute elevations in BP. Clonidine can be used prophylactically to reduce the hypertension resulting from bladder stimulation. Dangerous increases or decreases in body temperature may result from an inability to experience the sensory accompaniments of heat or cold exposure or control peripheral vasoconstriction or sweating below the level of the spinal cord injury.

www.ketabpezeshki.com (021) 66485457 - 66485438

PERIPHERAL NERVE AND NEUROMUSCULAR JUNCTION DISORDERS

Peripheral neuropathies **(Chap. 53)** are the most common cause of chronic autonomic insufficiency. Polyneuropathies that affect small myelinated and unmyelinated fibers of the sympathetic and parasympathetic nerves commonly occur in diabetes mellitus, amyloidosis, chronic alcoholism, porphyria, and Guillain-Barré syndrome. Neuromuscular junction disorders with autonomic involvement include botulism and Lambert-Eaton syndrome **(Chap. 55)**.

Diabetes mellitus

Autonomic neuropathy in patients with diabetes increases the mortality rate 1.5- to 3-fold, even after adjusting for other cardiovascular risk factors. Estimates of 5-year mortality risk among these patients range from 15 to 53%. Although many deaths are due to secondary vascular disease, there are patients who specifically suffer cardiac arrest due to autonomic neuropathy. The autonomic involvement is also predictive of other complications including renal disease, stroke, and sleep apnea.

Amyloidosis

Autonomic neuropathy occurs in both sporadic and familial forms of amyloidosis. The AL (immunoglobulin light chain) type is associated with primary amyloidosis or amyloidosis secondary to multiple myeloma. The ATTR type, with transthyretin as the primary protein component, is responsible for the most common form of inherited amyloidosis. Although patients usually present with a distal painful polyneuropathy accompanied by sensory loss, autonomic insufficiency can precede the development of the polyneuropathy or occur in isolation. The diagnosis can be made by protein electrophoresis of blood and urine, tissue biopsy (abdominal fat pad, rectal mucosa, or sural nerve) to search for amyloid deposits, and genetic testing for transthyretin mutations in familial cases. Treatment of familial cases with liver transplantation can be successful. The response of primary amyloidosis to melphalan and stem cell transplantation has been mixed. Death is usually due to cardiac or renal involvement. Postmortem studies reveal amyloid deposition in many organs, including two sites that contribute to autonomic failure: intraneural blood vessels and autonomic ganglia. Pathologic examination reveals a loss of both unmyelinated and myelinated nerve fibers.

Alcoholic neuropathy

Abnormalities in parasympathetic vagal and efferent sympathetic function are usually mild in alcoholic polyneuropathy. OH is usually due to brainstem involvement, rather than injury to the PNS. Impotence is a major problem, but concurrent gonadal hormone abnormalities may play a role in this symptom. Clinical symptoms of autonomic failure generally appear only when the stocking-glove polyneuropathy is severe, and there is usually coexisting Wernicke's encephalopathy **(Chap. 33)**. Autonomic involvement may contribute to the high mortality rates associated with alcoholism **(Chap. 63)**.

Porphyria

Autonomic dysfunction is most extensively documented in acute intermittent porphyria but can also occur with variegate porphyria and hereditary coproporphyria. Autonomic symptoms include tachycardia, sweating, urinary retention, abdominal pain, nausea and vomiting, insomnia, hypertension, and (less commonly) hypotension. Another prominent symptom is anxiety. Abnormal autonomic function can occur both during acute attacks and during remissions. Elevated catecholamine levels during acute attacks correlate with the degree of tachycardia and hypertension that is present.

Guillain-Barré syndrome

BP fluctuations and arrhythmias from autonomic instability can be severe **(Chap. 54)**. It is estimated that between 2 and 10% of patients with severe Guillain-Barré syndrome suffer fatal cardiovascular collapse. GI autonomic involvement, sphincter disturbances, abnormal sweating, and pupillary dysfunction can also occur. Demyelination has been described in the vagus and glossopharyngeal nerves, the sympathetic chain, and the white rami communicantes. Interestingly, the degree of autonomic involvement appears to be independent of the severity of motor or sensory neuropathy. Acute autonomic and sensory neuropathy is a variant that spares the motor system and presents with neurogenic OH and varying degrees of sensory loss. It is treated similarly to Guillain-Barré syndrome, but prognosis is less favorable, with persistent severe sensory deficits and variable degrees of OH in many patients.

Autoimmune autonomic ganglionopathy (AAG)

This disorder presents with the subacute development of autonomic disturbances including OH, enteric neuropathy (gastroparesis, ileus, constipation/diarrhea), flaccid bladder, and cholinergic failure (e.g., loss of sweating, sicca complex, and a tonic pupil). A chronic form of AAG resembles pure autonomic failure (see below). Autoantibodies against the ganglionic ACh receptor (A_3 AChR), which are present in approximately half of patients, are considered diagnostic of AAG. Pathology

www.ketabpezeshki.com (021) 66485457 - 66485438

shows preferential involvement of small unmyelinated nerve fibers, with sparing of larger myelinated ones. Onset of the neuropathy follows a viral infection in approximately half of cases. Up to one-third of untreated patients experience significant functional improvement over time. Immunotherapies that have been reported to be helpful include plasmapheresis, intravenous immune globulin, glucocorticoids, azathioprine, rituximab, and mycophenolate mofetil. OH, gastroparesis, and sicca symptoms can be managed symptomatically.

AAG can also occur on a paraneoplastic basis, with adenocarcinoma or small-cell carcinoma of the lung, lymphoma, or thymoma being the most common **(Chap. 50)**. In the paraneoplastic cases, distinctive additional features, such as cerebellar involvement or dementia, may be present **(see Tables 50-1, 50-2, and 50-3)**. T e neoplasm may be occult and possibly suppressed by the autoantibody.

Botulism

Botulinum toxin binds presynaptically to cholinergic nerve terminals and, after uptake into the cytosol, blocks ACh release. T is acute cholinergic neuropathy presents as motor paralysis and autonomic disturbances that include blurred vision, dry mouth, nausea, unreactive or sluggishly reactive pupils, constipation, and urinary retention.

PURE AUTONOMIC FAILURE (PAF)

T is sporadic syndrome consists of postural hypotension, impotence, bladder dysfunction, and impaired sweating. T e disorder begins in midlife and occurs in women more often than men. T e symptoms can be disabling, but the disease does not shorten life span. T e clinical and pharmacologic characteristics suggest primary involvement of postganglionic sympathetic neurons. A severe reduction in the density of neurons within sympathetic ganglia results in low supine plasma NE levels and noradrenergic supersensitivity. Some patients who are initially labeled with this diagnosis subsequently go on to develop AAG or MSA. Skin biopsies can demonstrate phosphorylated α-synuclein inclusions in postganglionic sympathetic adrenergic and cholinergic nerve fibers from some individuals with PAF, distinguishing them from AAG and suggesting that PAF is a synucleinopathy; patients with PD also have α-synuclein inclusions in sympathetic nerve biopsies.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

T is syndrome is characterized by symptomatic orthostatic intolerance without OH, accompanied by either an increase in heart rate to >120 beats/min or an increase of 30 beats/min with standing that subsides on sitting or lying down. Women are affected approximately five times more often than men, and most develop the syndrome between the ages of 15 and 50. Presyncopal symptoms (lightheadedness, weakness, blurred vision) combined with symptoms of autonomic overactivity (palpitations, tremulousness, nausea) are common. Recurrent unexplained episodes of dysautonomia and fatigue also occur. T e pathogenesis is unclear, but there is increasing evidence for sympathetic denervation distally in the legs with preserved cardiovascular function. Hypovolemia, venous pooling, impaired brainstem regulation, or increased sympathetic activity may play a role. Optimal treatment is uncertain, but expansion of fluid volume with water, salt, and fludrocortisone can be helpful as initial interventions. If this approach is inadequate, then midodrine, pyridostigmine, phenobarbital, beta blockers, or clonidine can be tried. Reconditioning and a sustained exercise program are important adjuncts to treatment.

INHERITED DISORDERS

T ere are five known hereditary sensory and autonomic neuropathies (HSAN I–V). T e most important autonomic variants are HSAN I and HSAN III. HSAN I is dominantly inherited and often presents as a distal small-fiber neuropathy (burning feet syndrome) associated with sensory loss and foot ulcers. T e most common responsible gene, on chromosome 9q, is SPTLC1. SPTLC is an important enzyme in the regulation of ceramide. Cells from HSAN I patients with the mutation produce higher-than-normal levels of glucosyl ceramide, perhaps triggering apoptosis. HSAN III (Riley-Day syndrome; familial dysautonomia) is an autosomal recessive disorder of Ashkenazi Jewish children and adults and is much less prevalent than HSAN I. Decreased tearing, hyperhidrosis, reduced sensitivity to pain, areflexia, absent fungiform papillae on the tongue, and labile BP may be present. Episodic abdominal crises and fever are common. Pathologic examination of nerves reveals a loss of sympathetic, parasympathetic, and sensory neurons. T e defective gene, IKBKAP, may prevent normal transcription of important molecules in neural development.

PRIMARY HYPERHIDROSIS

T is syndrome presents with excess sweating of the palms of the hands and soles of the feet beginning in childhood or early adulthood. T e condition tends to improve with age. T e disorder affects 0.6–1.0% of the population. T e etiology is unclear, but there may be a genetic component because 25% of patients have

www.ketabpezeshki.com (021) 66485457 - 66485438

a positive family history. T e condition can be socially embarrassing (e.g., shaking hands) or even disabling (e.g., inability to write without soiling the paper). Topical antiperspirants are occasionally helpful. More useful are potent anticholinergic drugs such as glycopyrrolate (1–2 mg PO tid). T2 ganglionectomy or sympathectomy is successful in >90% of patients with palmar hyperhidrosis. T e advent of endoscopic transaxillary T2 sympathectomy has lowered the complication rate of the procedure. T e most common postoperative complication is compensatory hyperhidrosis, which improves spontaneously over months. Other potential complications include recurrent hyperhidrosis (16%), Horner's syndrome (<2%), gustatory sweating, wound infection, hemothorax, and intercostal neuralgia. Local injection of botulinum toxin has also been used to block cholinergic, postganglionic sympathetic fibers to sweat glands in patients with palmar hyperhidrosis. T is approach is limited by the need for repetitive injections (the effect usually lasts 4 months before waning).

ACUTE SYMPATHETIC OVERACTIVITY SYNDROMES

T e physician may be confronted occasionally with an acute state of sympathetic overactivity.

An autonomic storm is an acute state of sustained sympathetic surge that results in variable combinations of alterations in BP and heart rate, body temperature, respiration, and sweating. Causes of autonomic storm include brain and spinal cord injury, toxins and drugs, autonomic neuropathy, and chemodectomas (e.g., pheochromocytoma). Brain injury is the most common cause of autonomic storm and typically follows severe head trauma and postresuscitation encephalopathy anoxic-ischemic brain injury. Autonomic storm can also occur with other acute intracranial lesions such as hemorrhage, cerebral infarction, rapidly expanding tumors, subarachnoid hemorrhage, hydrocephalus, or (less commonly) an acute spinal cord lesion. T e most consistent setting is that of an acute intracranial catastrophe of suf cient size and rapidity to produce a massive catecholaminergic surge. T e surge can cause seizures, neurogenic pulmonary edema, and myocardial injury. Manifestations include fever, tachycardia, hypertension, tachypnea, hyperhidrosis, pupillary dilatation, and flushing. Lesions of the afferent limb of the baroreflex can result in milder recurrent autonomic storms; many of these follow neck irradiation.

Drugs and toxins may also be responsible, including sympathomimetics such as phenylpropanolamine, cocaine, amphetamines, and tricyclic antidepressants; tetanus; and, less often, botulinum toxin. Cocaine, including "crack," can cause a hypertensive state with CNS hyperstimulation. Tricyclic overdose, such as from amitriptyline, can cause flushing, hypertension, tachycardia, fever, mydriasis, anhidrosis, and a toxic psychosis. T e hyperadrenergic state associated with Guillain-Barré syndrome can produce a moderate autonomic storm. Pheochromocytoma presents with a paroxysmal or sustained hyperadrenergic state, headache, hyperhidrosis, palpitations, anxiety, tremulousness, and hypertension. Neuroleptic malignant syndrome refers to a syndrome of muscle rigidity, hyperthermia, and hypertension in psychotic patients treated with phenothiazines **(Chap. 36)**. Management of autonomic storm includes ruling out other causes of autonomic instability, including malignant hyperthermia, porphyria, and seizures. Sepsis and encephalitis need to be excluded with appropriate studies. An electroencephalogram (EEG) should be done to search for seizure activity; MRI of the brain and spine is often necessary. T e patient should be managed in an intensive care unit. Management with morphine sulphate (10 mg every 4 h) and labetalol (100–200 mg twice daily) may be helpful. Supportive treatment may need to be maintained for several weeks. For chronic and milder autonomic storm, propranolol and/or clonidine can be effective.

MISCELLANEOUS

Other conditions associated with autonomic failure include infections, malignancy, poisoning (organophosphates), and aging. Disorders of the hypothalamus can affect autonomic function and produce abnormalities in temperature control, satiety, sexual function, and circadian rhythms **(Chap. 51)**.

REFLEX SYMPATHETIC DYSTROPHY AND CAUSALGIA

T e failure to identify a primary role of the ANS in the pathogenesis of these disorders has resulted in a change of nomenclature. T e terms complex regional pain syndrome (CRPS) types I and II are now used in place of reflex sympathetic dystrophy (RSD) and causalgia.

CRPS type I is a regional pain syndrome that often develops after tissue injury and most commonly affects one limb. Examples of associated injury include minor shoulder or limb trauma, fractures, myocardial infarction, or stroke. Allodynia (the perception of a nonpainful stimulus as painful), hyperpathia (an exaggerated pain response to a painful stimulus), and spontaneous pain occur. T e symptoms are unrelated to the severity of the initial trauma and are not confined to the distribution of a single peripheral nerve. CRPS type II is a regional pain syndrome that develops after injury to a specific peripheral nerve, often a major nerve trunk.

www.ketabpezeshki.com (021) 66485457 - 66485438

Spontaneous pain initially develops within the territory of the affected nerve but eventually may spread outside the nerve distribution.

Pain (usually burning or electrical in quality) is the primary clinical feature of CRPS. Vasomotor dysfunction, sudomotor abnormalities, or focal edema may occur alone or in combination but must be present for diagnosis. Limb pain syndromes that do not meet these criteria are best classified as "limb pain—not otherwise specified." In CRPS, localized sweating (increased resting sweat output) and changes in blood flow may produce temperature differences between affected and unaffected limbs.

CRPS type I (RSD) has been classically divided into three clinical phases. Phase I consists of pain and swelling in the distal extremity occurring within weeks to 3 months after the precipitating event. T e pain is diffuse, spontaneous, and either burning, throbbing, or aching in quality. T e involved extremity is warm and edematous, and the joints are tender. Increased sweating and hair growth develop. In phase II (3–6 months after onset), thin, shiny, cool skin appears. After an additional 3–6 months (phase III), atrophy of the skin and subcutaneous tissue plus flexion contractures complete the clinical picture. Autonomic testing or bone scans are occasionally useful when the diagnosis is in doubt.

T e natural history of typical CRPS may be more benign and more variable than previously recognized. A variety of surgical and medical treatments have been developed, with conflicting reports of ef cacy. Clinical trials suggest that early mobilization with physical therapy or a brief course of glucocorticoids may be helpful for CRPS type I or II. Other medical treatments include the use of adrenergic blockers, nonsteroidal anti-inflammatory drugs, calcium channel blockers, phenytoin, opioids, and calcitonin. Stellate ganglion blockade is a commonly used invasive technique that often provides temporary pain relief, but the ef cacy of repetitive blocks is uncertain.

TREATMENT Autonomic Failure

Management of autonomic failure is aimed at specific treatment of the cause and alleviation of symptoms. Of particular importance is the removal of drugs or amelioration of underlying conditions that cause or aggravate the autonomic symptoms, especially in the elderly. For example, OH can be caused or aggravated by angiotensin-converting enzyme inhibitors, calcium channel-blocking agents, tricyclic antidepressants, levodopa, alcohol, or insulin. A summary of drugs that can cause OH by class, putative mechanism, and magnitude of the BP drop is shown in Table 41-6.

PATIENT EDUCATION Only a minority of patients with OH require drug treatment. All patients should be taught the mechanisms of postural normotension (volume status, resistance and capacitance bed, autoregulation) and the nature of orthostatic stressors (time of day and the influence of meals, heat, standing, and exercise). Patients should learn to recognize orthostatic symptoms early (especially subtle cognitive symptoms, weakness, and fatigue) and to modify or avoid activities that provoke episodes. Other helpful measures may include keeping a BP log and dietary education (salt/fluids). Learning physical counter-maneuvers that reduce standing OH and practicing postural and resistance training are helpful measures.

SYMPTOMATIC TREATMENT Nonpharmacologic approaches are summarized in **Table 41-9**. Adequate intake of salt and fluids to produce a voiding volume between 1.5 and 2.5 L of urine (containing >170 meq/L of Na^+) each 24 h is essential. Sleeping with the head of the bed elevated will minimize the effects of supine nocturnal hypertension. Prolonged recumbency should be avoided when possible. Patients are advised to sit with legs dangling over the edge of the bed for several minutes before attempting to stand in the morning; other postural stresses should be similarly approached in a gradual manner. One maneuver that can reduce OH is leg-crossing with maintained contraction of leg muscles for 30 s; this compresses leg veins and increases systemic resistance. Compressive garments, such as compression stockings or abdominal binders, are helpful on occasion but uncomfortable for many patients. For transient worsening of OH, drinking two 250-mL (8-oz) glasses of water can raise standing BP 20–30 mmHg for about 2 h, beginning ~20 min after the fluid load. T e patient can increase intake of salt and fluids (bouillon treatment), increase use of physical counter-maneuvers (elevate the legs when supine), or temporarily resort to a full-body stocking (compression pressure 30–40 mmHg).

Anemia should be corrected with erythropoietin, administered subcutaneously at doses of 25–75 U/kg three times per week. T e hematocrit increases after 2–6 weeks. A weekly maintenance dose is usually necessary. However, the increased intravascular volume that accompanies the rise in hematocrit can exacerbate supine hypertension.

TABLE 41-9

INITIAL TREATMENT OF ORTHOSTATIC HYPOTENSION (OH)
Patient education: mechanisms and stressors of OH
High-salt diet (10–20 g/d)
High-f uid intake (2 L/d)
Elevate head of bed 10 cm (4 in.) to minimize supine hypertension
Maintain postural stimuli
Learn physical counter-maneuvers
Compression garments
Correct anemia

www.ketabpezeshki.com (021) 66485457 - 66485438

If these measures are not suf cient, pharmacologic treatment may be necessary. Midodrine, a directly acting α_1-agonist that does not cross the blood-brain barrier, is effective. It has a duration of action of 2–4 h. T e usual dose is 5–10 mg orally tid, but some patients respond best to a decremental dose (e.g., 15 mg on awakening, 10 mg at noon, and 5 mg in the afternoon). Midodrine should not be taken after 6:00 p.m. Side effects include pruritus, uncomfortable piloerection, and supine hypertension especially at higher doses. Droxidopa (Northera) was recently approved by the FDA for treatment of neurogenic OH associated with PAF, PD, or MSA; oral droxidopa is converted to NE and in short-term clinical trails was effective in decreasing symptoms of OH. Pyridostigmine (Mestinon) appears to improve OH without aggravating supine hypertension by enhancing ganglionic transmission (maximal when orthostatic, minimal when supine). Fludrocortisone will reduce OH but aggravates supine hypertension. At doses between 0.1 mg/d and 0.3 mg bid orally, it enhances renal sodium conservation and increases the sensitivity of arterioles to NE. Susceptible patients may develop fluid overload, congestive heart failure, supine hypertension, or hypokalemia. Potassium supplements are often necessary with chronic administration of fludrocortisone. Sustained elevations of supine BP >180/110 mmHg should be avoided. Supine hypertension (>180/110 mmHg) can be self-treated by avoiding the supine position (e.g., sleeping in a recumbent chair) and reducing fludrocortisone. A daily glass of wine, if requested by the patient, can be taken shortly before bedtime. If these simple measures are not adequate, drugs to be considered include oral hydralazine (25 mg qhs), oral nifedipine (Procardia; 10 mg qhs), or a nitroglycerin patch.

A promising drug combination (atomoxetine and yohimbine) has been studied for use in human subjects with severe OH not responsive to other agents, as can occur is some patients with diabetes and severe autonomic neuropathy not responsive to other medications. T e atomoxetine blocks the NE reuptake transporter, and yohimbine blocks α_2 receptors that mediate the sympathetic feedback loop for downregulation of BP in response to atomoxetine. T e result is a dramatic increase in BP and standing tolerance. T is combination is not FDA approved for this purpose. It is possible that the limited drug duration of action can be used to withdraw drug treatment when the patient anticipates becoming supine (e.g., before sleep).

Postprandial OH may respond to several measures. Frequent, small, low-carbohydrate meals may diminish splanchnic shunting of blood after meals and reduce postprandial OH. Prostaglandin inhibitors (ibuprofen or indomethacin) taken with meals or midodrine (10 mg with the meal) can be helpful. T e somatostatin analogue octreotide can be useful in the treatment of postprandial syncope by inhibiting the release of GI peptides that have vasodilator and hypotensive effects. T e subcutaneous dose ranges from 25 μg bid to 200 μg tid.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 42

TRIGEMINAL NEURALGIA, BELL'S PALSY, AND OTHER CRANIAL NERVE DISORDERS

M. Flint Beal ■ Stephen L. Hauser

Symptoms and signs of cranial nerve pathology are common in internal medicine. T ey often develop in the context of a widespread neurologic disturbance, and in such situations, cranial nerve involvement may represent the initial manifestation of the illness. In other disorders, involvement is largely restricted to one or several cranial nerves; these distinctive disorders are reviewed in this chapter. **Disorders of ocular movement are discussed in Chap. 25, disorders of hearing in Chap. 29, and vertigo and disorders of vestibular function in Chap. 12.**

FACIAL PAIN OR NUMBNESS

ANATOMIC CONSIDERATIONS

T e trigeminal (fifth cranial) nerve supplies sensation to the skin of the face and anterior half of the head **(Fig. 42-1)**. T e motor part innervates the muscles involved in chewing (including masseters and pterygoids) as well as the tensor tympani of the middle ear (hearing especially for high-pitched tones). It is the largest of the cranial nerves. It exits in the lateral midpons and traverses the middle cranial fossa to the semilunar (gasserian, trigeminal) ganglion in Meckel's cave, where the nerve divides into three divisions (ophthalmic [V1], maxillary [V2], and mandibular [V3]). V1 and V2 traverse the cavernous sinus to exit in the superior orbital fissure and foramen rotundum, located above and below the eye socket respectively; V3 exits through the foramen ovale. T e trigeminal nerve is predominantly sensory, and motor innervation is exclusively carried in V3. T e cornea is primarily innervated by V1, although an inferior crescent may be V2. Upon entering the pons, pain and temperature fibers descend ipsilaterally to the upper cervical spinal cord as the spinal tract of V, before synapsing with the spinal nucleus of V; this accounts for the facial numbness that can occur with spinal cord lesions above C2. In the brainstem, the spinal tract of V is also located adjacent to crossed ascending fibers of the spinothalamic tract, producing a "crossed" sensory loss for pain and temperature (ipsilateral face, contralateral arm/trunk/leg) with lesions of the lateral lower brainstem. CN V is also ensheathed by oligodendrocyte-derived, rather than Schwann cell–derived, myelin for up to 7 mm after it leaves the brainstem, unlike just a few millimeters for other cranial and spinal nerves; this may explain the high frequency of trigeminal neuralgia in multiple sclerosis **(Chap. 45)**, a disorder of oligodendrocyte myelin.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX)

Clinical manifestations

Trigeminal neuralgia is characterized by excruciating paroxysms of pain in the lips, gums, cheek, or chin and, very rarely, in the distribution of the ophthalmic division of the fifth nerve. T e pain seldom lasts more than a few seconds or a minute or two but may be so intense that the patient winces, hence the term tic. T e paroxysms, experienced as single jabs or clusters, tend to recur frequently, both day and night, for several weeks at a time. T ey may occur spontaneously or with movements of affected areas evoked by speaking, chewing, or smiling. Another characteristic feature is the presence of trigger zones, typically on the face, lips, or tongue, that provoke attacks; patients may report that tactile stimuli—e.g., washing the face, brushing the teeth, or exposure to a draft of air—generate excruciating pain. An essential feature of trigeminal neuralgia is that objective signs of sensory loss cannot be demonstrated on examination.

www.ketabpezeshki.com (021) 66485457 - 66485438

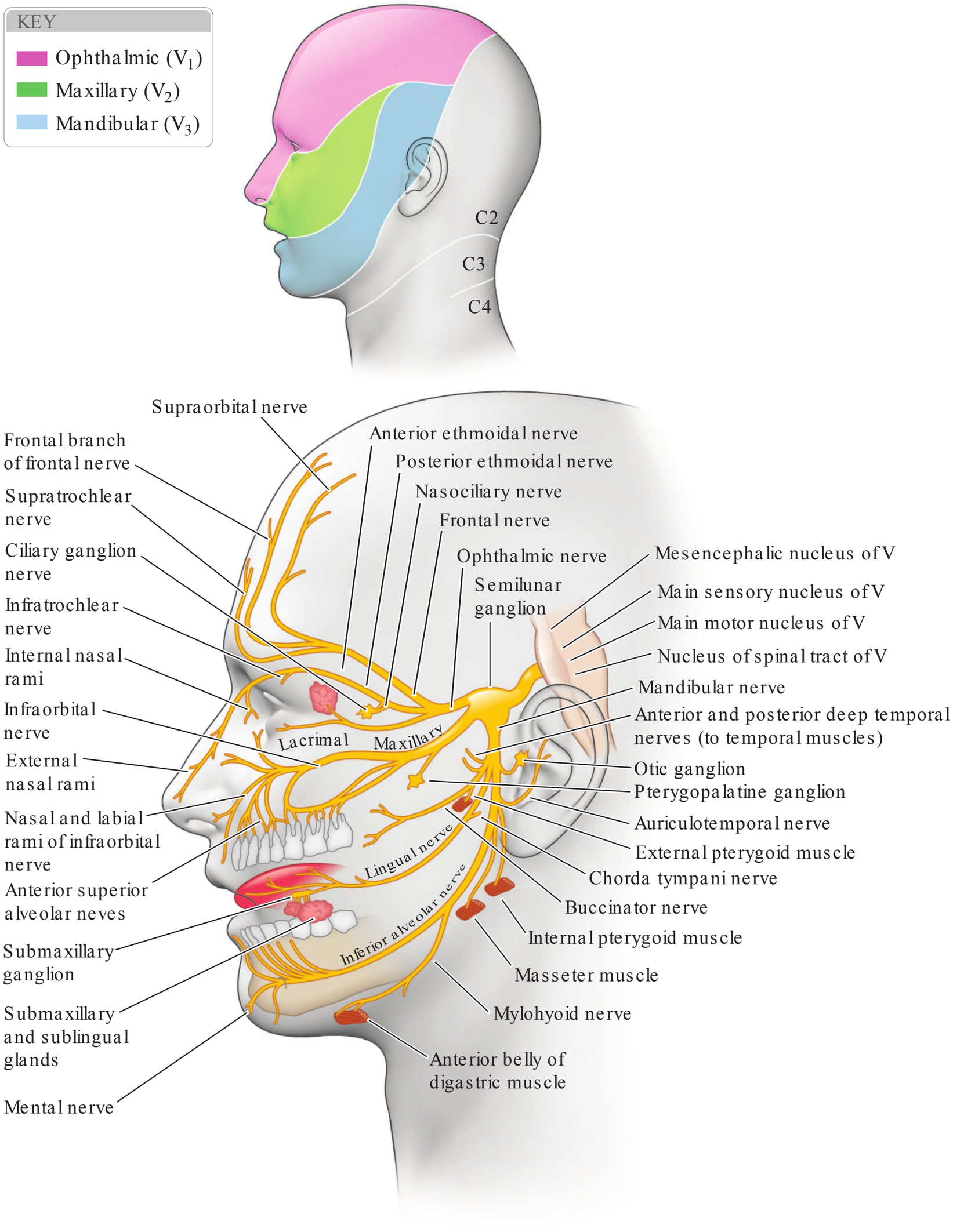


FIGURE 42-1
The trigeminal nerve and its branches and sensory distribution on the face. The three major sensory divisions of the trigeminal nerve consist of the ophthalmic, maxillary, and mandibular nerves. (Adapted from Waxman SG: Clinical Neuroanatomy, 26th ed. http://www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.)

Trigeminal neuralgia is relatively common, with an estimated annual incidence of 4–8 per 100,000 individuals. Middle-aged and elderly persons are affected primarily, and ~60% of cases occur in women. Onset is typically sudden, and bouts tend to persist for weeks or months before remitting spontaneously. Remissions may be long-lasting, but in most patients, the disorder ultimately recurs.

Pathophysiology

Symptoms result from ectopic generation of action potentials in pain-sensitive afferent fibers of the fifth cranial nerve root just before it enters the lateral surface of the pons. Compression or other pathology in the nerve leads to demyelination of large myelinated fibers that do not themselves carry pain sensation but

www.ketabpezeshki.com (021) 66485457 - 66485438

become hyperexcitable and electrically coupled with smaller unmyelinated or poorly myelinated pain fibers in close proximity; this may explain why tactile stimuli, conveyed via the large myelinated fibers, can stimulate paroxysms of pain. Compression of the trigeminal nerve root by a blood vessel, most often the superior cerebellar artery or on occasion a tortuous vein, is now believed to be the source of trigeminal neuralgia in most patients. In cases of vascular compression, age-related brain sagging and increased vascular thickness and tortuosity may explain the prevalence of trigeminal neuralgia in later life.

Differential diagnosis

Trigeminal neuralgia must be distinguished from other causes of face and head pain **(Chap. 9)** and from pain arising from diseases of the jaw, teeth, or sinuses. Pain from migraine or cluster headache tends to be deep-seated and steady, unlike the superficial stabbing quality of trigeminal neuralgia; rarely, cluster headache is associated with trigeminal neuralgia, a syndrome known as cluster-tic. In temporal arteritis, superficial facial pain is present but is not typically shock-like, the patient frequently complains of myalgias and other systemic symptoms, and an elevated erythrocyte sedimentation rate (ESR) is usually present. When trigeminal neuralgia develops in a young adult or is bilateral, multiple sclerosis (MS) is a key consideration, and in such cases, the cause is a demyelinating plaque near the root entry zone of the fifth nerve in the pons; often, evidence of facial sensory loss can be found on careful examination. Cases that are secondary to mass lesions—such as aneurysms, neurofibromas, acoustic schwannomas, or meningiomas—usually produce objective signs of sensory loss in the trigeminal nerve distribution (trigeminal neuropathy, see below).

Laboratory evaluation

An ESR is indicated if temporal arteritis is suspected. In typical cases of trigeminal neuralgia, neuroimaging studies are usually unnecessary but may be valuable if MS is a consideration or in assessing overlying vascular lesions in order to plan for decompression surgery.

TREATMENT Trigeminal Neuralgia

Drug therapy with carbamazepine is effective in ~50–75% of patients. Carbamazepine should be started as a single daily dose of 100 mg taken with food and increased gradually (by 100 mg daily in divided doses every 1–2 days) until substantial (>50%) pain relief is achieved. Most patients require a maintenance dose of 200 mg qid. Doses >1200 mg daily provide no additional benefit. Dizziness, imbalance, sedation, and rare cases of agranulocytosis are the most important side effects of carbamazepine. If treatment is effective, it is usually continued for 1 month and then tapered as tolerated. Oxcarbazepine (300–1200 mg bid) is an alternative to carbamazepine that has less bone marrow toxicity and probably is equally efficacious. If these agents are not well tolerated or are ineffective, lamotrigine, 400 mg daily, and phenytoin, 300–400 mg daily, are other options. Baclofen may also be tried, either alone or in combination with an anticonvulsant. The initial dose is 5–10 mg tid, gradually increasing as needed to 20 mg qid.

If drug treatment fails, surgical therapy should be offered. The most widely used method is currently microvascular decompression to relieve pressure on the trigeminal nerve as it exits the pons. This procedure requires a suboccipital craniotomy. This procedure appears to have a >70% efficacy rate and a low rate of pain recurrence in responders; the response is better for classic tic-like symptoms than for nonlancinating facial pains. In a small number of cases, there is perioperative damage to the eighth or seventh cranial nerves or to the cerebellum or a postoperative cerebrospinal fluid leak syndrome. High-resolution magnetic resonance angiography is useful preoperatively to visualize the relationships between the fifth cranial nerve root and nearby blood vessels.

Gamma knife radiosurgery of the trigeminal nerve root is also used for treatment and results in complete pain relief, sometimes delayed in onset, in more than two-thirds of patients and a low risk of persistent facial numbness; the response is sometimes long-lasting, but recurrent pain develops over 2–3 years in half of patients. Compared with surgical decompression, gamma knife surgery appears to be somewhat less effective but has few serious complications.

Another procedure, radiofrequency thermal rhizotomy, creates a heat lesion of the trigeminal ganglion or nerve. It is used less often now than in the past. Short-term relief is experienced by >95% of patients; however, long-term studies indicate that pain recurs in up to one-third of treated patients. Postoperatively, partial numbness of the face is common, masseter (jaw) weakness may occur especially following bilateral procedures, and corneal denervation with secondary keratitis can follow rhizotomy for first-division trigeminal neuralgia.

TRIGEMINAL NEUROPATHY

A variety of diseases can affect the trigeminal nerve **(Table 42-1)**. Most present with sensory loss on the face or with weakness of the jaw muscles. Deviation of the jaw on opening indicates weakness of the pterygoids on the side to which the jaw deviates. Some cases are due to Sjögren's syndrome or a collagen-vascular disease such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. Among infectious causes, herpes zoster (acute or postherpetic) and leprosy should be considered. Tumors of the

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 42-1

TRIGEMINAL NERVE DISORDERS

Nuclear (brainstem) lesions	**Peripheral nerve lesions**
Multiple sclerosis	Nasopharyngeal carcinoma
Stroke	Trauma
Syringobulbia	Guillain-Barré syndrome
Glioma	Sjögren's syndrome
Lymphoma	Collagen-vascular diseases
Preganglionic lesions	Sarcoidosis
Acoustic neuroma	Leprosy
Meningioma	Drugs (stilbamidine, trichloroethylene)
Metastasis	Idiopathic trigeminal neuropathy
Chronic meningitis	
Cavernous carotid aneurysm	
Gasserian ganglion lesions	
Trigeminal neuroma	
Herpes zoster	
Infection (spread from otitis media or mastoiditis)	

middle cranial fossa (meningiomas), of the trigeminal nerve (schwannomas), or of the base of the skull (metastatic tumors) may cause a combination of motor and sensory signs. Lesions in the cavernous sinus can affect the first and second divisions of the trigeminal nerve, and lesions of thesuperior orbital fissure can affect the first (ophthalmic) division; the accompanying corneal anesthesia increases the risk of ulceration (neurokeratitis).

Isolated sensory loss over the chin (mental neuropathy) can be the only manifestation of systemic malignancy. Rarely, an idiopathic form of trigeminal neuropathy is observed. It is characterized by numbness and paresthesias, sometimes bilaterally, with loss of sensation in the territory of the trigeminal nerve but without weakness of the jaw. Gradual recovery is the rule. Tonic spasm of the masticatory muscles, known as trismus, is symptomatic of tetanus or may occur in patients treated with phenothiazines.

FACIAL WEAKNESS

ANATOMIC CONSIDERATIONS

(Fig. 42-2) T e seventh cranial nerve supplies all the muscles concerned with facial expression. T e sensory component is small (the nervus intermedius); it conveys taste sensation from the anterior two-thirds of the tongue and probably cutaneous impulses from the anterior wall of the external auditory canal. T e motor nucleus of the seventh nerve lies anterior and lateral to the abducens nucleus. After leaving the pons, the seventh nerve enters the internal auditory meatus with the acoustic nerve. T e nerve continues its course in its own bony channel, the facial canal, and exits from the skull via the stylomastoid foramen. It then passes through the parotid gland and subdivides to supply the facial muscles.

A complete interruption of the facial nerve at the stylomastoid foramen paralyzes all muscles of facial expression. T e corner of the mouth droops, the creases and skinfolds are effaced, the forehead is unfurrowed, and the eyelids will not close. Upon attempted closure of the lids, the eye on the paralyzed side rolls upward (Bell's phenomenon). T e lower lid sags and falls away from the conjunctiva, permitting tears to spill over the cheek. Food collects between the teeth and lips, and saliva may dribble from the corner of the mouth. T e patient complains of a heaviness or numbness in the face, but sensory loss is rarely demonstrable and taste is intact.

If the lesion is in the middle-ear portion, taste is lost over the anterior two-thirds of the tongue on the same side. If the nerve to the stapedius is interrupted, there is hyperacusis (sensitivity to loud sounds). Lesions in the internal auditory meatus may affect the adjacent auditory and vestibular nerves, causing deafness, tinnitus, or dizziness. Intrapontine lesions that paralyze the face usually affect the abducens nucleus as well, and often the corticospinal and sensory tracts.

If the peripheral facial paralysis has existed for some time and recovery of motor function is incomplete, a continuous diffuse contraction of facial muscles may appear. T e palpebral fissure becomes narrowed, and the nasolabial fold deepens. Attempts to move one group of facial muscles may result in contraction of all (associated movements, or synkinesis). Facial spasms, initiated by movements of the face, may develop (hemifacial spasm). Anomalous regeneration of seventh nerve fibers may result in other troublesome phenomena. If fibers originally connected with the orbicularis oculi come to innervate the orbicularis oris, closure of the lids may cause a retraction of the mouth, or if fibers originally connected with muscles of the face later innervate the lacrimal gland, anomalous tearing ("crocodile tears") may occur with any activity of the facial muscles, such as eating. Another facial synkinesia is triggered by jaw opening, causing closure of the eyelids on the side of the facial palsy (jaw-winking).

BELL'S PALSY

T e most common form of facial paralysis is Bell's palsy. T e annual incidence of this idiopathic disorder is ~25 per 100,000 annually, or about 1 in 60 persons in a lifetime. Risk factors include pregnancy and diabetes mellitus.

www.ketabpezeshki.com (021) 66485457 - 66485438

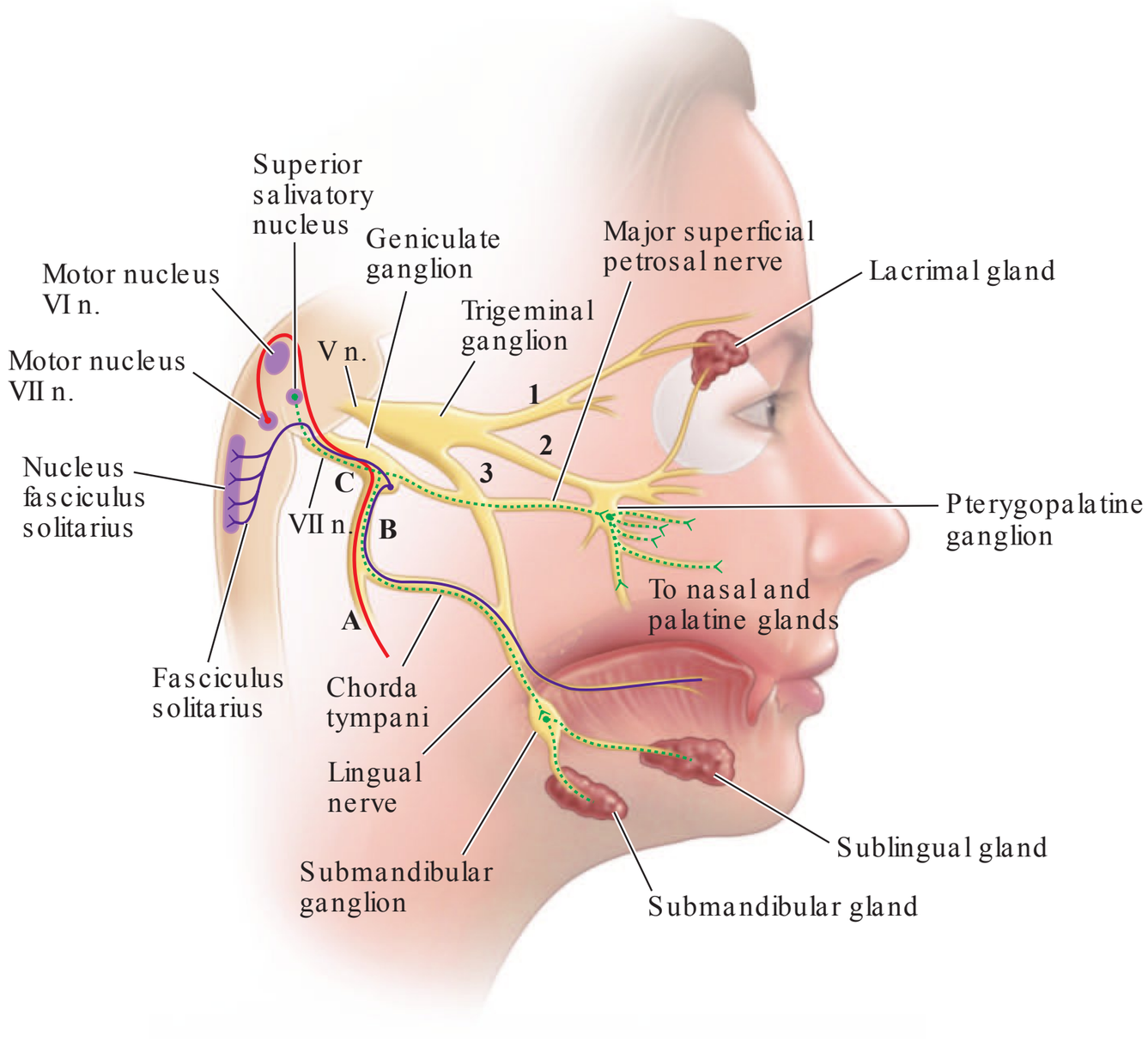


FIGURE 42-2

The facial nerve. A, B, and C denote lesions of the facial nerve at the stylomastoid foramen, distal and proximal to the geniculate ganglion, respectively. Green lines indicate the parasympathetic fibers, red line indicates motor fibers, and purple lines indicate visceral afferent fibers (taste). (Adapted from MB Carpenter: Core Text of Neuroanatomy, 2nd ed. Williams & Wilkins, 1978.)

Clinical manifestations

The onset of Bell's palsy is fairly abrupt, with maximal weakness being attained by 48 h as a general rule. Pain behind the ear may precede the paralysis for a day or two. Taste sensation may be lost unilaterally, and hyperacusis may be present. In some cases, there is mild cerebrospinal fluid lymphocytosis. Magnetic resonance imaging (MRI) may reveal swelling and uniform enhancement of the geniculate ganglion and facial nerve and, in some cases, entrapment of the swollen nerve in the temporal bone. Approximately 80% of patients recover within a few weeks or months. Electromyography may be of some prognostic value; evidence of denervation after 10 days indicates there has been axonal degeneration, that there will be a long delay (3 months as a rule) before regeneration occurs, and that it may be incomplete. The presence of incomplete paralysis in the first week is the most favorable prognostic sign. Recurrences are reported in approximately 7% of cases.

Pathophysiology

In acute Bell's palsy, there is inflammation of the facial nerve with mononuclear cells, consistent with an infectious or immune cause. Herpes simplex virus (HSV) type 1 DNA was frequently detected in endoneurial fluid and posterior auricular muscle, suggesting that a reactivation of this virus in the geniculate ganglion may be responsible for most cases. Reactivation of varicella-zoster virus is associated with Bell's palsy in up to one-third of cases and may represent the second most frequent cause. A variety of other viruses have also been implicated less commonly. An increased incidence of Bell's palsy was also reported among recipients of inactivated intranasal influenza vaccine, and it was hypothesized that this could have resulted from the Escherichia coli enterotoxin used as adjuvant or reactivation of latent virus.

Differential diagnosis

There are many other causes of acute facial palsy that must be considered in the differential diagnosis of Bell's palsy. Lyme disease can cause unilateral or bilateral facial palsies; in endemic areas, 10% or more of cases of facial palsy are likely due to infection with Borrelia burgdorferi. The Ramsay Hunt syndrome, caused by reactivation of herpes zoster in the geniculate ganglion, consists of a severe facial palsy associated with a vesicular eruption in the external auditory canal and sometimes in the pharynx and other parts of the cranial integument; often the eighth cranial nerve is affected as well.

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 42-3
Axial and coronal T1-weighted images after gadolinium with fat suppression demonstrate diffuse smooth linear enhancement of the left facial nerve, involving the genu, tympanic, and mastoid segments within the temporal bone (arrows), without evidence of mass lesion. Although highly suggestive of Bell's palsy, similar findings may be seen with other etiologies such as Lyme disease, sarcoidosis, and perineural malignant spread.

Facial palsy that is often bilateral occurs in sarcoidosis and in Guillain-Barré syndrome **(Chap. 54)**. Leprosy frequently involves the facial nerve, and facial neuropathy may also occur in diabetes mellitus, connective tissue diseases including Sjögren's syndrome, and amyloidosis. The rare Melkersson-Rosenthal syndrome consists of recurrent facial paralysis; recurrent—and eventually permanent—facial (particularly labial) edema; and, less constantly, plication of the tongue. Its cause is unknown. Acoustic neuromas frequently involve the facial nerve by local compression. Infarcts, demyelinating lesions of MS, and tumors are the common pontine lesions that interrupt the facial nerve fibers; other signs of brainstem involvement are usually present. Tumors that invade the temporal bone (carotid body, cholesteatoma, dermoid) may produce a facial palsy, but the onset is insidious and the course progressive.

All these forms of nuclear or peripheral facial palsy must be distinguished from the supranuclear type. In the latter, the frontalis and orbicularis oculi muscles of the forehead are involved less than those of the lower part of the face, since the upper facial muscles are innervated by corticobulbar pathways from both motor cortices, whereas the lower facial muscles are innervated only by the opposite hemisphere. In supranuclear lesions, there may be a dissociation of emotional and voluntary facial movements, and often some degree of paralysis of the arm and leg or an aphasia (in dominant hemisphere lesions) is present.

Laboratory evaluation

The diagnosis of Bell's palsy can usually be made clinically in patients with (1) a typical presentation, (2) no risk factors or preexisting symptoms for other causes of facial paralysis, (3) absence of cutaneous lesions of herpes zoster in the external ear canal, and (4) a normal neurologic examination with the exception of the facial nerve. Particular attention to the eighth cranial nerve, which courses near to the facial nerve in the pontomedullary junction and in the temporal bone, and to other cranial nerves is essential. In atypical or uncertain cases, an ESR, testing for diabetes mellitus, a Lyme titer, angiotensin-converting enzyme and chest imaging studies for possible sarcoidosis, a lumbar puncture for possible Guillain-Barré syndrome, or MRI scanning may be indicated. MRI often shows swelling and enhancement of the facial nerve in idiopathic Bell's palsy **(Fig. 42-3)**.

TREATMENT Bell's Palsy

Symptomatic measures include (1) the use of paper tape to depress the upper eyelid during sleep and prevent corneal drying, and (2) massage of the weakened muscles. A course of glucocorticoids, given as prednisone 60–80 mg daily during the first 5 days and then tapered over the next 5 days, modestly shortens the recovery period and improves the functional outcome. Although large and well-controlled randomized trials found no added benefit of the antiviral agents valacyclovir (1000 mg daily for 5–7 days) or acyclovir (400 mg five times daily for 10 days) compared to glucocorticoids alone, some earlier data suggested that combination therapy with prednisone plus valacyclovir might be marginally better than prednisolone alone, especially in patients with severe clinical presentations. For patients with permanent paralysis from Bell's palsy, a number of cosmetic surgical procedures have been used to restore a relatively symmetric appearance to the face.

www.ketabpezeshki.com (021) 66485457 - 66485438

OTHER MOTOR DISORDERS OF THE FACE

Hemifacial spasm consists of painless irregular involuntary contractions on one side of the face. Most cases appear related to vascular compression of the exiting facial nerve in the pons. Other cases develop as a sequela to Bell's palsy or are secondary to compression and/or demyelination of the nerve by tumor, infection, or MS. Mild cases can be treated with carbamazepine, gabapentin, or, if these drugs fail, baclofen. Local injections of botulinum toxin into affected muscles can relieve spasms for 3–4 months, and the injections can be repeated. Refractory cases due to vascular compression usually respond to surgical decompression of the facial nerve. Blepharospasm is an involuntary recurrent spasm of both eyelids that usually occurs in elderly persons as an isolated phenomenon or with varying degrees of spasm of other facial muscles. Severe, persistent cases of blepharospasm can be treated by local injection of botulinum toxin into the orbicularis oculi. Facial myokymia refers to a fine rippling activity of the facial muscles; it may be caused by MS or follow Guillain-Barré syndrome **(Chap. 54)**.

Facial hemiatrophy occurs mainly in women and is characterized by a disappearance of fat in the dermal and subcutaneous tissues on one side of the face. It usually begins in adolescence or the early adult years and is slowly progressive. In its advanced form, the affected side of the face is gaunt, and the skin is thin, wrinkled, and brown. T e facial hair may turn white and fall out, and the sebaceous glands become atrophic. Bilateral involvement may occur. A limited form of systemic sclerosis (scleroderma) may be the cause of some cases. Treatment is cosmetic, consisting of transplantation of skin and subcutaneous fat.

OTHER CRANIAL NERVE DISORDERS

GLOSSOPHARYNGEAL NEURALGIA

T is form of neuralgia involves the ninth (glossopharyngeal) and sometimes portions of the tenth (vagus) cranial nerves. It resembles trigeminal neuralgia in many respects but is much less common. T e pain is intense and paroxysmal; it originates on one side of the throat, approximately in the tonsillar fossa. In some cases, the pain is localized in the ear or may radiate from the throat to the ear because of involvement of the tympanic branch of the glossopharyngeal nerve. Spasms of pain may be initiated by swallowing or coughing. T ere is no demonstrable motor or sensory deficit; the glossopharyngeal nerve supplies taste sensation to the posterior third of the tongue and, together with the vagus nerve, sensation to the posterior pharynx. Cardiac symptoms—bradycardia or asystole, hypotension, and fainting—have been reported. Glossopharyngeal neuralgia can result from vascular compression, MS, or tumors, but many cases are idiopathic. Medical therapy is similar to that for trigeminal neuralgia, and carbamazepine is generally the first choice. If drug therapy is unsuccessful, surgical procedures—including microvascular decompression if vascular compression is evident—or rhizotomy of glossopharyngeal and vagal fibers in the jugular bulb is frequently successful.

Glossopharyngeal neuropathy in conjunction with vagus and accessory nerve palsies may occur with herpes zoster infection or with a tumor or aneurysm in the posterior fossa or in the jugular foramen. Hoarseness due to vocal cord paralysis, some difficulty in swallowing, deviation of the soft palate to the intact side, anesthesia of the posterior wall of the pharynx, and weakness of the upper part of the trapezius and sternocleidomastoid muscles make up the jugular foramen syndrome **(Table 42-2)**.

DYSPHAGIA AND DYSPHONIA

When the intracranial portion of one vagus (tenth cranial) nerve is interrupted, the soft palate droops ipsilaterally and does not rise in phonation. T ere is loss of the gag ref ex on the affected side, as well as of the "curtain movement" of the lateral wall of the pharynx, whereby the faucial pillars move medially as the palate rises in saying "ah." T e voice is hoarse and slightly nasal, and the vocal cord lies immobile midway between abduction and adduction. Loss of sensation at the external auditory meatus and the posterior pinna may also be present.

T e pharyngeal branches of both vagal nerves may be affected in diphtheria; the voice has a nasal quality, and regurgitation of liquids through the nose occurs during swallowing.

Injury to the vagus nerve in the carotid sheath can also occur with carotid dissection or following endarterectomy. T e vagus nerve may be involved at the meningeal level by neoplastic and infectious processes and within the medulla by tumors, vascular lesions (e.g., the lateral medullary syndrome), and motor neuron disease. T is nerve may be involved by infection with varicella zoster virus. Polymyositis and dermatomyositis, which cause hoarseness and dysphagia by direct involvement of laryngeal and pharyngeal muscles, may be confused with diseases of the vagus nerves. Dysphagia is also a symptom in some patients with myotonic dystrophy. **Nonneurologic causes of dysphagia are discussed in Chap. 53.**

T e recurrent laryngeal nerves, especially the left, are most often damaged as a result of intrathoracic disease. Aneurysm of the aortic arch, an enlarged left atrium, and tumors of the mediastinum and bronchi are much more

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 42-2

CRANIAL NERVE SYNDROMES

SITE	CRANIAL NERVES	USUAL CAUSE
Sphenoid fissure (superior orbital)	III, IV, first division V, VI	Invasive tumors of sphenoid bone; aneurysms
Lateral wall of cavernous sinus	III, IV, first division V, VI, often with proptosis	Infection, thrombosis, aneurysm, or fistula of cavernous sinus; invasive tumors from sinuses and sella turcica; benign granuloma responsive to glucocorticoids
Retrosphenoid space	II, III, IV, V, VI	Large tumors of middle cranial fossa
Apex of petrous bone	V, VI	Petrositis; tumors of petrous bone
Internal auditory meatus	VII, VIII	Tumors of petrous bone (dermoids, etc.); infectious processes; acoustic neuroma
Pontocerebellar angle	V, VII, VIII, and sometimes IX	Acoustic neuroma; meningioma
Jugular foramen	IX, X, XI	Tumors and aneurysms
Posterior laterocondylar space	IX, X, XI, XII	Tumors of parotid gland and carotid body and metastatic tumors
Posterior retroparotid space	IX, X, XI, XII, and Horner's syndrome	Tumors of parotid gland, carotid body, lymph nodes; metastatic tumor; tuberculous adenitis

frequent causes of an isolated vocal cord palsy than are intracranial disorders. However, a substantial number of cases of recurrent laryngeal palsy remain idiopathic.

When confronted with a case of laryngeal palsy, the physician must attempt to determine the site of the lesion. If it is intramedullary, there are usually other signs, such as ipsilateral cerebellar dysfunction, loss of pain and temperature sensation over the ipsilateral face and contralateral arm and leg, and an ipsilateral Horner's syndrome. If the lesion is extramedullary, the glossopharyngeal and spinal accessory nerves are frequently involved (jugular foramen syndrome). If it is extracranial in the posterior laterocondylar or retroparotid space, there may be a combination of ninth, tenth, eleventh, and twelfth cranial nerve palsies and a Horner's syndrome (Table 42-2). If there is no sensory loss over the palate and pharynx and no palatal weakness or dysphagia, the lesion is below the origin of the pharyngeal branches, which leave the vagus nerve high in the cervical region; the usual site of disease is then the mediastinum.

NECK WEAKNESS

Isolated involvement of the accessory (eleventh cranial) nerve can occur anywhere along its route, resulting in partial or complete paralysis of the sternocleidomastoid and trapezius muscles. More commonly, involvement occurs in combination with deficits of the ninth and tenth cranial nerves in the jugular foramen or after exit from the skull (Table 42-2). An idiopathic form of accessory neuropathy, akin to Bell's palsy, has been described, and it may be recurrent in some cases. Most but not all patients recover.

TONGUE PARALYSIS

T e hypoglossal (twelfth cranial) nerve supplies the ipsilateral muscles of the tongue. T e nucleus of the nerve or its fibers of exit may be involved by intramedullary lesions such as tumor, poliomyelitis, or most often motor neuron disease. Lesions of the basal meninges and the occipital bones (platybasia, invagination of occipital condyles, Paget's disease) may compress the nerve in its extramedullary course or in the hypoglossal canal. Isolated lesions of unknown cause can occur. Atrophy and fasciculation of the tongue develop weeks to months after interruption of the nerve.

MULTIPLE CRANIAL NERVE PALSIES

Several cranial nerves may be affected by the same disease process. In this situation, the main clinical problem is to determine whether the lesion lies within the brainstem or outside it. Lesions that lie on the surface of the brainstem are characterized by involvement of adjacent cranial nerves (often occurring in succession) and late and rather slight involvement of the long sensory and motor pathways and segmental structures lying within the brainstem. T e opposite is true of primary lesions within the brainstem. T e extramedullary lesion is more likely to cause bone erosion or enlargement of the foramens of exit of cranial nerves. T e intramedullary lesion involving cranial nerves often produces a crossed sensory or motor paralysis (cranial nerve signs on one side of the body and tract signs on the opposite side).

Involvement of multiple cranial nerves outside the brainstem is frequently the result of trauma, localized

www.ketabpezeshki.com (021) 66485457 - 66485438

infections including varicella-zoster virus, infectious and noninfectious (especially carcinomatous) causes of meningitis **(Chaps. 46 and 47)**, granulomatous diseases such as Wegener's granulomatosis, Behçet's disease, vascular disorders including those associated with diabetes, enlarging aneurysms, or locally infiltrating tumors. Among the tumors, nasopharyngeal cancers, lymphomas, neurofibromas, meningiomas, chordomas, cholesteatomas, carcinomas, and sarcomas have all been observed to involve a succession of lower cranial nerves. Owing to their anatomic relationships, the multiple cranial nerve palsies form a number of distinctive syndromes, listed in Table 42-2. Sarcoidosis is the cause of some cases of multiple cranial neuropathy; tuberculosis, the Chiari malformation, platybasia, and basilar invagination of the skull are additional causes. A purely motor disorder without atrophy always raises the question of myasthenia gravis **(Chap. 55)**. As noted above, Guillain-Barré syndrome commonly affects the facial nerves bilaterally. In the Fisher variant of the Guillain-Barré syndrome, oculomotor paresis occurs with ataxia and areflexia in the limbs **(Chap. 54)**. Wernicke's encephalopathy can cause a severe ophthalmoplegia combined with other brainstem signs **(Chap. 33)**.

The cavernous sinus syndrome **(Fig. 42-4)** is a distinctive and frequently life-threatening disorder. It often presents as orbital or facial pain; orbital swelling and chemosis due to occlusion of the ophthalmic veins; fever; oculomotor neuropathy affecting the third, fourth, and sixth cranial nerves; and trigeminal neuropathy affecting the ophthalmic (V1) and occasionally the maxillary (V2) divisions of the trigeminal nerve. Cavernous sinus thrombosis, often secondary to infection from orbital cellulitis (frequently Staphylococcus aureus), a cutaneous source on the face, or sinusitis (especially with mucormycosis in diabetic patients), is the most frequent cause; other etiologies include aneurysm of the carotid artery, a carotid-cavernous fistula (orbital bruit may be present), meningioma, nasopharyngeal carcinoma, other tumors, or an idiopathic granulomatous disorder (Tolosa-Hunt syndrome). The two cavernous sinuses directly communicate via intercavernous channels; thus, involvement on one side may extend to become bilateral. Early diagnosis is essential, especially when due to infection, and treatment depends on the underlying etiology.

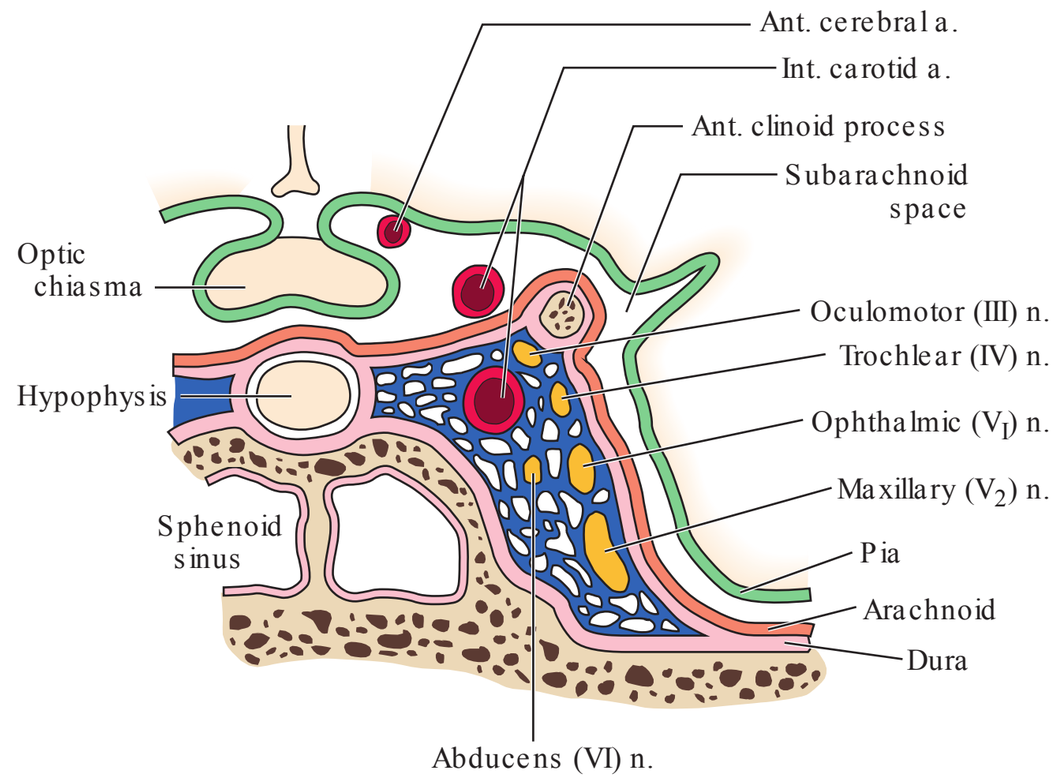


FIGURE 42-4
Anatomy of the cavernous sinus in coronal section, illustrating the location of the cranial nerves in relation to the vascular sinus, internal carotid artery (which loops anteriorly to the section), and surrounding structures.

In infectious cases, prompt administration of broad-spectrum antibiotics, drainage of any abscess cavities, and identification of the offending organism are essential. Anticoagulant therapy may benefit cases of primary thrombosis. Repair or occlusion of the carotid artery may be required for treatment of fistulas or aneurysms. The Tolosa-Hunt syndrome generally responds to glucocorticoids. A dramatic improvement in pain is usually evident within a few days; oral prednisone (60 mg daily) is usually continued for 2 weeks and then gradually tapered over a month, or longer if pain recurs. Occasionally an immunosuppressive medication, such as azathioprine or methotrexate, needs to be added to maintain an initial response to glucocorticoids.

An idiopathic form of multiple cranial nerve involvement on one or both sides of the face is occasionally seen. The syndrome consists of a subacute onset of boring facial pain, followed by paralysis of motor cranial nerves. The clinical features overlap those of the Tolosa-Hunt syndrome and appear to be due to idiopathic inflammation of the dura mater, which may be visualized by MRI. The syndrome is usually responsive to glucocorticoids.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 43

DISEASES OF THE SPINAL CORD

Stephen L. Hauser ■ Allan H. Ropper

Diseases of the spinal cord are frequently devastating. T ey produce quadriplegia, paraplegia, and sensory deficits far beyond the damage they would inflict elsewhere in the nervous system because the spinal cord contains, in a small cross-sectional area, almost the entire motor output and sensory input of the trunk and limbs. Many spinal cord diseases are reversible if recognized and treated at an early stage **(Table 43-1)**; thus, they are among the most critical of neurologic emergencies. T e efficient use of diagnostic procedures, guided by knowledge of the anatomy and the clinical features of spinal cord diseases, is required to maximize the likelihood of a successful outcome.

APPROACH TO THE PATIENT: Spinal Cord Disease

SPINAL CORD ANATOMY RELEVANT TO CLINICAL SIGNS T e spinal cord is a thin, tubular extension of the central nervous system contained within the bony spinal canal. It originates at the medulla and continues caudally to the conus medullaris at the lumbar level; its fibrous extension, the filum terminale, terminates at the coccyx. T e adult spinal cord is ~46 cm (18 in.) long, oval in shape, and enlarged in the cervical and lumbar regions, where neurons that innervate the upper and lower extremities, respectively, are located. T e white matter tracts containing ascending sensory and descending motor pathways are located peripherally, whereas nerve cell bodies are clustered in an inner region of gray matter shaped like a four-leaf clover that surrounds the central canal (anatomically an extension of the fourth ventricle). T e membranes that cover the spinal cord—the pia, arachnoid, and dura—are continuous with those of the brain, and the cerebrospinal fluid is contained within the subarachnoid space between the pia and arachnoid.

TABLE 43-1 TREATABLE SPINAL CORD DISORDERS

Compressive
- Epidural, intradural, or intramedullary neoplasm
- Epidural abscess
- Epidural hemorrhage
- Cervical spondylosis
- Herniated disk
- Posttraumatic compression by fractured or displaced vertebra or hemorrhage

Vascular
- Arteriovenous malformation and dural fistula
- Antiphospholipid syndrome and other hypercoagulable states

Inf ammatory
- Multiple sclerosis
- Neuromyelitis optica
- Transverse myelitis
- Sarcoidosis
- Sjögren-related myelopathy
- Systemic lupus erythematosus-related myelopathy
- Vasculitis

Infectious
- Viral: VZV, HSV-1 and -2, CMV, HIV, HTLV-1, others
- Bacterial and mycobacterial: Borrelia, Listeria, syphilis, others
- Mycoplasma pneumoniae
- Parasitic: schistosomiasis, toxoplasmosis

Developmental
- Syringomyelia
- Meningomyelocele
- Tethered cord syndrome

Metabolic
- Vitamin B_{12} deficiency (subacute combined degeneration)
- Copper deficiency

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; VZV, varicella-zoster virus.

T e spinal cord has 31 segments, each defined by an exiting ventral motor root and entering dorsal sensory root. During embryologic development, growth of the

www.ketabpezeshki.com (021) 66485457 - 66485438

cord lags behind that of the vertebral column, and the mature spinal cord ends at approximately the first lumbar vertebral body. The lower spinal nerves take an increasingly downward course to exit via intervertebral foramina. The first seven pairs of cervical spinal nerves exit above the same-numbered vertebral bodies, whereas all the subsequent nerves exit below the same-numbered vertebral bodies because of the presence of eight cervical spinal cord segments but only seven cervical vertebrae. The relationship between spinal cord segments and the corresponding vertebral bodies is shown in **Table 43-2**. These relationships assume particular importance for localization of lesions that cause spinal cord compression. Sensory loss below the circumferential level of the umbilicus, for example, corresponds to the T10 cord segment but indicates involvement of the cord adjacent to the seventh or eighth thoracic vertebral body **(see Figs. 31-2 and 31-3)**. In addition, at every level, the main ascending and descending tracts are somatotopically organized with a laminated distribution that reflects the origin or destination of nerve fibers.

Determining the level of the lesion The presence of a horizontally defined level below which sensory, motor, and autonomic function is impaired is a hallmark of a lesion of the spinal cord. This sensory level is sought by asking the patient to identify a pinprick or cold stimulus applied to the proximal legs and lower trunk and successively moved up toward the neck on each side. Sensory loss below this level is the result of damage to the spinothalamic tract on the opposite side, one to two segments higher in the case of a unilateral spinal cord lesion, and at the level of a bilateral lesion. The discrepancy in the level of a unilateral lesion is the result of the course of the second-order sensory fibers, which originate in the dorsal horn, and ascend for one or two levels as they cross anterior to the central canal to join the opposite spinothalamic tract. Lesions that transect the descending corticospinal and other motor tracts cause paraplegia or quadriplegia with heightened deep tendon reflexes, Babinski signs, and eventual spasticity (the upper motor neuron syndrome). Transverse damage to the cord also produces autonomic disturbances consisting of absent sweating below the implicated cord level and bladder, bowel, and sexual dysfunction.

The uppermost level of a spinal cord lesion can also be localized by attention to the segmental signs corresponding to disturbed motor or sensory innervation by an individual cord segment. A band of altered sensation (hyperalgesia or hyperpathia) at the upper end of the sensory disturbance, fasciculations or atrophy in muscles innervated by one or several segments, or a muted or absent deep tendon reflex may be noted at this level. These signs also can occur with focal root or peripheral nerve disorders; thus, they are most useful when they occur together with signs of long tract damage. With severe and acute transverse lesions, the limbs initially may be flaccid rather than spastic. This state of "spinal shock" lasts for several days, rarely for weeks, and may be mistaken for extensive damage to the anterior horn cells over many segments of the cord or for an acute polyneuropathy.

The main features of transverse damage at each level of the spinal cord are summarized below.

Cervical cord Upper cervical cord lesions produce quadriplegia and weakness of the diaphragm. The uppermost level of weakness and reflex loss with lesions at C5-C6 is in the biceps; at C7, in finger and wrist extensors and triceps; and at C8, finger and wrist flexion. Horner's syndrome (miosis, ptosis, and facial hypohidrosis) may accompany a cervical cord lesion at any level.

Thoracic cord Lesions here are localized by the sensory level on the trunk and, if present, by the site of midline back pain. Useful markers of the sensory level on the trunk are the nipples (T4) and umbilicus (T10). Leg weakness and disturbances of bladder and bowel function accompany the paralysis. Lesions at T9-T10 paralyze the lower—but not the upper—abdominal muscles, resulting in upward movement of the umbilicus when the abdominal wall contracts (Beevor's sign).

Lumbar cord Lesions at the L2-L4 spinal cord levels paralyze flexion and adduction of the thigh, weaken leg extension at the knee, and abolish the patellar reflex. Lesions at L5-S1 paralyze only movements of the foot and ankle, flexion at the knee, and extension of the thigh, and abolish the ankle jerks (S1).

Sacral cord/conus medullaris The conus medullaris is the tapered caudal termination of the spinal cord, comprising the sacral and single coccygeal segments. The distinctive conus syndrome consists of bilateral saddle anesthesia (S3-S5), prominent bladder and bowel dysfunction (urinary retention and incontinence with lax anal tone), and impotence. The bulbocavernosus (S2-S4) and anal (S4-S5) reflexes are absent **(Chap. 1)**. Muscle strength is largely preserved. By contrast, lesions of the cauda equina, the nerve roots derived from the lower cord, are characterized

TABLE 43-2

SPINAL CORD LEVELS RELATIVE TO THE VERTEBRAL BODIES

SPINAL CORD LEVEL	CORRESPONDING VERTEBRAL BODY
Upper cervical	Same as cord level
Lower cervical	1 level higher
Upper thoracic	2 levels higher
Lower thoracic	2 to 3 levels higher
Lumbar	T10-T12
Sacral	T12-L1

www.ketabpezeshki.com (021) 66485457 - 66485438

by low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function. Mass lesions in the lower spinal canal often produce a mixed clinical picture with elements of both cauda equina and conus medullaris syndromes. **Cauda equina syndromes are also discussed in Chap. 10.**

Special patterns of spinal cord disease The location of the major ascending and descending pathways of the spinal cord are shown in **Fig. 43-1**. Most fiber tracts—including the posterior columns and the spinocerebellar and pyramidal tracts—are situated on the side of the body they innervate. However, afferent fibers mediating pain and temperature sensation ascend in the spinothalamic tract contralateral to the side they supply. The anatomic configurations of these tracts produce characteristic syndromes that provide clues to the underlying disease process.

Brown-Sequard hemicord syndrome This consists of ipsilateral weakness (corticospinal tract) and loss of joint position and vibratory sense (posterior column), with contralateral loss of pain and temperature sense (spinothalamic tract) one or two levels below the lesion. Segmental signs, such as radicular pain, muscle atrophy, or loss of a deep tendon reflex, are unilateral. Partial forms are more common than the fully developed syndrome.

Central cord syndrome This syndrome results from selective damage to the gray matter nerve cells and crossing spinothalamic tracts surrounding the central canal. In the cervical cord, the central cord syndrome produces arm weakness out of proportion to leg weakness and a "dissociated" sensory loss, meaning loss of pain and temperature sensations over the shoulders, lower neck, and upper trunk (cape distribution), in contrast to preservation of light touch, joint position, and vibration sense in these regions. Spinal trauma, syringomyelia, and intrinsic cord tumors are the main causes.

Anterior spinal artery syndrome Infarction of the cord is generally the result of occlusion or diminished flow in this artery. The result is bilateral tissue destruction at several contiguous levels that spares the posterior columns. All spinal cord functions—motor, sensory, and autonomic—are lost below the level of the lesion, with the striking exception of retained vibration and position sensation.

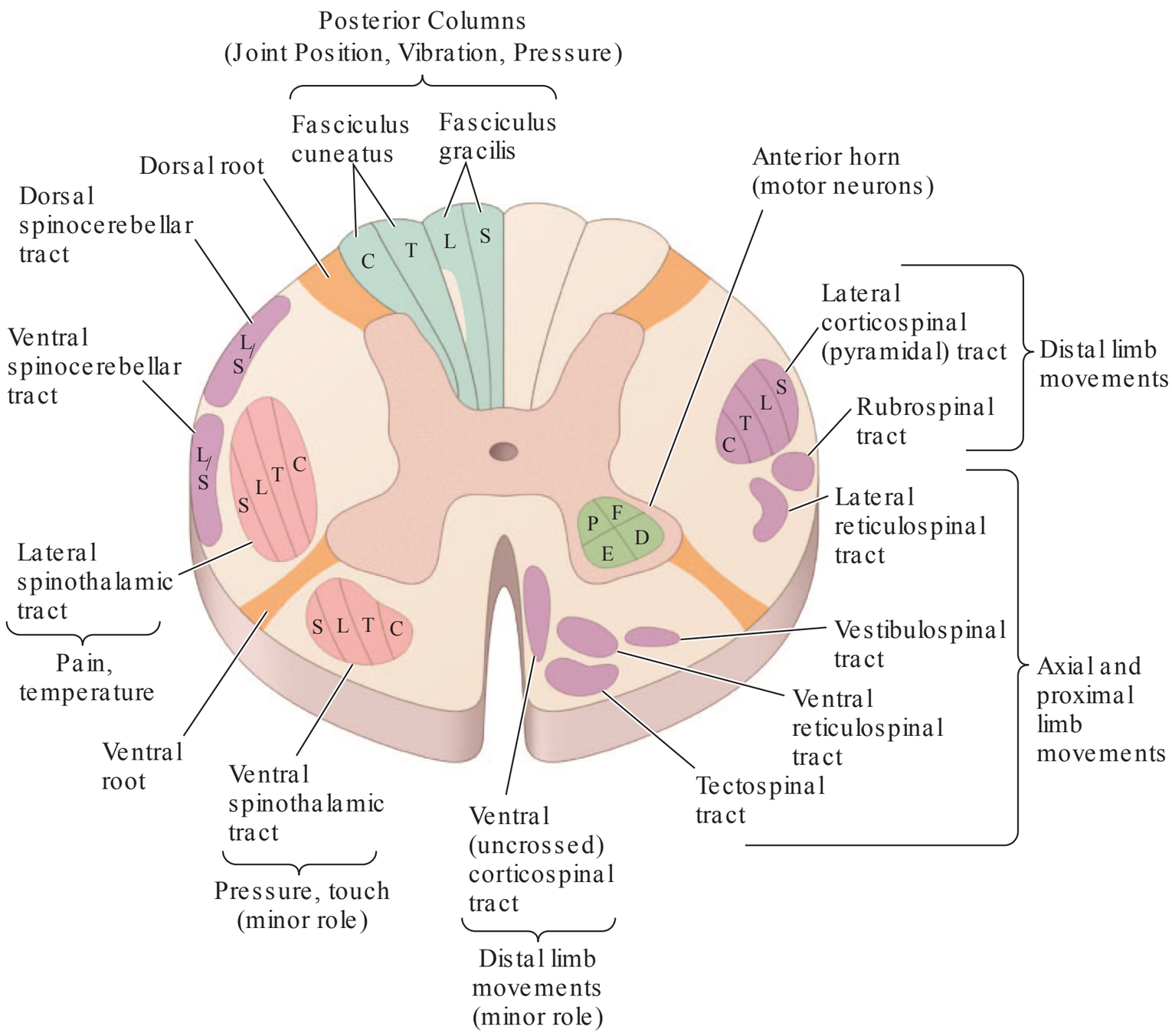


FIGURE 43-1
Transverse section through the spinal cord, composite representation, illustrating the principal ascending (left) and descending (right) pathways. The lateral and ventral spinothalamic tracts ascend contralateral to the side of the body that is innervated. C, cervical; D, distal; E, extensors; F, flexors; L, lumbar; P, proximal; S, sacral; T, thoracic.

www.ketabpezeshki.com (021) 66485457 - 66485438

Foramen magnum syndrome Lesions in this area interrupt decussating pyramidal tract fibers destined for the legs, which cross caudal to those of the arms, resulting in weakness of the legs (crural paresis). Compressive lesions near the foramen magnum may produce weakness of the ipsilateral shoulder and arm followed by weakness of the ipsilateral leg, then the contralateral leg, and finally the contralateral arm, an "around the clock" pattern that may begin in any of the four limbs. There is typically suboccipital pain spreading to the neck and shoulders.

Intramedullary and extramedullary syndromes It is useful to differentiate intramedullary processes, arising within the substance of the cord, from extramedullary ones that lie outside the cord and compress the spinal cord or its vascular supply. The differentiating features are only relative and serve as clinical guides. With extramedullary lesions, radicular pain is often prominent, and there is early sacral sensory loss and spastic weakness in the legs with incontinence due to the superficial location of the corresponding sensory and motor fibers in the spinothalamic and corticospinal tracts (Fig. 43-1). Intramedullary lesions tend to produce poorly localized burning pain rather than radicular pain and to spare sensation in the perineal and sacral areas ("sacral sparing"), reflecting the laminated configuration of the spinothalamic tract with sacral fibers outermost; corticospinal tract signs appear later. Regarding extramedullary lesions, a further distinction is made between extradural and intradural masses, as the former are generally malignant and the latter benign (neurofibroma being a common cause). Consequently, a long duration of symptoms favors an intradural origin.

ACUTE AND SUBACUTE SPINAL CORD DISEASES

The initial symptoms of structural diseases of the cord that evolve over days or weeks are focal neck or back pain, followed by various combinations of paresthesias, sensory loss, motor weakness, and sphincter disturbance. There may be only mild sensory symptoms or a devastating functional transection of the cord. Partial lesions selectively involve the posterior columns or anterior spinothalamic tracts or are limited to one side of the cord. Paresthesias or numbness typically begins in the feet and ascend symmetrically or asymmetrically. These symptoms simulate a polyneuropathy, but a sharply demarcated spinal cord level indicates the myelopathic nature of the process.

In severe and abrupt cases, areflexia reflecting spinal shock may be present, but hyperreflexia supervenes over days or weeks; persistent areflexic paralysis with a sensory level usually indicates necrosis over multiple segments of the spinal cord.

APPROACH TO THE PATIENT: Compressive and Noncompressive Myelopathy

DISTINGUISHING COMPRESSIVE FROM NONCOMPRESSIVE MYELOPATHY
The first priority is to exclude a treatable compression of the cord by a mass that may be amenable to treatment. The common causes are tumor, epidural abscess or hematoma, herniated disk, and vertebral pathology. Epidural compression due to malignancy or abscess often causes warning signs of neck or back pain, bladder disturbances, and sensory symptoms that precede the development of paralysis. Spinal subluxation, hemorrhage, and noncompressive etiologies such as infarction are more likely to produce myelopathy without antecedent symptoms. Magnetic resonance imaging (MRI) with gadolinium, centered on the clinically suspected level, is the initial diagnostic procedure if it is available; in some cases, it is appropriate to image the entire spine (cervical through sacral regions) to search for additional clinically inapparent lesions. Once compressive lesions have been excluded, noncompressive causes of acute myelopathy that are intrinsic to the cord are considered, primarily vascular, inflammatory, and infectious etiologies.

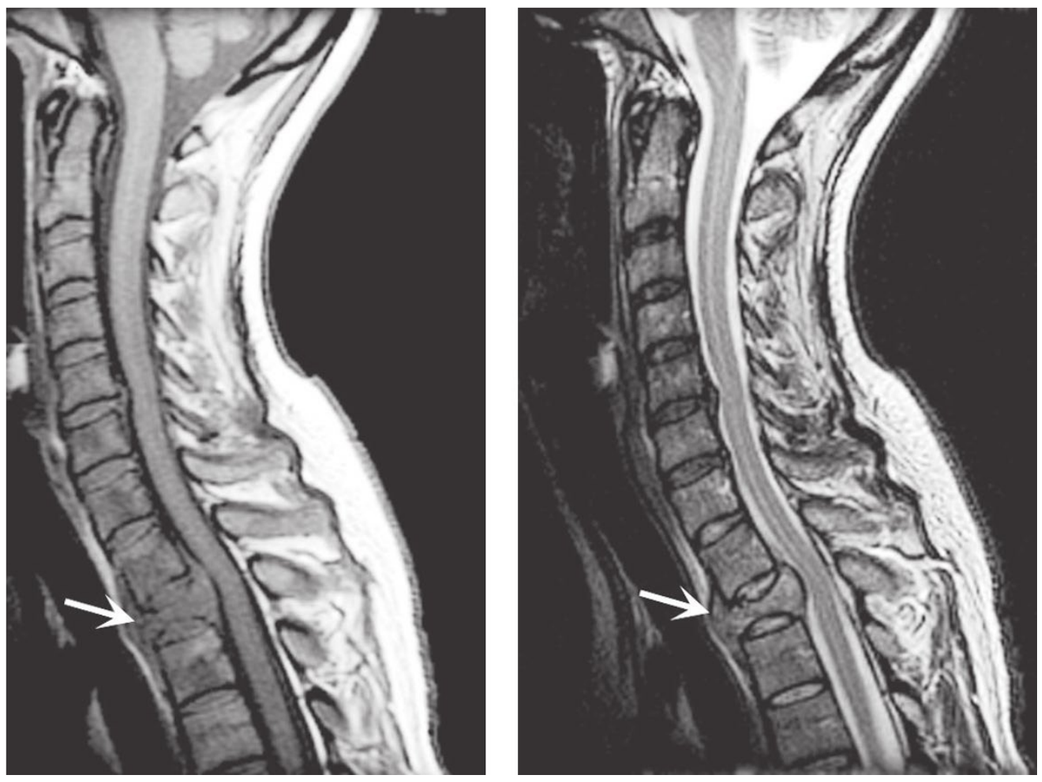
COMPRESSIVE MYELOPATHIES

Neoplastic spinal cord compression

In adults, most neoplasms are epidural in origin, resulting from metastases to the adjacent vertebral column. The propensity of solid tumors to metastasize to the vertebral column probably reflects the high proportion of bone marrow located in the axial skeleton. Almost any malignant tumor can metastasize to the spinal column, with breast, lung, prostate, kidney, lymphoma, and myeloma being particularly frequent. The thoracic spinal column is most commonly involved; exceptions are metastases from prostate and ovarian cancer, which occur disproportionately in the sacral and lumbar vertebrae, probably from spread through Batson's plexus, a network of veins along the anterior epidural space. Retroperitoneal neoplasms (especially lymphomas or sarcomas) enter the spinal canal laterally through the intervertebral foramina and produce radicular pain with signs of weakness that corresponds to the level of involved nerve roots.

Pain is usually the initial symptom of spinal metastasis; it may be aching and localized or sharp and radiating in quality and typically worsens with movement, coughing, or sneezing and characteristically awakens patients at night. A recent onset of persistent back pain, particularly if in the thoracic spine (which is uncommonly involved by spondylosis), should prompt consideration of vertebral metastasis.

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 43-2
Epidural spinal cord compression due to breast carcinoma. Sagittal T1-weighted (A) and T2-weighted (B) magnetic resonance imaging scans through the cervicothoracic junction reveal an infiltrated and collapsed second thoracic vertebral body with posterior displacement and compression of the upper thoracic spinal cord. The low-intensity bone marrow signal in A signifies replacement by tumor.

Rarely, pain is mild or absent. Plain radiographs of the spine and radionuclide bone scans have a limited role in diagnosis because they do not identify 15–20% of metastatic vertebral lesions and fail to detect paravertebral masses that reach the epidural space through the intervertebral foramina. MRI provides excellent anatomic resolution of the extent of spinal tumors **(Fig. 43-2)** and is able to distinguish between malignant lesions and other masses—epidural abscess, tuberculoma, lipoma, or epidural hemorrhage, among others—that present in a similar fashion. Vertebral metastases are usually hypointense relative to a normal bone marrow signal on T1-weighted MRI; after the administration of gadolinium, contrast enhancement may deceptively "normalize" the appearance of the tumor by increasing its intensity to that of normal bone marrow. Infections of the spinal column (osteomyelitis and related disorders) are distinctive in that, unlike tumor, they often cross the disk space to involve the adjacent vertebral body.

If spinal cord compression is suspected, imaging should be obtained promptly. If there are radicular symptoms but no evidence of myelopathy, it may be safe to defer imaging for 24–48 h. Up to 40% of patients who present with cord compression at one level are found to have asymptomatic epidural metastases elsewhere; thus, the length of the spine is often imaged when epidural malignancy is in question.

TREATMENT Neoplastic Spinal Cord Compression

Management of cord compression includes glucocorticoids to reduce cord edema, local radiotherapy (initiated as early as possible) to the symptomatic lesion, and specific therapy for the underlying tumor type. Glucocorticoids (dexamethasone, up to 40 mg daily) can be administered before an imaging study if there is clinical suspicion of cord compression and the medication is continued at a lower dose until definitive treatment with radiotherapy (generally 3000 cGy administered in 15 daily fractions) and/or surgical decompression is completed. In one randomized controlled trial, initial management with surgery followed by radiotherapy was more effective than radiotherapy alone for patients with a single area of spinal cord compression by extradural tumor; however, patients with recurrent cord compression, brain metastases, radiosensitive tumors, or severe motor symptoms of >48 h in duration were excluded from this study. Radiotherapy alone may be effective even for some typically radioresistant metastases. A good response to therapy can be expected in individuals who are ambulatory at presentation. Treatment usually prevents new weakness, and some recovery of motor function occurs in up to one-third of patients. Motor deficits (paraplegia or quadriplegia), once established for >12 h, do not usually improve, and beyond 48 h the prognosis for substantial motor recovery is poor. Although most patients do not experience recurrences in the months following radiotherapy, with survival beyond 2 years, recurrence becomes increasingly likely and can be managed with additional radiotherapy. Newer techniques such as stereotactic radiosurgery can deliver high doses of focused radiation and with similar rates of response compared to traditional radiotherapy. Biopsy of the epidural mass is unnecessary in patients with known primary cancer, but it is indicated if a history of underlying cancer is lacking. Surgery, either decompression by laminectomy or vertebral body resection, is also indicated when signs of cord compression worsen despite radiotherapy, when the maximum-tolerated dose of radiotherapy has been delivered previously to the site, or when a vertebral compression fracture or spinal instability contributes to cord compression.

In contrast to tumors of the epidural space, most intradural mass lesions are slow-growing and benign. Meningiomas and neurofibromas account for most of these, with occasional cases caused by chordoma, lipoma, dermoid, or sarcoma. Meningiomas **(Fig. 43-3)** are often located posterior to the thoracic cord or near the foramen magnum, although they can arise from the meninges anywhere along the spinal canal. Neurofibromas are benign tumors of the nerve sheath that typically arise from the posterior root; when multiple, neurofibromatosis is the likely etiology. Symptoms usually begin with radicular sensory symptoms followed

www.ketabpezeshki.com (021) 66485457 - 66485438

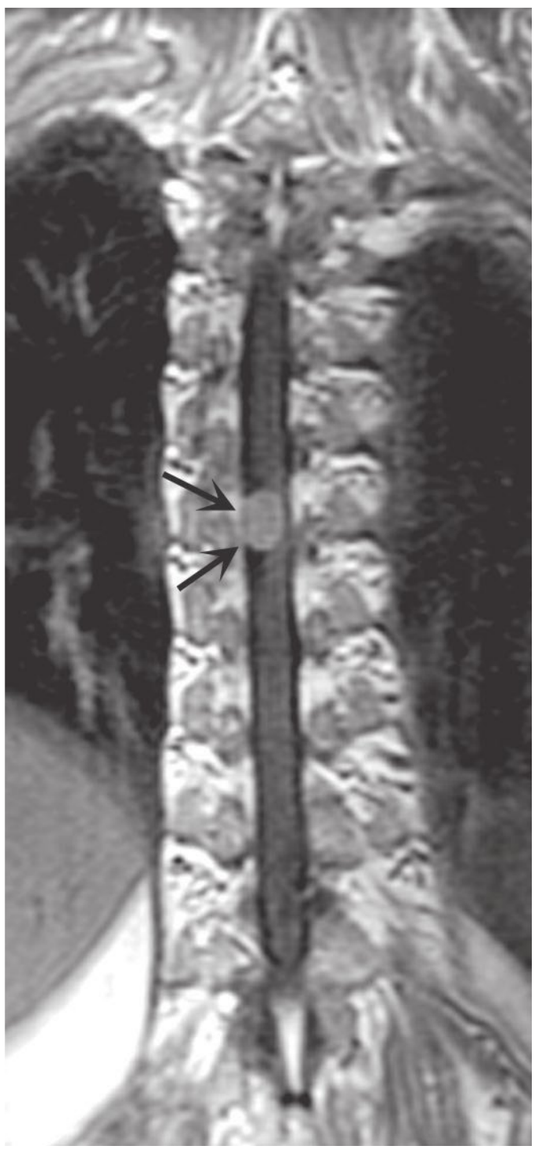


FIGURE 43-3
Magnetic resonance imaging of a thoracic meningioma. Coronal T1-weighted postcontrast image through the thoracic spinal cord demonstrates intense and uniform enhancement of a well-circumscribed extramedullary mass (arrows) that displaces the spinal cord to the left.

by an asymmetric, progressive spinal cord syndrome. Therapy is surgical resection.

Primary intramedullary tumors of the spinal cord are uncommon. They present as central cord or hemicord syndromes, often in the cervical region. There may be poorly localized burning pain in the extremities and sparing of sacral sensation. In adults, these lesions are ependymomas, hemangioblastomas, or low-grade astrocytomas **(Fig. 43-4)**. Complete resection of an intramedullary ependymoma is often possible with microsurgical techniques. Debulking of an intramedullary astrocytoma can also be helpful, as these are often slowly growing lesions; the value of adjunctive radiotherapy and chemotherapy is uncertain. Secondary (metastatic) intramedullary tumors also occur, especially in patients with advanced metastatic disease **(Chap. 49)**, although these are not nearly as frequent as brain metastases.

Spinal epidural abscess

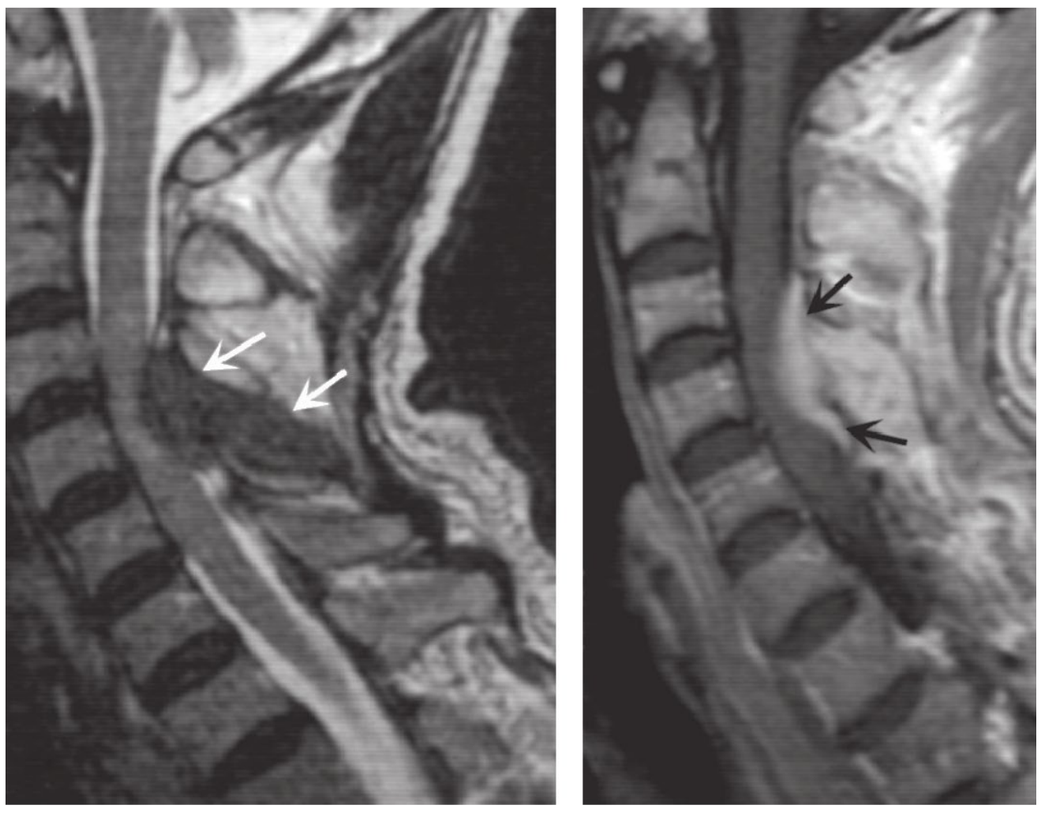
Spinal epidural abscess presents with midline back or neck pain, fever, and progressive limb weakness. Prompt recognition of this distinctive process may prevent permanent sequelae. Aching pain is almost always present, either over the spine or in a radicular pattern. The duration of pain prior to presentation is generally ≤2 weeks but may on occasion be several months or longer. Fever is typically but not invariably present, accompanied by elevated white blood cell count, sedimentation rate, and C-reactive protein. As the abscess expands, further spinal cord damage results from venous congestion and thrombosis. Once weakness and other signs of myelopathy appear, progression may be rapid and irreversible. A more chronic sterile granulomatous form of abscess is also known, usually after treatment of an acute epidural infection.

Risk factors include an impaired immune status (HIV, diabetes mellitus, renal failure, alcoholism, malignancy), intravenous drug abuse, and infections of the skin or other tissues. Two-thirds of epidural infections result from hematogenous spread of bacteria from the skin (furunculosis), soft tissue (pharyngeal or dental abscesses; sinusitis), or deep viscera (bacterial endocarditis). The remainder arises from direct extension of a local infection to the subdural space; examples of local predisposing conditions are vertebral osteomyelitis, decubitus ulcers, lumbar puncture, epidural anesthesia, or spinal surgery. Most cases are due to Staphylococcus aureus; gram-negative bacilli, Streptococcus, anaerobes, and fungi can also cause epidural abscesses. Tuberculosis from an adjacent vertebral source (Pott's disease) remains an important cause in the developing world.

MRI **(Fig. 43-5)** localizes the abscess and excludes other causes of myelopathy. Blood cultures are positive

FIGURE 43-4
Magnetic resonance imaging of an intramedullary astrocytoma. Sagittal T1-weighted postcontrast image through the cervical spine demonstrates expansion of the upper cervical spine by a mass lesion emanating from within the spinal cord at the cervicomedullary junction. Irregular peripheral enhancement occurs within the mass (arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 43-5
Magnetic resonance (MR) imaging of a spinal epidural abscess due to tuberculosis. A. Sagittal T2-weighted free spin-echo MR sequence. A hypointense mass replaces the posterior elements of C3 and extends epidurally to compress the spinal cord (arrows). B. Sagittal T1-weighted image after contrast administration reveals a diffuse enhancement of the epidural process (arrows) with extension into the epidural space.

in more than half of cases, but direct aspiration of the abscess at surgery is often required for a microbiologic diagnosis. Lumbar puncture is only required if encephalopathy or other clinical signs raise the question of associated meningitis, a feature that is found in <25% of cases. The level of the puncture should be planned to minimize the risk of meningitis due to passage of the needle through infected tissue. A high cervical tap is sometimes the safest approach. Cerebrospinal fluid (CSF) abnormalities in epidural and subdural abscess consist of pleocytosis with a preponderance of polymorphonuclear cells, an elevated protein level, and a reduced glucose level, but the responsible organism is not cultured unless there is associated meningitis.

TREATMENT Spinal Epidural Abscess

Treatment is by decompressive laminectomy with debridement combined with long-term antibiotic treatment. Surgical evacuation prevents development of paralysis and may improve or reverse paralysis in evolution, but it is unlikely to improve deficits of more than several days in duration. Broad-spectrum antibiotics should be started empirically before surgery and then modified on the basis of culture results; medication is generally continued for at least 6 weeks. If surgery is contraindicated or if there is a fixed paraplegia or quadriplegia that is unlikely to improve following surgery, long-term administration of systemic and oral antibiotics can be used; in such cases, the choice of antibiotics may be guided by results of blood cultures. Surgical management remains the treatment of choice unless the abscess is limited in size and causes few or no neurologic signs.

With prompt diagnosis and treatment of spinal epidural abscess, up to two-thirds of patients experience significant recovery.

Spinal epidural hematoma

Hemorrhage into the epidural (or subdural) space causes acute focal or radicular pain followed by variable signs of a spinal cord or conus medullaris disorder. Therapeutic anticoagulation, trauma, tumor, or blood dyscrasias are predisposing conditions. Rare cases complicate lumbar puncture or epidural anesthesia. MRI and computed tomography (CT) confirm the clinical suspicion and can delineate the extent of the bleeding. Treatment consists of prompt reversal of any underlying clotting disorder and surgical decompression. Surgery may be followed by substantial recovery, especially in patients with some preservation of motor function preoperatively. Because of the risk of hemorrhage, lumbar puncture should be avoided whenever possible in patients with severe thrombocytopenia or other coagulopathies.

Hematomyelia

Hemorrhage into the substance of the spinal cord is a rare result of trauma, intraparenchymal vascular malformation (see below), vasculitis due to polyarteritis nodosa or systemic lupus erythematosus (SLE), bleeding disorders, or a spinal cord neoplasm. Hematomyelia presents as an acute painful transverse myelopathy. With large lesions, extension into the subarachnoid space results in subarachnoid hemorrhage **(Chap. 33)**. Diagnosis is by MRI or CT. Therapy is supportive, and surgical intervention is generally not useful. An exception is hematomyelia due to an underlying vascular malformation, for which spinal angiography and endovascular occlusion may be indicated, or surgery to evacuate the clot and remove the underlying vascular lesion.

NONCOMPRESSIVE MYELOPATHIES

The most frequent causes of noncompressive acute transverse myelopathy are spinal cord infarction; systemic inflammatory disorders, including SLE and sarcoidosis; demyelinating diseases, including multiple sclerosis (MS); neuromyelitis optica (NMO); postinfectious or idiopathic transverse myelitis, which is presumed to be an immune condition related to acute disseminated encephalomyelitis **(Chap. 45)**; and infectious (primarily viral) causes. After spinal cord compression is excluded, the evaluation generally requires a lumbar puncture and a search for underlying systemic disease **(Table 43-3)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 43-3

EVALUATION OF ACUTE TRANSVERSE MYELOPATHY

1. MRI of spinal cord with and without contrast (exclude compressive causes).
2. CSF studies: Cell count, protein, glucose, IgG index/synthesis rate, oligoclonal bands, VDRL; Gram's stain, acid-fast bacilli, and India ink stains; PCR for VZV, HSV-2, HSV-1, EBV, CMV, HHV-6, enteroviruses, HIV; antibody for HTLV-1, Borrelia burgdorferi, Mycoplasma pneumoniae, and Chlamydia pneumoniae; viral, bacterial, mycobacterial, and fungal cultures.
3. Blood studies for infection: HIV; RPR; IgG and IgM enterovirus antibody; IgM mumps, measles, rubella, group B arbovirus, Brucella melitensis, Chlamydia psittaci, Bartonella henselae, schistosomal antibody; cultures for B. melitensis. Also consider nasal/pharyngeal/anal cultures for enteroviruses; stool O&P for Schistosoma ova.
4. Immune-mediated disorders: ESR; ANA; ENA; dsDNA; rheumatoid factor; anti-SSA; anti-SSB, complement levels; antiphospholipid and anticardiolipin antibodies; p-ANCA; antimicrosomal and antithyroglobulin antibodies; if Sjögren's syndrome suspected, Schirmer test, salivary gland scintigraphy, and salivary/lacrimal gland biopsy.
5. Sarcoidosis: Serum angiotensin-converting enzyme; serum Ca; 24-h urine Ca; chest x-ray; chest CT; total-body gallium scan; lymph node biopsy.
6. Demyelinating disease: Brain MRI scan, evoked potentials, CSF oligoclonal bands, neuromyelitis optica antibody (anti-aquaporin-4 [NMO] antibody).
7. Vascular causes: MRI, CT myelogram; spinal angiogram.

Abbreviations: ANA, antinuclear antibodies; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ENA, epithelial neutrophil-activating peptide; ESR, erythrocyte sedimentation rate; HHV, human herpes virus; HSV, herpes simplex virus; HTLV, human T cell leukemia/lymphoma virus; MRI, magnetic resonance imaging; O&P, ova and parasites; p-ANCA, perinuclear antineutrophilic cytoplasmic antibodies; PCR, polymerase chain reaction; RPR, rapid plasma reagin (test); VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus.

Spinal cord infarction

The cord is supplied by three arteries that course vertically over its surface: a single anterior spinal artery and paired posterior spinal arteries. The anterior spinal artery originates in paired branches of the vertebral arteries at the cranciocervical junction and is fed by additional radicular vessels that arise at C6, at an upper thoracic level, and, most consistently, at T11-L2 (artery of Adamkiewicz). At each spinal cord segment, paired penetrating vessels branch from the anterior spinal artery to supply the anterior two-thirds of the cord; the posterior spinal arteries, which often become less distinct below the midthoracic level, supply the posterior columns.

Spinal cord ischemia can occur at any level; however, the presence of the artery of Adamkiewicz below, and the anterior spinal artery circulation above, creates a region of marginal blood flow in the upper thoracic segments. With hypotension or cross-clamping of the aorta, cord infarction typically occurs at the level of T3-T4, and also at boundary zones between the anterior and posterior spinal artery territories. The latter may result in a rapidly progressive syndrome over hours of weakness and spasticity with little sensory change.

Acute infarction in the territory of the anterior spinal artery produces paraplegia or quadriplegia, dissociated sensory loss affecting pain and temperature sense but sparing vibration and position sense, and loss of sphincter control ("anterior cord syndrome"). Onset may be sudden but more typically is progressive over minutes or a few hours, quite unlike stroke in the cerebral hemispheres. Sharp midline or radiating back pain localized to the area of ischemia is frequent. Areflexia due to spinal shock is often present initially; with time, hyperreflexia and spasticity appear. Less common is infarction in the territory of the posterior spinal arteries, resulting in loss of posterior column function either on one side or bilaterally.

Causes of spinal cord infarction include aortic atherosclerosis, dissecting aortic aneurysm, vertebral artery occlusion or dissection in the neck, aortic surgery, or profound hypotension from any cause. A "surfer's myelopathy" in the cervical region is probably vascular in origin. Cardiogenic emboli, vasculitis, and collagen vascular disease (particularly SLE, Sjögren's syndrome, and the antiphospholipid antibody syndrome are other etiologies. Occasional cases develop from embolism of nucleus pulposus material into spinal vessels, usually from local spine trauma. In a substantial number of cases, no cause can be found, and thromboembolism in arterial feeders is suspected. MRI may fail to demonstrate infarctions of the cord, especially in the first day, but often the imaging becomes abnormal at the affected level.

In cord infarction due to presumed thromboembolism, acute anticoagulation is not indicated, with the possible exception of the unusual transient ischemic attack or incomplete infarction with a stuttering or progressive course. The antiphospholipid antibody syndrome is treated with anticoagulation. Lumbar drainage of spinal fluid has reportedly been successful in some cases of cord infarction and has been used prophylactically during aortic surgery, but it has not been studied systematically.

Inflammatory and immune myelopathies (myelitis)

This is broad category includes the demyelinating conditions MS, NMO, and postinfectious myelitis, as well as sarcoidosis and systemic autoimmune disease. In approximately one-quarter of cases of myelitis, no underlying cause can be identified. Some will later manifest additional symptoms of an immune-mediated

www.ketabpezeshki.com (021) 66485457 - 66485438

disease. Recurrent episodes of myelitis are usually due to one of the immune-mediated diseases or to infection with herpes simplex virus (HSV) type 2 (below).

Multiple sclerosis

MS may present with acute myelitis, particularly in individuals of Asian or African ancestry. In Caucasians, MS attacks rarely cause a transverse myelopathy (i.e., attacks of bilateral sensory disturbances, unilateral or bilateral weakness, and bladder or bowel symptoms), but it is among the most common causes of a partial cord syndrome. MRI findings in MS-associated myelitis typically consist of mild swelling of the cord and diffuse or multifocal "shoddy" areas of abnormal signal on T2-weighted sequences. Contrast enhancement, indicating disruption in the blood-brain barrier associated with inflammation, is present in many acute cases. A brain MRI is most helpful in gauging the likelihood that a case of myelitis represents an initial attack of MS. A normal scan indicates that the risk of evolution to MS is low, ~10–15% over 5 years; in contrast, the finding of multiple periventricular T2-bright lesions indicates a much higher risk, >50% over 5 years and >90% by 14 years. The CSF may be normal, but more often there is a mild mononuclear cell pleocytosis, with normal or mildly elevated CSF protein levels; the presence of oligoclonal bands is variable, but when they are found, a diagnosis of MS is more likely.

There are no adequate trials of therapy for MS-associated transverse myelitis. Intravenous methylprednisolone (500 mg qd for 3 days) followed by oral prednisone (1 mg/kg per day for several weeks, then gradual taper) has been used as initial treatment. A course of plasma exchange may be indicated for severe cases if glucocorticoids are ineffective. **MS is discussed in Chap. 45**.

Neuromyelitis optica

NMO is an immune-mediated demyelinating disorder consisting of a severe myelopathy that is typically longitudinally extensive, meaning that the lesion spans three or more vertebral segments. NMO is associated with optic neuritis that is often bilateral and may precede or follow myelitis by weeks or months, and also by brainstem and, in some cases, hypothalamic involvement. Recurrent myelitis without optic nerve involvemement can also occur in NMO; affected individuals are usually female and often of Asian ancestry. CSF studies reveal a variable mononuclear pleocytosis of up to several hundred cells per microliter; unlike MS, oligoclonal bands are generally absent. Diagnostic serum autoantibodies against the water channel protein aquaporin-4 are present in 60–70% of patients with NMO. NMO has also been associated with SLE and antiphospholipid antibodies (see below) as well as with other systemic autoimmune diseases; rare cases are paraneoplastic in origin. Treatment is with glucocorticoids and, for refractory cases, plasma exchange (as for MS, above). Preliminary studies suggest that treatment with azathioprine, mycophenylate, or anti-CD20 (anti–B cell) monoclonal antibody may protect against subsequent relapses; treatment for 5 years or longer is generally recommended. **NMO is discussed in Chap. 45**.

Systemic immune-mediated disorders

Myelitis occurs in a small number of patients with SLE, many cases of which are associated with antibodies to antiphospholipids and/or to aquaporin-4. Patients with aquaporin-4 antibodies are likely to have longitudinally extensive myelitis by MRI, are considered to have an NMO-spectrum disorder, and are at high risk of developing future episodes of myelitis and/or optic neuritis. The CSF in SLE myelitis is usually normal or shows a mild lymphocytic pleocytosis; oligoclonal bands are a variable finding. Although there are no systematic trials of therapy for SLE myelitis, based on limited data, high-dose glucocorticoids followed by cyclophosphamide have been recommended. Acute severe episodes of transverse myelitis that do not initially respond to glucocorticoids are often treated with a course of plasma exchange. Sjögren's syndrome can also be associated with NMO spectrum disorder and also with cases of acute transverse or chronic progressive myelopathy. Other immune-mediated myelitides include antiphospholipid antibody syndrome, mixed connective tissue disease, Behçet's syndrome, and vasculitis related to polyarteritis nodosa, perinuclear antineutrophilic cytoplasmic (p-ANCA) antibodies, or primary central nervous system vasculitis.

Another important consideration in this group is sarcoid myelopathy that may present as a slowly progressive or relapsing disorder. MRI reveals an edematous swelling of the spinal cord that may mimic tumor; there is almost always gadolinium enhancement of active lesions and in some cases nodular enhancement of the adjacent surface of the cord; lesions may be single or multiple, and on axial images, enhancement of the central cord is usually present. The typical CSF profile consists of a mild lymphocytic pleocytosis and mildly elevated protein level; in a minority of cases, reduced glucose and oligoclonal bands are found. The diagnosis is particularly difficult when systemic manifestations of sarcoid are minor or absent (nearly 50% of cases) or when other typical neurologic manifestations of the disease—such as cranial neuropathy, hypothalamic involvement, or meningeal enhancement visualized by MRI—are lacking. A slit-lamp examination of the eye to search for uveitis, chest x-ray and CT to assess pulmonary involvement and mediastinal lymphadenopathy, serum or CSF angiotensin-converting enzyme (ACE; CSF values elevated in only a minority of cases), serum calcium, and a gallium scan may assist in the diagnosis.

www.ketabpezeshki.com (021) 66485457 - 66485438

T e usefulness of spinal fluid ACE is uncertain. Initial treatment is with oral glucocorticoids; immunosuppressant drugs, including the tumor necrosis factor α inhibitor infliximab, have been used for resistant cases.

Postinfectious myelitis

Many cases of myelitis, termed postinfectious or postvaccinal, follow an infection or vaccination. Numerous organisms have been implicated, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), mycoplasma, influenza, measles, varicella, and mumps. As in the related disorder acute disseminated encephalomyelitis **(Chap. 45)**, postinfectious myelitis often begins as the patient appears to be recovering from an acute febrile infection, or in the subsequent days or weeks, but an infectious agent cannot be isolated from the nervous system or CSF. T e presumption is that the myelitis represents an autoimmune disorder triggered by infection and is not due to direct infection of the spinal cord. No randomized controlled trials of therapy exist; treatment is usually with glucocorticoids or, in fulminant cases, plasma exchange.

Acute infectious myelitis

Many viruses have been associated with an acute myelitis that is infectious in nature rather than postinfectious. Nonetheless, the two processes are often difficult to distinguish. Herpes zoster is the best characterized viral myelitis, but HSV types 1 and 2, EBV, CMV, and rabies virus are other well-described causes. HSV-2 (and less commonly HSV-1) produces a distinctive syndrome of recurrent sacral cauda equina neuritis in association with outbreaks of genital herpes (Elsberg's syndrome). Poliomyelitis is the prototypic viral myelitis, but it is more or less restricted to the anterior gray matter of the cord containing the spinal motoneurons. A polio-like syndrome can also be caused by a large number of enteroviruses (including enterovirus 71 and coxsackie), and with West Nile virus and other flaviviruses. Recently, cases of paralysis in children and adolescents were associated with enterovirus D-68 infection but a causal role for this virus has not been established. Chronic viral myelitic infections, such as those due to HIV or human T cell lymphotropic virus type 1 (HTLV-1), are discussed below.

Bacterial and mycobacterial myelitis (most are essentially abscesses) are less common than viral causes and much less frequent than cerebral bacterial abscess. Almost any pathogenic species may be responsible, including Borrelia burgdorferi (Lyme disease), Listeria monocytogenes, Mycobacterium tuberculosis, and Treponema pallidum (syphilis). Mycoplasma pneumoniae may be a cause of myelitis, but its status is uncertain because many cases are more properly classified as postinfectious.

Schistosomiasis is an important cause of parasitic myelitis in endemic areas. T e process is intensely inflammatory and granulomatous, caused by a local response to tissue-digesting enzymes from the ova of the parasite, typically Schistosoma mansoni. Toxoplasmosis can occasionally cause a focal myelopathy, and this diagnosis should especially be considered in patients with AIDS **(Chap. 48)**.

In cases of suspected viral myelitis, it may be appropriate to begin specific therapy pending laboratory confirmation. Herpes zoster, HSV, and EBV myelitis are treated with intravenous acyclovir (10 mg/kg q8h) or oral valacyclovir (2 g tid) for 10–14 days; CMV is treated with ganciclovir (5 mg/kg IV bid) plus foscarnet (60 mg/kg IV tid) or cidofovir (5 mg/kg per week for 2 weeks).

High-voltage electrical injury

Spinal cord injuries are prominent following electrocution from lightning strikes or other accidental electrical exposures. T e syndrome consists of transient weakness acutely (often with an altered sensorium and focal cerebral disturbances), followed several days or even weeks later by a myelopathy that can be severe and permanent. T is is a rare injury type, and limited data incriminate a vascular pathology involving the anterior spinal artery and its branches in some cases. T erapy is supportive.

CHRONIC MYELOPATHIES

SPONDYLOTIC MYELOPATHY

Spondylotic myelopathy is one of the most common causes of chronic cord compression and of gait difficulty in the elderly. Neck and shoulder pain with stiffness are early symptoms; impingement of bone and soft tissue overgrowth on nerve roots results in radicular arm pain, most often in a C5 or C6 distribution. Compression of the cervical cord, which occurs in fewer than one-third of cases, produces a slowly progressive spastic paraparesis, at times asymmetric and often accompanied by paresthesias in the feet and hands. Vibratory sense is diminished in the legs, there is a Romberg sign, and occasionally there is a sensory level for vibration or pinprick on the upper thorax. In some cases, coughing or straining produces leg weakness or radiating arm or shoulder pain. Dermatomal sensory loss in the arms, atrophy of intrinsic hand muscles, increased deep-tendon reflexes in the legs, and extensor plantar responses are common. Urinary urgency or incontinence occurs in advanced cases, but there are many alternative causes of these problems in older individuals. A tendon reflex in the arms is often diminished at some level; most often at the biceps (C5-C6).

www.ketabpezeshki.com (021) 66485457 - 66485438

In individual cases, radicular, myelopathic, or combined signs may predominate. T e diagnosis should be considered in appropriate cases of progressive cervical myelopathy, paresthesias of the feet and hands, or wasting of the hands.

Diagnosis is usually made by MRI and may be suspected from CT images; plain x-rays are less helpful. Extrinsic cord compression and deformation are appreciated on axial MRI views, and T2-weighted sequences may reveal areas of high signal intensity within the cord adjacent to the site of compression. A cervical collar may be helpful in milder cases, but definitive therapy consists of surgical decompression. Posterior laminectomy or an anterior approach with resection of the protruded disk and bony material may be required. **Cervical spondylosis and related degenerative diseases of the spine are discussed in Chap. 10**.

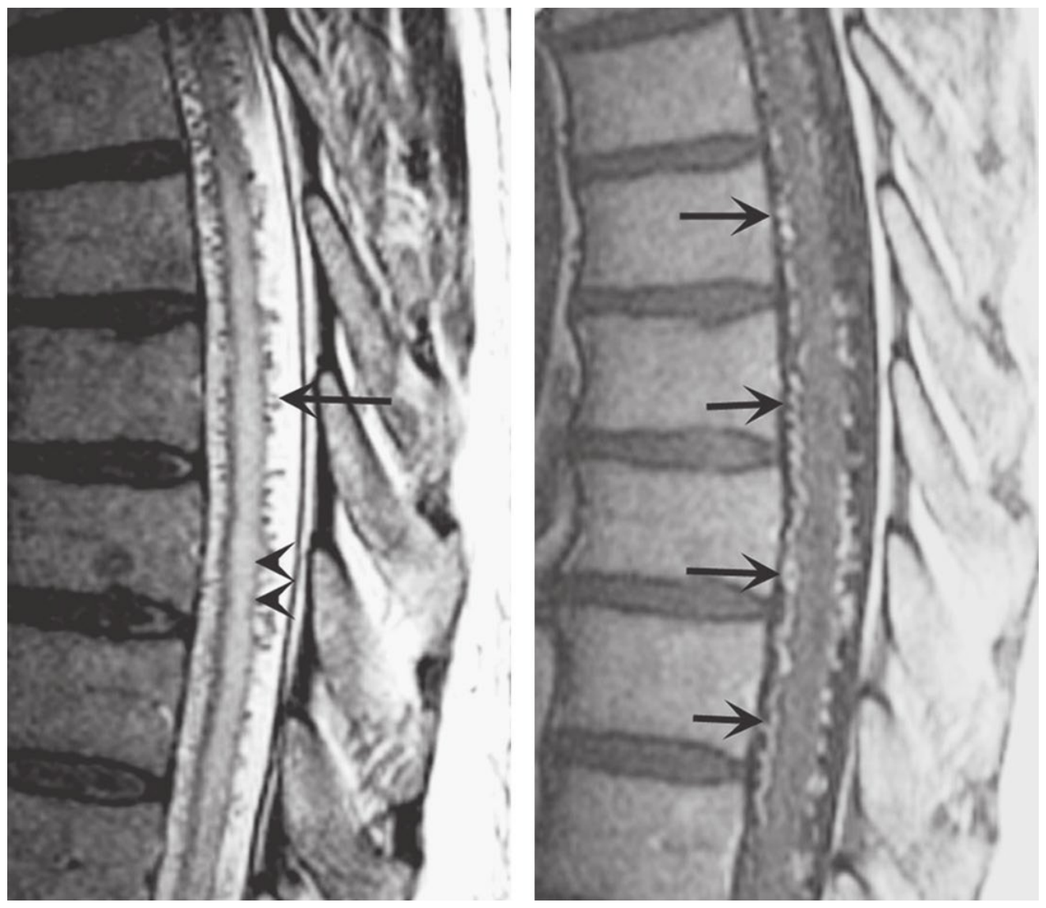


FIGURE 43-6
Arteriovenous malformation. Sagittal magnetic resonance scans of the thoracic spinal cord: T2 fast spin-echo technique (left) and T1 postcontrast image (right). On the T2-weighted image (left), abnormally high signal intensity is noted in the central aspect of the spinal cord (arrowheads). Numerous punctate flow voids indent the dorsal and ventral spinal cord (arrow). These represent the abnormally dilated venous plexus supplied by a dural arteriovenous fistula. After contrast administration (right), multiple, serpentine, enhancing veins (arrows) on the ventral and dorsal aspect of the thoracic spinal cord are visualized, diagnostic of arteriovenous malformation. This patient was a 54-year-old man with a 4-year history of progressive paraparesis.

VASCULAR MALFORMATIONS OF THE CORD AND DURA

Vascular malformations of the cord and overlying dura are treatable causes of progressive myelopathy. Most common are fistulas located within the dura or posteriorly along the surface of the cord. Most dural arteriovenous (AV) fistulas are located at or below the midthoracic level, usually consisting of a direct connection between a radicular feeding artery in the nerve root sleeve with dural veins. T e typical presentation is a middle-aged man with a progressive myelopathy that worsens slowly or intermittently and may have periods of remission, sometimes mimicking MS. Acute deterioration due to hemorrhage into the spinal cord (hematomyelia) or subarachnoid space may also occur but is rare. A saltatory progression is most common and appears to be the result of local ischemia and edema from venous congestion. Most patients have incomplete sensory, motor, and bladder disturbances. T e motor disorder may predominate and produce a mixture of upper and restricted lower motor neuron signs, simulating amyotrophic lateral sclerosis (ALS). Pain over the dorsal spine, dysesthesias, or radicular pain may be present. Other symptoms suggestive of AV malformation (AVM) or dural fistula include intermittent claudication; symptoms that change with posture, exertion, Valsalva maneuver, or menses; and fever.

Less commonly, AVM disorders are intramedullary rather than dural. One unusual disorder is a progressive thoracic myelopathy with paraparesis developing over weeks or months, characterized pathologically by abnormally thick, hyalinized vessels within the cord (subacute necrotic myelopathy, or Foix-Alajouanine syndrome).

Spinal bruits are infrequent but may be sought at rest and after exercise in suspected cases. A vascular nevus on the overlying skin may indicate an underlying vascular malformation as occurs with Klippel-Trenaunay-Weber syndrome. High-resolution MRI with contrast administration detects the draining vessels of many but not all AVMs **(Fig. 43-6)**. An uncertain proportion may be visualized by CT myelography as enlarged vessels along the surface of the cord. Definitive diagnosis requires selective spinal angiography, which defines the feeding vessels and the extent of the malformation. Endovascular embolization of the major feeding vessels may stabilize a progressive neurologic deficit or allow for gradual recovery. Some lesions, especially small dural fistulas, can be resected surgically.

RETROVIRUS-ASSOCIATED MYELOPATHIES

T e myelopathy associated with HTLV-1, formerly called tropical spastic paraparesis, is a slowly progressive spastic syndrome with variable sensory and bladder disturbance. Approximately half of patients have mild back or leg pain. T e neurologic signs may be asymmetric, often lacking a well-defined sensory level; the only sign in the arms may be hyperreflexia

www.ketabpezeshki.com (021) 66485457 - 66485438

after several years of illness. T e onset is insidious, and the illness is slowly progressive at a variable rate; most patients are unable to walk within 10 years of onset. T is presentation may resemble primary progressive MS or a thoracic AVM. Diagnosis is made by demonstration of HTLV-1-specific antibody in serum by enzyme-linked immunosorbent assay (ELISA), confirmed by radioimmunoprecipitation or Western blot analysis. Especially in endemic areas, a finding of HTLV-1 seropositivity in a patient with myelopathy does not necessarily prove that HTLV-1 is causative. T e CSF/serum antibody index may provide support by establishing intrathecal synthesis of antibodies favoring HTVL-1 myelopathy over asymptomatic carriage. Measuring proviral DNA by polymerase chain reaction (PCR) in serum and CSF cells can be useful as an ancillary part of diagnosis, because proviral DNA levels may be higher in patients with myelopathy. T e myelopathy appears to result from an immune-mediated attack on the spinal cord rather than the result of direct viral infection. T ere is no ef ective treatment, but symptomatic therapy for spasticity and bladder symptoms may be helpful.

A progressive myelopathy may also result from HIV infection **(Chap. 48)**. It is characterized by vacuolar degeneration of the posterior and lateral tracts, resembling subacute combined degeneration (see below).

SYRINGOMYELIA

Syringomyelia is a developmental cavity of the cervical cord that may enlarge and produce progressive myelopathy or may remain asymptomatic. Symptoms begin insidiously in adolescence or early adulthood, progress irregularly, and may undergo spontaneous arrest for several years. Many young patients acquire a cervicalthoracic scoliosis. More than half of all cases are associated with Chiari type 1 malformations in which the cerebellar tonsils protrude through the foramen magnum and into the cervical spinal canal. T e pathophysiology of syrinx expansion is controversial, but some interference with the normal flow of CSF seems likely, perhaps by the Chiari malformation. Acquired cavitations of the cord in areas of necrosis are also termed syrinx cavities; these follow trauma, myelitis, necrotic spinal cord tumors, and chronic arachnoiditis due to tuberculosis and other etiologies.

T e presentation is a central cord syndrome consisting of a regional dissociated sensory loss (loss of pain and temperature sensation with sparing of touch and vibration) and areflexic weakness in the upper limbs. T e sensory deficit has a distribution that is "suspended" over the nape of the neck, shoulders, and upper arms (cape distribution) or in the hands. Most cases begin asymmetrically with unilateral sensory loss in the hands that leads to injuries and burns that are not appreciated by the patient. Muscle wasting in the lower neck, shoulders, arms, and hands with asymmetric or absent reflexes in the arms reflects expansion of the cavity in the gray matter of the cord. As the cavity enlarges and compresses the long tracts, spasticity and weakness of the legs, bladder and bowel dysfunction, and a Horner's syndrome appear. Some patients develop facial numbness and sensory loss from damage to the descending tract of the trigeminal nerve (C2 level or above). In cases with Chiari malformations, cough-induced headache and neck, arm, or facial pain may be reported. Extension of the syrinx into the medulla, syringobulbia, causes palatal or vocal cord paralysis, dysarthria, horizontal or vertical nystagmus, episodic dizziness or vertigo, and tongue weakness with atrophy.

MRI accurately identifies developmental and acquired syrinx cavities and their associated spinal cord enlargement **(Fig. 43-7)**. Images of the brain and the entire spinal cord should be obtained to delineate the full longitudinal extent of the syrinx, assess posterior fossa structures for the Chiari malformation, and determine whether hydrocephalus is present.

FIGURE 43-7
Magnetic resonance imaging of syringomyelia associated with a Chiari malformation. Sagittal T1-weighted image through the cervical and upper thoracic spine demonstrates descent of the cerebellar tonsils below the level of the foramen magnum (black arrows). Within the substance of the cervical and thoracic spinal cord, a cerebrospinal fluid collection dilates the central canal (white arrows).

www.ketabpezeshki.com (021) 66485457 - 66485438

TREATMENT Syringomyelia

Treatment of syringomyelia is generally unsatisfactory. The Chiari tonsillar herniation may be decompressed, generally by suboccipital craniectomy, upper cervical laminectomy, and placement of a dural graft. Fourth ventricular outflow is reestablished by this procedure. If the syrinx cavity is large, some surgeons recommend direct decompression or drainage by one of a number of methods, but the added benefit of this procedure is uncertain, and complications are common. With Chiari malformations, shunting of hydrocephalus generally precedes any attempt to correct the syrinx. Surgery may stabilize the neurologic deficit, and some patients improve. Patients with few symptoms and signs from the syrinx do not require surgery and are followed by serial clinical and imaging examinations.

Syrinx cavities secondary to trauma or infection, if symptomatic, are treated with a decompression and drainage procedure in which a small shunt is inserted between the cavity and subarachnoid space; alternatively, the cavity can be fenestrated. Cases due to intramedullary spinal cord tumor are generally managed by resection of the tumor.

CHRONIC MYELOPATHY OF MULTIPLE SCLEROSIS

A chronic progressive myelopathy is the most frequent cause of disability in both primary progressive and secondary progressive forms of MS. Involvement is typically bilateral but asymmetric and produces motor, sensory, and bladder/bowel disturbances. Fixed motor disability appears to result from extensive loss of axons in the corticospinal tracts. Diagnosis is facilitated by identification of earlier attacks such as optic neuritis. MRI, CSF, and evoked response testing are confirmatory. Disease-modifying therapy is indicated for patients with progressive myelopathy who also have coexisting MS relapses. Therapy is sometimes offered to patients who have a progressive course without relapses but with "active" MRI scans (e.g., the presence of new focal demyelinating lesions) despite the lack of evidence supporting the value of treatment in this setting. **MS is discussed in Chap. 45**.

SUBACUTE COMBINED DEGENERATION (VITAMIN B_{12} DEFICIENCY)

This treatable myelopathy presents with subacute paresthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness. Loss of reflexes due to an associated peripheral neuropathy in a patient who also has Babinski signs is an important diagnostic clue. Optic atrophy and irritability or other cognitive changes may be prominent in advanced cases and are occasionally the presenting symptoms. The myelopathy of subacute combined degeneration tends to be diffuse rather than focal; signs are generally symmetric and reflect predominant involvement of the posterior and lateral tracts, including Romberg's sign. The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B_{12} concentration, elevated serum levels of homocysteine and methylmalonic acid, and in uncertain cases, testing for anti–parietal cell antibodies and a Schilling test. Treatment is by replacement therapy, beginning with 1000 μg of intramuscular vitamin B_{12} repeated at regular intervals or by subsequent oral treatment.

HYPOCUPRIC MYELOPATHY

This myelopathy is similar to subacute combined degeneration (described above), except there is no neuropathy, and explains cases with normal serum levels of B_{12}. Low levels of serum copper are found, and often there is also a low level of serum ceruloplasmin. Some cases follow gastrointestinal procedures, particularly bariatric surgery, that result in impaired copper absorption; others have been associated with excess zinc from health food supplements or, until recently, zinc-containing denture creams, all of which impair copper absorption via induction of metallothionein, a copper-binding protein. Many cases are idiopathic. Improvement or at least stabilization may be expected with reconstitution of copper stores by oral supplementation. There is microcytic or macrocytic anemia. The pathophysiology and pathology of the idiopathic form are not known.

TABES DORSALIS

The classic syphilitic syndromes of tabes dorsalis and meningovascular inflammation of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders. The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15–30% of patients. The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg's sign; and, in almost all cases, bilateral Argyll Robertson pupils, which fail to constrict to light but accommodate. Diabetic polyradiculopathy may simulate tabes.

FAMILIAL SPASTIC PARAPLEGIA

Many cases of slowly progressive myelopathy are genetic in origin **(Chap. 39)**. More than 30 different causative loci have been identified, including autosomal dominant, autosomal recessive, and X-linked forms. Especially for

www.ketabpezeshki.com (021) 66485457 - 66485438

the recessive and X-linked forms, a family history of myelopathy may be lacking. Most patients present with almost imperceptibly progressive spasticity and weakness in the legs, usually but not always symmetrical. Sensory symptoms and signs are absent or mild, but sphincter disturbances may be present. In some families, additional neurologic signs are prominent, including nystagmus, ataxia, or optic atrophy. T e onset may be as early as the first year of life or as late as middle adulthood. Only symptomatic therapies are available.

ADRENOMYELONEUROPATHY

T is X-linked disorder is a variant of adrenoleukodystrophy. Most af ected males have a history of adrenal insufficiency and then develop a progressive spastic (or ataxic) paraparesis beginning in early or sometimes middle adulthood; some patients also have a mild peripheral neuropathy. Female heterozygotes may develop a slower, insidiously progressive spastic myelopathy beginning later in adulthood and without adrenal insufficiency. Diagnosis is usually made by demonstration of elevated levels of very-long-chain fatty acids in plasma and in cultured fibroblasts. T e responsible gene encodes the adrenoleukodystrophy protein (ADLP), a peroxisomal membrane transporter involved in carrying long-chain fatty acids to peroxisomes for degradation. Corticosteroid replacement is indicated if hypoadrenalism is present, and bone marrow transplantation and nutritional supplements have been attempted for this condition without clear evidence of efficacy.

OTHER CHRONIC MYELOPATHIES

Primary lateral sclerosis **(Chap. 39)** is a degenerative disorder characterized by progressive spasticity with weakness, eventually accompanied by dysarthria and dysphonia; bladder symptoms occur in approximately half of patients. Sensory function is spared. T e disorder resembles ALS and is considered a variant of the motor neuron degenerations, but without the characteristic lower motor neuron disturbance. Some cases may represent familial spastic paraplegia, particularly autosomal recessive or X-linked varieties in which a family history may be absent.

Tethered cord syndrome is a developmental disorder of the lower spinal cord and nerve roots that rarely presents in adulthood as low back pain accompanied by a progressive lower spinal cord and/or nerve root syndrome. Some patients have a small leg or foot deformity indicating a long-standing process, and in others, a dimple, patch of hair, or sinus tract on the skin overlying the lower back is the clue to a congenital lesion. Diagnosis is made by MRI, which demonstrates a low-lying conus medullaris and thickened filum terminale. T e MRI may also reveal diastematomyelia (division of the lower spinal cord into two halves), lipomas, cysts, or other congenital abnormalities of the lower spine coexisting with the tethered cord. Treatment is with surgical release.

T ere are a number of rare toxic causes of spastic myelopathy, including lathyrism due to ingestion of chickpeas containing the excitotoxin β-N-oxalylamino-l-alanine (BOAA), seen primarily in the developing world, and nitrous oxide inhalation producing a myelopathy identical to subacute combined degeneration. SLE, Sjögren's syndrome, and sarcoidosis may each cause a myelopathy without overt evidence of systemic disease. Cancer-related causes of chronic myelopathy, besides the common neoplastic compressive myelopathy discussed earlier, include radiation injury **(Chap. 49)** and rare paraneoplastic myelopathies. T e last of these are most often associated with lung or breast cancer and anti-Hu antibodies **(Chap. 50)** or with lymphoma that causes a syndrome of destruction of anterior horn cells; NMO **(Chap. 45)** can also rarely be paraneoplastic in origin. Metastases to the cord are probably more common than either of these in patients with cancer. Often, a cause of intrinsic myelopathy can be identified only through periodic reassessment.

REHABILITATION OF SPINAL CORD DISORDERS

T e prospects for recovery from an acute destructive spinal cord lesion fade after ~6 months. T ere are currently no ef ective means to promote repair of injured spinal cord tissue; promising but entirely experimental approaches include the use of factors that influence reinnervation by axons of the corticospinal tract, nerve and neural sheath graft bridges, forms of electrical stimulation at the site of injury, and the local introduction of stem cells. T e disability associated with irreversible spinal cord damage is determined primarily by the level of the lesion and by whether the disturbance in function is complete or incomplete **(Table 43-4)**. Even a complete high cervical cord lesion may be compatible with a productive life. T e primary goals are development of a rehabilitation plan framed by realistic expectations and attention to the neurologic, medical, and psychological complications that commonly arise.

Many of the usual symptoms associated with medical illnesses, especially somatic and visceral pain, may be lacking because of the destruction of af erent pain pathways. Unexplained fever, worsening of spasticity, or deterioration in neurologic function should prompt a search for infection, thrombophlebitis, or an intraabdominal pathology. T e loss of normal

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 43-4

EXPECTED NEUROLOGIC FUNCTION FOLLOWING COMPLETE CORD LESIONS			
LEVEL	SELF-CARE	TRANSFERS	MAXIMUM MOBILITY
High quadriplegia (C1-C4)	Dependent on others; requires respiratory support	Dependent on others	Motorized wheelchair
Low quadriplegia (C5-C8)	Partially independent with adaptive equipment	May be dependent or independent	May use manual wheelchair, drive an automobile with adaptive equipment
Paraplegia (below T1)	Independent	Independent	Ambulates short distances with aids

Source: Adapted from JF Ditunno, CS Formal: Chronic spinal cord injury. N Engl J Med 330:550, 1994; with permission.

thermoregulation and inability to maintain normal body temperature can produce recurrent fever (quadriplegic fever), although most episodes of fever are due to infection of the urinary tract, lung, skin, or bone.

Bladder dysfunction generally results from loss of supraspinal innervation of the detrusor muscle of the bladder wall and the sphincter musculature. Detrusor spasticity is treated with anticholinergic drugs (oxybutynin, 2.5–5 mg qid) or tricyclic antidepressants with anticholinergic properties (imipramine, 25–200 mg/d). Failure of the sphincter muscle to relax during bladder emptying (urinary dyssynergia) may be managed with the α-adrenergic blocking agent terazosin hydrochloride (1–2 mg tid or qid), with intermittent catheterization, or, if that is not feasible, by use of a condom catheter in men or a permanent indwelling catheter. Surgical options include the creation of an artificial bladder by isolating a segment of intestine that can be catheterized intermittently (enterocystoplasty) or can drain continuously to an external appliance (urinary conduit). Bladder areflexia due to acute spinal shock or conus lesions is best treated by catheterization. Bowel regimens and disimpaction are necessary in most patients to ensure at least biweekly evacuation and avoid colonic distention or obstruction.

Patients with acute cord injury are at risk for venous thrombosis and pulmonary embolism. Use of calf-compression devices and anticoagulation with low-molecular-weight heparin is recommended. In cases of persistent paralysis, anticoagulation should probably be continued for 3 months.

Prophylaxis against decubitus ulcers should involve frequent changes in position in a chair or bed, the use of special mattresses, and cushioning of areas where pressure sores often develop, such as the sacral prominence and heels. Early treatment of ulcers with careful cleansing, surgical or enzyme debridement of necrotic tissue, and appropriate dressing and drainage may prevent infection of adjacent soft tissue or bone.

Spasticity is aided by stretching exercises to maintain mobility of joints. Drug treatment is effective but may result in reduced function, as some patients depend on spasticity as an aid to stand, transfer, or walk. Baclofen (up to 240 mg/d in divided doses) is effective; it acts by facilitating γ-aminobutyric acid–mediated inhibition of motor reflex arcs. Diazepam acts by a similar mechanism and is useful for leg spasms that interrupt sleep (2–4 mg at bedtime). Tizanidine (2–8 mg tid), an α_2 adrenergic agonist that increases presynaptic inhibition of motor neurons, is another option. For nonambulatory patients, the direct muscle inhibitor dantrolene (25–100 mg qid) may be used, but it is potentially hepatotoxic. In refractory cases, intrathecal baclofen administered via an implanted pump, botulinum toxin injections, or dorsal rhizotomy may be required to control spasticity.

Despite the loss of sensory function, many patients with spinal cord injury experience chronic pain sufficient to diminish their quality of life. Randomized controlled studies indicate that gabapentin or pregabalin is useful in this setting. Epidural electrical stimulation and intrathecal infusion of pain medications have been tried with some success. **Management of chronic pain is discussed in Chap. 8**.

A paroxysmal autonomic hyperreflexia may occur following lesions above the major splanchnic sympathetic outflow at T6. Headache, flushing, and diaphoresis above the level of the lesion, as well as hypertension with bradycardia or tachycardia, are the major symptoms. The trigger is typically a noxious stimulus—for example, bladder or bowel distention, a urinary tract infection, or a decubitus ulcer—below the level of the cord lesion. Treatment consists of removal of offending stimuli; ganglionic blocking agents (mecamylamine, 2.5–5 mg) or other short-acting antihypertensive drugs are useful in some patients.

Attention to these details allows longevity and a productive life for patients with complete transverse myelopathies.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 44

CONCUSSION AND OTHER TRAUMATIC BRAIN INJURIES

Allan H. Ropper

Almost 10 million head injuries occur annually in the United States, about 20% of which are serious enough to cause brain damage. Among men <35 years, accidents, usually motor vehicle collisions, are the chief cause of death and >70% of these involve head injury. Furthermore, minor head injuries are so common that almost all physicians will be called upon to provide immediate care or to see patients who are suffering from various sequelae.

Medical personnel caring for head injury patients should be aware that (1) spinal injury often accompanies head injury, and care must be taken in handling the patient to prevent compression of the spinal cord due to instability of the spinal column; (2) intoxication is frequently associated with traumatic brain injury, and thus testing for drugs and alcohol should be carried out when appropriate; and (3) additional injuries, including rupture of abdominal organs, may produce vascular collapse, shock, or respiratory distress that requires immediate attention.

TYPES OF HEAD INJURIES

CONCUSSION

T is form of minor head injury had in the past referred to an immediate and transient loss of consciousness that was associated with a short period of amnesia. Many patients, however, do not lose consciousness after a minor head injury but instead are dazed or confused, or feel stunned or "star struck," and the term concussion is now applied to all such cognitive and perceptual changes experienced after a blow to the head. Severe concussion may precipitate a brief convulsion or autonomic signs such as facial pallor, bradycardia, faintness with mild hypotension, or sluggish pupillary reaction, but most patients quickly return to a neurologically normal state.

T e mechanics of a typical concussion involve sudden deceleration of the head when hitting a blunt stationary object. T is creates an anterior-posterior movement of the brain within the skull due to inertia and rotation of the cerebral hemispheres on the fulcrum of the relatively fixed upper brainstem. Loss of consciousness in concussion is believed to result from a transient electrophysiologic dysfunction of the reticular activating system in the upper midbrain that is at the site of rotation **(Chap. 19)**. T e transmission of a wave of kinetic energy throughout the brain is an alternative explanation for the disruption in consciousness.

Gross and light-microscopic changes in the brain are usually absent following concussion, but biochemical and ultrastructural changes, such as mitochondrial ATP depletion and local disruption of the blood-brain barrier, may be transient abnormalities. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are usually normal; however, a small number of patients will be found to have a skull fracture, an intracranial hemorrhage, or a brain contusion.

A brief period of both retrograde and anterograde amnesia is characteristic of concussion, and it recedes rapidly in alert patients. Memory loss spans the moments before impact but may encompass the previous days or weeks (rarely months). With severe injuries, the extent of retrograde amnesia roughly correlates with the severity of injury. Memory is regained erratically from the most distant to more recent memories, with islands of amnesia occasionally remaining. T e mechanism of amnesia is not known. Hysterical posttraumatic amnesia is not uncommon after head injury and should be suspected when inexplicable behavioral abnormalities occur, such as recounting events that cannot be recalled on later testing, a bizarre affect, forgetting

www.ketabpezeshki.com (021) 66485457 - 66485438

one's own name, or a persistent anterograde deficit that is excessive in comparison with the degree of injury. **Amnesia is discussed in Chap. 22**.

A single, uncomplicated concussion only infrequently produces permanent neurobehavioral changes in patients who are free of preexisting psychiatric and neurologic problems. Nonetheless, residual problems in memory and concentration may have an anatomic correlate in microscopic cerebral lesions (see below).

The mechanisms by which a blast injury affects the brain and causes symptoms that are associated with concussion, a problem mainly in military medicine, are not known. The energy of a blast wave can enter the cranium through the openings of the orbits, auditory canals, and foramen magnum. There are not consistent changes in cerebral imaging studies but more subtle indications of tissue disruption have been found, comparable to those of mild concussion. It has been difficult to separate the direct effects of the blast from the consequences of being thrown against fixed objects or injured by flying debris.

CONTUSION, BRAIN HEMORRHAGE, AND AXONAL SHEARING LESIONS

These pathologic changes are the result of severe cranial trauma. A surface bruise of the brain, or contusion, consists of varying degrees of petechial hemorrhage, edema, and tissue destruction. Contusions and deeper hemorrhages result from mechanical forces that displace and compress the hemispheres forcefully and by deceleration of the brain against the inner skull, either under a point of impact (coup lesion) or, as the brain swings back, in the antipolar area (contrecoup lesion). Trauma sufficient to cause prolonged unconsciousness usually produces some degree of contusion. Blunt deceleration impact, as occurs against an automobile dashboard or from falling forward onto a hard surface, causes contusions on the orbital surfaces of the frontal lobes and the anterior and basal portions of the temporal lobes. With lateral forces, as from impact on an automobile door frame, contusions are situated on the lateral convexity of the hemisphere. The clinical signs of contusion are determined by the location and size of the lesion; often, there are no focal neurologic abnormalities, but these injured regions are later the sites of gliotic scars that may produce seizures. A hemiparesis or gaze preference is fairly typical of moderately sized contusions. Large bilateral contusions produce stupor with extensor posturing, while those limited to the frontal lobes cause a taciturn state. Contusions in the temporal lobe may cause delirium or an aggressive, combative syndrome.

Acute contusions are easily visible on CT and MRI scans, appearing as inhomogeneous hyperdensities on CT and as hyperintensities on T2 and fluid-attenuated

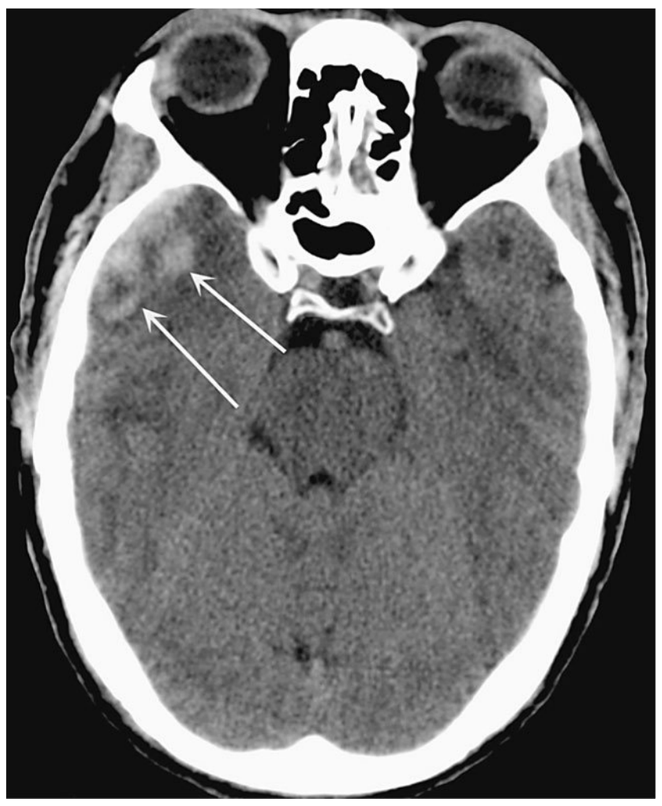


FIGURE 44-1
Traumatic cerebral contusion. Noncontrast computed tomography scan demonstrating a hyperdense hemorrhagic region in the anterior temporal lobe.

inversion recovery (FLAIR) MRI sequences; there is usually surrounding localized brain edema **(Fig. 44-1)** and some subarachnoid bleeding. Blood in the cerebrospinal fluid (CSF) due to trauma may provoke a mild inflammatory reaction. Over a few days, contusions acquire a surrounding contrast enhancement and edema that may be mistaken for tumor or abscess. Glial and macrophage reactions result in chronic, scarred, hemosiderin-stained depressions on the cortex (plaques jaunes) that are the main source of posttraumatic epilepsy.

Torsional or shearing forces within the brain cause hemorrhages of the basal ganglia and other deep regions. Large hemorrhages after minor trauma suggest that there is a bleeding diathesis or cerebrovascular amyloidosis. For unexplained reasons, deep cerebral hemorrhages may not develop until several days after injury. Sudden neurologic deterioration in a comatose patient or a sudden rise in intracranial pressure (ICP) suggests this complication has occurred and should therefore prompt investigation with a CT scan.

A special type of deep white matter lesion consists of widespread mechanical disruption, or shearing, of axons at the time of impact. Most characteristic are small areas of tissue injury in the corpus callosum and dorsolateral pons. The presence of widespread multifocal axonal damage in both hemispheres, a state called diffuse axonal injury (DAI), has been proposed to explain persistent coma and the vegetative state after closed head injury **(Chap. 19)**, but small ischemic-hemorrhagic lesions in the midbrain and thalamus are an alternative explanation. Only severe shearing lesions that contain blood are visualized by CT, usually in the corpus callosum and centrum semiovale **(Fig. 44-2)**;

www.ketabpezeshki.com (021) 66485457 - 66485438

FIGURE 44-2
Multiple small areas of hemorrhage and tissue disruption in the white matter of the frontal lobes on noncontrast computed tomography scan. These appear to reflect an extreme type of the dif use axonal shearing lesions that occur with closed head injury.

however, special MRI sequences that detect small amounts of blood and diffusion tensor imaging can demonstrate numerous such lesions throughout the white matter.

SKULL FRACTURES

A blow to the skull that exceeds the elastic tolerance of the bone causes a fracture. Intracranial lesions accompany roughly two-thirds of skull fractures, and the presence of a fracture increases many-fold the chances of an underlying subdural or epidural hematoma. Consequently, fractures are primarily markers of the site and severity of injury. If the underlying arachnoid membrane has been torn, fractures also provide potential pathways for entry of bacteria to the CSF with a risk of meningitis and for leakage of CSF outward through the dura. If there is leakage of CSF, severe orthostatic headache results from lowered pressure in the spinal fuid compartment.

Most fractures are linear and extend from the point of impact toward the base of the skull. Basilar skull fractures are often extensions of adjacent linear fractures over the convexity of the skull but may occur independently owing to stresses on the foor of the middle cranial fossa or occiput. Basilar fractures are usually parallel to the petrous bone or along the sphenoid bone and directed toward the sella turcica and ethmoidal groove. Although most basilar fractures are uncomplicated, they can cause CSF leakage, pneumocephalus, and delayed cavernous-carotid fistulas. Hemotympanum (blood behind the tympanic membrane), ecchymosis over the mastoid process (Battle sign), and periorbital ecchymosis (“raccoon sign”) are associated with basilar fractures. Because routine x-ray examination may fail to disclose basilar fractures, they should be suspected if these clinical signs are present.

CSF may leak through the cribriform plate or the adjacent sinus and cause CSF rhinorrhea (a watery discharge from the nose). Persistent rhinorrhea and recurrent meningitis usually require surgical repair of torn dura underlying the fracture. T e site of the leak is often difficult to determine, but useful diagnostic tests include the instillation of water-soluble contrast into the CSF followed by CT with the patient in various positions, or injection of radionuclide compounds or fuorescein into the CSF and the insertion of absorptive nasal pledgets. T e location of an intermittent leak is infrequently delineated, and many resolve spontaneously.

Sellar fractures, even those associated with serious neuroendocrine dysfunction, may be radiologically occult or evident only by an air-fuid level in the sphenoid sinus. Fractures of the dorsum sella cause sixth or seventh nerve palsies or optic nerve damage.

Petrous bone fractures, especially those oriented along the long axis of the bone, may be associated with facial palsy, disruption of ear ossicles, and CSF otorrhea. Transverse petrous fractures are less common; they almost always damage the cochlea or labyrinths and often the facial nerve as well. External bleeding from the ear is usually from local abrasion of the external canal but can also result from petrous fracture.

Fractures of the frontal bone are usually depressed, involving the frontal and paranasal sinuses and the orbits. Depressed skull fractures are typically compound, but they may be asymptomatic because the impact energy is dissipated in breaking the bone; some have underlying brain contusions. Debridement and exploration of compound fractures are required in order to avoid infection; simple fractures usually do not require surgery.

CRANIAL NERVE INJURIES

T e cranial nerves most often injured with head trauma are the olfactory, optic, oculomotor, and trochlear; the first and second branches of the trigeminal nerve; and the facial and auditory nerves. Anosmia and an apparent loss of taste (actually a loss of perception of aromatic favors, with retained elementary taste perception) occur in ~10% of persons with serious head injuries, particularly from falls on the back of the head. T is is the result of displacement of the brain and shearing of the fine olfactory nerve filaments that course through the cribriform bone. At least partial recovery of olfactory and gustatory function is expected, but if bilateral anosmia persists for several months, the prognosis is poor. Partial optic nerve injuries from closed trauma result in blurring

www.ketabpezeshki.com (021) 66485457 - 66485438

of vision, central or paracentral scotomas, or sector defects. Direct orbital injury may cause short-lived blurred vision for close objects due to reversible iridoplegia. Diplopia limited to downward gaze and corrected when the head is tilted away from the side of the affected eye indicates trochlear (fourth nerve) nerve damage. It occurs frequently as an isolated problem after minor head injury or may develop for unknown reasons after a delay of several days. Facial nerve injury caused by a basilar fracture is present immediately in up to 3% of severe injuries; it may also be delayed for 5–7 days. Fractures through the petrous bone, particularly the less common transverse type, are liable to produce facial palsy. Delayed facial palsy occurring up to a week after injury, the mechanism of which is unknown, has a good prognosis. Injury to the eighth cranial nerve from a fracture of the petrous bone causes loss of hearing, vertigo, and nystagmus immediately after injury. Deafness from eighth nerve injury is rare and must be distinguished from blood in the middle ear or disruption of the middle ear ossicles. Dizziness, tinnitus, and high-tone hearing loss occur from cochlear concussion, most typically after blast injury.

SEIZURES

Convulsions are surprisingly uncommon immediately after a head injury, but a brief period of tonic extensor posturing or a few clonic movements of the limbs just after the moment of impact can occur. However, the cortical scars that evolve from contusions are highly epileptogenic and may later manifest as seizures, even after many months or years **(Chap. 31)**. T e severity of injury roughly determines the risk of future seizures. It has been estimated that 17% of individuals with brain contusion, subdural hematoma, or prolonged loss of consciousness will develop a seizure disorder and that this risk extends for an indefinite period of time, whereas the risk is ≤2% after mild injury. T e majority of convulsions in the latter group occur within 5 years of injury but may be delayed for decades. Penetrating injuries have a much higher rate of subsequent epilepsy.

SUBDURAL AND EPIDURAL HEMATOMAS

Hemorrhages beneath the dura (subdural) or between the dura and skull (epidural) have characteristic clinical and imaging features. T ey are sometimes associated with underlying contusions and other injuries, often making it difficult to determine the relative contribution of each component to the clinical state. T e mass effect and raised ICP caused by these hematomas can be life threatening, making it imperative to identify them rapidly by CT or MRI scan and to remove them when appropriate.

Acute subdural hematoma

Direct cranial trauma may be minor and is not required for acute subdural hemorrhage to occur, especially in the elderly and those taking anticoagulant medications **(Fig. 44-3)**. Acceleration forces alone, as from whiplash, are sometimes sufficient to produce subdural hematoma. Up to one-third of patients have a lucid interval lasting minutes to hours before coma supervenes, but most are drowsy or comatose from the moment of injury. A unilateral headache and slightly enlarged pupil on the side of the hematoma are frequently, but not invariably, present. Stupor or coma, hemiparesis, and unilateral pupillary enlargement are signs of larger hematomas. In an acutely deteriorating patient, burr (drainage) holes or an emergency craniotomy are required. Small subdural hematomas may be asymptomatic and usually do not require evacuation if they do not enlarge.

A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis, usually in alcoholics and in the elderly and often after only minor trauma. On imaging studies, subdural hematomas appear as crescentic collections over the convexity of one or both hemispheres, most commonly in the frontotemporal region, and less often in the inferior middle fossa or over the occipital poles (Fig. 44-3). Interhemispheric, posterior fossa, or bilateral convexity hematomas are less frequent and are difficult to diagnose clinically, although drowsiness and the neurologic signs expected from damage in each region can usually be detected. T e bleeding that causes larger hematomas

FIGURE 44-3
Acute subdural hematoma. Noncontrast computed tomography scan reveals a hyperdense clot that has an irregular border with the brain and causes more horizontal displacement (mass effect) than might be expected from its thickness. The disproportionate mass effect is the result of the large rostral-caudal extent of these hematomas. Compare to Fig. 44-4.

www.ketabpezeshki.com (021) 66485457 - 66485438

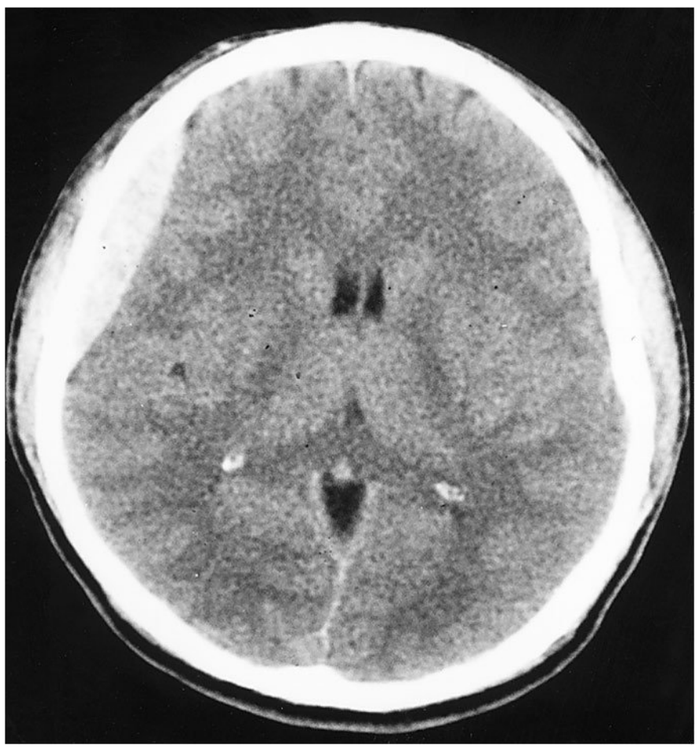


FIGURE 44-4
Acute epidural hematoma. The tightly attached dura is stripped from the inner table of the skull, producing a characteristic lenticular-shaped hemorrhage on noncontrast computed tomography scan. Epidural hematomas are usually caused by tearing of the middle meningeal artery following fracture of the temporal bone.

FIGURE 44-5
Computed tomography scan of chronic bilateral subdural hematomas of different ages. The collections began as acute hematomas and have become hypodense in comparison to the adjacent brain after a period during which they were isodense and difficult to appreciate. Some areas of resolving blood are contained on the more recently formed collection on the left (arrows).

is primarily venous in origin, although additional arterial bleeding sites are sometimes found at operation, and a few large hematomas have a purely arterial origin.

Epidural hematoma

These usually evolve more rapidly than subdural hematomas and are correspondingly more treacherous **(Fig. 44-4)**. They occur in up to 10% of cases of severe head injury but are associated with underlying cortical damage less often than for subdural hematomas. Most patients are unconscious when first seen. A "lucid interval" of several minutes to hours before coma supervenes is most characteristic of epidural hemorrhage, but it is still uncommon, and epidural hemorrhage is not the only cause of this temporal sequence. Rapid surgical evacuation and ligation or cautery of the damaged vessel is indicated, usually the middle meningeal artery that has been lacerated by an overlying skull fracture.

Chronic subdural hematoma

A subacutely evolving syndrome due to subdural hematoma occurs days or weeks after injury with drowsiness, headache, confusion, or mild hemiparesis, usually in alcoholics and in the elderly and often after only minor or unnoticed trauma **(Fig. 44-5)**. On imaging studies, chronic subdural hematomas appear as crescentic clots over the convexity of one or both hemispheres, most commonly in the frontotemporal region **(**Fig. 44-3**)**. A history of trauma may or may not be elicited in relation to chronic subdural hematoma; the injury may have been trivial and forgotten, particularly in the elderly and those with clotting disorders. Headache is common but not invariable. Additional features that may appear weeks later include slowed thinking, vague change in personality, seizure, or a mild hemiparesis. Headache fluctuates in severity, sometimes with changes in head position.

Bilateral chronic subdural hematomas produce perplexing clinical syndromes, and the initial clinical impression may be of a stroke, brain tumor, drug intoxication, depression, or a dementing illness. Drowsiness, inattentiveness, and incoherence of thought are generally more prominent than focal signs such as hemiparesis. Rarely, chronic hematomas cause brief episodes of hemiparesis or aphasia that are indistinguishable from transient ischemic attacks. Patients with undetected bilateral subdural hematomas have a low tolerance for surgery, anesthesia, and drugs that depress the nervous system; drowsiness or confusion persists for long periods postoperatively.

CT without contrast initially shows a low-density mass over the convexity of the hemisphere (Fig. 44-5). Between 2 and 6 weeks after the initial bleeding, the clot becomes isodense compared to adjacent brain and may be inapparent. Many subdural hematomas that are several weeks in age contain areas of blood and intermixed serous fluid. Bilateral chronic hematomas may fail to be detected because of the absence of lateral tissue shifts; this circumstance in an older patient is suggested by a "hypernormal" CT scan with fullness of the cortical sulci and small ventricles. Infusion of contrast material demonstrates enhancement of the vascular fibrous capsule surrounding the collection. MRI reliably identifies subacute and chronic hematomas.

www.ketabpezeshki.com (021) 66485457 - 66485438

Clinical observation coupled with serial imaging is a reasonable approach to patients with few symptoms, such as headache alone, and in those with small chronic subdural collections. Treatment of minimally symptomatic chronic subdural hematoma with glucocorticoids is favored by some clinicians, but surgical evacuation is more often successful. T e fibrous membranes that grow from the dura and encapsulate the collection require removal to prevent recurrent f uid accumulation. Small hematomas are resorbed, leaving only the organizing membranes. On imaging studies, very chronic subdural hematomas are difficult to distinguish from hygromas, which are collections of CSF from a rent in the arachnoid membrane.

CLINICAL SYNDROMES AND TREATMENT OF HEAD INJURY

MINOR INJURY

T e patient who has brief y lost consciousness or been stunned after a minor head injury usually becomes fully alert and attentive within minutes but may complain of headache, dizziness, faintness, nausea, a single episode of emesis, difficulty with concentration, a brief amnestic period, or slight blurring of vision. T is typical concussion syndrome has a good prognosis with little risk of subsequent deterioration. Children are particularly prone to drowsiness, vomiting, and irritability, symptoms that are sometimes delayed for several hours after apparently minor injuries. Vasovagal syncope that follows injury may cause undue concern. Generalized or frontal headache is common in the following days. It may be migrainous (throbbing and hemicranial) in nature or aching and bilateral. After several hours of observation, patients with minor injury may be accompanied home and observed for a day by a family member or friend, with written instructions to return if symptoms worsen.

Persistent severe headache and repeated vomiting in the context of normal alertness and no focal neurologic signs is usually benign, but CT should be obtained and a longer period of observation is appropriate. T e decision to perform imaging tests also depends on clinical signs that indicate that the impact was severe (e.g., persistent confusion, periorbital or mastoid hematoma, repeated vomiting, palpable skull fracture), on the seriousness of other bodily injuries, and on the degree of surveillance that can be anticipated after discharge. Two studies have indicated that older age, two or more episodes of vomiting, >30 min of retrograde or persistent anterograde amnesia, seizure, and concurrent drug or alcohol intoxication are sensitive (but not specific) indicators of intracranial hemorrhage that justify CT scanning. It may be appropriate to be more liberal in obtaining CT scans in children because a small number, even without loss of consciousness, will have intracranial traumatic lesions but this exposes the child to radiation.

Concussion in sports

In the current absence of adequate data, a common sense approach to athletic concussion has been to remove the individual from play immediately and avoid contact sports for at least several days after a mild injury and for a longer period if there are more severe injuries or if there are protracted neurologic symptoms such as headache and difficulty concentrating. No individual should return to play unless all symptoms have resolved and an assessment has been made by a health care professional who has experience with treatment of concussion. Once cleared, the individual can then begin a graduated program of increasing activity. Younger athletes are particularly likely to experience protracted concussive symptoms, and a slower return to play in this age group may be reasonable. T ese guidelines are designed in part to avoid a perpetuation of symptoms but also to prevent the rare second impact syndrome, in which diffuse and fatal cerebral swelling follows a second minor head injury.

In the past, mental decline in boxers late in their careers had been called dementia pugilistica. T ere is some evidence that repeated concussions from other sports are associated with a similar delayed and progressive cognitive disorder that is due mainly to the deposition of tau protein in cortical neurons. T e brains of these patients display deposition of tau protein in the superficial cortical layers, and particularly in the depths of sulci within the frontal cortices, a pattern named chronic traumatic encephalopathy (CTE) that is quite unlike other degenerative conditions. CTE is an intensively studied and provocative entity. Its contribution, if any, to late-life dementia and parkinsonism in former athletes, soldiers, or others who have sustained repeated concussive injuries is unknown. **CTE is also discussed in Chap. 30**.

INJURY OF INTERMEDIATE SEVERITY

Patients who are not fully alert or have persistent confusion, behavioral changes, extreme dizziness, or focal neurologic signs such as hemiparesis should be admitted to the hospital and have cerebral imaging. A cerebral contusion or hematoma will usually be found. Common syndromes include: (1) delirium with a disinclination to be examined or moved, expletive speech, and resistance if disturbed (anterior temporal lobe contusions); (2) a quiet, disinterested, slowed mental state (abulia) alternating with irascibility (inferior frontal and frontopolar contusions); (3) a focal deficit such as aphasia or mild hemiparesis (due to subdural

www.ketabpezeshki.com (021) 66485457 - 66485438

hematoma or convexity contusion or, less often, carotid artery dissection); (4) confusion and inattention, poor performance on simple mental tasks, and fluctuating orientation (associated with several types of injuries, including those described above, and with medial frontal contusions and interhemispheric subdural hematoma); (5) repetitive vomiting, nystagmus, drowsiness, and unsteadiness (labyrinthine concussion, but occasionally due to a posterior fossa subdural hematoma or vertebral artery dissection); and (6) diabetes insipidus (damage to the median eminence or pituitary stalk). Injuries of this degree are often complicated by drug or alcohol intoxication, and clinically inapparent cervical spine injury may be present. Blast injuries are often accompanied by rupture of the tympanic membranes.

After surgical removal of hematomas, most patients in this category improve over weeks. During the first week, the state of alertness, memory, and other cognitive functions often fluctuate, and agitation and somnolence are common. Behavioral changes tend to be worse at night, as with many other encephalopathies, and may be treated with small doses of antipsychotic medications. Subtle abnormalities of attention, intellect, spontaneity, and memory return toward normal weeks or months after the injury, sometimes abruptly. Persistent cognitive problems are discussed below.

SEVERE INJURY

Patients who are comatose from the moment of injury require immediate neurologic attention and resuscitation. After intubation, with care taken to immobilize the cervical spine, the depth of coma, pupillary size and reactivity, limb movements, and Babinski responses are assessed. As soon as vital functions permit and cervical spine x-rays and a CT scan have been obtained, the patient should be transported to a critical care unit. Hypoxia should be reversed, and normal saline used as the resuscitation fluid in preference to albumin. The finding of an epidural or subdural hematoma or large intracerebral hemorrhage is usually an indication for prompt surgery and intracranial decompression in an otherwise salvageable patient. Measurement of ICP with a ventricular catheter or fiberoptic device in order to guide treatment has been favored by many units but has not improved outcome. Hyperosmolar intravenous solutions are used in various regimens to limit intracranial pressure. The inherently appealing approach of removing portions of the skull in order to decompress the intracranial contents, as has been successful for brain swelling after cerebral infarction, has so far not proven effective for traumatic brain injury. The use of prophylactic antiepileptic medications has been recommended, but there is little supportive data. **Management of raised ICP, a frequent feature of severe head injury, is discussed in Chap. 33**.

GRADING AND PROGNOSIS

In severe head injury, the clinical features of eye opening, motor responses of the limbs, and verbal output have been found to be generally predictive of outcome. These three responses are assessed by the Glasgow Coma Scale; a score between 3 and 15 is assigned **(Table 44-1)**. Over 85% of patients with aggregate scores of <5 die within 24 h. However, a number of

TABLE 44-1

GLASGOW COMA SCALE FOR HEAD INJURY

EYE OPENING (E)		VERBAL RESPONSE (V)	
Spontaneous	4	Oriented	5
To loud voice	3	Confused, disoriented	4
To pain	2	Inappropriate words	3
Nil	1	Incomprehensible sounds	2
		Nil	1
Best Motor Response (M)			
Obeys	6		
Localizes	5		
Withdraws (flexion)	4		
Abnormal flexion posturing	3		
Extension posturing	2		
Nil	1		

Note: Coma score = E + M + V. Patients scoring 3 or 4 have an 85% chance of dying or remaining vegetative, whereas scores >11 indicate only a 5–10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of recovery.

www.ketabpezeshki.com (021) 66485457 - 66485438

patients with slightly higher scores, including a few without pupillary light responses, survive, suggesting that an initially aggressive approach is justified in most patients. Patients <20 years old, particularly children, may make remarkable recoveries after having grave early neurologic signs. In one large study of severe head injury, 55% of children had a good outcome at 1 year, compared with 21% of adults. Older age, increased ICP, early hypoxia or hypotension, compression of the brainstem on CT or MRI, and a delay in the evacuation of large intracranial hemorrhages are indicators of a poor prognosis.

POSTCONCUSSION SYNDROME

T e postconcussion syndrome refers to a state following minor head injury consisting of combinations of fatigue, dizziness, headache, and difficulty in concentration. T e syndrome simulates asthenia and anxious depression. Based on experimental models, it has been proposed that subtle axonal shearing lesions or as yet undefined biochemical alterations account for the cognitive symptoms. In moderate and severe trauma, neuropsychological changes such as difficulty with attention and memory and other cognitive deficits are undoubtedly present, sometimes severe, but many problems identified by formal testing do not affect daily functioning. Test scores tend to improve rapidly during the first 6 months after injury and then more slowly for years.

Management of the postconcussive syndrome requires the identification and treatment of each separate element of depression, sleeplessness, anxiety, persistent headache, and dizziness. A clear explanation of the problems that may follow concussion has been shown to reduce subsequent complaints. Care is taken to avoid prolonged use of drugs that produce dependence. Headache may initially be treated with acetaminophen and small doses of amitriptyline. Vestibular exercises **(Chap. 12)** and small doses of vestibular suppressants such as promethazine (Phenergan) may be helpful when dizziness is the main problem. Patients who after minor or moderate injury have difficulty with memory or with complex cognitive tasks at work may be reassured that these problems usually improve over 6–12 months, and workload may be reduced in the interim. It is sometimes helpful to obtain serial and quantified neuropsychological testing in order to adjust the work environment to the patient's abilities and to document improvement over time. Whether cognitive exercises are useful in contrast to rest and a reduction in mental challenges is uncertain. Previously energetic and resilient individuals usually have the best recoveries. In patients with persistent symptoms, the possibility exists of malingering or prolongation as a result of litigation.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 45

MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES

Stephen L. Hauser ■ Douglas S. Goodin

Demyelinating disorders are immune-mediated conditions characterized by preferential destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared, and most patients have no evidence of an associated systemic illness. Multiple sclerosis, the most common disease in this category, is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by chronic inflammation, demyelination, gliosis (scarring), and neuronal loss; the course can be relapsing-remitting or progressive. Lesions of MS typically develop at different times and in different CNS locations (i.e., MS is said to be disseminated in time and space). Approximately 350,000 individuals in the United States and 2.5 million individuals worldwide are affected. The clinical course can be extremely variable, ranging from a benign condition to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

PATHOGENESIS

Pathology

New MS lesions begin with perivenular cuffing by inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. Involvement of the humoral immune system is also evident; small numbers of B lymphocytes also infiltrate the nervous system, myelin-specific autoantibodies are present on degenerating myelin sheaths, and complement is activated. Demyelination is the hallmark of the pathology, and evidence of myelin degeneration is found at the earliest time points of tissue injury. A remarkable feature of MS plaques is that oligodendrocyte precursor cells survive—and in many lesions are present in even greater numbers than in normal tissue—but these cells fail to differentiate into mature myelin-producing cells. In some lesions, surviving oligodendrocytes or those that differentiate from precursor cells partially remyelinate the surviving naked axons, producing so-called shadow plaques. As lesions evolve, there is prominent astrocytic proliferation (gliosis). Over time, ectopic lymphocyte follicle-like structures, consisting of aggregates of T and B cells resembling secondary lymphoid tissue, appear in the meninges and especially overlying deep cortical sulci and also in perivascular spaces. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. Thus MS is not solely a disease of myelin, and neuronal pathology is increasingly recognized as a major contributor to irreversible neurologic disability. Inflammation, demyelination, and plaque formation are also present in the cerebral cortex, and significant axon loss indicating death of neurons is widespread, especially in advanced cases (see "Neurodegeneration," below).

Physiology

Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath

www.ketabpezeshki.com (021) 66485457 - 66485438

between nodes (Fig. 45-1). T is produces considerably faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. T is can happen when the resting axon membrane becomes hyperpolarized due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block of en follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 45-1). T is redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. Conduction block may be incomplete, affecting high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments of the axonal membrane are reorganized to support continuous (slow) nerve impulse propagation.

Epidemiology

MS is approximately threefold more common in women than men. T e age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before age 18 years of age, and a small percentage of cases begin before the age of 10 years.

Geographical gradients have been repeatedly observed in MS, with the highest known prevalence for MS (250 per 100,000) in the Orkney Islands, located north of Scotland. In other temperate zone areas (e.g., northern North America, northern Europe, southern Australia, and southern New Zealand), the prevalence of MS is 0.1–0.2%. By contrast, in the tropics (e.g., Asia, equatorial Africa, and the Middle East), the prevalence is of en 10- to 20-fold less.

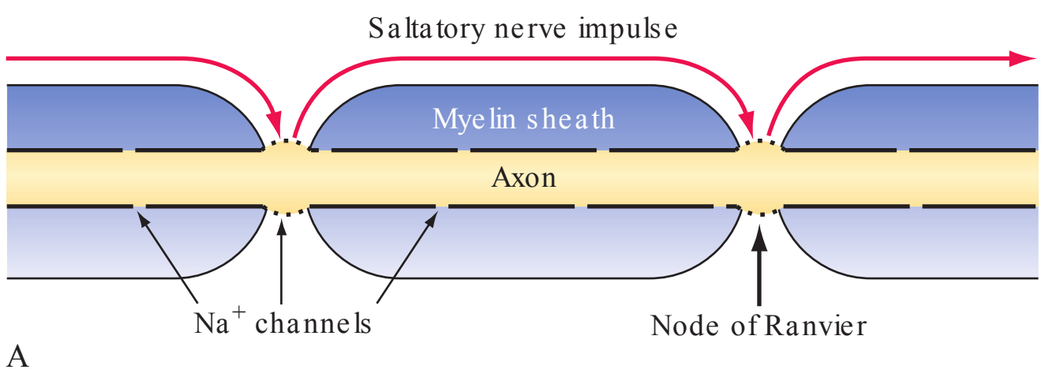
T e prevalence of MS has increased steadily (and dramatically) in several regions around the world over the past half-century, presumably reflecting the impact of some environmental shif . Moreover, the fact that this increase has occurred primarily (or exclusively) in women indicates that women are more responsive to this environmental change.

Well-established risk factors for MS include vitamin D deficiency, exposure to Epstein-Barr virus (EBV) af er early childhood, and cigarette smoking.

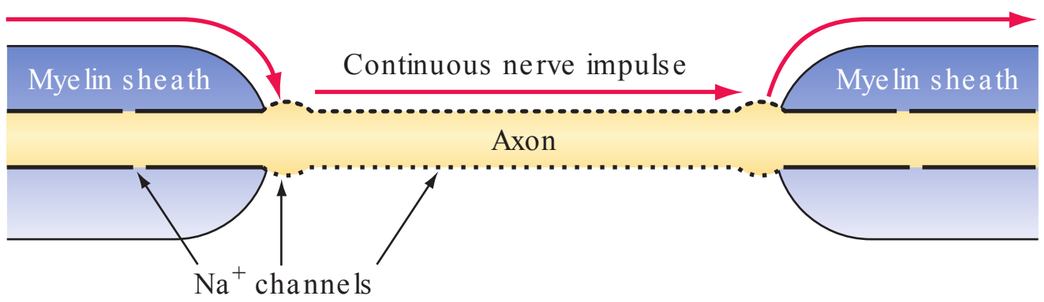
Vitamin D deficiency is associated with an increase in MS risk, and data suggest that ongoing deficiency may also increase disease activity af er MS begins. Immunoregulatory effects of vitamin D could explain these apparent relationships. Exposure of the skin to ultraviolet-B (UVB) radiation from the sun is essential for the biosynthesis of vitamin D, and this endogenous production is the most important source of vitamin D in most individuals; a diet rich in fatty fish represents another source of vitamin D. At high latitudes, the amount of UVB radiation reaching the earth's surface is of en insufficient, particularly during winter months, and consequently, low serum levels of vitamin D are common in temperate zones. T e common practice to avoid direct sun exposure and the widespread use of sun block, which (at sun protection factor [SPF] 15) blocks 94% of the incoming UVB radiation, would be expected to exacerbate any population-wide vitamin D deficiency.

Evidence of a remote EBV infection playing some role in MS is supported by numerous epidemiologic and laboratory studies. A higher risk of infectious mononucleosis (associated with relatively late EBV infection) and higher antibody titers to latency-associated EBV nuclear antigen have been repeatedly associated with MS risk, although a causal role for EBV has not been established.

A history of cigarette smoking has also been associated with MS risk. Interestingly, in an animal model of MS, the lung was identified as a critical site for activation of pathogenic T lymphocytes responsible for autoimmune demyelination.



A



B

FIGURE 45-1
Nerve conduction in myelinated and demyelinated axons. A. Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. B. Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

www.ketabpezeshki.com (021) 66485457 - 66485438

Recent data in MS models have also shown that high levels of dietary sodium activate pathogenic autoreactive T lymphocytes, suggesting that consumption of a high-salt diet, now widespread in the Western world, might be part of the explanation for the observed increase in the prevalence of MS in recent years.

GENETIC CONSIDERATIONS

Whites are inherently at higher risk for MS than Africans or Asians, even when residing in a similar environment. MS also aggregates within some families, and adoption, half-sibling, twin, and spousal studies indicate that familial aggregation is due to genetic, and not environmental, factors **(Table 45-1)**.

Susceptibility to MS is polygenic, with each gene contributing a relatively small amount to the overall risk. T e strongest susceptibility signal in genome-wide studies maps to the HLA-DRB1 gene in the class II region of the major histocompatibility complex (MHC), and this association accounts for approximately 10% of the disease risk. T is HLA association, which was first described several decades ago, suggests that MS, at its core, is an antigen-specific autoimmune disease. Whole-genome association studies have now identified approximately 110 other MS susceptibility variants, each of which individually has only a modest effect on MS risk. Most of these MS-associated genes have known roles in the adaptive immune system, for example the genes for the interleukin (IL) 7 receptor (CD127), IL-2 receptor (CD25), and T cell costimulatory molecule LFA-3 (CD58); some variants also influence susceptibility to other autoimmune diseases in addition to MS. T e variants identified so far all lack specificity and sensitivity for MS; thus, at present, they are not useful for diagnosis or to predict the future course of the disease.

Immunology

A proinflammatory autoimmune response directed against a component of CNS myelin, and perhaps other neural elements as well, remains the cornerstone of current concepts of MS pathogenesis.

TABLE 45-1

RISK OF DEVELOPING MULTIPLE SCLEROSIS (MS)	
1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half-sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

Autoreactive T lymphocytes

Myelin basic protein (MBP), an intracellular protein involved in myelin compaction, is an important T cell antigen in experimental allergic encephalomyelitis (EAE), a laboratory model, and probably also in human MS. Activated MBP-reactive T cells have been identified in the blood, in cerebrospinal fluid (CSF), and within MS lesions. Moreover, DRB1*15:01 may influence the autoimmune response because it binds with high affinity to a fragment of MBP (spanning amino acids 89–96), stimulating T cell responses to this self-protein. Two different populations of proinflammatory T cells are likely to mediate autoimmunity in MS. T-helper type 1 (T_H1) cells producing interferon γ (IFN-γ) are one key effector population, and more recently, a role for highly proinflammatory T_H17 T cells has been established. T_H17 cells are induced by transforming growth factor β (TGF-β) and IL-6 and are amplified by IL-21 and IL-23. T_H17 cells, and levels of their corresponding cytokine IL-17, are increased in MS lesions and also in the circulation of people with active MS. High circulating levels of IL-17 may also be a marker of a more severe course of MS. T_H1 cytokines, including IL-2, tumor necrosis factor (TNF)-α, and IFN-γ, also play key roles in activating and maintaining autoimmune responses, and TNF-α and IFN-γ may directly injure oligodendrocytes or the myelin membrane.

Humoral autoimmunity

B cell activation and antibody responses also appear to be necessary for the full development of demyelinating lesions to occur, both in experimental models and in human MS. Clonally restricted populations of activated, antigen-experienced, memory B cells and plasma cells are present in MS lesions, in lymphoid follicle-like structures in the meninges overlying the cerebral cortex, and in the CSF. Similar or identical clonal populations are found in each compartment, indicating that a highly focused B cell response is occurring locally within the CNS in MS. Myelin-specific autoantibodies, some directed against an extracellular myelin protein, myelin oligodendrocyte glycoprotein (MOG), have been detected bound to vesiculated myelin debris in MS plaques. In the CSF, elevated levels of locally synthesized immunoglobulins and oligoclonal antibodies, derived from clonally restricted CNS B cells and plasma cells, are also characteristic of MS. T e pattern of oligoclonal banding is unique to each individual, and attempts to identify the targets of these antibodies have been largely unsuccessful.

Triggers

Serial magnetic resonance imaging (MRI) studies in early relapsing-remitting MS reveal that bursts of focal inflammatory disease activity occur far more frequently

www.ketabpezeshki.com (021) 66485457 - 66485438

than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent. Although the triggers causing these bursts are unknown, molecular mimicry between environmental agents, presumably pathogens, and myelin antigens activating pathogenic T cells may be responsible.

Neurodegeneration

Axonal damage occurs in every newly formed MS lesion, and cumulative axonal loss is considered to be one important cause of irreversible neurologic disability in MS. As many as 70% of axons are lost from the lateral corticospinal (e.g., motor) tracts in patients with advanced paraparesis from MS, and longitudinal MRI studies suggest there is progressive axonal loss over time within established, inactive lesions. Demyelination can result in reduced trophic support for axons, redistribution of ion channels, and destabilization of action potential membrane potentials. Axons can adapt initially to these injuries, but over time, distal and retrograde degeneration often occurs. Therefore, promoting remyelination remains an important therapeutic goal.

In progressive MS, a key unresolved question is whether the primary neurodegenerative process occurs primarily in the cerebral cortex, the white matter, or in some combination of the two sites. As noted above, meningeal infiltrates of B and T cells are particularly prominent in progressive MS cases, and these "lymphoid follicles" are associated with underlying microglial activation, gray matter plaques, and loss of cortical neurons. White matter lesions may also contribute to late progressive MS; inactive plaques are often non-inflammatory at the center, but at the edges, microglia and macrophages and evidence of ongoing axonal injury can be found. This suggests that a simmering, and possibly concentrically expanding, axonopathy may be present, even in the most chronic cases. In addition, a diffuse low-grade inflammation across large areas of white matter may be present, associated with reduced myelin staining and axonal injury ("dirty white matter"). Another characteristic of progressive MS is that inflammation is often present without a concomitant disruption of the BBB; possibly, this feature might explain the failure of immunotherapies not capable of crossing the BBB to benefit patients with progressive MS.

Evidence supports a role of one, or more likely several, of the following mechanisms in progressive MS. Axonal and neuronal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure either occurring as a consequence of free-radical damage or due to accumulation of deletions in mitochondrial DNA.

CLINICAL MANIFESTATIONS

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Indeed, at autopsy, approximately 0.1% of individuals who were asymptomatic during life will be found, unexpectedly, to have pathologic evidence of MS. Similarly, in the modern era, an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS **(Table 45-2)**. Examination often reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

Weakness *of* the limbs may manifest as loss of strength, speed, or dexterity, as fatigue, or as a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the upper motor neuron type **(Chap. 14)** and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and Babinski signs. Occasionally a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord **(see Fig. 14-2)**.

Spasticity **(Chap. 14)** is commonly associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms interfering with ambulation, work, or self-care. Occasionally spasticity provides support for the body weight during ambulation, and in these cases, treatment of spasticity may actually do more harm than good.

TABLE 45-2

INITIAL SYMPTOMS OF MS

SYMPTOM	PERCENTAGE OF CASES	SYMPTOM	PERCENTAGE OF CASES
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Source: After WB Matthews et al: McAlpine's Multiple Sclerosis. New York, Churchill Livingstone, 1991.

www.ketabpezeshki.com (021) 66485457 - 66485438

Optic neuritis (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. T ese symptoms can be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) of en precedes or accompanies the visual loss. An afferent pupillary defect **(Chap. 25)** is usually present. Funduscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON. Uveitis is uncommon and should raise the possibility of alternative diagnoses such as sarcoid or lymphoma.

Visual blurring in MS may result from ON or diplopia (double vision); if the symptom resolves when either eye is covered, the cause is diplopia.

Diplopia may result from internuclear ophthalmoplegia (INO) or from palsy of the sixth cranial nerve (rarely the third or fourth). An INO consists of impaired adduction of one eye due to a lesion in the ipsilateral medial longitudinal fasciculus **(Chaps. 27 and 28)**. Prominent nystagmus is of en observed in the abducting eye, along with a small skew deviation. A bilateral INO is particularly suggestive of MS. Other common gaze disturbances in MS include (1) a horizontal gaze palsy, (2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus.

Sensory symptoms are varied and include both paresthesias (e.g., tingling, prickling sensations, formications, "pins and needles," or painful burning) and hypesthesia (e.g., reduced sensation, numbness, or a "dead" feeling). Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common. Sensory impairment of the trunk and legs below a horizontal line on the torso (a sensory level) indicates that the spinal cord is the origin of the sensory disturbance. It is of en accompanied by a bandlike sensation of tightness around the torso. Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time.

Ataxia usually manifests as cerebellar tremors **(Chap. 37)**. Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech).

Bladder dys*f*unction is present in >90% of MS patients, and in a third of patients, dysfunction results in weekly or more frequent episodes of incontinence. During normal reflex voiding, relaxation of the bladder sphincter (α-adrenergic innervation) is coordinated with contraction of the detrusor muscle in the bladder wall (muscarinic cholinergic innervation). Detrusor hyperre*fl*exia, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncontrolled bladder emptying. Detrusor sphincter dyssynergia, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

Constipation occurs in >30% of patients. Fecal urgency or bowel incontinence is less common (<15%) but can be socially debilitating.

Cognitive dys*f*unction can include memory loss; impaired attention; difficulties in executive functioning, memory, and problem solving; slowed information processing; and problems shif ing between cognitive tasks. Euphoria (elevated mood) was once thought to be characteristic of MS but is actually uncommon, occurring in <20% of patients. Cognitive dysfunction sufficient to impair activities of daily living is rare.

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue.

Fatigue **(Chap. 13)** is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, depression, expending exceptional effort to accomplish basic activities of daily living, or sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

Sexual dys*f*unction may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

Facial weakness due to a lesion in the pons may resemble idiopathic Bell's palsy **(Chap. 42)**. Unlike Bell's palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis **(Chap. 12)**. Hearing loss **(Chap. 29)** may also occur in MS but is uncommon.

Ancillary symptoms

Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (Uhthof 's symptom). It is also common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses (see "Acute Attacks or Initial Demyelinating Episodes," below). Such heat-related symptoms probably result from transient conduction block (see above).

Lhermitte's symptom is an electric shock–like sensation (typically induced by flexion or other movements

www.ketabpezeshki.com (021) 66485457 - 66485438

of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms. It is generally self-limited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day), lack of any alteration of consciousness or change in background electroencephalogram during episodes, and a self-limited course (generally lasting weeks to months). They may be precipitated by hyperventilation or movement. These syndromes may include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other less well-characterized syndromes. Paroxysmal symptoms probably result from spontaneous discharges, arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts.

Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia **(Chap. 42)** can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lancinating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise the possibility that MS could be responsible.

Facial myokymia consists of either persistent rapid flickering contractions of the facial musculature (especially the lower portion of the orbicularis oculus) or a contraction that slowly spreads across the face. It results from lesions of the corticobulbar tracts or brainstem course of the facial nerve.

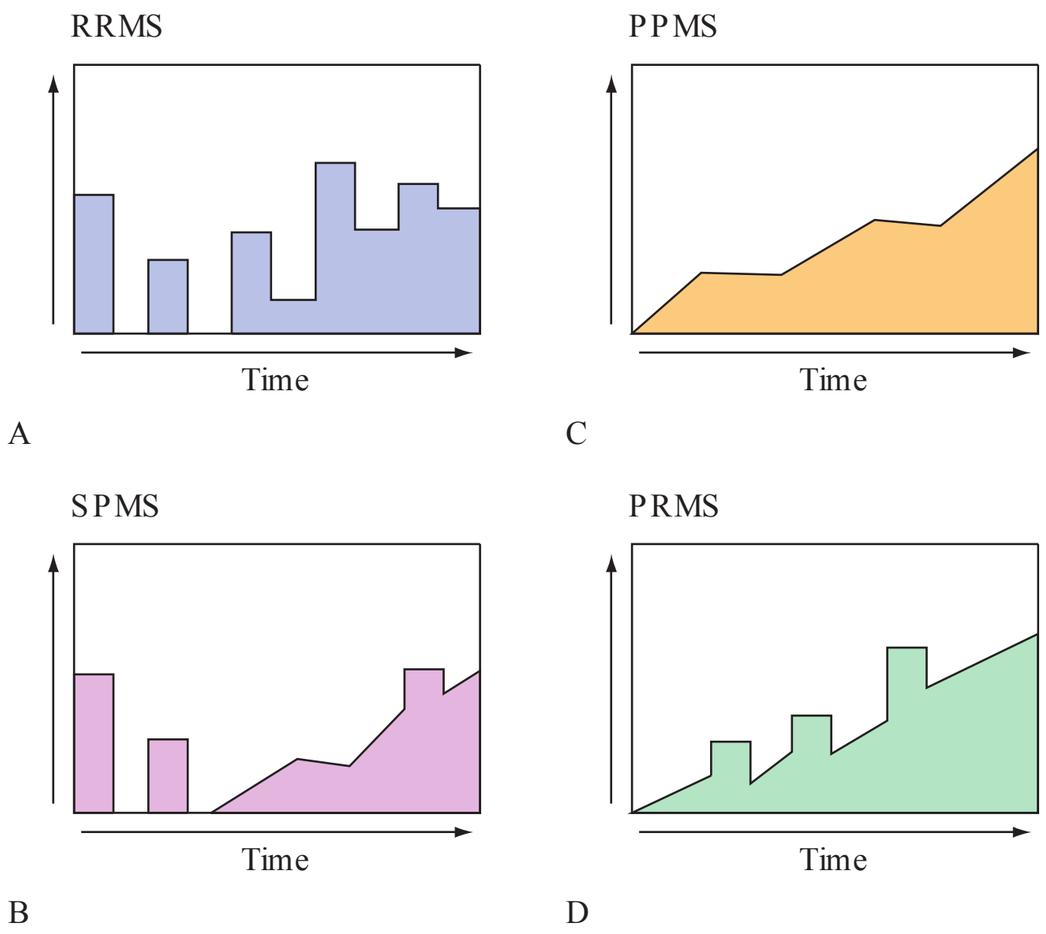


FIGURE 45-2
Clinical course of multiple sclerosis (MS). A. Relapsing/remitting MS (RRMS). B. Secondary progressive MS (SPMS). C. Primary progressive MS (PPMS). D. Progressive/relapsing MS (PRMS).

DISEASE COURSE

Four clinical types of MS exist **(Fig. 45-2)**:

1. Relapsing/remitting MS (RRMS) accounts for 85% of MS cases at onset and is characterized by discrete attacks that generally evolve over days to weeks (rarely over hours). With initial attacks, there is often substantial or complete recovery over the ensuing weeks to months, but as attacks continue over time recovery may be less evident **(Fig. 45-2A)**. Between attacks, patients are neurologically stable.
2. Secondary progressive MS (SPMS) always begins as RRMS **(Fig. 45-2B)**. At some point, however, the clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase). SPMS produces a greater amount of fixed neurologic disability than RRMS. For a patient with RRMS, the risk of developing SPMS is ~2% each year, meaning that the great majority of RRMS ultimately evolves into SPMS. SPMS appears to represent a late stage of the same underlying illness as RRMS.
3. Primary progressive MS (PPMS) accounts for ~15% of cases. These patients do not experience attacks but only a steady functional decline from disease onset **(Fig. 45-2C)**. Compared to RRMS, the sex distribution is more even, the disease begins later in life (mean age ~40 years), and disability develops faster (at least relative to the onset of the first clinical symptom). Despite these differences, PPMS appears to represent the same underlying illness as RRMS.
4. Progressive/relapsing MS (PRMS) overlaps PPMS and SPMS and accounts for ~5% of MS patients. Like patients with PPMS, these patients experience a steady deterioration in their condition from disease onset. However, like SPMS patients, they experience occasional attacks superimposed upon their progressive course **(Fig. 45-2D)**.

DIAGNOSIS

There is no definitive diagnostic test for MS. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS **(Table 45-3)**. Symptoms must last for >24 h and occur as distinct episodes

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 45-3

DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space • ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a second clinical attack implicating a different CNS site AND For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) PLUS 2 out of the 3 following criteria Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.
Source: From CH Polman et al: Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the "McDonald Criteria." Ann Neurol 69:292, 2011.

that are separated by a month or more. In patients who have only one of the two required signs on neurologic examination, the second may be documented by abnormal tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnostic scheme, the second clinical event (in time) may be supported solely by MRI findings, consisting of either the development of new focal white matter lesions on MRI or the simultaneous presence of both an enhancing lesion and a nonenhancing lesion in an asymptomatic location. In patients whose course is progressive from onset for ≥6 months without superimposed relapses, documentation of intrathecal IgG synthesis may be used to support a diagnosis of PPMS.

DIAGNOSTIC TESTS

Magnetic resonance imaging

MRI has revolutionized the diagnosis and management of MS **(Fig. 45-3)**; characteristic abnormalities are found in >95% of patients, although more than

www.ketabpezeshki.com (021) 66485457 - 66485438

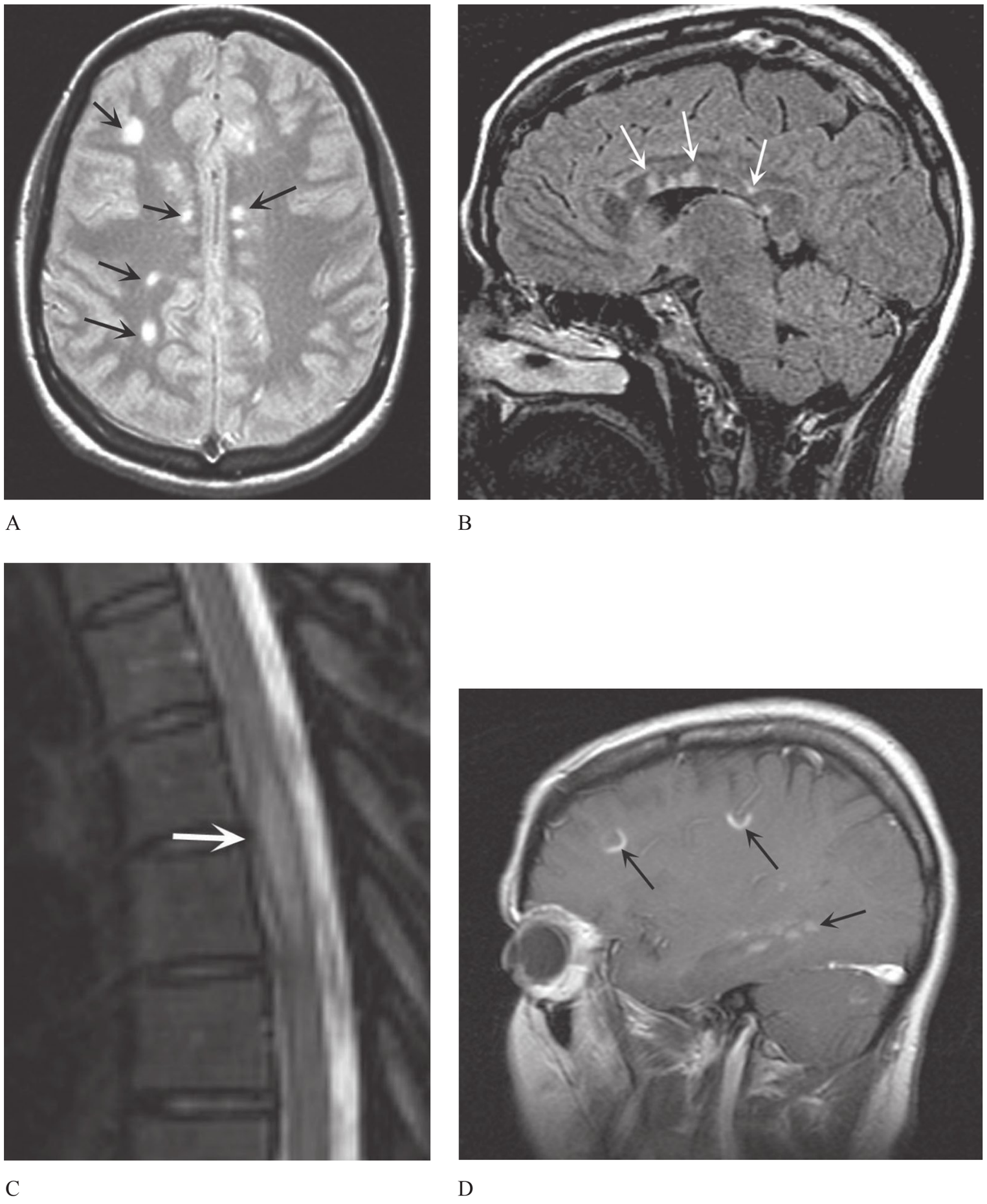


FIGURE 45-3
Magnetic resonance imaging findings in multiple sclerosis (MS). A. Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. B. Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image in which the high signal of cerebrospinal fluid (CSF) has been suppressed. CSF appears dark, whereas areas of brain edema or demyelination appear high in signal as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. C. Sagittal T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. D. Sagittal T1-weighted image obtained after the intravenous administration of gadolinium DTPA reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (arrows).

90% of the lesions visualized by MRI are asymptomatic. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a useful marker of inflammation. Gd enhancement typically persists for approximately 1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on spin-echo (T2-weighted) and proton-density images. Lesions are frequently oriented perpendicular to the ventricular surface, corresponding to the pathologic pattern of perivenous demyelination (Dawson's fingers). Lesions are multifocal within the brain, brainstem, and spinal cord. Lesions larger than 6 mm located in the corpus callosum, periventricular white matter, brainstem,

www.ketabpezeshki.com (021) 66485457 - 66485438

cerebellum, or spinal cord are particularly helpful diagnostically. Current criteria for the use of MRI in the diagnosis of MS are shown in Table 45-3.

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability, as do measures of brain atrophy. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

Newer MRI methods such as magnetization transfer ratio (MTR) imaging and proton magnetic resonance spectroscopic imaging (MRSI) may ultimately serve as surrogate markers of clinical disability. MRSI can quantitate molecules such as N-acetyl aspartate, which is a marker of axonal integrity, and MTR may be able to distinguish demyelination from edema.

Evoked potentials

EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways. EPs use computer averaging to measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain. These tests provide the most information when the pathways studied are clinically uninvolved. For example, in a patient with a remitting and relapsing spinal cord syndrome with sensory deficits in the legs, an abnormal somatosensory EP following posterior tibial nerve stimulation provides little new information. By contrast, an abnormal visual EP in this circumstance would permit a diagnosis of clinically definite MS (Table 45-3). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted waveshape) is suggestive of demyelination.

Cerebrospinal fluid

CSF abnormalities found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal. Various formulas distinguish intrathecally synthesized IgG from IgG that may have entered the CNS passively from the serum. One formula, the CSF IgG index, expresses the ratio of IgG to albumin in the CSF divided by the same ratio in the serum. The IgG synthesis rate uses serum and CSF IgG and albumin measurements to calculate the rate of CNS IgG synthesis. The measurement of oligoclonal bands (OCBs) by agarose gel electrophoresis in the CSF also assesses intrathecal production of IgG. Two or more discrete OCBs, not present in a paired serum sample, are found in >75% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients, the number of bands may increase with time.

A mild CSF pleocytosis (>5 cells/μL) is present in ~25% of cases, usually in young patients with RRMS. A pleocytosis of >75 cells/μL, the presence of polymorphonuclear leukocytes, or a protein concentration >1 g/L (>100 mg/dL) in CSF should raise concern that the patient may not have MS.

DIFFERENTIAL DIAGNOSIS

No single clinical sign or test is diagnostic of MS. The diagnosis is readily made in a young adult with relapsing and remitting symptoms involving different areas of CNS white matter. The possibility of an alternative diagnosis should always be considered **(Table 45-4)**, particularly when (1) symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient is <15 or >60 years of age;

TABLE 45-4

DISORDERS THAT CAN MIMIC MULTIPLE SCLEROSIS (MS)
Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

Abbreviations: AV, arteriovenous; CNS, central nervous system; HTLV, human T cell lymphotropic virus.

www.ketabpezeshki.com (021) 66485457 - 66485438

(3) the clinical course is progressive from onset; (4) the patient has never experienced visual, sensory, or bladder symptoms; or (5) laboratory findings (e.g., MRI, CSF, or EPs) are atypical. Similarly, uncommon or rare symptoms in MS (e.g., aphasia, parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, or coma) should increase concern about an alternative diagnosis. Diagnosis is also difficult in patients with a rapid or explosive (stroke-like) onset or with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic tumor. In the current era, the disorders most likely to be mistaken for MS are neuromyelitis optica (see below), sarcoid, vascular disorders (including antiphospholipid syndrome and vasculitis), and rarely CNS lymphoma. T e specific tests required to exclude alternative diagnoses will vary with each clinical situation; however, an erythrocyte sedimentation rate, serum B_{12} level, ANA, and treponemal antibody should probably be obtained in all patients with suspected MS.

PROGNOSIS

Most patients with clinically evident MS ultimately experience progressive neurologic disability. In older studies conducted mostly before disease-modifying therapies for MS were widely available, 15 years af er onset, only 20% of patients had no functional limitation, and between one-third and one-half progressed to SPMS and required assistance with ambulation; furthermore, 25 years af er onset, ~80% of MS patients reached this level of disability. T e long-term prognosis for untreated MS appears to have improved in recent years, at least in part because of the development of therapies for the early relapsing form of the disease. Although the prognosis in an individual is difficult to establish, certain clinical features suggest a more favorable prognosis. T ese include ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment af er 5 years. By contrast, patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled. Patients with a long-term favorable course are likely to have developed fewer MRI lesions during the early years of disease, and vice versa. Importantly, some MS patients have a benign variant of MS and never develop neurologic disability. T e likelihood of having benign MS is thought to be <20%. Patients with benign MS 15 years af er onset who have entirely normal neurologic examinations are likely to maintain their benign course

In patients with their first demyelinating event (i.e., a clinically isolated syndrome), the brain MRI provides prognostic information. With three or more typical T2-weighted lesions, the risk of developing MS af er 20 years is ~80%. Conversely, with a normal brain MRI, the likelihood of developing MS is <20%. Similarly, the presence of two or more Gd-enhancing lesions at baseline is highly predictive of future MS, as is the appearance of either new T2-weighted lesions or new Gd enhancement ≥3 months af er the initial episode.

Mortality as a direct consequence of MS is uncommon, although it has been estimated that the 25-year survival is only 85% of expected. Death can occur during an acute MS attack, although this is distinctly rare. More commonly, death occurs as a complication of MS (e.g., pneumonia in a debilitated individual). Death can also result from suicide. Early disease-modifying therapy seems to reduce this excess mortality.

Ef ect of pregnancy

Pregnant MS patients experience fewer attacks than expected during gestation (especially in the last trimester), but more attacks than expected in the first 3 months postpartum. When considering the pregnancy year as a whole (i.e., 9 months of pregnancy plus 3 months postpartum), the overall disease course is unaffected. Decisions about childbearing should thus be made based on (1) the mother's physical state, (2) her ability to care for the child, and (3) the availability of social support. Disease-modifying therapy is generally discontinued during pregnancy, although the actual risk from the interferons and glatiramer acetate (see below) appears to be low.

TREATMENT Multiple Sclerosis

T erapy for MS can be divided into several categories: (1) treatment of acute attacks, (2) treatment with disease-modifying agents that reduce the biologic activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist, but several promising approaches are being actively investigated.

T e Expanded Disability Status Score (EDSS) is a widely used measure of neurologic impairment in MS **(Table 45-5)**. Most patients with EDSS scores <3.5 have RRMS, walk normally, and are generally not disabled; by contrast, patients with EDSS scores >5.5 have progressive MS (SPMS or PPMS), are gait-impaired, and, typically, are occupationally disabled.

ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an increase in ambient temperature, fever, or an infection. When the clinical change is thought to reflect a pseudoexacerbation, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 45-5

SCORING SYSTEMS FOR MULTIPLE SCLEROSIS (MS)

Kurtzke Expanded Disability Status Score (EDSS)

0.0 = Normal neurologic exam (all grade 0 in functional status [FS])
1.0 = No disability, minimal signs in one FS (i.e., grade 1)
1.5 = No disability, minimal signs in more than one FS (more than one grade 1)
2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) although fully ambulatory
3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0 = Ambulatory without aid or rest for –500 m
4.5 = Ambulatory without aid or rest for –300 m
5.0 = Ambulatory without aid or rest for –200 m
5.5 = Ambulatory without aid or rest for –100 m
6.0 = Unilateral assistance required to walk about 100 m with or without resting
6.5 = Constant bilateral assistance required to walk about 20 m without resting
7.0 = Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone
7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer
8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 = Helpless bed patient; can communicate and eat
9.5 = Totally helpless bed patient; unable to communicate or eat
10.0 = Death due to MS

Functional Status (FS) Score

A. Pyramidal functions
0 = Normal
1 = Abnormal signs without disability
2 = Minimal disability
3 = Mild or moderate paraparesis or hemiparesis, or severe monoparesis
4 = Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia
5 = Paraplegia, hemiplegia, or marked quadriparesis
6 = Quadriplegia

B. Cerebellar functions
0 = Normal
1 = Abnormal signs without disability
2 = Mild ataxia
3 = Moderate truncal or limb ataxia
4 = Severe ataxia all limbs
5 = Unable to perform coordinated movements due to ataxia

C. Brainstem functions
0 = Normal
1 = Signs only
2 = Moderate nystagmus or other mild disability
3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 = Marked dysarthria or other marked disability
5 = Inability to swallow or speak

D. Sensory functions
0 = Normal
1 = Vibration or figure-writing decrease only, in 1 or 2 limbs
2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs
3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
5 = Loss (essentially) of sensation in 1 or 2 limbs or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 = Sensation essentially lost below the head

E. Bowel and bladder functions
0 = Normal
1 = Mild urinary hesitancy, urgency, or retention
2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
3 = Frequent urinary incontinence
4 = In need of almost constant catheterization
5 = Loss of bladder function
6 = Loss of bowel and bladder function

F. Visual (or optic) functions
0 = Normal
1 = Scotoma with visual acuity (corrected) better than 20/30
2 = Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99
4 = Worse eye with marked decrease of fields and maximal acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 = Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6 = Grade 5 plus maximal visual acuity of better eye of 20/60 or less

G. Cerebral (or mental) functions
0 = Normal
1 = Mood alteration only (does not affect EDSS score)
2 = Mild decrease in mentation
3 = Moderate decrease in mentation
4 = Marked decrease in mentation
5 = Chronic brain syndrome—severe or incompetent

Source: Adapted from JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983.

www.ketabpezeshki.com (021) 66485457 - 66485438

attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Orally administered methylprednisolone or dexamethasone (in equivalent dosages) can be substituted for the intravenous portion of the therapy, although gastrointestinal complications are more common by this route. Outpatient treatment is almost always possible.

Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics are advisable. Lithium carbonate (300 mg orally bid) may help to manage emotional lability and insomnia associated with glucocorticoid therapy. Patients with a history of peptic ulcer disease may require cimetidine (400 mg bid) or ranitidine (150 mg bid). Proton pump inhibitors such as pantoprazole (40 mg orally bid) may reduce the likelihood of gastritis, especially when large doses are administered orally. Plasma exchange (five to seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination that are unresponsive to glucocorticoids. However, the cost is high, and conclusive evidence of efficacy is lacking.

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS) Ten such agents are approved by the U.S. Food and Drug Administration (FDA): (1) IFN-β-1a (Avonex), (2) IFN-β-1a (Rebif), (3) IFN-β-1b (Betaseron or Extavia), (4) glatiramer acetate (Copaxone), (5) natalizumab (Tysabri), (6) fingolimod (Gilenya), (7) dimethyl fumarate (Tecfidera), (8) teriflunomide (Aubagio), (9) mitoxantrone (Novantrone), and (10) alemtuzumab (Lemtrada). Several other promising agents are in varying stages of product development. Each of these treatments can also be used in SPMS patients who continue to experience attacks, both because SPMS can be difficult to distinguish from RRMS and because the available clinical trials, although not definitive, suggest that such patients may sometimes derive therapeutic benefit. Thus, in several phase 3 clinical trials, recipients of each of these agents experienced fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients **(Table 45-6)**. Because of its potential toxicity as an

TABLE 45-6

TWO-YEAR OUTCOMES FOR FDA-APPROVED THERAPIES FOR MULTIPLE SCLEROSIS[a]

	CLINICAL OUTCOMES[b]		MRI OUTCOMES[c]	
DOSE, ROUTE, AND SCHEDULE	ATTACK RATE, MEAN	CHANGE IN DISEASE SEVERITY	NEW T2 LESIONS[d]	TOTAL BURDEN OF DISEASE
IFN-β-1b, 250 μg SC qod	–34%[e]	–29% (NS)	–83%[f]	–17%[e]
IFN-β-1a, 30 μg IM qw	–18%[g]	–37%[g]	–36%[f]	–4% (NS)
IFN-β-1a, 44 μg SC tiw	–32%[e]	–30%[g]	–78%[e]	–15%[e]
GA, 20 mg SC qd	–29%[f]	–12% (NS)	–38%[f]	–8%[f]
MTX, 12 mg/m^2 IV q3mo	–66%[e]	–75%[g]	–79%[g]	NR
NTZ, 300 mg IV qmo	–68%[e]	–42%[e]	–83%[e]	–18%[e]
FGM, 0.5 mg PO qd	–55%[e]	–34%[f]	–74%[e]	–23%[e]
DMF, 240 mg PO bid	–52%[e]	–40%[f]	–71%e	NR
TF, 14 mg PO qd	–31%[e]	–26%[g]	–70%[e]	–20%[g]

[a]Percentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for magnetic resonance imaging (MRI) disease burden, which was calculated as the difference in the median percent change between the treated and placebo groups.
[b]Severity = 1 point Expanded Disability Status Score progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years).
[c]Different studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best case scenario for each trial).
[d]New lesions seen on T2-weighted MRI.
[e]$p = .001$.
[f]$p = .01$.
[g]$p = .05$.
Abbreviations: DMF, dimethyl fumarate; FDA, U.S. Food and Drug Administration; FGM, fingolimod; GA, glatiramer acetate; IFN-β, interferon β; IM, intramuscular; IV, intravenous; MTX, mitoxantrone; NR, not reported; NS, not significant; NTZ, natalizumab; PO, oral; q3mo, once every 3 months; qd, daily; qmo, once per month; qod, every other day; qw, once per week; qyr, once per year; SC, subcutaneous; TF, terifunomide; tiw, three times per week.

www.ketabpezeshki.com (021) 66485457 - 66485438

immunosuppressant, mitoxantrone is generally reserved for patients with progressive disability who have failed other treatments. When considering the data in Table 45-6, however, it is important to note that the relative efficacy of the different agents cannot be determined by cross-trial comparisons. Relative efficacy can only be assessed from nonbiased head-to-head clinical trials.

Interferon-β IFN-β is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including (1) downregulating expression of MHC molecules on antigen-presenting cells, (2) reducing proinflammatory and increasing regulatory cytokine levels, (3) inhibiting T cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS. IFN-β reduces the attack rate and improves disease severity measures such as EDSS progression and MRI-documented disease burden. IFN-β should be considered in patients with either RRMS or SPMS with superimposed relapses. In patients with SPMS but without relapses, efficacy has not been established. Head-to-head trials suggest that dosing IFN-β more frequently and at higher doses has better efficacy but is also more likely to induce neutralizing antibodies (see below). IFN-β-1a (Avonex), 30 μg, is administered by intramuscular injection once every week. IFN-β-1a (Rebif), 44 μg, is administered by subcutaneous injection three times per week. IFN-β-1b (Betaseron or Extavia), 250 μg, is administered by subcutaneous injection every other day.

Common side effects of IFN-β therapy include flulike symptoms (e.g., fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia). Rarely, more severe hepatotoxicity may occur. Subcutaneous IFN-β also causes reactions at the injection site (e.g., pain, redness, induration, or, rarely, skin necrosis). Side effects can usually be managed with concomitant nonsteroidal anti-inflammatory medications. Depression, increased spasticity, and cognitive changes have been reported, although these symptoms can also be due to the underlying disease. In any event, side effects due to IFN-β therapy usually subside over time.

Approximately 2–10% of IFN-β-1a (Avonex) recipients, 15–25% of IFN-β-1a (Rebif) recipients, and 30–40% of IFN-β-1b (Betaseron/Extavia) recipients develop neutralizing antibodies to IFN-β, which may disappear over time. Two very large randomized trials (one with >2000 patients) provide unequivocal evidence that neutralizing antibodies reduce efficacy as determined by several MRI outcomes. Paradoxically, however, these same trials, despite abundant statistical power, failed to demonstrate any concomitant impact on the clinical outcomes of disability and relapse rate. T e reason for this clinical-radiologic dissociation is unresolved. For a patient doing well on therapy, the presence of antibodies should not affect treatment. Conversely, for a patient doing poorly on therapy, alternative treatment should be considered, even if there are no detectable antibodies.

Glatiramer acetate Glatiramer acetate is a synthetic, random polypeptide composed of four amino acids (l-glutamic acid, l-lysine, l-alanine, and l-tyrosine). Its mechanism of action may include (1) induction of antigen-specific suppressor T cells; (2) binding to MHC molecules, thereby displacing bound MBP; or (3) altering the balance between proinflammatory and regulatory cytokines. Glatiramer acetate reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate also benefits disease severity measures, although, for clinical disability, this is less well established than for IFN-β. Nevertheless, two very large head-to-head trials demonstrated that the impact of glatiramer acetate on clinical relapse rates and disability was comparable to high-dose, high-frequency IFN-β. Therefore, glatiramer acetate should be considered as an equally effective alternative to IFN-β in RRMS patients. Its usefulness in progressive disease is unknown. Glatiramer acetate is administered by subcutaneous injection of either 20 mg every day or 40 mg thrice weekly. Injection-site reactions also occur with glatiramer acetate. Initially, these were thought to be less severe than with IFN-β, although two recent head-to-head comparisons of high-dose, high-frequency IFN-β to daily glatiramer acetate did not bear out this impression. In addition, approximately 15% of patients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, brief (duration <1 h), and tends not to recur. Finally, some patients experience lipoatrophy, which, on occasion, can be disfiguring and require cessation of treatment.

Natalizumab Natalizumab is a humanized monoclonal antibody directed against the α_4 subunit of $\alpha_4\beta_1$ integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It prevents lymphocytes from binding to endothelial cells, thereby preventing lymphocytes from penetrating the BBB and entering the CNS. Natalizumab is highly effective in reducing the attack rate and significantly improves all measures of disease severity in MS (both clinical and MRI). Moreover, it is well-tolerated, and the dosing schedule of monthly intravenous infusions makes it very convenient for patients. However, progressive multifocal leukoencephalopathy (PML), a life-threatening condition resulting from infection by the John Cunningham (JC) virus, has occurred in approximately 0.3% of patients treated with natalizumab. The incidence of PML is very low in the first year of treatment but then rises by the second year to reach a level of about 2 cases per 1000 patients per year. Nevertheless, the measurement of antibodies against the JC virus in the serum can be used to stratify this risk. Thus, in patients who do not have these antibodies, the risk of PML is either minimal or nonexistent (as long as they remain JC antibody free). Conversely, in patients who have these antibodies (especially those who have them in high titer), the risk may be as high as 0.6% or greater. The risk is also high in patients who have previously received immunosuppressive therapy. Natalizumab is currently recommended only for JC antibody–negative patients, unless they have failed

www.ketabpezeshki.com (021) 66485457 - 66485438

alternative therapies or if they have a particularly aggressive disease course. Head-to-head data show that natalizumab is superior to low-dose (weekly) IFN-β-1a in RRMS. However, its relative efficacy compared to other agents has not been established conclusively.

Natalizumab, 300 mg, is administered by IV infusion each month. Treatment with natalizumab is, in general, well tolerated. A small percentage (<10%) of patients experience hypersensitivity reactions (including anaphylaxis), and ~6% develop neutralizing antibodies to the molecule (only half of which persist).

The major concern with long-term treatment is the risk of PML. Approximately half of the adult population is JC antibody positive, indicating that they experienced an asymptomatic infection with the JC virus at some time in the past. Nevertheless, because the risk is extremely low during the first year of treatment with natalizumab (regardless of antibody status), natalizumab can still be used safely in JC antibody–positive patients for a period of 12 months. After this time, in antibody-positive patients, a change to another disease-modifying therapy should be strongly considered. By contrast, persistently antibody-negative patients can be continued on treatment indefinitely. Up to 2% of seronegative MS patients undergoing treatment with natalizumab seroconvert annually; thus it is recommended that JC antibody status be assessed at 6-month intervals in all patients receiving treatment with this agent.

Fingolimod Fingolimod is a sphingosine-1-phosphate (S1P) inhibitor that prevents the egress of lymphocytes from the secondary lymphoid organs such as the lymph nodes and spleen. Its mechanism of action is probably due, in part, to the trapping of lymphocytes in the periphery and inhibiting their trafficking to the CNS. Fingolimod reduces the attack rate and significantly improves all measures of disease severity in MS. It is well tolerated, and the daily oral dosing schedule makes it very convenient for patients. A large head-to-head phase 3 randomized study demonstrated the superiority of fingolimod over low-dose (weekly) IFN-β-1a. However, its relative efficacy compared to other agents has not been established conclusively.

Fingolimod, 0.5 mg, is administered orally each day. Treatment with fingolimod is also, in general, well tolerated. Mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia) are more common than in controls, sometimes requiring discontinuation of the medication. First- and second-degree heart block and bradycardia can also occur when fingolimod therapy is initiated. A 6-h period of observation (including electrocardiogram monitoring) is recommended for all patients receiving their first dose, and individuals with preexisting cardiac disease should probably not be treated with this agent. Other side effects include macular edema and, rarely, disseminated varicella-zoster virus (VZV) infection; prior to initiating therapy with fingolimod, an ophthalmic exam and VZV vaccination for seronegative individuals are indicated.

Dimethyl fumarate (DMF) Although the precise mechanisms of action of DMF are not fully understood, it seems to have anti-inflammatory effects through its modulation of the expression of proinflammatory and anti-inflammatory cytokines. Also, DMF inhibits the ubiquitylation and degradation of nuclear factor E2-related factor 2 (Nrf2)—a transcription factor that binds to the antioxidant response elements (AREs) located on the DNA and thereby induces the transcription of several antioxidant proteins. DMF reduces the attack rate and significantly improves all measures of disease severity in MS patients. However, its twice-daily oral dosing schedule makes it somewhat less convenient for patients than daily oral therapies. In addition, compliance is likely to be less with a twice-daily dosing regimen—a factor that could be of concern given the observation (in a small clinical trial) that once-daily DMF lacks efficacy. A head-to-head trial provided evidence that DMF was superior to glatiramer acetate on some outcome measures.

DMF, 240 mg, is administered orally twice each day. Gastrointestinal side effects (abdominal discomfort, nausea, vomiting, flushing, and diarrhea) are common at the start of therapy but generally subside with continued administration. Other adverse events included mild decreases in neutrophil and lymphocyte counts and mild elevations in liver enzymes. Nevertheless, in general, treatment with DMF is well tolerated after an initial period of adjustment. Following the release of DMF, four cases of PML were reported in patients receiving other products (not Tecfidera) that contained DMF. Each of these patients was lymphocytopenic, and most had received previous immunosuppressant therapy so that the relationship of DMF to the PML (if any) in these cases is uncertain. Nevertheless, these reports underscore the fact, stated previously, that long-term safety can never be guaranteed by the results of short-term trials. In the case of DMF for MS, only time and experience will tell us whether or not there is any cause for concern.

Teriflunomide Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, which is a key part of the pathway for de novo pyrimidine biosynthesis from carbamoyl phosphate and aspartate. It is the active metabolite of the drug leflunomide (FDA-approved for rheumatoid arthritis), and it exerts its anti-inflammatory effects by limiting the proliferation of rapidly dividing T and B cells. This enzyme is not involved in the so-called "salvage pathway," by which existing pyrimidine pools are recycled for DNA and RNA synthesis in resting and homeostatically proliferating cells. Consequently, teriflunomide is considered to be cytostatic rather than cytotoxic. Teriflunomide reduces the attack rate and significantly improves all measures of disease severity in MS patients. It is well tolerated, and its daily oral dosing schedule makes it very convenient for patients. A head-to-head trial suggested the equivalence, but not superiority, of teriflunomide and high-dose (thrice-weekly) IFN-β-1a. Teriflunomide, either 7 or 14 mg, is administered orally each day. In the pivotal clinical trials, mild hair thinning and gastrointestinal symptoms (nausea

www.ketabpezeshki.com (021) 66485457 - 66485438

and diarrhea) were more common than in controls, but in general, treatment with teriflunomide was well tolerated. As with any new agent, the long-term safety is not guaranteed by the results of short-term trials. A major limitation, especially in women of childbearing age, is its possible teratogenicity (pregnancy category X); teriflunomide can remain in the bloodstream for 2 years, and it is recommended that exposed men and women who wish to conceive receive cholestyramine or activated charcoal to eliminate residual drug.

Mitoxantrone hydrochloride Mitoxantrone, an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The FDA approved mitoxantrone on the basis of a single (relatively small) phase 3 clinical trial in Europe, in addition to an even smaller phase 2 study completed earlier. Mitoxantrone received (from the FDA) the broadest indication of any current treatment for MS. Thus, mitoxantrone is indicated for use in SPMS, in PRMS, and in patients with worsening RRMS (defined as patients whose neurologic status remains significantly abnormal between MS attacks). Despite this broad indication, however, the data supporting its efficacy are weaker than for other approved therapies.

Mitoxantrone can be cardiotoxic (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose >140 mg/m^2 is not recommended. At currently approved doses (12 mg/m^2 every 3 months), the maximum duration of therapy can be only 2–3 years. Furthermore, >40% of women will experience amenorrhea, which may be permanent. Finally, there is risk of acute leukemia from mitoxantrone, estimated as at least a 1% lifetime risk, and this complication has been reported in several mitoxantrone-treated MS patients.

Because of these risks, and a growing list of alternative therapies, mitoxantrone is now only rarely used for MS. It should not be used as a first-line agent in either RRMS or relapsing SPMS, but might be considered in selected patients with a progressive course who have failed other therapies.

Alemtuzumab Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, which is expressed on both monocytes and lymphocytes. It causes lymphocyte depletion (of both B and T cells) and a change in the composition of lymphocyte subsets. Both of these changes, particularly the impact on lymphocyte subsets, are long lasting. In preliminary trials, alemtuzumab markedly reduced the attack rate and significantly improved all measures of disease severity in MS patients. In two phase 3 trials, however, its impact on clinical disability was less convincing. Notably, both trials used the active comparator of thrice-weekly, high-dose IFN-β-1a. The European and Canadian drug agencies were the first to approve this agent for use in RRMS; the FDA has also approved alemtuzumab, but only after an appeal following initial disapproval. The reasons for the initial disapproval were based on a perceived lack of a convincing disability effect and concerns over potential toxicity. The toxicities of concern were the occurrence (during the trial or thereafter) of (1) autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia, hemolytic anemia, pancytopenia, antiglomerular basement membrane disease, and membranous glomerulonephritis; (2) malignancies including thyroid cancer, melanoma, breast cancer, and human papillomavirus (HPV)–related cancers; (3) serious infections; and (4) infusion reactions.

Ocrelizumab Ocrelizumab (Ocrevus) is a humanized monoclonal antibody directed against the CD20 molecule present on the surface of mature B-cells. CD20 is not expressed on early B-cell precursers or on antibody-producing plasma cells, thus treatment with ocrelizumab selectively depletes mature B-cells while preserving preexisting humoral immunity and the capacity for B-cell reconstitution by lymphoid stem cells. In two phase 3 trials, ocrelizumab demonstrated a high degree of efficacy against RRMS, reducing annualized relapse rates by 47%, reducing new MRI lesions by 95%, and improving other measures of inflammatory and degenerative disease activity, compared with three times per week interferon-β (Rebif). A favorable safety profile over 96 weeks was also observed with ocrelizumab. Infusion-related reactions, most commonly observed with the first infusion and usually mild in degree, were the most significant side effect noted. Ocrelizumab 600 mg is administered by intravenous infusion every 24 weeks (administered as two 300-mg infusions spaced two weeks apart for the first dose, and as a single 600-mg infusion thereafter); intravenous methylprednisolone 100 mg is given prior to each infusion and optional prophylaxis with analgesics/antipyretics and antihistamines are recommended, along with adjustment of the infusion rate to manage infusion-related reactions. At the time of this writing, ocrelizumab is undergoing review by the FDA and other regulatory bodies.

Initiating and changing treatment Previously, most patients with relapsing forms of MS received injectable agents (IFN-β or glatiramer acetate) as first-line therapy. However, with the introduction of effective and probably safe oral agents, including DMF, fingolimod, and teriflunomide, this has begun to change. In addition, the monthly infusion therapy natalizumab, which is highly effective, well tolerated, and apparently safe in JC antibody–negative patients, provides an attractive option in many cases. As noted above, with the exception of the first-generation injectable agents, long-term safety data are not available, and for the most part, comparative data are lacking. The value of combination therapy is also largely unknown, although a recent clinical trial demonstrated no added benefit to the combination of glatiramer acetate with low-dose, once-weekly IFN-β-1a.

Despite these unknowns, clinicians need to make decisions based on the best available evidence, coupled with practical considerations. One reasonable approach stratifies initial decision-making based on two levels of disease aggressiveness **(Fig. 45-4)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

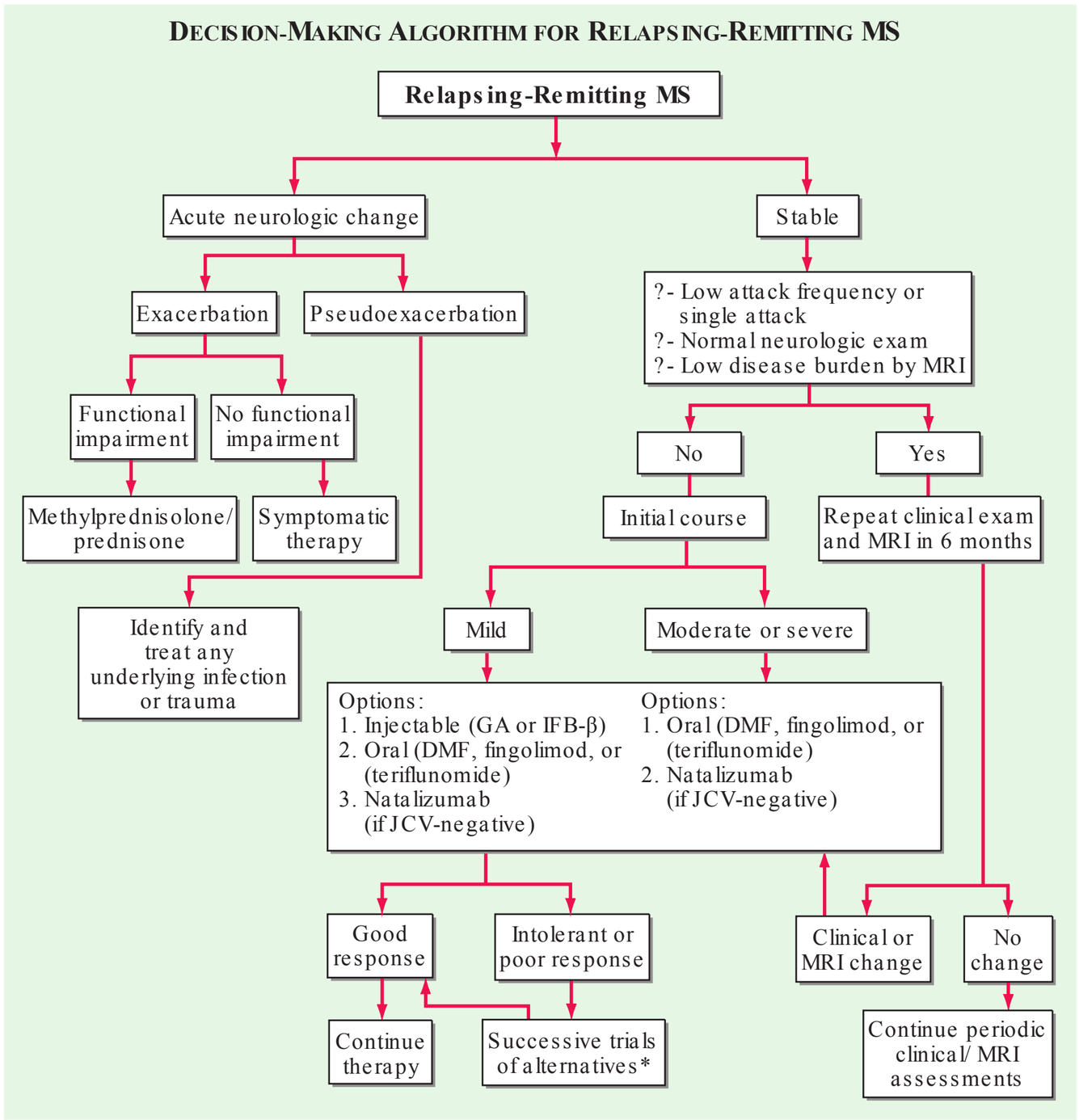


FIGURE 45-4

Therapeutic decision-making for multiple sclerosis (MS). *Can include trials of different preparations of interferon β (IFN-β, particularly advancing from once-weekly (Avonex) to a more frequent (e.g., Rebif, Betaseron/Extavia) dosing regimen. Options also include use of natalizumab in JC virus–positive patients. MRI, magnetic resonance imaging.

Mild initial course In the case of recent onset, normal exam or minimal impairment (EDSS ≤2.5 or less), or low disease activity, either an injectable (IFN-β or glatiramer acetate) or an oral (DMF, fingolimod, or teriflunomide) agent is reasonable. Although head-to-head comparisons are not available, natalizumab is thought to be more effective than these other agents, and therefore, this therapy can be considered even in minimally affected, JCV antibody–seronegative patients. The injectable agents (IFN-β and glatiramer acetate) have a superb track record for safety but have a high nuisance factor due to the need for frequent injections, as well as bothersome side effects that contribute to noncompliance. Some of the oral agents (DMF and fingolimod) are probably more effective than the injectables, but long-term risks are mostly unknown; DMF produces bothersome gastrointestinal symptoms in many patients at least initially (can be mitigated by beginning at one-quarter strength and gradually advancing to full dose), and fingolimod can lead to bradycardia and other cardiac disturbances of unclear clinical significance. Teriflunomide may be less effective than the other oral agents, and there are concerns about its possible long-lasting pregnancy risks. Nevertheless, its long-term safety has likely been established because of its extensive human exposure as the active metabolite of leflunomide—a drug long approved by the FDA.

Moderate or severe initial course In highly active disease or moderate impairment (EDSS >2.5), either a highly effective oral agent (DMF or fingolimod) or, if the patient is JC virus antibody seronegative, infusion therapy with natalizumab is recommended.

Regardless of which agent is chosen first, treatment should probably be changed in patients who continue to have relapses, progressive neurologic impairment or, arguably, ongoing evidence of subclinical MRI activity (Fig. 45-4).

The long-term impact of these treatments on the disease course remains controversial, although several recent studies have shown that these agents improve the long-term outcome of MS including a prolongation of the time to reach certain disability outcomes (e.g., SPMS and requiring assistance to ambulate) and reduction in MS-related mortality. These benefits seem most conspicuous when treatment begins early in the RRMS stage of the illness. Unfortunately, however, already established progressive symptoms do not respond well to treatment with these disease-modifying therapies.

www.ketabpezeshki.com (021) 66485457 - 66485438

Because progressive symptoms are likely to result from accumulated axonal and neuronal loss, many experts now believe that very early treatment with a disease-modifying drug is appropriate for most MS patients. It may also be reasonable to delay initiating treatment in patients with (1) normal neurologic exams, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients, however, should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease. Finally, vitamin D deficiency should be corrected in all patients with MS, and generally this requires oral supplementation with vitamin D_3, 4000 to 5000 IU daily.

DISEASE-MODIFYING THERAPIES FOR PROGRESSIVE MS SPMS High-dose IFN-β probably has a beneficial effect in patients with SPMS who are still experiencing acute relapses. IFN-β is probably ineffective in patients with SPMS who are not having acute attacks. All of the other agents have not yet been studied in this patient population. Although mitoxantrone has been approved for patients with progressive MS, this is not the population studied in the pivotal trial. Therefore no evidence-based recommendation can be made with regard to its use in this setting.

PPMS No approved therapies are currently available. Ocrelizumab (Ocrevus) [see above], a humanized monoclonal antibody that targets CD20 B-cells, was reported in a single phase 3 trial to reduce progression of clinical disability in PPMS by 24%, and also to improve other clinical and MRI markers of inflammatory and degenerative disease activity, compared with placebo treatment. A favorable safety profile was also observed over 120 weeks. Ocrelizumab appears to be the first investigational agent to convincingly modify the course of PPMS. It has received breakthrough therapy designation by the FDA permitting expedited review, and is also undergoing review by other regulatory bodies. It is unclear at this time if approval of ocrelizumab might extend to SPMS. The dosing of ocrelizumab for progressive forms of MS is likely to be identical as for RRMS (above).

OFF-LABEL TREATMENT OPTIONS FOR RRMS AND SPMS Azathioprine (2–3 mg/kg per day) has been used primarily in SPMS. Meta-analysis of published trials suggests that azathioprine is marginally effective at lowering relapse rates, although a benefit on disability progression has not been demonstrated.

Methotrexate (7.5–20 mg/week) was shown in one study to slow the progression of upper extremity dysfunction in SPMS. Because of the possibility of developing irreversible liver damage, some experts recommend a blind liver biopsy af er 2 years of therapy.

Cyclophosphamide (700 mg/m^2, every other month) may be helpful for treatment-refractory patients who are (1) otherwise in good health, (2) ambulatory, and (3) <40 years of age. Because cyclophosphamide can be used for periods in excess of 3 years, it may be preferable to mitoxantrone in these circumstances.

Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about its having any impact on long-term disability.

Methylprednisolone, administered in one study as monthly high-dose intravenous pulses, reduced disability progression (see above).

OTHER THERAPEUTIC CLAIMS Many purported treatments for MS have never been subjected to scientific scrutiny. T ese include dietary therapies (e.g., the Swank diet, in addition to others), megadose vitamins, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury-amalgam tooth fillings, among many others. Patients should avoid costly or potentially hazardous unproven treatments. Many such treatments lack biologic plausibility. For example, no reliable case of mercury poisoning resembling typical MS has ever been described.

Although potential roles for EBV, human herpesvirus (HHV) 6, or chlamydia have been suggested for MS, these reports are unconfirmed, and treatment with antiviral agents or antibiotics is not recommended.

Most recently, chronic cerebrospinal insufficiency (CCSVI) has been proposed as a cause of MS, and vascular-surgical intervention is recommended. However, the failure of independent investigators to even approximate the initial claims of 100% sensitivity and 100% specificity for the diagnostic procedure have raised considerable doubt that CCSVI is a real entity. Certainly, any potentially dangerous surgery should be avoided until more rigorous science is available.

SYMPTOMATIC THERAPY For all patients, it is useful to encourage attention to a healthy lifestyle, including maintaining an optimistic outlook, a healthy diet, and regular exercise as tolerated (swimming is often well-tolerated because of the cooling effect of cold water). It is reasonable also to correct vitamin D deficiency with oral vitamin D and to recommend dietary supplementation with long-chain (omega-3) unsaturated fatty acids (present in oily fish such as salmon), because of their biologic plausibility for MS pathogenesis, safety, and general health benefits.

Ataxia/tremor is of en intractable. Clonazepam, 1.5–20 mg/d; primidone, 50–250 mg/d; propranolol, 40–200 mg/d; or ondansetron, 8–16 mg/d, may help. Wrist weights occasionally reduce tremor in the arm or hand. T alamotomy or deep-brain stimulation has been tried with mixed success.

Spasticity and spasms may improve with physical therapy, regular exercise, and stretching. Avoidance of triggers (e.g., infections, fecal impactions, bed sores) is extremely important. Effective medications include baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydrochloride (10–60 mg/d). For severe spasticity, a baclofen pump (delivering medication directly into the CSF) can provide substantial relief.

www.ketabpezeshki.com (021) 66485457 - 66485438

Weakness can sometimes be improved with the use of potassium channel blockers such as 4-aminopyridine (10–40 mg/d) and 3,4-di-aminopyridine (40–80 mg/d), particularly in the setting where lower extremity weakness interferes with the patient's ability to ambulate. The FDA has approved 4-aminopyridine (at 20 mg/d), and this can be obtained either as dalfampridine (Ampyra) or, more cheaply, through a compounding pharmacy. The principle concern with the use of these agents is the possibility of inducing seizures at high doses.

Pain is treated with anticonvulsants (carbamazepine, 100–1000 mg/d; phenytoin, 300–600 mg/d; gabapentin, 300–3600 mg/d; or pregabalin, 50–300 mg/d), antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; desipramine, 100–300 mg/d; or venlafaxine, 75–225 mg/d), or antiarrhythmics (mexiletine, 300–900 mg/d). If these approaches fail, patients should be referred to a comprehensive pain management program.

Bladder dysfunction management is best guided by urodynamic testing. Evening fluid restriction or frequent voluntary voiding may help detrusor hyperreflexia. If these methods fail, propantheline bromide (10–15 mg/d), oxybutynin (5–15 mg/d), hyoscyamine sulfate (0.5–0.75 mg/d), tolterodine tartrate (2–4 mg/d), or solifenacin (5–10 mg/d) may help. Coadministration of pseudoephedrine (30–60 mg) is sometimes beneficial.

Detrusor/sphincter dyssynergia may respond to phenoxybenzamine (10–20 mg/d) or terazosin hydrochloride (1–20 mg/d). Loss of reflex bladder wall contraction may respond to bethanechol (30–150 mg/d). However, both conditions often require catheterization.

Urinary tract infections should be treated promptly. Patients with large postvoid residual urine volumes are predisposed to infections. Prevention by urine acidification (with cranberry juice or vitamin C) inhibits some bacteria. Prophylactic administration of antibiotics is sometimes necessary but may lead to colonization by resistant organisms. Intermittent catheterization may help to prevent recurrent infections.

Treatment of constipation includes high-fiber diets and fluids. Natural or other laxatives may help. Fecal incontinence may respond to a reduction in dietary fiber.

Depression should be treated. Useful drugs include the selective serotonin reuptake inhibitors (fluoxetine, 20–80 mg/d, or sertraline, 50–200 mg/d), the tricyclic antidepressants (amitriptyline, 25–150 mg/d; nortriptyline, 25–150 mg/d; or desipramine, 100–300 mg/d), and the nontricyclic antidepressants (venlafaxine, 75–225 mg/d).

Fatigue may improve with assistive devices, help in the home, or successful management of spasticity. Patients with frequent nocturia may benefit from anticholinergic medication at bedtime. Primary MS fatigue may respond to amantadine (200 mg/d), methylphenidate (5–25 mg/d), or modafinil (100–400 mg/d).

Cognitive problems may respond to the cholinesterase inhibitor donepezil hydrochloride (10 mg/d).

Paroxysmal symptoms respond dramatically to low-dose anticonvulsants (acetazolamide, 200–600 mg/d; carbamazepine, 50–400 mg/d; phenytoin, 50–300 mg/d; or gabapentin, 600–1800 mg/d).

Heat sensitivity may respond to heat avoidance, air-conditioning, or cooling garments.

Sexual dysfunction may be helped by lubricants to aid in genital stimulation and sexual arousal. Management of pain, spasticity, fatigue, and bladder/bowel dysfunction may also help. Sildenafil (50–100 mg), tadalafil (5–20 mg), or vardenafil (5–20 mg), taken 1–2 h before sex, is now the standard treatment for maintaining erections.

PROMISING EXPERIMENTAL THERAPIES Numerous clinical trials are currently under way. These include studies on (1) monoclonal antibodies against CD20 to deplete B cells and against the IL-2 receptor; (2) selective oral sphingosine-1-phosphate receptor antagonists to sequester lymphocytes in secondary lymphoid organs; (3) estriol to induce a pregnancy-like state; (4) molecules to promote remyelination; and (4) bone marrow transplantation.

CLINICAL VARIANTS OF MS

Acute MS (Marburg's variant) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. When acute MS presents as a solitary, usually cavitary, lesion, a brain tumor is often suspected. In such cases, a brain biopsy is usually required to establish the diagnosis. An antibody-mediated process appears to be responsible for most cases. Marburg's variant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO; Devic's disease) is an aggressive inflammatory disorder characterized by recurrent attacks of ON and myelitis **(Table 45-7)**.

TABLE 45-7

DIAGNOSTIC CRITERIA FOR NEUROMYELITIS OPTICA

Required:
1. Optic neuritis
2. Acute transverse myelitis

Supportive (2 of 3 criteria required):
1. Longitudinally extensive cord lesion extending over 3 or more vertebral segments
2. Brain magnetic resonance imaging normal or not meeting criteria for multiple sclerosis
3. Aquaporin-4 seropositivity

Source: Adapted from DM Wingerchuk et al: Neurology 66:1485, 2006.

www.ketabpezeshki.com (021) 66485457 - 66485438

کتاب پزشکی

66485457 - 66485438

www.ketabpezeshki.com

NMO is more frequent in women than men (>3:1), typically begins in childhood or early adulthood but can arise at any age, and is uncommon in whites compared with individuals of Asian and African ancestry. Attacks of ON can be bilateral (rare in MS) or unilateral; myelitis can be severe and transverse (rare in MS) and is typically longitudinally extensive, involving three or more contiguous vertebral segments. Also in contrast to MS, progressive symptoms do not occur in NMO. T e brain MRI was earlier thought to be normal in NMO, but it is now recognized that in approximately half of cases, there are lesions involving the hypothalamus causing an endocrinopathy; the lower brainstem presenting as intractable hiccoughs or vomiting from involvement of the area postrema in the lower medulla; or the cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres can be asymptomatic, sometimes have a "cloud-like" appearance and, unlike MS lesions, are of en not destructive, and can resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the gray matter of the cord. CSF findings include pleocytosis greater than that observed in MS, with neutrophils and eosinophils present in some cases; OCBs are uncommon, occurring in fewer than 30% of NMO patients. T e pathology of NMO is a distinctive astrocytopathy with inflammation, a loss of astrocytes, and an absence of staining of the water channel protein aquaporin-4 by immunohistochemistry, plus thickened blood vessel walls, demyelination, and deposition of antibody and complement.

NMO is best understood as a syndrome with diverse causes. Up to 40% of patients have a systemic autoimmune disorder, of en systemic lupus erythematosus, Sjögren's syndrome, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)–associated vasculitis, myasthenia gravis, Hashimoto's thyroiditis, or mixed connective tissue disease. In others, onset may be associated with acute infection with VZV, EBV, HIV, or tuberculosis. Rare cases appear to be paraneoplastic and associated with breast, lung, or other cancers. NMO is of en idiopathic, however. NMO is usually disabling over time; in one series, respiratory failure from cervical myelitis was present in one-third of patients, and 8 years af er onset, 60% of patients were blind and more than half had permanent paralysis of one or more limbs.

A highly specific autoantibody directed against aquaporin-4 is present in the sera of approximately two-thirds of patients with a clinical diagnosis of NMO. Seropositive patients have a very high risk for future relapses; more than half will relapse within 1 year if untreated. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that aquaporin-4 antibodies are pathogenic, as passive transfer of antibodies from NMO patients into laboratory animals reproduce histologic features of the disease.

When MS affects individuals of African or Asian ancestry, there is a propensity for demyelinating lesions to involve predominantly the optic nerve and spinal cord, an MS subtype termed opticospinal MS. Interestingly, some individuals with opticospinal MS are seropositive for aquaporin-4 antibodies, suggesting that such cases represent an NMO spectrum disorder.

TREATMENT Neuromyelitis Optica

Disease-modifying therapies have not been rigorously studied in NMO. Acute attacks of NMO are usually treated with high-dose glucocorticoids (solumedrol 1–2 g/d for 5–10 days followed by a prednisone taper). Plasma exchange (typically 7 qod exchanges of 1.5 plasma volumes) has also been used empirically for acute episodes that fail to respond to glucocorticoids. Given the unfavorable natural history of untreated NMO, prophylaxis against relapses is recommended for most patients using one of the following regimens: mycophenylate mofetil (250 mg bid gradually increasing to 1000 mg bid); B cell depletion with anti-CD20 monoclonal antibody (rituximab); or a combination of glucocorticoids (500 mg IV methylprednisolone daily for 5 days; then oral prednisone 1 mg/kg per day for 2 months, followed by slow taper) plus azathioprine (2 mg/kg per day started on week 3). Available evidence suggests that use of IFN-β is ineffective and paradoxically may increase the risk of NMO relapses.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) has a monophasic course and is most frequently associated with an antecedent infection (postinfectious encephalomyelitis); approximately 5% of ADEM cases follow immunization (postvaccinal encephalomyelitis). ADEM is far more common in children than adults, and many adult cases initially thought to represent ADEM subsequently experience late relapses qualifying as either MS or another chronic inflammatory disorder such as vasculitis, sarcoid, or lymphoma. T e hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination, in contrast to larger confluent demyelinating lesions typical of MS. In the most explosive form of ADEM, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

www.ketabpezeshki.com (021) 66485457 - 66485438

Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence in developed countries. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 10^6 immunizations). ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, EBV, HHV-6, HIV, other viruses, and Mycoplasma pneumoniae. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness. In addition to measles, postvaccinal encephalomyelitis may also follow the administration of vaccines for smallpox (5 cases per million), the Semple rabies, and Japanese encephalitis. Modern vaccines that do not require viral culture in CNS tissue have reduced the ADEM risk.

All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent or vaccine that then triggers an inflammatory demyelinating response. Autoantibodies to MBP and to other myelin antigens have been detected in the CSF from some patients with ADEM. Attempts to demonstrate direct viral invasion of the CNS have been unsuccessful.

CLINICAL MANIFESTATIONS

In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neurologic disease are consistently present (e.g., hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). In ADEM due to chickenpox, cerebellar involvement is of en conspicuous. CSF protein is modestly elevated (0.5–1.5 g/L [50–150 mg/dL]). Lymphocytic pleocytosis, generally 200 cells/μL or greater, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pattern during the initial days of the illness. Transient CSF oligoclonal banding has been reported. MRI usually reveals extensive changes in the brain and spinal cord, consisting of white matter hyperintensities on T2 and fluid-attenuated inversion recovery sequences with Gd enhancement on T1-weighted sequences.

DIAGNOSIS

T e diagnosis is most reliably established when there is a history of recent vaccination or viral exanthematous illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses including HIV may be difficult to exclude **(Chap. 46)**; other considerations include hypercoagulable states including the antiphospholipid antibody syndrome, vasculitis, neurosarcoid, primary CNS lymphoma, or metastatic cancer. An explosive presentation of MS can mimic ADEM, and especially in adults, it may not be possible to distinguish these conditions at onset. T e simultaneous onset of disseminated symptoms and signs is common in ADEM and rare in MS. Similarly, meningismus, drowsiness, coma, and seizures suggest ADEM rather than MS. Unlike MS, in ADEM, optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that favor ADEM include extensive and relatively symmetric white matter abnormalities, basal ganglia or cortical gray matter lesions, and Gd enhancement of all abnormal areas. By contrast, OCBs in the CSF are more common in MS. In one study of adult patients initially thought to have ADEM, 30% experienced additional relapses over a follow-up period of 3 years, and they were reclassified as having MS. Occasional patients with "recurrent ADEM" have also been reported, especially children; however, it is not possible to distinguish this entity from atypical MS.

TREATMENT Acute Disseminated Encephalomyelitis

Initial treatment is with high-dose glucocorticoids as for exacerbations of NMO (see above); depending on the response, treatment may need to be continued for 8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or intravenous immunoglobulin. T e prognosis reflects the severity of the underlying acute illness. In recent case series of presumptive ADEM in adults, mortality rates of 5–20% are reported, and many survivors have permanent neurologic sequelae.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 46

MENINGITIS, ENCEPHALITIS, BRAIN ABSCESS, AND EMPYEMA

Karen L. Roos ■ Kenneth L. Tyler

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision making, and rapid institution of therapy can be lifesaving. These distinct clinical syndromes include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and infectious thrombophlebitis. Each may present with a nonspecific prodrome of fever and headache, which in a previously healthy individual may initially be thought to be benign, until (with the exception of viral meningitis) altered consciousness, focal neurologic signs, or seizures appear. Key goals of early management are to emergently distinguish between these conditions, identify the responsible pathogen, and initiate appropriate antimicrobial therapy.

APPROACH TO THE PATIENT: Meningitis, Encephalitis, Brain Abscess, and Empyema

(Figure 46-1) The first task is to identify whether an infection predominantly involves the subarachnoid space (meningitis) or whether there is evidence of either generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem. When brain tissue is directly injured by a bacterial or viral infection, the disease is referred to as encephalitis, whereas focal infections involving brain tissue are classified as either cerebritis or abscess, depending on the presence or absence of a capsule.

Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation. Kernig's sign is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. Brudzinski's sign is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

Initial management can be guided by several considerations: (1) Empirical therapy should be initiated promptly whenever bacterial meningitis is a significant diagnostic consideration. (2) All patients who have had recent head trauma, are immunocompromised, have known malignant lesions or central nervous system (CNS) neoplasms, or have focal neurologic findings, papilledema, or a depressed level of consciousness should undergo computed tomography (CT) or magnetic resonance imaging (MRI) of the brain prior to lumbar puncture (LP). In these cases empirical antibiotic therapy should not be delayed pending test results but should be administered prior to neuroimaging and LP. (3) A significantly depressed level of consciousness (e.g., somnolence, coma), seizures, or focal neurologic deficits do not occur in viral meningitis; patients with these symptoms should be hospitalized for further evaluation and treated empirically for bacterial and viral meningoencephalitis. (4) Immunocompetent patients with a normal level of consciousness, no prior antimicrobial treatment, and a cerebrospinal fluid (CSF) profile consistent with viral meningitis (lymphocytic pleocytosis and a normal glucose concentration) can often be

www.ketabpezeshki.com (021) 66485457 - 66485438

treated as outpatients if appropriate contact and monitoring can be ensured. Failure of a patient with suspected viral meningitis to improve within 48 h should prompt a reevaluation including follow-up neurologic and general medical examination and repeat imaging and laboratory studies, of en including a second LP.

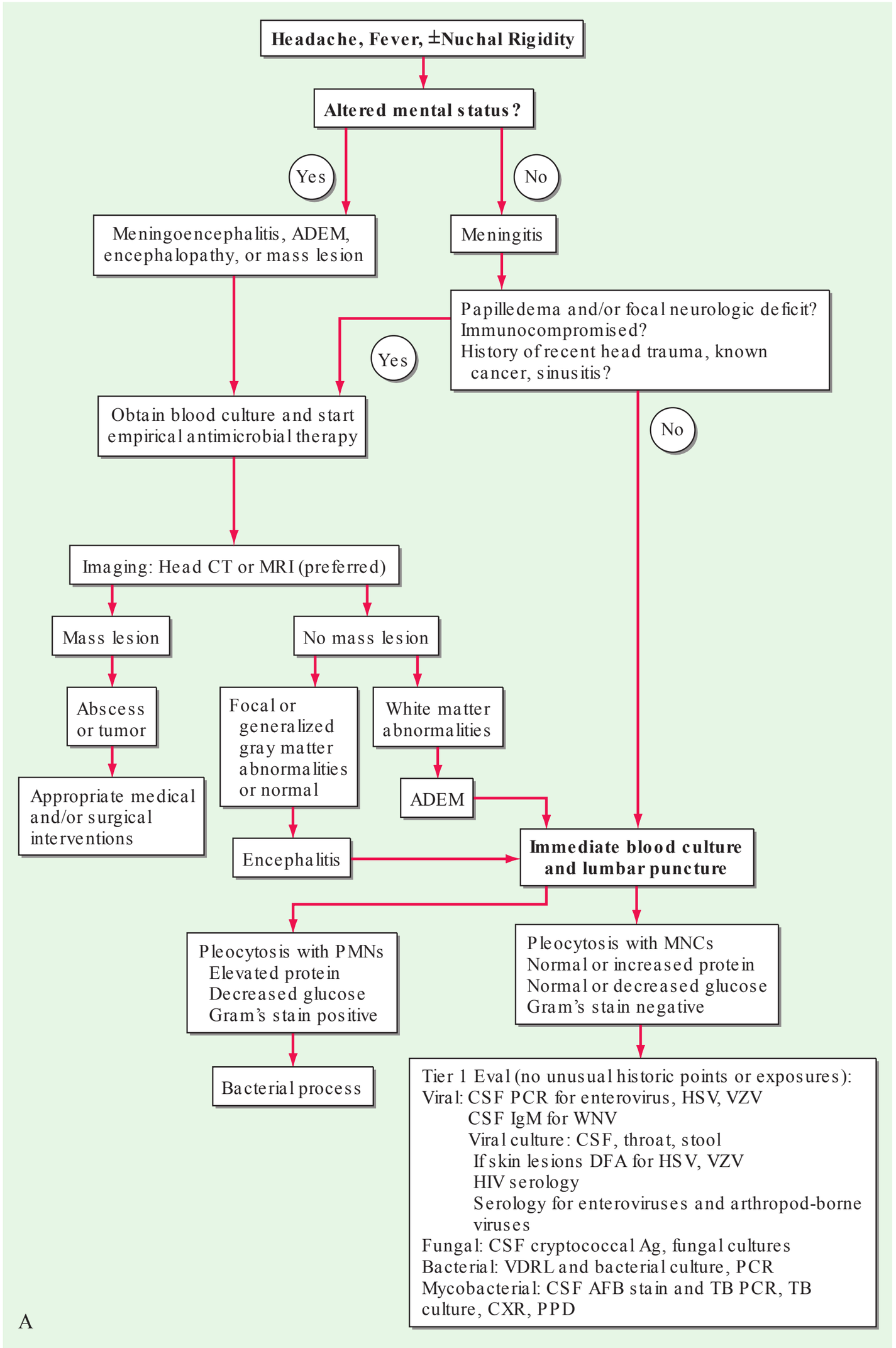


FIGURE 46-1

The management of patients with suspected central nervous system (CNS) infection. ADEM, acute disseminated encephalomyelitis; AFB, acid-fast bacillus; Ag, antigen; CSF, cerebrospinal fluid; CT, computed tomography; CTFV, Colorado tick fever virus; CXR, chest x-ray; DFA, direct fluorescent antibody; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MNCs, mononuclear cells; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear leukocytes; PPD, purified protein derivative; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus; WNV, West Nile virus.

www.ketabpezeshki.com (021) 66485457 - 66485438

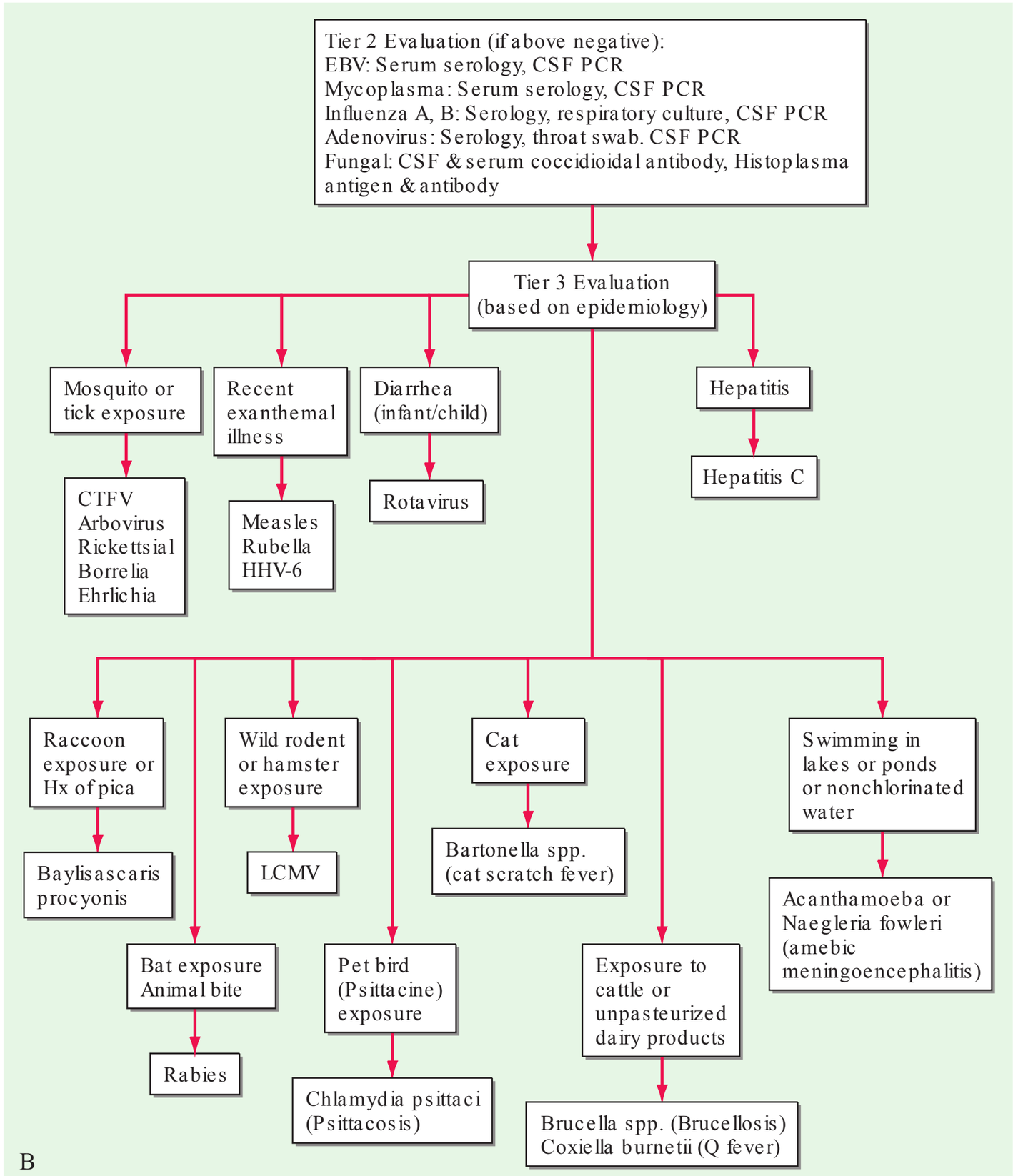


FIGURE 46-1 (Continued)

ACUTE BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space. It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. T e meninges, subarachnoid space, and brain parenchyma are all frequently involved in the inflammatory reaction (meningoencephalitis).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. T e organisms most of en responsible for community-acquired bacterial meningitis are Streptococcus pneumoniae (~50%), Neisseria meningitidis (~25%), group B streptococci (~15%), and Listeria monocytogenes (~10%). Haemophilus in*fl*uenzae type b accounts for <10% of cases of bacterial meningitis in most series. N. meningitidis is the causative organism of recurring epidemics of meningitis every 8 to 12 years.

ETIOLOGY

S. pneumoniae is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). T ere are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and CSF rhinorrhea. T e mortality rate remains ~20% despite antibiotic therapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

The incidence of meningitis due to N. meningitidis has decreased with the routine immunization of 11- to 18-year-olds with the quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine. The vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Gram-negative bacilli cause meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy, and head trauma associated with CSF rhinorrhea or otorrhea.

Otitis, mastoiditis, and sinusitis are predisposing and associated conditions for meningitis due to Streptococci sp., gram-negative anaerobes, Staphylococcus aureus, Haemophilus sp., and Enterobacteriaceae. Meningitis complicating endocarditis may be due to viridans streptococci, S. aureus, Streptococcus bovis, the HACEK group (Haemophilus sp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae), or enterococci.

Group B Streptococcus, or Streptococcus agalactiae, was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals >50 years of age, particularly those with underlying diseases.

L. monocytogenes is an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by Listeria. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs.

The frequency of H. in*fl*uenzae type b (Hib) meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, H. in*fl*uenzae causes meningitis in unvaccinated children and older adults, and non-b H. in*fl*uenzae is an emerging pathogen.

S. aureus and coagulase-negative staphylococci are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, S. pneumoniae and N. meningitidis, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the CSF. Some bacteria, such as S. pneumoniae, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the subarachnoid space is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the subarachnoid space **(Fig. 46-2)**. Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid

www.ketabpezeshki.com (021) 66485457 - 66485438

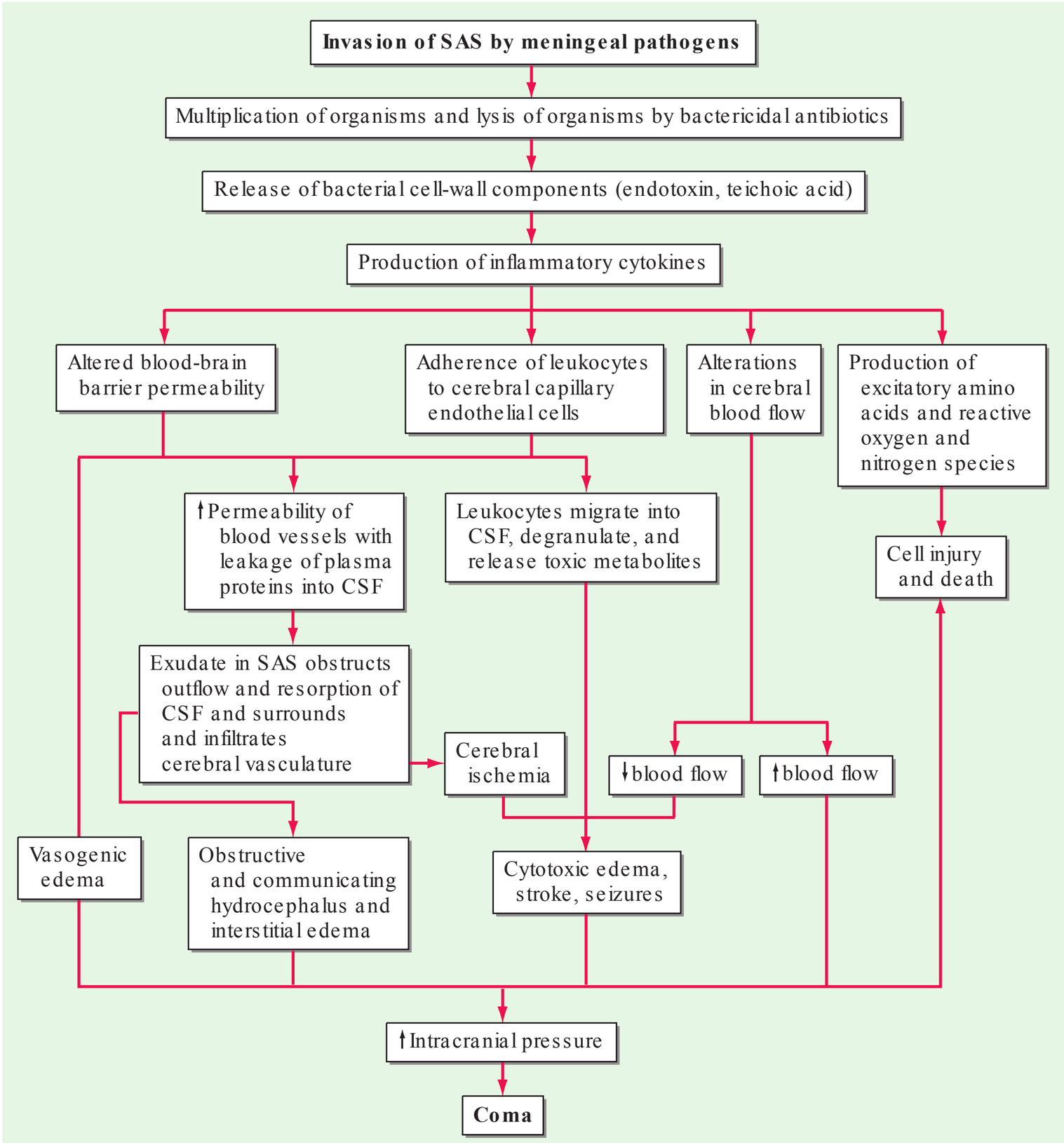


FIGURE 46-2
The pathophysiology of the neurologic complications of bacterial meningitis. CSF, cerebrospinal fluid; SAS, subarachnoid space.

and peptidoglycans of S. pneumoniae, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor alpha (TNF-α) and interleukin 1β (IL-1β) are present in CSF within 1–2 h of intracisternal inoculation of LPS. T is cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1β and TNF-α. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells, especially in the dentate gyrus of the hippocampus.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF-α and IL-1β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the subarachnoid space (Fig. 46-2). T e subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. T e adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites

www.ketabpezeshki.com (021) 66485457 - 66485438

that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation **(Chap. 33)**. Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the subarachnoid space and infiltration of the arterial wall by inflammatory cells with intimal thickening (vasculitis) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. T e combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. T e classic clinical triad of meningitis is fever, headache, and nuchal rigidity, but the classic triad may not be present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Fever and either headache, stiff neck, or an altered level of consciousness will be present in nearly every patient with bacterial meningitis. Nausea, vomiting, and photophobia are also common complaints.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents.

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH_2O, and 20% have opening pressures >400 mmH_2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). T e most disastrous complication of increased ICP is cerebral herniation. T e incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters devoted to individual pathogens. T e most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay **(Table 46-1)**. T e diagnosis of bacterial meningitis is made by examination of the CSF **(Table 46-2)**. T e need to obtain neuroimaging studies (CT or MRI) prior to LP requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated af er blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay.

T e classic CSF abnormalities in bacterial meningitis (Table 46-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration (<2.2 mmol/L [<40 mg/dL] and/or CSF/serum glucose ratio of <0.4 in ~60%), (3) increased protein concentration (>0.45 g/L [>45 mg/dL] in 90%), and (4) increased opening pressure (>180 mmH_2O in 90%). CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. T e CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 46-1

ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CENTRAL NERVOUS SYSTEM INFECTIONS[A]

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

	TOTAL DAILY DOSE AND DOSING INTERVAL	
ANTIMICROBIAL AGENT	**CHILD (>1 MONTH)**	**ADULT**
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225-300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8hb	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45-60 (mg/kg)/d, q6h	45-60 (mg/kg)d, q6–12hb

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function.
[b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

TABLE 46-2

CEREBROSPINAL FLUID (CSF) ABNORMALITIES IN BACTERIAL MENINGITIS

Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
Latex agglutination	May be positive in patients with meningitis due to Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b, Escherichia coli, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis
PCR	Detects bacterial DNA

Abbreviation: PCR, polymerase chain reaction

bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.

A 16S rRNA conserved sequence broad-based bacterial PCR can detect small numbers of viable and nonviable organisms in CSF and is expected to be useful for making a diagnosis of bacterial meningitis in patients who have been pretreated with oral or parenteral antibiotics and in whom Gram's stain and CSF culture are negative. When the broad-range PCR is positive, a PCR that uses specific bacterial primers to detect the nucleic acid of S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae, and S. agalactiae can be obtained based on the clinical suspicion of the meningeal pathogen. The latex agglutination (LA) test for the detection of bacterial antigens of S. pneumoniae, N. meningitidis, H. influenzae type b, group B Streptococcus, and E. coli K1 strains in the CSF has been useful for making a diagnosis of bacterial meningitis but is being replaced by the CSF bacterial PCR assay. The CSF LA test has a specificity of 95–100% for S. pneumoniae and N. meningitidis, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the sensitivity of the CSF LA test is only 70–100% for detection of S. pneumoniae and 33–70% for detection of N. meningitidis antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in

www.ketabpezeshki.com (021) 66485457 - 66485438

CSF and thus for making a diagnosis of gram-negative bacterial meningitis. T e test has a specificity of 85–100% and a sensitivity approaching 100%. T us, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false positives may occur.

Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is of en seen af er the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. T e rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis (see "Viral Encephalitis," below). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI images, high signal intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG (see below).

Rickettsial disease can resemble bacterial meningitis. Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria Rickettsia rickettsii. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash, and if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. Anaplasma phagocytophilum causes human granulocytic ehrlichiosis (anaplasmosis), and Ehrlichia cha*ff*eensis causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, confusion, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia, and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Focal suppurative CNS infections (see below), including subdural and epidural empyema and brain abscess, should also be considered, especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones.

A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; **Chap. 33**) is generally the major consideration. Other possibilities include chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma or craniopharyngioma epidermoid or dermoid cyst); drug-induced hypersensitivity meningitis; carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis **(Chap. 47)** may be considered in the differential diagnosis of acute meningitis. T e principal causes include Mycobacterium tuberculosis, Cryptococcus neo*f*ormans, Histoplasma capsulatum, Coccidioides immitis, and *T*reponema pallidum.

www.ketabpezeshki.com (021) 66485457 - 66485438

EMPIRICAL ANTIMICROBIAL THERAPY (Table 46-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. S. pneumoniae and N. meningitidis are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant S. pneumoniae, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provides good coverage for susceptible S. pneumoniae, group B streptococci, and H. influenzae and adequate coverage for N. meningitidis. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against S. pneumoniae and N. meningitidis and greater activity against Enterobacter species and Pseudomonas aeruginosa. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to Enterobacter species and P. aeruginosa. Ampicillin should be added to the empirical regimen for coverage of L. monocytogenes in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Metronidazole is added to the empirical regimen to cover gram-negative anaerobes in patients with otitis, sinusitis, or mastoiditis. In hospital-acquired meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including P. aeruginosa are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime, cefepime, or meropenem. Ceftazidime, cefepime, or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, because ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with P. aeruginosa. Meropenem is a carbapenem antibiotic that is highly active in vitro against L. monocytogenes, has been demonstrated to be effective in cases of meningitis caused by P. aeruginosa, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

SPECIFIC ANTIMICROBIAL THERAPY

Meningococcal meningitis Although ceftriaxone and cefotaxime provide adequate empirical coverage for N. meningitidis, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. **(Table 46-3)** Isolates of N. meningitidis with moderate resistance to penicillin have been identified and are increasing in incidence worldwide. CSF isolates of N. meningitidis should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one

TABLE 46-3

ANTIMICROBIAL THERAPY OF CENTRAL NERVOUS SYSTEM BACTERIAL INFECTIONS BASED ON PATHOGEN[A]

ORGANISM	ANTIBIOTIC
Neisseria meningitides	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except Pseudomonas spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococci spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 46-1.

www.ketabpezeshki.com (021) 66485457 - 66485438

dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

Pneumococcal meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of S. pneumoniae should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 46-3). For S. pneumoniae meningitis, an isolate of S. pneumoniae is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL and to be resistant when the MIC is >0.12 μg/mL. Isolates of S. pneumoniae that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci, with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. For MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone.

A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Patients with S. pneumoniae meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of S. pneumoniae who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

Listeria meningitis Meningitis due to L. monocytogenes is treated with ampicillin for at least 3 weeks (Table 46-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal meningitis Meningitis due to susceptible strains of S. aureus or coagulase-negative staphylococci is treated with nafcillin (Table 46-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

Gram-negative bacillary meningitis The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to P. aeruginosa, which should be treated with ceftazidime, cefepime, or meropenem (Table 46-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

ADJUNCTIVE THERAPY The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1β and TNF-α in the subarachnoid space. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1β and TNF-α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF-α by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF-α production once it has been induced. The results of clinical trials of dexamethasone therapy in meningitis due to H. influenzae, S. pneumoniae, and N. meningitidis have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss.

A prospective European trial of adjunctive therapy for acute bacterial meningitis in 301 adults found that dexamethasone reduced the number of unfavorable outcomes (15 vs. 25%, p = 0.03) including death (7 vs. 15%, p = 0.04). The benefits were most striking in patients with pneumococcal meningitis. Dexamethasone (10 mg intravenously) was administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of S. pneumoniae meningitis. As a result, to assure reliable penetration of vancomycin into the CSF, children and adults are treated with vancomycin in a dose of 45–60 mg/kg per day. Alternatively, vancomycin can be administered by the intraventricular route.

One of the concerns for using dexamethasone in adults with bacterial meningitis is that in experimental models of meningitis, dexamethasone therapy increased hippocampal cell injury and reduced learning capacity. This has not been the case in clinical series. The efficacy of dexamethasone therapy in preventing neurologic sequelae is different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast

www.ketabpezeshki.com (021) 66485457 - 66485438

Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone.

INCREASED INTRACRANIAL PRESSURE Emergency treatment of increased ICP includes elevation of the patient's head to 30–45°, intubation and hyperventilation ($Paco_2$ 25–30 mmHg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device.

Treatment of increased intracranial pressure is discussed in detail in Chap. 33.

PROGNOSIS

Mortality rate is 3–7% for meningitis caused by H. in*fl*uenzae, N. meningitidis, or group B streptococci; 15% for that due to L. monocytogenes; and 20% for S. pneumoniae. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration (<2.2 mmol/L [<40 mg/dL]) and markedly increased CSF protein concentration (>3 g/L [> 300 mg/dL]) have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

ACUTE VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Immunocompetent adult patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see below). Headache is almost invariably present and often characterized as frontal or retroorbital and frequently associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion, do not occur in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.

ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases of viral meningitis. The most important agents are enteroviruses (including echoviruses and coxsackieviruses in addition to numbered enteroviruses), varicella-zoster virus (VZV), HSV (HSV-2 > HSV-1), HIV, and arboviruses **(Table 46-4)**. CSF cultures are positive in 30–70% of patients, with the frequency of isolation depending on the specific

TABLE 46-4

VIRUSES CAUSING ACUTE MENINGITIS AND ENCEPHALITIS IN NORTH AMERICA

ACUTE MENINGITIS

Common	Less Common
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Herpes simplex virus 1
Varicella-zoster virus	Human herpesvirus 6
Herpes simplex virus 2	Cytomegalovirus
Epstein-Barr virus	Lymphocytic choriomeningitis virus
Arthropod-borne viruses	Mumps
HIV	

ACUTE ENCEPHALITIS

Common	Less Common
Herpesviruses	Rabies
Cytomegalovirus[a]	Eastern equine encephalitis virus
Herpes simplex virus 1[b]	Powassan virus
Herpes simplex virus 2	Cytomegalovirus[a]
Human herpesvirus 6	Colorado tick fever virus
Varicella-zoster virus	Mumps
Epstein-Barr virus	
Arthropod-borne viruses	
La Crosse virus	
West Nile virus[c]	
St. Louis encephalitis virus	
Enteroviruses	

[a]Immunocompromised host.
[b]The most common cause of sporadic encephalitis.
[c]The most common cause of epidemic encephalitis.

www.ketabpezeshki.com (021) 66485457 - 66485438

viral agent. Approximately two-thirds of culture-negative cases of "aseptic" meningitis have a specific viral etiology identified by CSF PCR testing (see below).

EPIDEMIOLOGY

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~60,000–75,000 cases per year. In temperate climates, there is a substantial increase in cases during the non-winter months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections in the summer and fall, with a peak monthly incidence of about 1 reported case per 100,000 population.

LABORATORY DIAGNOSIS

CSF examination

The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a pleocytosis, a normal or slightly elevated protein concentration (0.2–0.8 g/L [20–80 mg/dL]), a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are not seen on Gram's stain of CSF. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. Lymphocytes are typically the predominant cell. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, West Nile virus, eastern equine encephalitis (EEE) virus, or mumps. A PMN pleocytosis occurs in 45% of patients with West Nile virus (WNV) meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. PMN pleocytosis with low glucose may also be a feature of cytomegalovirus (CMV) infections in immunocompromised hosts. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis in whom a specific diagnosis has not been established should prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and VZV. As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, Listeria meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, IL-1β, IL-6, soluble IL-2 receptor, β_2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but they remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase chain reaction amplification of viral nucleic acid

Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, CSF PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV CSF PCR is also an important diagnostic test in patients with recurrent episodes of "aseptic" meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. CSF PCR is also used routinely to diagnose CNS viral infections caused by CMV, Epstein-Barr virus (EBV), VZV, and human herpesvirus 6 (HHV-6). CSF PCR tests are available for WNV but are not as sensitive as detection of WNV-specific CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by Mycoplasma pneumoniae, which can mimic viral meningitis and encephalitis. PCR of throat washings may assist in diagnosis of enteroviral and mycoplasmal CNS infections. PCR of stool specimens may also assist in diagnosis of enteroviral infections (see below).

Viral culture

The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic studies

For many arboviruses including WNV, serologic studies remain important diagnostic tools. Serum antibody determination is less useful for viruses with high

www.ketabpezeshki.com (021) 66485457 - 66485438

seroprevalence rates in the general population such as HSV, VZV, CMV, and EBV. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. For viruses with high seroprevalence such as VZV and HSV, demonstration of synthesis of virus-specific antibodies in CSF, as shown by an increased IgG index or the presence of CSF IgM antibodies, may be useful and can provide presumptive evidence of CNS infection. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule. For example, WNV serum IgM has been shown to persist in some patients for >1 year following acute infection. Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in aiding acute diagnosis or management. In the case of EBV, demonstration of antibody responses consistent with recent/acute infection (e.g., IgM viral capsid antibody, antibody against early antigen, absence of antibody against EBV-associated nuclear antigen) may assist in diagnosis.

CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands also occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other laboratory studies

All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR), and C-reactive protein, electrolytes, glucose, creatine kinase, aldolase, amylase, and lipase. Neuroimaging studies (MRI preferable to CT) are not absolutely necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms, atypical CSF profiles, or underlying immunocompromising treatments or conditions.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as Mycoplasma, Listeria spp., Brucella spp., Coxiella spp., Leptospira spp., and Rickettsia spp.; (4) parameningeal infections; (5) neoplastic meningitis; and (6) meningitis secondary to noninfectious inflammatory diseases, including autoimmune and hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes. Studies in children >28 days of age suggest that the presence of CSF protein >0.5 g/L (sensitivity 89%, specificity 78%) and elevated serum procalcitonin levels >0.5 ng/mL (sensitivity 89%, specificity 89%) were clues to the presence of bacterial as opposed to "aseptic" meningitis. A variety of clinical algorithms for differentiating bacterial from aseptic meningitis have been developed. One such prospectively validated system, the bacterial meningitis score, suggests that the probability of bacterial meningitis is 0.3% or less (negative predictive value 99.7%, 95% confidence interval 99.6–100%) in children with CSF pleocytosis who have (1) a negative CSF Gram's stain, (2) CSF neutrophil count <1000 cells/μL, (3) CSF protein <80 mg/dL, (4) peripheral absolute neutrophil count of <10,000 cells/μL, and (5) no prior history or current presence of seizures.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses (EV) are the most common cause of viral meningitis, accounting for >85% of cases in which a specific etiology can be identified. Cases may either be sporadic or occur in clusters. EV71 has produced large epidemics of neurologic disease outside the United States, especially in Southeast Asia, but most recently reported cases in the United States have been sporadic. Enteroviruses are the most likely cause of viral meningitis in the summer and fall months, especially in children (<15 years), although cases occur at reduced frequency year round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of enterovirus infection, including exanthems, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. However, up to 15% of patients,

www.ketabpezeshki.com (021) 66485457 - 66485438

most commonly young infants rather than older children or adults, have a normal CSF leukocyte count. In rare cases, PMNs may predominate during the first 48 h of illness. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). CSF PCR has the highest sensitivity if performed within 48 h of symptom onset, with sensitivity declining rapidly af er day 5 of symptoms. PCR of throat washings or stool specimens may be positive for several weeks, and positive results can help support the diagnosis of an acute enteroviral infection. T e sensitivity of routine enteroviral PCRs for detecting EV71 is low, and specific testing may be required. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus in*f*ections occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In the United States, the most important causes of arboviral meningitis and encephalitis are WNV, St. Louis encephalitis virus, and the California encephalitis group of viruses. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningoencephalitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However, ~45% of patients with WNV meningoencephalitis have CSF neutrophilia, which can persist for a week or more. T e rarity of hypoglycorrhachia in WNV infection, the absence of positive Gram's stains, and the negative cultures help distinguish these patients from those with bacterial meningitis. Definitive diagnosis of arboviral meningoencephalitis is based on demonstration of viral-specific IgM in CSF or seroconversion. T e prevalence of CSF IgM increases progressively during the first week af er infection, peaking at >80% in patients with neuroinvasive disease; as a result, repeat studies may be needed when disease suspicion is high and an early study is negative. CSF PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF PCR is less than that of CSF serology. WNV CSF PCR may be useful in immunocompromised patients who may have absent or reduced antibody responses.

HSV meningitis has been increasingly recognized as a major cause of viral meningitis in adults, and overall, it is probably second in importance to enteroviruses as a cause of viral meningitis, accounting for 5% of total cases overall and undoubtedly a higher frequency of those cases occurring in adults and/or outside of the summer-fall period when enterovirus infections are increasingly common. In adults, the majority of cases of uncomplicated meningitis are due to HSV-2, whereas HSV-1 is responsible for 90% of cases of HSV encephalitis. HSV meningitis occurs in ~25–35% of women and ~10–15% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. Diagnosis of HSV meningitis is usually by HSV CSF PCR because cultures may be negative, especially in patients with recurrent meningitis. Demonstration of intrathecal synthesis of HSV-specific antibody may also be useful in diagnosis, although antibody tests are less sensitive and less specific than PCR and may not become positive until af er the first week of infection. Although a history of or the presence of HSV genital lesions is an important diagnostic clue, many patients with HSV meningitis give no history and have no evidence of active genital herpes at the time of presentation. Most cases of recurrent viral or "aseptic" meningitis, including cases previously diagnosed as Mollaret's meningitis, are due to HSV.

VZV meningitis should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that VZV is being increasingly identified as an important cause of both meningitis and encephalitis in patients without rash. T e frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. Diagnosis is usually based on CSF PCR, although the sensitivity of this test may not be as high as for the other herpesviruses. VZV serologic studies complement PCR testing, and the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures.

EBV in*f*ections may also produce aseptic meningitis, with or without associated infectious mononucleosis. T e presence of atypical lymphocytes in the CSF or peripheral blood is suggestive of EBV infection but may occasionally be seen with other viral infections. EBV is almost never cultured from CSF. Serum and CSF serology can help establish the presence of acute infection, which is characterized by IgM viral capsid antibodies (VCAs), antibodies to early antigens (EAs), and the absence of antibodies to EBV-associated nuclear antigen (EBNA). CSF PCR is another important diagnostic test, although false-positive results may reflect viral reactivation associated with other infectious or inflammatory processes or the presence of latent viral DNA

www.ketabpezeshki.com (021) 66485457 - 66485438

in lymphocytes recruited due to other inflammatory conditions.

HIV meningitis should be suspected in any patient presenting with a viral meningitis with known or suspected risk factors for HIV infection. Meningitis may occur following primary infection with HIV in 5–10% of cases and less commonly at later stages of illness. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. Diagnosis can be confirmed by detection of HIV genome in blood or CSF. Seroconversion may be delayed, and patients with negative HIV serologies who are suspected of having HIV meningitis should be monitored for delayed seroconversion. **For further discussion of HIV infection, see Chap. 48**.

Mumps should be considered when meningitis occurs in the late winter or early spring, especially in males (male-to-female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%; however, mumps remains a potential source of infection in nonimmunized individuals and populations. Rare cases (10–100:100,000 vaccinated individuals) of vaccine-associated mumps meningitis have been described, with onset typically 2–4 weeks after vaccination. The presence of parotitis, orchitis, oophoritis, pancreatitis, or elevations in serum lipase and amylase is suggestive of mumps meningitis; however, their absence does not exclude the diagnosis. Clinical meningitis was previously estimated to occur in 10–30% of patients with mumps parotitis; however, in a recent U.S. outbreak of nearly 2600 cases of mumps, only 11 cases of meningitis were identified, suggesting the incidence may be lower than previously suspected. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. Patients with meningitis have a CSF pleocytosis that can exceed 1000 cells/μL in 25%. Lymphocytes predominate in 75%, although CSF neutrophilia occurs in 25%. Hypoglycorrhachia, occurs in 10–30% of patients and may be a clue to the diagnosis when present. Diagnosis is typically made by culture of virus from CSF or by detecting IgM antibodies or seroconversion. CSF PCR is available in some diagnostic and research laboratories.

LCMV infection should be considered when aseptic meningitis occurs in the late fall or winter and in individuals with a history of exposure to house mice (Mus musculus), pet or laboratory rodents (e.g., hamsters, rats, mice), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted above, may include the presence of leukopenia, thrombocytopenia, or abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells/μL) and hypoglycorrhachia (<30%). Diagnosis is based on serology and/or culture of virus from CSF.

TREATMENT Acute Viral Meningitis

Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics, and antiemetics. Fluid and electrolyte status should be monitored. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see above). Hospitalization may not be required in immunocompetent patients with presumed viral meningitis and no focal signs or symptoms, no significant alteration in consciousness, and a classic CSF profile (lymphocytic pleocytosis, normal glucose, negative Gram's stain) if adequate provision for monitoring at home and medical follow-up can be ensured. Immunocompromised patients; patients with significant alteration in consciousness, seizures, or the presence of focal signs and symptoms suggesting the possibility of encephalitis or parenchymal brain involvement; and patients who have an atypical CSF profile should be hospitalized. Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous acyclovir (15–30 mg/kg per day in three divided doses), which can be followed by an oral drug such as acyclovir (800 mg five times daily), famciclovir (500 mg tid), or valacyclovir (1000 mg tid) for a total course of 7–14 days. Patients who are less ill can be treated with oral drugs alone. Patients with HIV meningitis should receive highly active antiretroviral therapy **(Chap. 48)**. There is no specific therapy of proven benefit for patients with arboviral encephalitis, including that caused by WNV.

Patients with viral meningitis who are known to have deficient humoral immunity (e.g., X-linked agammaglobulinemia) and who are not already receiving either intramuscular gamma globulin or intravenous immunoglobulin (IVIg) should be treated with these agents. Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, measles, rubella, and varicella infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70–90% for this vaccine, but a booster may be required after ~10 years to maintain immunity. A related vaccine (Zostavax) is recommended for

www.ketabpezeshki.com (021) 66485457 - 66485438

prevention of herpes zoster (shingles) in adults over the age of 60. An inactivated varicella vaccine is available for transplant recipients and others for whom live viral vaccines are contraindicated

PROGNOSIS

In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. T e outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

VIRAL ENCEPHALITIS

DEFINITION

In contrast to viral meningitis, where the infectious process and associated inflammatory response are limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyeloradiculitis).

CLINICAL MANIFESTATIONS

In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. T e most commonly encountered focal findings are aphasia, ataxia, upper or lower motor neuron patterns of weakness, involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Even though neurotropic viruses typically cause pathologic injury in distinct regions of the CNS, variations in clinical presentations make it impossible to reliably establish the etiology of a specific case of encephalitis on clinical grounds alone (see "Differential Diagnosis," below).

ETIOLOGY

In the United States, there are an estimated ~20,000 cases of encephalitis per year, although the actual number of cases is likely to be significantly larger. Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology remain of unknown cause. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified (Table 46-4). T e most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (HSV, VZV, EBV). Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including Alphaviruses (e.g., EEE virus, western equine encephalitis virus), Flaviviruses (e.g., WNV, St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus), and Bunyaviruses (e.g., California encephalitis virus serogroup, La Crosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States. WNV caused 2873 confirmed cases of neuroinvasive disease (encephalitis, meningitis, or myelitis) in 2012 with 286 deaths. States reporting >200 cases included Texas (1868 cases), California (479), Louisiana (335), Illinois (290), Mississippi (249), South Dakota (203), and Michigan (202). In 2013, there were 1140 neuroinvasive cases with 100 deaths. States reporting >100 cases included California (357 cases), Colorado (315), Nebraska (213), Texas (157), South Dakota (148), North Dakota (123), and Illinois (106). It is important to recognize that WNV epidemics are unpredictable and that cases have occurred in every state in the continental United States. New causes of viral CNS infections are constantly appearing, as evidenced by the outbreak of cases of encephalitis in Southeast Asia caused by Nipah virus, a newly identified member of the Paramyxoviridae family; of meningitis in Europe caused by Toscana virus, an arbovirus belonging to the Bunyavirus family; and of neurologic disorders associated with major epidemics of Chikungunya virus, a togavirus, in Africa, India, and Southeast Asia. Parechoviruses including human parechovirus 3 (HPeV3), members of the Picornavirus family, have recently been reported as causes of fever,

www.ketabpezeshki.com (021) 66485457 - 66485438

sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

LABORATORY DIAGNOSIS

CSF examination

CSF examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased ICP. Ideally at least 20 mL should be collected with 5–10 mL stored frozen for later studies as needed. The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of immunocompetent patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial LP but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/μL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and LCMV may occasionally result in cell counts >1000/μL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including CMV, HSV, and enteroviruses. Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis. Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients. Large numbers of CSF PMNs may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses. However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL)in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

CSF PCR

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, HHV-6, and enteroviruses (see "Viral Meningitis," above). In the case of VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis. The sensitivity and specificity of CSF PCRs vary with the virus being tested. The sensitivity (~96%) and specificity (~99%) of HSV CSF PCR are equivalent to or exceed those of brain biopsy. It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory abnormalities significantly reduces the likelihood of HSV encephalitis but does not exclude it. For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%. In both situations, a positive test makes the diagnosis almost certain (98–99%). There have been several recent reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset and that became positive when repeated 1–3 days later. The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining positive after ≥14 days. PCR results are generally not affected by ≤1 week of antiviral therapy. In one study, 98% of CSF specimens remained PCR-positive during the first week of initiation of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than HSV have not been definitively characterized. Enteroviral (EV) CSF PCR appears to have a sensitivity and specificity of >95%. EV PCR sensitivity for EV71 may be considerably lower (~30% in some reports). Parechoviruses are also not detected by standard EV RT-PCRs. The specificity of EBV CSF PCR has not been established. Positive EBV CSF PCRs associated with positive tests for other pathogens have been reported and may reflect reactivation of EBV latent in lymphocytes that enter the CNS as a result of an unrelated infectious or inflammatory process. In patients with CNS infection due to VZV, CSF antibody and PCR

www.ketabpezeshki.com (021) 66485457 - 66485438

studies should be considered complementary, because patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs. In the case of WNV infection, CSF PCR appears to be less sensitive (~70% sensitivity) than detection of WNV-specific CSF IgM, although PCR testing remains useful in immunocompromised patients who may not mount an effective anti-WNV antibody response.

CSF culture

CSF culture is generally of limited utility in the diagnosis of acute viral encephalitis. Culture may be insensitive (e.g., >95% of patients with HSV encephalitis have negative CSF cultures as do virtually all patients with EBV-associated CNS disease) and often takes too long to significantly affect immediate therapy.

Serologic studies and antigen detection

The basic approach to the serodiagnosis of viral encephalitis is identical to that discussed earlier for viral meningitis. Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis because IgM antibodies do not cross the blood-brain barrier, and their presence in CSF is therefore indicative of intrathecal synthesis. Timing of antibody collection may be important because the rate of CSF WNV IgM seropositivity increases by ~10% per day during the first week after illness onset, reaching 80% or higher on day 7 after symptom onset. In patients with HSV encephalitis, both antibodies to HSV-1 glycoproteins and glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, HSV CSF antibody testing is of value in selected patients whose illness is >1 week in duration and who are CSF PCR–negative for HSV. In the case of VZV infection, CSF antibody tests may be positive when PCR fails to detect viral DNA, and both tests should be considered complementary rather than mutually exclusive.

MRI, CT, and EEG

Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often EEG. These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to a diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, FLAIR, or diffusion-weighted MRI **(Fig. 46-3)**; (2) focal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 80% will have abnormalities in the temporal lobe, and an additional 10% in extratemporal regions. These lesions are typically hyperintense on T2-weighted images. The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity. Children with HSV encephalitis may have atypical patterns of MRI lesions and often show involvement of brain regions outside the frontotemporal areas. CT is less sensitive than MRI and is normal in up to 20–35% of patients. EEG abnormalities occur in >75% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific. Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped, sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2–3 s. The periodic complexes are typically noted between days 2 and 15 of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

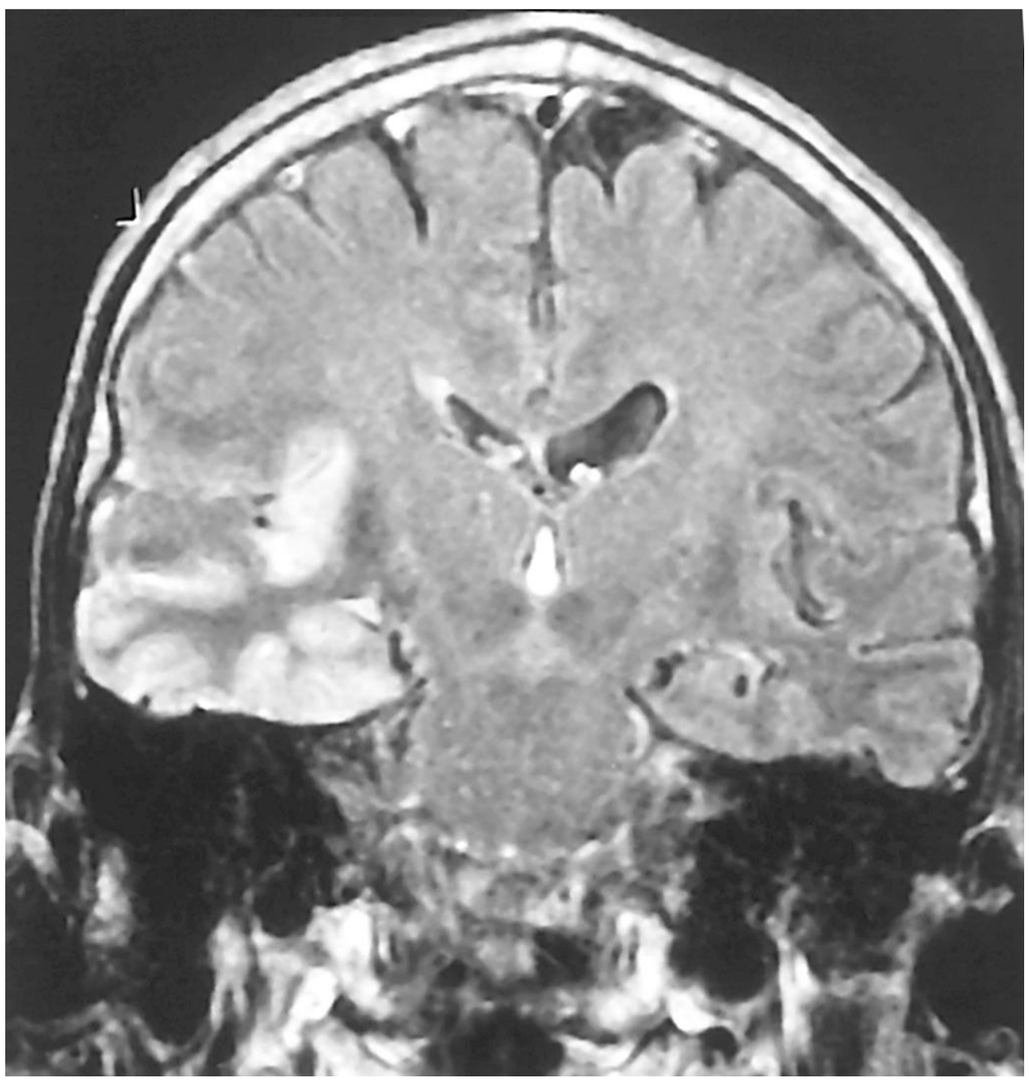


FIGURE 46-3
Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

www.ketabpezeshki.com (021) 66485457 - 66485438

Significant MRI abnormalities are found in only approximately two-thirds of patients with WNV encephalitis, a frequency less than that with HSV encephalitis. When present, abnormalities often involve deep brain structures, including the thalamus, basal ganglia, and brainstem, rather than the cortex and may only be apparent on FLAIR images. EEGs in patients with WNV encephalitis typically show generalized slowing that may be more anteriorly prominent rather than the temporally predominant pattern of sharp or periodic discharges more characteristic of HSV encephalitis. Patients with VZV encephalitis may show multifocal areas of hemorrhagic and ischemic infarction, reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis. Immunocompromised adult patients with CMV often have enlarged ventricles with areas of increased T2 signal on MRI outlining the ventricles and subependymal enhancement on T1-weighted postcontrast images. **Table 46-5** highlights specific diagnostic test results in encephalitis that can be useful in clinical decision making.

Brain biopsy

Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy.

DIFFERENTIAL DIAGNOSIS

Infection by a variety of other organisms can mimic viral encephalitis. In studies of biopsy-proven HSV encephalitis, common infectious mimics of focal viral encephalitis included mycobacteria, fungi, rickettsiae, Listeria, Mycoplasma, and other bacteria (including Bartonella sp.). Autoimmune causes of encephalitis, including those associated with antibodies against N-methyl-d-aspartate (NMDA) receptor, voltage-gated potassium channels (VGKC), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and γ-aminobutyric acid (GABA) receptors, and GAD-65, have been increasingly recognized as causes of encephalitis that can mimic that caused by viral infection. In most cases, diagnosis is made by detection of the specific autoantibodies in serum and/or CSF. NMDA receptor antibodies have recently been reported in some patients with HSE encephalitis, and their presence should not exclude appropriate testing and treatment for HSV encephalitis. Autoimmune encephalitis may also be associated with specific cancers (paraneoplastic) and onconeuronal antibodies (e.g., anti-Hu, Yo, Ma2, amphiphysin, CRMP5, CV2) **(Chap. 50)**. Subacute or chronic forms of encephalitis may occur in association with autoantibodies against thyroglobulin and thyroperoxidase (Hashimoto's encephalopathy) and with prion diseases.

Infection caused by the ameba Naegleria *f*owleri can also cause acute meningoencephalitis (primary amebic meningoencephalitis), whereas that caused by Acanthamoeba and Balamuthia more typically produces subacute or chronic granulomatous amebic meningoencephalitis. Naegleria thrive in warm, iron-rich pools of water, including those found in drains, canals, and both

TABLE 46-5

USE OF DIAGNOSTIC TESTS IN ENCEPHALITIS

The best test for WNV encephalitis is the CSF IgM antibody test. The prevalence of positive CSF IgM tests increases by about 10% per day after illness onset and reaches 70–80% by the end of the first week. Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).
Approximately 80% of patients with proven HSV encephalitis have MRI abnormalities involving the temporal lobes. This percentage likely increases to >90% when FLAIR and diffusion-weighted MRI sequences are also used. The absence of temporal lobe lesions on MRI reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.
The CSF HSV PCR test may be negative in the first 72 h of symptoms of HSV encephalitis. A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.
Detection of intrathecal synthesis (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of HSV-specific antibody may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative. Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.
Negative CSF viral cultures are of no value in excluding the diagnosis of HSV or EBV encephalitis.
VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.
The specificity of EBV CSF PCR for diagnosis of CNS infection is unknown. Positive tests may occur in patients with a CSF pleocytosis due to other causes. Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis. Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EA, early antigen; EBNA, EBV-associated nuclear antigen; EBV, Epstein-Barr virus; FLAIR, fluid-attenuated inversion recovery; HSV, herpes simplex virus; IgM, immunoglobulin M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VCA, viral capsid antibody; VZV, varicella-zoster virus; WNV, West Nile virus.

www.ketabpezeshki.com (021) 66485457 - 66485438

natural and human-made outdoor pools. Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water. T e CSF, in contrast to the typical profile seen in viral encephalitis, of en resembles that of bacterial meningitis with a neutrophilic pleocytosis and hypoglycorrhachia. Motile trophozoites can be seen in a wet mount of warm, fresh CSF. T ere have been an increasing number of cases of Balamuthia mandrillaris amebic encephalitis mimicking acute viral encephalitis in children and immunocompetent adults. T is organism has also been associated with encephalitis in recipients of transplanted organs from a donor with unrecognized infection. No effective treatment has been identified, and mortality approaches 100%.

Encephalitis can be caused by the raccoon pinworm Baylisascaris procyonis. Clues to the diagnosis include a history of raccoon exposure, especially of playing in or eating dirt potentially contaminated with raccoon feces. Most patients are children, and many have an associated eosinophilia.

Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis. T is distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggesting involvement of the inferomedial frontotemporal regions of the brain are present, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with signs and symptoms consistent with acute encephalitis with focal findings on clinical examination, neuroimaging studies, or EEG. T e diagnostic procedure of choice in these patients is CSF PCR analysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see above).

T e anatomic distribution of lesions may provide an additional clue to diagnosis. Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms, or neuroimaging abnormalities may be infected by flaviviruses (WNV, St. Louis encephalitis virus, Japanese encephalitis virus), HSV, rabies, or L. monocytogenes. Significant involvement of deep gray matter structures, including the basal ganglia and thalamus, should also suggest possible flavivirus infection. T ese patients may present clinically with prominent movement disorders (tremor, myoclonus) or parkinsonian features. Patients with WNV infection can also present with a poliomyelitis-like acute flaccid paralysis, as can patients infected with EV71 and, less commonly, other enteroviruses. Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation. T e complete eradication of polio remains an ongoing challenge despite a continuing World Health Organization poliovirus elimination campaign. T ree hundred forty-one cases of polio (almost all due to serotype 1) have been reported in 2013 from eight countries (Somalia 183 cases, Pakistan 63, Nigeria 51, Kenya 14, Syria 13, Afghanistan 9, Ethiopia 6, and Cameroon 2). T ere have been small outbreaks of poliomyelitis associated with vaccine strains of virus that have reverted to virulence through mutation or recombination with circulating wild-type enteroviruses in Hispaniola, China, the Philippines, Indonesia, Nigeria, and Madagascar.

Epidemiologic factors may provide important clues to the diagnosis of viral meningitis or encephalitis. Particular attention should be paid to the season of the year; the geographic location and travel history; and possible exposure to animal bites or scratches, rodents, and ticks. Although transmission from the bite of an infected dog remains the most common cause of rabies worldwide, in the United States very few cases of dog rabies occur, and the most common risk factor is exposure to bats—although a clear history of a bite or scratch is of en lacking. T e classic clinical presentation of encephalitic (furious) rabies is fever, fluctuating consciousness, and autonomic hyperactivity. Phobic spasms of the larynx, pharynx, neck muscles, and diaphragm can be triggered by attempts to swallow water (hydrophobia) or by inspiration (aerophobia). Patients may also present with paralytic (dumb) rabies characterized by acute ascending paralysis. Rabies due to the bite of a bat has a different clinical presentation than classic rabies due to a dog or wolf bite. Patients present with focal neurologic deficits, myoclonus, seizures, and hallucinations; phobic spasms are not a typical feature. Patients with rabies have a CSF lymphocytic pleocytosis and may show areas of increased T2 signal abnormality in the brainstem, hippocampus, and hypothalamus. Diagnosis can be made by finding rabies virus antigen in brain tissue or in the neural innervation of hair follicles at the nape of the neck. PCR amplification of viral nucleic acid from CSF and saliva or tears may also enable diagnosis. Serology is frequently negative in both serum and CSF in the first week af er onset of infection, which limits its acute diagnostic utility. No specific therapy is available, and cases are almost invariably fatal, with isolated survivors having devastating neurologic sequelae.

State public health authorities provide a valuable resource concerning isolation of particular agents in

www.ketabpezeshki.com (021) 66485457 - 66485438

individual regions. Regular updates concerning the number, type, and distribution of cases of arboviral encephalitis can be found on the CDC and U.S. Geological Survey (USGS) websites (http://www.cdc.gov and http://diseasemaps.usgs.gov).

TREATMENT Viral Encephalitis

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction, avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis. As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures, deep venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme, deoxypyrimidine (thymidine) kinase, that phosphorylates acyclovir to produce acyclovir-5′-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. T e specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5′-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for 14–21 days. CSF PCR can be repeated at the completion of this course, with PCR-positive patients receiving additional treatment, followed by a repeat CSF PCR test. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration ≤7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h, rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. T e alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels ~50% of serum levels. Complications of therapy include elevations in blood urea nitrogen and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course of parenteral acyclovir. A recently completed National Institute of Allergy and Infectious Disease (NIAID)/National Institute of Neurological Disorders and Stroke–sponsored phase III trial of supplemental oral valacyclovir therapy (2 g tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir (www.clinicaltrials.gov, identifier NCT00031486) was terminated early due to low enrollment. Although analysis was compromised due to low numbers, no differences were seen in the 12-month endpoints including dementia rating scale, mini-mental state exam, and Glasgow coma score in patients receiving valacyclovir versus placebo. T e role of adjunctive intravenous glucocorticoids in treatment of HSV and VZV infection remains unclear, with most guidelines considering the existing supportive evidence weak and recommendation for possible use based on expert opinion only.

Ganciclovir and foscarnet, either alone or in combination, are of en used in the treatment of CMV-related CNS infections, although their efficacy remains unproven. Cidofovir (see below) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2′-deoxyguanosine. T e drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25–70% of coincident plasma levels. T e usual dose for treatment of severe

www.ketabpezeshki.com (021) 66485457 - 66485438

neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain, occur in ~20% of patients. Some patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear. Valganciclovir is an orally bioavailable prodrug that can generate high serum levels of ganciclovir, although studies of its efficacy in treating CMV CNS infections are limited.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14–21 days is followed by maintenance therapy (60–120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reductions in serum calcium, magnesium, and potassium occur in ~15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent to or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for two or more additional doses, depending on clinical response. Patients must be prehydrated with normal saline (e.g., 1 L over 1–2 h) prior to each dose and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavirin (15–25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (La Crosse) virus. Ribavirin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis and in patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

No specific antiviral therapy of proven efficacy is currently available for treatment of WNV encephalitis. Patients have been treated with a-interferon, ribavirin, an Israeli IVIg preparation that contains high-titer anti-WNV antibody (Omr-IgG-am) (www.clinicaltrials.gov, identifier NCT00069316 and 0068055), and humanized monoclonal antibodies directed against the viral envelope glycoprotein (www.clinicaltrials.gov, identifier NCT00927953 and 00515385). WNV chimeric vaccines, in which WNV envelope and premembrane proteins are inserted into the background of another flavivirus, are already undergoing human clinical testing and have been found to be both safe and immunogenic in healthy adults but have not yet been tested for disease prevention in humans (www.clinicaltrials.gov, identifier NCT00746798, 00442169, 00094718, and 00537147). Both chimeric and killed inactivated WNV vaccines have been found to be safe and effective in preventing equine WNV infection, and several effective flavivirus vaccines are already in human use, creating optimism that a safe and effective human WNV vaccine can also be developed.

SEQUELAE

There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of EEE virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, approximately 5–15% of children infected with La Crosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir is available from the NIAID-Collaborative Antiviral Study Group (CASG) trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment (Glasgow coma score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years; 64% survival, 57% no or mild sequelae).

www.ketabpezeshki.com (021) 66485457 - 66485438

Some recent studies using quantitative HSV CSF PCR tests indicate that clinical outcome following treatment also correlates with the amount of HSV DNA present in CSF at the time of presentation. Many patients with WNV infection have sequelae, including cognitive impairment; weakness; and hyper- or hypokinetic movement disorders, including tremor, myoclonus, and parkinsonism. In a large longitudinal study of prognosis in 156 patients with WNV infection, the mean time to achieve recovery (defined as 95% of maximal predicted score on specific validated tests) was 112–148 days for fatigue, 121–175 days for physical function, 131–139 days for mood, and 302–455 days for mental function (the longer interval in each case representing patients with neuroinvasive disease).

SUBACUTE MENINGITIS

CLINICAL MANIFESTATIONS

Patients with subacute meningitis typically have an unrelenting headache, stiff neck, low-grade fever, and lethargy for days to several weeks before they present for evaluation. Cranial nerve abnormalities and night sweats may be present. **T is syndrome overlaps that of chronic meningitis, discussed in detail in Chap. 47**.

ETIOLOGY

Common causative organisms include M. tuberculosis, C. neoformans, H. capsulatum, C. immitis, and *T.* pallidum. Initial infection with M. tuberculosis is acquired by inhalation of aerosolized droplet nuclei. Tuberculous meningitis in adults does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, millet seed–sized (miliary) tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection. T ese tubercles enlarge and are usually caseating. T e propensity for a caseous lesion to produce meningitis is determined by its proximity to the subarachnoid space (SAS) and the rate at which fibrous encapsulation develops. Subependymal caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the SAS. Mycobacterial antigens produce an intense inflammatory reaction that leads to the production of a thick exudate that fills the basilar cisterns and surrounds the cranial nerves and major blood vessels at the base of the brain.

Fungal infections are typically acquired by the inhalation of airborne fungal spores. T e initial pulmonary infection may be asymptomatic or present with fever, cough, sputum production, and chest pain. T e pulmonary infection is of en self-limited. A localized pulmonary fungal infection can then remain dormant in the lungs until there is an abnormality in cell-mediated immunity that allows the fungus to reactivate and disseminate to the CNS. T e most common pathogen causing fungal meningitis is C. neoformans. T is fungus is found worldwide in soil and bird excreta. H. capsulatum is endemic to the Ohio and Mississippi River valleys of the central United States and to parts of Central and South America. C. immitis is endemic to the desert areas of the southwest United States, northern Mexico, and Argentina.

Syphilis is a sexually transmitted disease that is manifest by the appearance of a painless chancre at the site of inoculation. *T.* pallidum invades the CNS early in the course of syphilis. Cranial nerves VII and VIII are most frequently involved.

LABORATORY DIAGNOSIS

T e classic CSF abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis (10–500 cells/μL), (3) elevated protein concentration in the range of 1–5 g/L, and (4) decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL). T e combination of unrelenting headache, stif neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis. T e last tube of fluid collected at LP is the best tube to send for a smear for acid-fast bacilli (AFB). If there is a pellicle in the CSF or a cobweb-like clot on the surface of the fluid, AFB can best be demonstrated in a smear of the clot or pellicle. Positive smears are typically reported in only 10–40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4–8 weeks to identify the organism and are positive in ~50% of adults. Culture remains the gold standard to make the diagnosis of tuberculous meningitis. PCR for the detection of M. tuberculosis DNA should be sent on CSF if available, but the sensitivity and specificity on CSF have not been defined. T e CDC recommends the use of nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis.

T e characteristic CSF abnormalities in fungal meningitis are a mononuclear or lymphocytic pleocytosis, an increased protein concentration, and a decreased glucose concentration. T ere may be eosinophils in the CSF in C. immitis meningitis. Large volumes of CSF are of en required to demonstrate the organism on India ink smear or grow the organism in culture. If spinal fluid examined by LP on two separate occasions fails to yield an organism, CSF should be obtained by high-cervical or cisternal puncture.

T e cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal

www.ketabpezeshki.com (021) 66485457 - 66485438

meningitis. A reactive CSF cryptococcal antigen test establishes the diagnosis. T e detection of the Histoplasma polysaccharide antigen in CSF establishes the diagnosis of a fungal meningitis but is not specific for meningitis due to H. capsulatum. It may be falsely positive in coccidioidal meningitis. T e CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% for coccidioidal meningitis.

T e diagnosis of syphilitic meningitis is made when a reactive serum treponemal test (fluorescent treponemal antibody absorption test [FTA-ABS] or microhemagglutination assay–*T.* pallidum [MHA-TP]) is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration, or when the CSF Venereal Disease Research Laboratory (VDRL) test is positive. A reactive CSF FTA-ABS is not definitive evidence of neurosyphilis. T e CSF FTA-ABS can be falsely positive from blood contamination. A negative CSF VDRL does not rule out neurosyphilis. A negative CSF FTA-ABS or MHA-TP rules out neurosyphilis.

TREATMENT Subacute Meningitis

Empirical therapy of tuberculous meningitis is of en initiated on the basis of a high index of suspicion without adequate laboratory support. Initial therapy is a combination of isoniazid (300 mg/d), rifampin (10 mg/kg per day), pyrazinamide (30 mg/kg per day in divided doses), ethambutol (15–25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). When the antimicrobial sensitivity of the M. tuberculosis isolate is known, ethambutol can be discontinued. If the clinical response is good, pyrazinamide can be discontinued af er 8 weeks and isoniazid and rifampin continued alone for the next 6–12 months. A 6-month course of therapy is acceptable, but therapy should be prolonged for 9–12 months in patients who have an inadequate resolution of symptoms of meningitis or who have positive mycobacterial cultures of CSF during the course of therapy. Dexamethasone therapy is recommended for HIV-negative patients with tuberculous meningitis. T e dose is 12–16 mg/d for 3 weeks, and then tapered over 3 weeks.

Meningitis due to C. neo*f*ormans in non-HIV, nontransplant patients is treated with induction therapy with amphotericin B (AmB) (0.7 mg/kg IV per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 4 weeks if CSF culture results are negative af er 2 weeks of treatment. T erapy should be extended for a total of 6 weeks in the patient with neurologic complications. Induction therapy is followed by consolidation therapy with fluconazole 400 mg/d for 8 weeks. Organ transplant recipients are treated with liposomal AmB (3–4 mg/kg per day) or AmB lipid complex (ABLC) 5 mg/kg per day plus flucytosine (100 mg/kg per day in four divided doses) for at least 2 weeks or until CSF culture is sterile. Follow CSF yeast cultures for sterilization rather than the cryptococcal antigen titer. T is treatment is followed by an 8- to 10-week course of fluconazole (400–800 mg/d [6–12 mg/kg] PO). If the CSF culture is sterile af er 10 weeks of acute therapy, the dose of fluconazole is decreased to 200 mg/d for 6 months to a year. Patients with HIV infection are treated with AmB or a lipid formulation plus flucytosine for at least 2 weeks, followed by fluconazole for a minimum of 8 weeks. HIV-infected patients may require indefinite maintenance therapy with fluconazole 200 mg/d. Meningitis due to H. capsulatum is treated with AmB (0.7–1.0 mg/kg per day) for 4–12 weeks. A total dose of 30 mg/kg is recommended. T erapy with AmB is not discontinued until fungal cultures are sterile. Af er completing a course of AmB, maintenance therapy with itraconazole 200 mg two or three times daily is initiated and continued for at least 9 months to a year. C. immitis meningitis is treated with either high-dose fluconazole (1000 mg daily) as monotherapy or intravenous AmB (0.5–0.7 mg/kg per day) for >4 weeks. Intrathecal AmB (0.25–0.75 mg/d three times weekly) may be required to eradicate the infection. Lifelong therapy with fluconazole (200–400 mg daily) is recommended to prevent relapse. AmBisome (5 mg/kg per day) or AmB lipid complex (5 mg/kg per day) can be substituted for AmB in patients who have or who develop significant renal dysfunction. T e most common complication of fungal meningitis is hydrocephalus. Patients who develop hydrocephalus should receive a CSF diversion device. A ventriculostomy can be used until CSF fungal cultures are sterile, at which time the ventriculostomy is replaced by a ventriculoperitoneal shunt.

Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3–4 million units intravenously every 4 h for 10–14 days. An alternative regimen is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either regimen is followed with 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks. T e standard criterion for treatment success is reexamination of the CSF. T e CSF should be reexamined at 6-month intervals for 2 years. T e cell count is expected to normalize within 12 months, and the VDRL titer to decrease by two dilutions or revert to nonreactive within 2 years of completion of therapy. Failure of the CSF pleocytosis to resolve or an increase in the CSF VDRL titer by two or more dilutions requires retreatment.

CHRONIC ENCEPHALITIS

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical features and pathology

Progressive multifocal leukoencephalopathy (PML) is characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves.

www.ketabpezeshki.com (021) 66485457 - 66485438

In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia. Seizures occur in ~20% of patients, predominantly in those with lesions abutting the cortex.

Almost all patients have an underlying immunosuppressive disorder or are receiving immunomodulatory therapy. In recent series, the most common associated conditions were AIDS (80%), hematologic malignancies (13%), transplant recipients (5%), and chronic inflammatory diseases (2%). It has been estimated that up to 5% of AIDS patients will develop PML. There have been over 400 reported cases of PML occurring in patients being treated for multiple sclerosis and inflammatory bowel disease with natalizumab, a humanized monoclonal antibody that inhibits lymphocyte trafficking into CNS and bowel mucosa by binding to α_4 integrins. Overall risk in these patients has been estimated at ~3.4 PML cases per 1000 treated patients, but the risk depends on a variety of factors including anti-JCV antibody serostatus, prior immunosuppressive therapy use, and duration of natalizumab therapy. Patients who lack detectable JCV antibody have a risk of developing PML of <0.1 case/1000 patients, whereas those who are JCV seropositive and have been exposed to prior immunosuppressive therapy and have received >24 months of natalizumab therapy have a risk of >1 case/100 treated patients. PML cases have also been reported in patients receiving other humanized monoclonal antibodies with immunomodulatory activity including efalizumab and rituximab, although the relative risks have not been clearly established. The basic clinical and diagnostic features appear to be similar in HIV-associated PML and PML associated with immunomodulatory drugs with the exception of an increased likelihood of peripheral enhancement in MRIs of PML lesions in immunomodulatory cases. In natalizumab-associated PML, patients will also almost invariably develop clinical and radiographic worsening of lesions with discontinuation of therapy, attributed to development of immune reconstitution inflammatory syndrome (IRIS).

Diagnostic studies

The diagnosis of PML is frequently suggested by MRI. MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased signal on T2 and FLAIR images and decreased signal on T1-weighted images. HIV-PML lesions are classically nonenhancing (90%), but patients with immunomodulatory drug associated PML may have peripheral ring enhancement. PML lesions are not typically associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JCV DNA from CSF has become an important diagnostic tool. The presence of a positive CSF PCR for JCV DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML, reflecting the assay's relatively high specificity (92–100%); however, sensitivity is variable, and a negative CSF PCR does not exclude the diagnosis. In HIV-negative patients and HIV-positive patients not receiving highly active antiviral therapy (HAART), sensitivity is likely 70–90%. In HAART-treated patients, sensitivity may be closer to 60%, reflecting the lower JCV CSF viral load in this relatively more immunocompetent group. Studies with quantitative JCV CSF PCR indicate that patients with low JCV loads (<100 copies/μL) have a generally better prognosis than those with higher viral loads. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis. In biopsy or necropsy specimens of brain, JCV antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification.

Serologic studies are of no utility in diagnosis due to high basal seroprevalence level, but may contribute to risk stratification in patients contemplating therapy with immunomodulatory drugs such as natalizumab.

TREATMENT Progressive Multifocal Leukoencephalopathy

No effective therapy for PML is available. There are case reports of potential beneficial effects of the 5-HT_{2a} receptor antagonist mirtazapine, which may inhibit binding of JCV to its receptor on oligodendrocytes. Retrospective noncontrolled studies have also suggested a possible beneficial effect of treatment with interferon-α. Neither of these agents has been tested in randomized controlled clinical trials. A prospective multicenter clinical trial to evaluate the efficacy of the antimalarial drug mefloquine failed to show benefit. Intravenous and/or intrathecal cytarabine were not shown to be of benefit in a randomized controlled trial in HIV-associated PML, although some experts suggest that cytarabine may have therapeutic efficacy in situations where

www.ketabpezeshki.com (021) 66485457 - 66485438

breakdown of the blood-brain barrier allows sufficient CSF penetration. A randomized controlled trial of cidofovir in HIV-associated PML also failed to show significant benefit. Because PML almost invariably occurs in immunocompromised individuals, any therapeutic interventions designed to enhance or restore immunocompetence should be considered. Perhaps the most dramatic demonstration of this is disease stabilization and, in rare cases, improvement associated with the improvement in the immune status of HIV-positive patients with AIDS following institution of HAART. In HIV-positive PML patients treated with HAART, 1-year survival is ~50%, although up to 80% of survivors may have significant neurologic sequelae. HIV-positive PML patients with higher CD4 counts (>300/μL) and low or nondetectable HIV viral loads have a better prognosis than those with lower CD4 counts and higher viral loads. Although institution of HAART enhances survival in HIV-positive PML patients, the associated immune reconstitution in patients with an underlying opportunistic infection such as PML may also result in a severe CNS inflammatory syndrome (IRIS) associated with clinical worsening, CSF pleocytosis, and the appearance of new enhancing MRI lesions. Patients receiving natalizumab or other immunomodulatory antibodies, who are suspected of having PML, should have therapy immediately halted and circulating antibodies removed by plasma exchange. Patients should be closely monitored for development of IRIS, which is generally treated with intravenous glucocorticoids, although controlled clinical trials of efficacy remain lacking.

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

SSPE is a rare chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus. The frequency has been estimated at 1 in 100,000–500,000 measles cases. An average of five cases per year are reported in the United States. The incidence has declined dramatically since the introduction of a measles vaccine. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of a progressive neurologic disorder. Some 85% of patients are between 5 and 15 years old at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic studies

MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brainstem as disease progresses. The EEG may initially show only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein concentration and a markedly elevated gamma globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification.

TREATMENT Subacute Sclerosing Panencephalitis

No definitive therapy for SSPE is available. Treatment with isoprinosine (Inosiplex, 100 mg/kg per day), alone or in combination with intrathecal or intraventricular interferon-α, has been reported to prolong survival and produce clinical improvement in some patients but has never been subjected to a controlled clinical trial.

PROGRESSIVE RUBELLA PANENCEPHALITIS

This is an extremely rare disorder that primarily affects males with congenital rubella syndrome, although isolated cases have been reported following childhood rubella. After a latent period of 8–19 years, patients develop progressive neurologic deterioration. The manifestations are similar to those seen in SSPE. CSF shows a mild lymphocytic pleocytosis, slightly elevated protein concentration, markedly increased gamma globulin, and rubella virus–specific oligoclonal bands. No therapy is available. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease.

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term cerebritis is often employed to describe a nonencapsulated brain abscess.

www.ketabpezeshki.com (021) 66485457 - 66485438

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~0.3–1.3:100,000 persons per year. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, penetrating head trauma or neurosurgical procedures, and dental infections. In immunocompetent individuals the most important pathogens are Streptococcus spp. (anaerobic, aerobic, and viridans [40%]), Enterobacteriaceae (Proteus spp., E. coli sp., Klebsiella spp. [25%]), anaerobes (e.g., Bacteroides spp., Fusobacterium spp. [30%]), and staphylococci (10%). In immunocompromised hosts with underlying HIV infection, organ transplantation, cancer, or immunosuppressive therapy, most brain abscesses are caused by Nocardia spp., *T*oxoplasma gondii, Aspergillus spp., Candida spp., and C. neo*f*ormans. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *T*aenia solium (neurocysticercosis). In India and East Asia, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2) following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In up to 25% of cases, no obvious primary source of infection is apparent (cryptogenic brain abscess).

Approximately one-third of brain abscesses are associated with otitis media and mastoiditis, of en with an associated cholesteatoma. Otogenic abscesses occur predominantly in the temporal lobe (55–75%) and cerebellum (20–30%). In some series, up to 90% of cerebellar abscesses are otogenic. Common organisms include streptococci, Bacteroides spp., Pseudomonas spp., Haemophilus spp., and Enterobacteriaceae. Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. Approximately 10% of brain abscesses are associated with paranasal sinusitis, and this association is particularly strong in young males in their second and third decades of life. T e most common pathogens in brain abscesses associated with paranasal sinusitis are streptococci (especially Streptococcus milleri), Haemophilus spp., Bacteroides spp., Pseudomonas spp., and S. aureus. Dental infections are associated with ~2% of brain abscesses, although it is of en suggested that many "cryptogenic" abscesses are in fact due to dental infections. T e most common pathogens in this setting are streptococci, staphylococci, Bacteroides spp., and Fusobacterium spp.

Hematogenous abscesses account for ~25% of brain abscesses. Hematogenous abscesses are of en multiple, and multiple abscesses of en (50%) have a hematogenous origin. T ese abscesses show a predilection for the territory of the middle cerebral artery (i.e., posterior frontal or parietal lobes). Hematogenous abscesses are of en located at the junction of the gray and white matter and are of en poorly encapsulated. T e microbiology of hematogenous abscesses is dependent on the primary source of infection. For example, brain abscesses that develop as a complication of infective endocarditis are of en due to viridans streptococci or S. aureus. Abscesses associated with pyogenic lung infections such as lung abscess or bronchiectasis are of en due to streptococci, staphylococci, Bacteroides spp., Fusobacterium spp., or Enterobacteriaceae. Abscesses that follow penetrating head trauma or neurosurgical procedures are frequently due to methicillin-resistant S. aureus (MRSA), S. epidermidis, Enterobacteriaceae, Pseudomonas spp., and Clostridium spp. Enterobacteriaceae and P. aeruginosa are important causes of abscesses associated with urinary sepsis. Congenital cardiac malformations that produce a right-to-lef shunt, such as tetralogy of Fallot, patent ductus arteriosus, and atrial and ventricular septal defects, allow bloodborne bacteria to bypass the pulmonary capillary bed and reach the brain. Similar phenomena can occur with pulmonary arteriovenous malformations. T e decreased arterial oxygenation and saturation from the right-to-lef shunt and polycythemia may cause focal areas of cerebral ischemia, thus providing a nidus for microorganisms that bypassed the pulmonary circulation to multiply and form an abscess. Streptococci are the most common pathogens in this setting.

PATHOGENESIS AND HISTOPATHOLOGY

Results of experimental models of brain abscess formation suggest that for bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant areas of ischemia, necrosis, or hypoxemia in brain tissue. T e intact brain parenchyma is relatively resistant to infection. Once bacteria have established infection, brain abscess frequently evolves through a series of stages, influenced by the nature of the infecting organism and by the immunocompetence of the host. T e early cerebritis stage (days 1–3) is characterized by a perivascular infiltration of inflammatory cells, which surround a central core of coagulative necrosis. Marked edema surrounds the lesion at this stage. In the late cerebritis stage (days 4–9), pus formation leads to enlargement of the necrotic center, which is surrounded

www.ketabpezeshki.com (021) 66485457 - 66485438

at its border by an inflammatory infiltrate of macrophages and fibroblasts. A thin capsule of fibroblasts and reticular fibers gradually develops, and the surrounding area of cerebral edema becomes more distinct than in the previous stage. T e third stage, early capsule formation (days 10–13), is characterized by the formation of a capsule that is better developed on the cortical than on the ventricular side of the lesion. T is stage correlates with the appearance of a ring-enhancing capsule on neuroimaging studies. T e final stage, late capsule formation (day 14 and beyond), is defined by a well-formed necrotic center surrounded by a dense collagenous capsule. T e surrounding area of cerebral edema has regressed, but marked gliosis with large numbers of reactive astrocytes has developed outside the capsule. T is gliotic process may contribute to the development of seizures as a sequela of brain abscess.

CLINICAL PRESENTATION

A brain abscess typically presents as an expanding intracranial mass lesion rather than as an infectious process. Although the evolution of signs and symptoms is extremely variable, ranging from hours to weeks or even months, most patients present to the hospital 11–12 days following onset of symptoms. T e classic clinical triad of headache, fever, and a focal neurologic deficit is present in <50% of cases. T e most common symptom in patients with a brain abscess is headache, occurring in >75% of patients. T e headache is of en characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis. T e new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients. Focal neurologic deficits including hemiparesis, aphasia, or visual field defects are part of the initial presentation in >60% of patients.

T e clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of the ICP. Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. Signs of raised ICP—papilledema, nausea and vomiting, and drowsiness or confusion—can be the dominant presentation of some abscesses, particularly those in the cerebellum. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space.

DIAGNOSIS

Diagnosis is made by neuroimaging studies. MRI **(Fig. 46-4)** is better than CT for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa. Cerebritis appears on MRI as an area of low-signal intensity on T1-weighted images with irregular postgadolinium enhancement and as an area of increased signal intensity on T2-weighted images. Cerebritis is of en not visualized by CT scan, but when present, appears as an area of hypodensity. On a contrast-enhanced CT

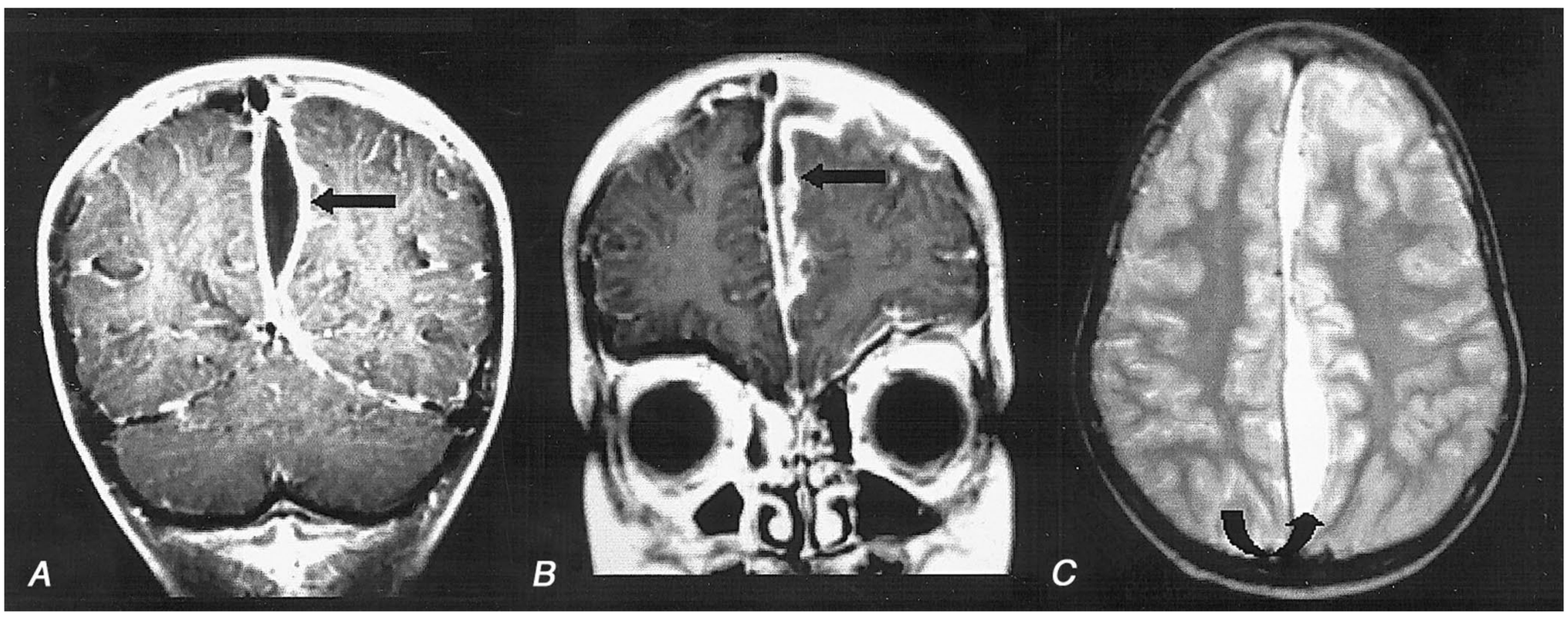


FIGURE 46-4

Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted magnetic resonance imaging (MRI) (A, black arrow), hypointense signal on the axial proton density images (B, black arrow), and enhances prominently after gadolinium administration on the coronal T1-weighted image (C). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (C, white arrow). (Courtesy of Joseph Lurito, MD; with permission.)

www.ketabpezeshki.com (021) 66485457 - 66485438

scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement with surrounding edema (hypodensity). On contrast-enhanced T1-weighted MRI, a mature brain abscess has a capsule that enhances surrounding a hypodense center and surrounded by a hypodense area of edema. On T2-weighted MRI, there is a hyperintense central area of pus surrounded by a well-defined hypointense capsule and a hyperintense surrounding area of edema. It is important to recognize that the CT and MRI appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal CNS lesions such as primary or metastatic tumors may be facilitated by the use of diffusion-weighted imaging sequences on which a brain abscess typically shows increased signal due to restricted diffusion of the abscess cavity with corresponding low signal on apparent diffusion coefficient images.

Microbiologic diagnosis of the etiologic agent is most accurately determined by Gram's stain and culture of abscess material obtained by CT-guided stereotactic needle aspiration. Aerobic and anaerobic bacterial cultures and mycobacterial and fungal cultures should be obtained. Up to 10% of patients will also have positive blood cultures. LP should not be performed in patients with known or suspected focal intracranial infections such as abscess or empyema; CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

Additional laboratory studies may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion. About 50% of patients have a peripheral leukocytosis, 60% an elevated ESR, and 80% an elevated C-reactive protein. Blood cultures are positive in ~10% of cases overall but may be positive in >85% of patients with abscesses due to Listeria.

DIFFERENTIAL DIAGNOSIS

Conditions that can cause headache, fever, focal neurologic signs, and seizure activity include brain abscess, subdural empyema, bacterial meningitis, viral meningoencephalitis, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. When fever is absent, primary and metastatic brain tumors become the major differential diagnosis. Less commonly, cerebral infarction or hematoma can have an MRI or CT appearance resembling brain abscess.

TREATMENT Brain Abscess

Optimal therapy of brain abscesses involves a combination of high-dose parenteral antibiotics and neurosurgical drainage. Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole (see Table 46-1 for antibiotic dosages). In patients with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of Pseudomonas spp. and vancomycin for coverage of staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.

Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and therapy. Empirical antibiotic coverage should be modified based on the results of Gram's stain and culture of the abscess contents. Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful.

Medical therapy alone is not optimal for treatment of brain abscess and should be reserved for patients whose abscesses are neurosurgically inaccessible, for patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and for patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy. The role, if any, of supplemental oral antibiotic therapy following completion of a standard course of parenteral therapy has never been adequately studied.

In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures. Anticonvulsant therapy is continued for at least 3 months after resolution of the abscess, and decisions regarding withdrawal are then based on the EEG. If the EEG is abnormal, anticonvulsant therapy should be continued. If the EEG is normal, anticonvulsant therapy can be slowly withdrawn, with close follow-up and repeat EEG after the medication has been discontinued.

Glucocorticoids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP. Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess. More frequent studies (e.g., weekly) are probably warranted in the subset of patients who are receiving antibiotic therapy alone. A small amount of enhancement may remain for months after the abscess has been successfully treated.

PROGNOSIS

The mortality rate of brain abscess has declined in parallel with the development of enhanced neuroimaging techniques, improved neurosurgical procedures

www.ketabpezeshki.com (021) 66485457 - 66485438

for stereotactic aspiration, and improved antibiotics. In modern series, the mortality rate is typically <15%. Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% of survivors.

NONBACTERIAL CAUSES OF INFECTIOUS FOCAL CNS LESIONS

ETIOLOGY

Neurocysticercosis is the most common parasitic disease of the CNS worldwide. Humans acquire cysticercosis by the ingestion of food contaminated with the eggs of the parasite *T.* solium. Toxoplasmosis is a parasitic disease caused by *T.* gondii and acquired from the ingestion of undercooked meat and from handling cat feces.

CLINICAL PRESENTATION

T e most common manifestation of neurocysticercosis is new-onset partial seizures with or without secondary generalization. Cysticerci may develop in the brain parenchyma and cause seizures or focal neurologic deficits. When present in the subarachnoid or ventricular spaces, cysticerci can produce increased ICP by interference with CSF flow. Spinal cysticerci can mimic the presentation of intraspinal tumors. When the cysticerci first lodge in the brain, they frequently cause little in the way of an inflammatory response. As the cysticercal cyst degenerates, it elicits an inflammatory response that may present clinically as a seizure. Eventually the cyst dies, a process that may take several years and is typically associated with resolution of the inflammatory response and, of en, abatement of seizures.

Primary *T*oxoplasma infection is of en asymptomatic. However, during this phase parasites may spread to the CNS, where they become latent. Reactivation of CNS infection is almost exclusively associated with immunocompromised hosts, particularly those with HIV infection. During this phase patients present with headache, fever, seizures, and focal neurologic deficits.

DIAGNOSIS

T e lesions of neurocysticercosis are readily visualized by MRI or CT scans. Lesions with viable parasites appear as cystic lesions. T e scolex can of en be visualized on MRI. Lesions may appear as contrast-enhancing lesions surrounded by edema. A very early sign of cyst death is hypointensity of the vesicular fluid on T2-weighted images when compared with CSF. Parenchymal brain calcifications are the most common finding and evidence that the parasite is no longer viable. MRI findings of toxoplasmosis consist of multiple lesions in the deep white matter, the thalamus, and basal ganglia and at the gray-white junction in the cerebral hemispheres. With contrast administration, the majority of the lesions enhance in a ringed, nodular, or homogeneous pattern and are surrounded by edema. In the presence of the characteristic neuroimaging abnormalities of *T.* gondii infection, serum IgG antibody to *T.* gondii should be obtained and, when positive, the patient should be treated.

TREATMENT Infectious Focal CNS Lesions

Anticonvulsant therapy is initiated when the patient with neurocysticercosis presents with a seizure. T ere is controversy about whether or not anthelmintic therapy should be given to all patients, and recommendations are based on the stage of the lesion. Cysticerci appearing as cystic lesions in the brain parenchyma with or without pericystic edema or in the subarachnoid space at the convexity of the cerebral hemispheres should be treated with anticysticidal therapy. Cysticidal drugs accelerate the destruction of the parasites, resulting in a faster resolution of the infection. Albendazole and praziquantel are used in the treatment of neurocysticercosis. Approximately 85% of parenchymal cysts are destroyed by a single course of albendazole, and ~75% are destroyed by a single course of praziquantel. T e dose of albendazole is 15 mg/kg per day in two doses for 8 days. T e dose of praziquantel is 50 mg/kg per day for 15 days, although a number of other dosage regimens are also frequently cited. Prednisone or dexamethasone is given with anticysticidal therapy to reduce the host inflammatory response to degenerating parasites. Many, but not all, experts recommend anticysticidal therapy for lesions that are surrounded by a contrast-enhancing ring. T ere is universal agreement that calcified lesions do not need to be treated with anticysticidal therapy. Antiepileptic therapy can be stopped once the follow-up CT scan shows resolution of the lesion. Long-term antiepileptic therapy is recommended when seizures occur af er resolution of edema and resorption or calcification of the degenerating cyst.

CNS toxoplasmosis is treated with a combination of sulfadiazine, 1.5–2.0 g orally qid, plus pyrimethamine, 100 mg orally to load, then 75–100 mg orally qd, plus folinic acid, 10–15 mg orally qd. Folinic acid is added to the regimen to prevent megaloblastic anemia. T erapy is continued until there is no evidence of active disease on neuroimaging studies, which typically takes at least 6 weeks, and then the dose of sulfadiazine is reduced to 2–4 g/d and pyrimethamine to 50 mg/d. Clindamycin plus pyrimethamine is an alternative therapy for patients who cannot tolerate sulfadiazine, but the combination of pyrimethamine and sulfadiazine is more effective.

www.ketabpezeshki.com (021) 66485457 - 66485438

SUBDURAL EMPYEMA

A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes **(Fig. 46-5)**.

EPIDEMIOLOGY

SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. Sinusitis is the most common predisposing condition and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis-associated empyema has a striking predilection for young males, possibly reflecting sex-related differences in sinus anatomy and development. It has been suggested that SDE may complicate 1–2% of cases of frontal sinusitis severe enough to require hospitalization. As a consequence of this epidemiology, SDE shows an ~3:1 male/female predominance, with 70% of cases occurring in the second and third decades of life. SDE may also develop as a complication of head trauma or neurosurgery. Secondary infection of a subdural effusion may also result in empyema, although secondary infection of hematomas, in the absence of a prior neurosurgical procedure, is rare.

ETIOLOGY

Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. Staphylococci and gram-negative bacilli are of en the etiologic organisms when SDE follows neurosurgical procedures or head trauma. Up to one-third of cases are culture-negative, possibly reflecting difficulty in obtaining adequate anaerobic cultures.

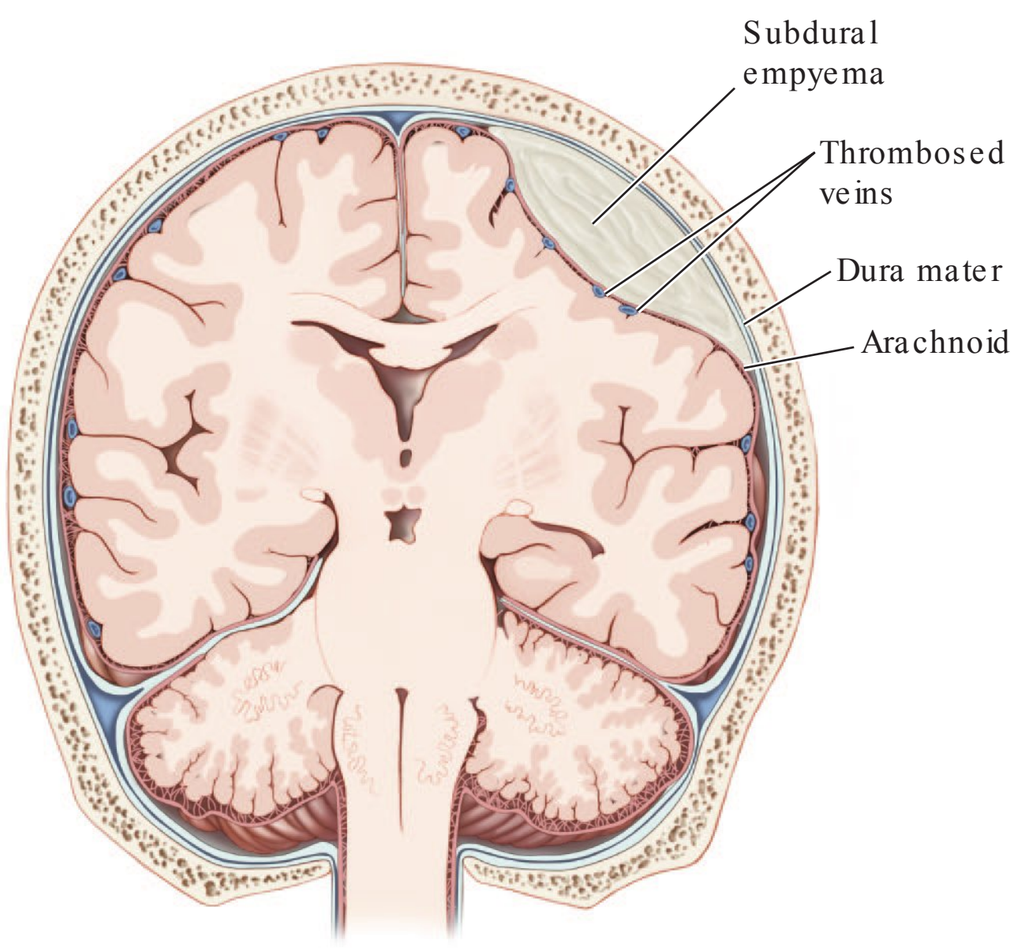


FIGURE 46-5
Subdural empyema.

PATHOPHYSIOLOGY

Sinusitis-associated SDE develops as a result of either retrograde spread of infection from septic thrombophlebitis of the mucosal veins draining the sinuses or contiguous spread of infection to the brain from osteomyelitis in the posterior wall of the frontal or other sinuses. SDE may also develop from direct introduction of bacteria into the subdural space as a complication of a neurosurgical procedure. T e evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection. In patients with sinusitis-associated SDE, suppuration typically begins in the upper and anterior portions of one cerebral hemisphere and then extends posteriorly. SDE is of en associated with other intracranial infections, including epidural empyema (40%), cortical thrombophlebitis (35%), and intracranial abscess or cerebritis (>25%). Cortical venous infarction produces necrosis of underlying cerebral cortex and subcortical white matter, with focal neurologic deficits and seizures (see below).

CLINICAL PRESENTATION

A patient with SDE typically presents with fever and a progressively worsening headache. T e diagnosis of SDE should always be suspected in a patient with known sinusitis who presents with new CNS signs or symptoms. Patients with underlying sinusitis frequently have symptoms related to this infection. As the infection progresses, focal neurologic deficits, seizures, nuchal rigidity, and signs of increased ICP commonly occur. Headache is the most common complaint at the time of presentation; initially it is localized to the side of the subdural infection, but then it becomes more severe and generalized. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. Seizures begin as partial motor seizures that then become secondarily generalized. Seizures may be due to the direct irritative effect of the SDE on the underlying cortex or result from cortical venous infarction (see above). In untreated SDE, the increasing mass effect and increase in ICP cause progressive deterioration in consciousness, leading ultimately to coma.

www.ketabpezeshki.com (021) 66485457 - 66485438

DIAGNOSIS

MRI **(Fig. 46-6)** is superior to CT in identifying SDE and any associated intracranial infections. T e administration of gadolinium greatly improves diagnosis by enhancing the rim of the empyema and allowing the empyema to be clearly delineated from the underlying brain parenchyma. Cranial MRI is also extremely valuable in identifying sinusitis, other focal CNS infections, cortical venous infarction, cerebral edema, and cerebritis. CT may show a crescent-shaped hypodense lesion over one or both hemispheres or in the interhemispheric fissure. Frequently the degree of mass effect, exemplified by midline shif , ventricular compression, and sulcal effacement, is far out of proportion to the mass of the SDE.

CSF examination should be avoided in patients with known or suspected SDE because it adds no useful information and is associated with the risk of cerebral herniation.

DIFFERENTIAL DIAGNOSIS

T e differential diagnosis of the combination of headache, fever, focal neurologic signs, and seizure activity that progresses rapidly to an altered level of consciousness includes subdural hematoma, bacterial meningitis, viral encephalitis, brain abscess, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. T e presence of nuchal rigidity is unusual with brain abscess or epidural empyema and should suggest the possibility of SDE when associated with significant focal neurologic signs and fever. Patients with bacterial meningitis also have nuchal rigidity but do not typically have focal deficits of the severity seen with SDE.

TREATMENT Subdural Empyema

SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through craniotomy, craniectomy, or burr-hole drainage, is the definitive step in the management of this infection. Empirical antimicrobial therapy for community-acquired SDE should include a combination of a third-generation cephalosporin (e.g., cefotaxime or cef riaxone), vancomycin, and metronidazole (see Table 46-1 for dosages). Patients with hospital-acquired SDE may have infections due to Pseudomonas spp. or MRSA and should receive coverage with a carbapenem (e.g., meropenem) and vancomycin. Metronidazole is not necessary for antianaerobic therapy when meropenem is being used. Parenteral antibiotic therapy should be continued for a minimum of 3–4 weeks af er SDE drainage. Patients with associated cranial osteomyelitis may require longer therapy. Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy; the initial empirical antibiotic coverage can be modified accordingly.

PROGNOSIS

Prognosis is influenced by the level of consciousness of the patient at the time of hospital presentation, the size of the empyema, and the speed with which therapy is instituted. Long-term neurologic sequelae, which include seizures and hemiparesis, occur in up to 50% of cases.

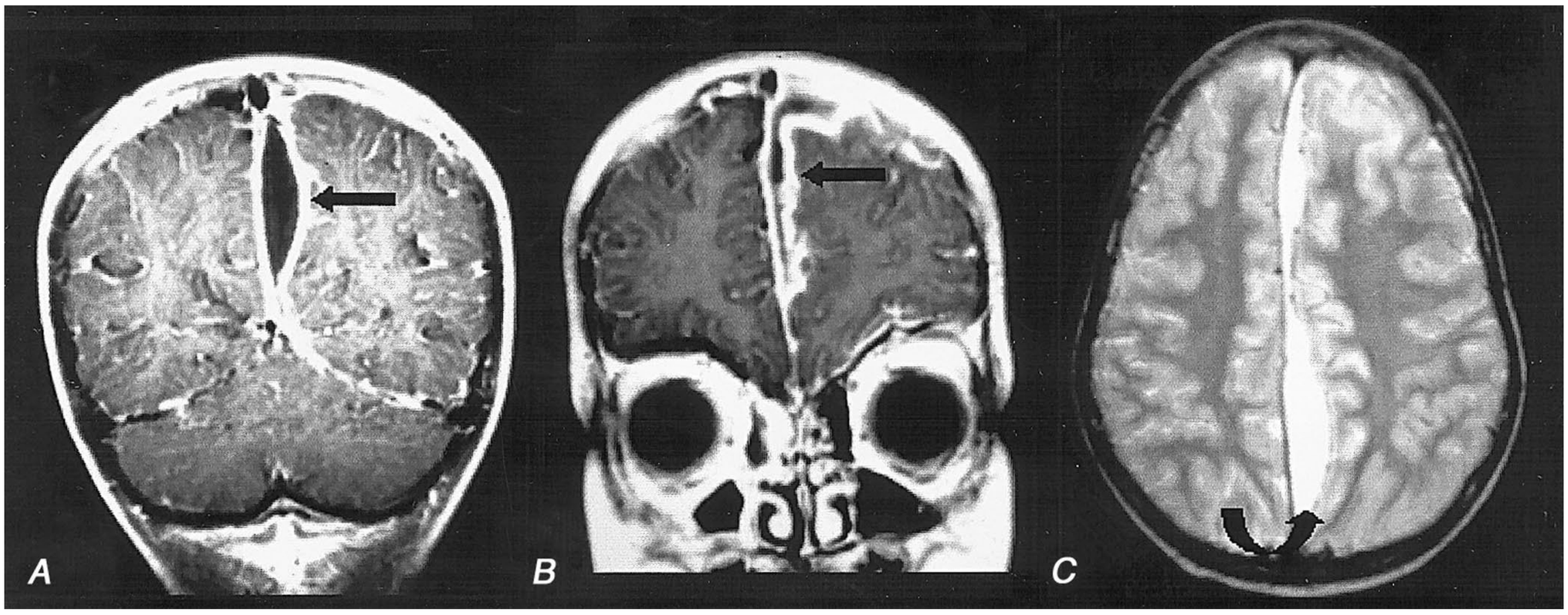


FIGURE 46-6
Subdural empyema. There is marked enhancement of the dura and leptomeninges (A, B, straight arrows) along the left medial hemisphere. The pus is hypointense on T1-weighted images (A, B) but markedly hyperintense on the proton density–weighted (C, curved arrow) image. (Courtesy of Joseph Lurito, MD; with permission.)

www.ketabpezeshki.com (021) 66485457 - 66485438

CRANIAL EPIDURAL ABSCESS

Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura **(Fig. 46-7)**.

ETIOLOGY AND PATHOPHYSIOLOGY

Cranial epidural abscess is less common than either brain abscess or SDE and accounts for <2% of focal suppurative CNS infections. A cranial epidural abscess develops as a complication of a craniotomy or compound skull fracture or as a result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. An epidural abscess may develop contiguous to an area of osteomyelitis, when craniotomy is complicated by infection of the wound or bone flap, or as a result of direct infection of the epidural space. Infection in the frontal sinus, middle ear, mastoid, or orbit can reach the epidural space through retrograde spread of infection from septic thrombophlebitis in the emissary veins that drain these areas or by way of direct spread of infection through areas of osteomyelitis. Unlike the subdural space, the epidural space is really a potential rather than an actual compartment. T e dura is normally tightly adherent to the inner skull table, and infection must dissect the dura away from the skull table as it spreads. As a result, epidural abscesses are of en smaller than SDEs. Cranial epidural abscesses, unlike brain abscesses, only rarely result from hematogenous spread of infection from extracranial primary sites. T e bacteriology of a cranial epidural abscess is similar to that of SDE (see above). T e etiologic organisms of an epidural abscess that arises from frontal sinusitis, middle-ear infections, or mastoiditis are usually streptococci or anaerobic organisms. Staphylococci or gram-negative organisms are the usual cause of an epidural abscess that develops as a complication of craniotomy or compound skull fracture.

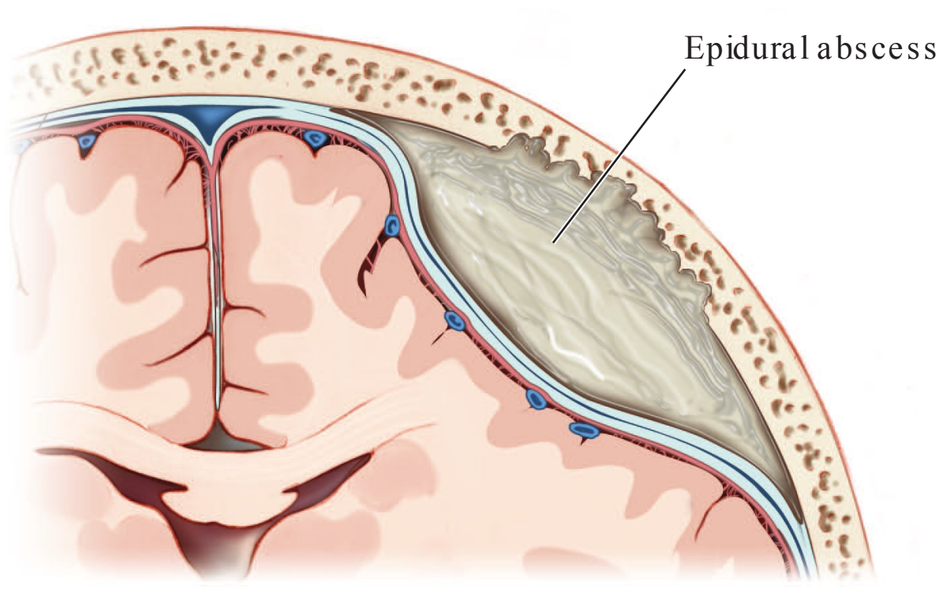


FIGURE 46-7
Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

CLINICAL PRESENTATION

Patients present with fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%). Development of symptoms may be insidious, as the empyema usually enlarges slowly in the confined anatomic space between the dura and the inner table of the skull. Periorbital edema and Pott's puffy tumor, reflecting underlying associated frontal bone osteomyelitis, are present in ~40%. In patients with a recent neurosurgical procedure, wound infection is invariably present, but other symptoms may be subtle and can include altered mental status (45%), fever (35%), and headache (20%). T e diagnosis should be considered when fever and headache follow recent head trauma or occur in the setting of frontal sinusitis, mastoiditis, or otitis media.

DIAGNOSIS

Cranial MRI with gadolinium enhancement is the procedure of choice to demonstrate a cranial epidural abscess. T e sensitivity of CT is limited by the presence of signal artifacts arising from the bone of the inner skull table. T e CT appearance of an epidural empyema is that of a lens or crescent-shaped hypodense extraaxial lesion. On MRI, an epidural empyema appears as a lentiform or crescent-shaped fluid collection that is hyperintense compared to CSF on T2-weighted images. On T1-weighted images, the fluid collection may be either isointense or hypointense compared to brain. Following the administration of gadolinium, there is linear enhancement of the dura on T1-weighted images. In distinction to subdural empyema, signs of mass effect or other parenchymal abnormalities are uncommon.

TREATMENT Epidural Abscess

Immediate neurosurgical drainage is indicated. Empirical antimicrobial therapy, pending the results of Gram's stain and culture of the purulent material obtained at surgery, should include a combination of a third-generation cephalosporin, vancomycin, and metronidazole (Table 46-1). Cef azidime or meropenem should be substituted for cef riaxone or cefotaxime in neurosurgical patients. Metronidazole is not necessary for antianaerobic coverage in patients receiving meropenem. When the organism has been identified, antimicrobial therapy can be modified accordingly. Antibiotics should be continued for 3–6 weeks af er surgical drainage. Patients with associated osteomyelitis may require additional therapy.

PROGNOSIS

T e mortality rate is <5% in modern series, and full recovery is the rule in most survivors.

www.ketabpezeshki.com (021) 66485457 - 66485438

SUPPURATIVE THROMBOPHLEBITIS

DEFINITION

Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. T is may occur as a complication of bacterial meningitis; SDE; epidural abscess; or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.

ANATOMY AND PATHOPHYSIOLOGY

T e cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. T e superior sagittal sinus is the largest of the venous sinuses **(Fig. 46-8)**. It receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Bacterial meningitis is a common predisposing condition for septic thrombosis of the superior sagittal sinus. T e diploic veins, which drain into the superior sagittal sinus, provide a route for the spread of infection from the meninges, especially in cases where there is purulent exudate near areas of the superior sagittal sinus. Infection can also spread to the superior sagittal sinus from nearby SDE or epidural abscess. Dehydration from vomiting, hypercoagulable states, and immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, also contribute to cerebral venous sinus thrombosis. T rombosis may extend from one sinus to another, and at autopsy, thrombi of different histologic ages can of en be detected in several sinuses. T rombosis of the superior sagittal sinus is of en associated with thrombosis of superior cortical veins and small parenchymal hemorrhages.

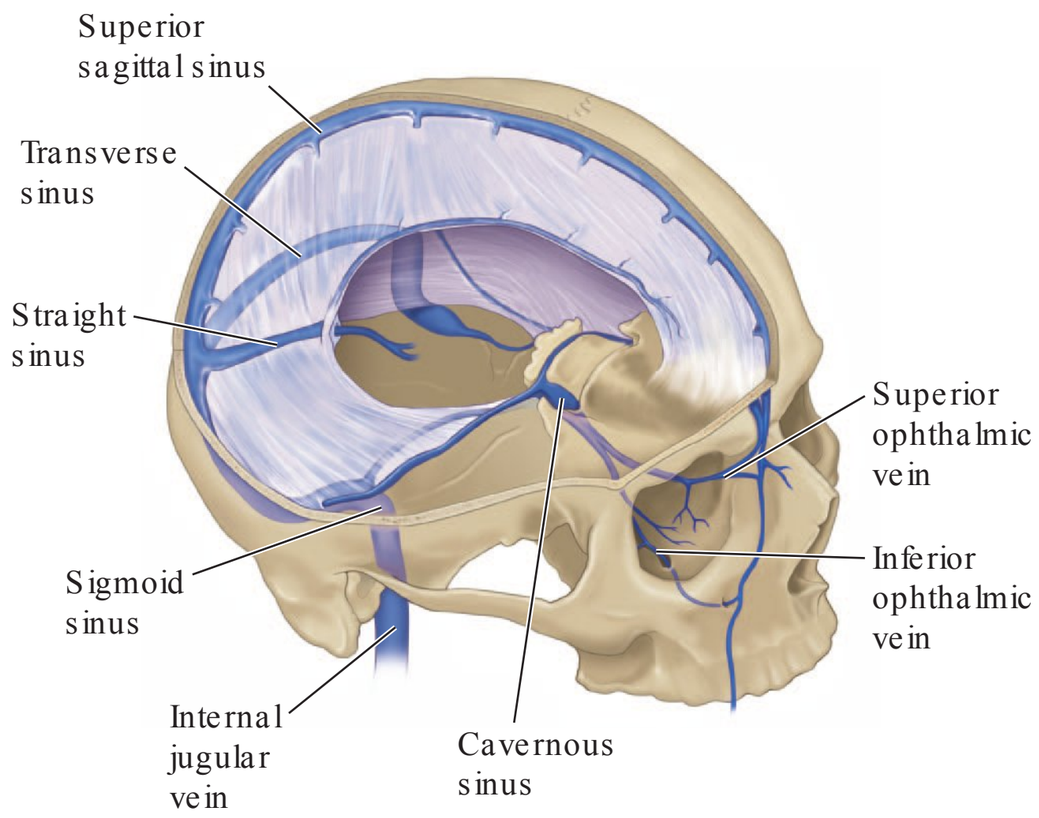


FIGURE 46-8
Anatomy o**f** the cerebral venous sinuses.

T e superior sagittal sinus drains into the transverse sinuses (Fig. 46-8). T e transverse sinuses also receive venous drainage from small veins from both the middle ear and mastoid cells. T e transverse sinus becomes the sigmoid sinus before draining into the internal jugular vein. Septic transverse/sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion. T e cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull. T e cavernous sinuses receive blood from the facial veins via the superior and inferior ophthalmic veins. Bacteria in the facial veins enter the cavernous sinus via these veins. Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins. T e sphenoid and ethmoid sinuses are the most common sites of primary infection resulting in septic cavernous sinus thrombosis.

CLINICAL MANIFESTATIONS

Septic thrombosis o*f* the superior sagittal sinus presents with headache, fever, nausea and vomiting, confusion, and focal or generalized seizures. T ere may be a rapid development of stupor and coma. Weakness of the lower extremities with bilateral Babinski's signs or hemiparesis is of en present. When superior sagittal sinus thrombosis occurs as a complication of bacterial meningitis, nuchal rigidity and Kernig's and Brudzinski's signs may be present.

T e oculomotor nerve, the trochlear nerve, the abducens nerve, the ophthalmic and maxillary branches of the trigeminal nerve, and the internal carotid artery all pass through the cavernous sinus **(see Fig. 42-4)**. T e symptoms of septic cavernous sinus thrombosis are fever, headache, frontal and retroorbital pain, and diplopia. T e classic signs are ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI; hyperesthesia of the ophthalmic and maxillary divisions of the fif h cranial nerve and a decreased corneal reflex may be detected. T ere may be evidence of dilated, tortuous retinal veins and papilledema.

Headache and earache are the most frequent symptoms of transverse sinus thrombosis. A transverse sinus thrombosis may also present with otitis media, sixth nerve palsy, and retroorbital or facial pain (Gradenigo's syndrome). Sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

DIAGNOSIS

T e diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the affected venous

www.ketabpezeshki.com (021) 66485457 - 66485438

sinus on MRI and confirmed by magnetic resonance venography, CT angiogram, or the venous phase of cerebral angiography. T e diagnosis of thrombophlebitis of intracerebral and meningeal veins is suggested by the presence of intracerebral hemorrhage but requires cerebral angiography for definitive diagnosis.

TREATMENT Suppurative Thrombophlebitis

Septic venous sinus thrombosis is treated with antibiotics, hydration, and removal of infected tissue and thrombus in septic lateral or cavernous sinus thrombosis. T e choice of antimicrobial therapy is based on the bacteria responsible for the predisposing or associated condition. Optimal duration of therapy is unknown, but antibiotics are usually continued for 6 weeks or until there is radiographic evidence of resolution of thrombosis. Anticoagulation with dose-adjusted intravenous heparin is recommended for aseptic venous sinus thrombosis and in the treatment of septic venous sinus thrombosis complicating bacterial meningitis in patients who have progressive neurologic deterioration despite antimicrobial therapy and intravenous fluids. T e presence of a small intracerebral hemorrhage from septic thrombophlebitis is not an absolute contraindication to heparin therapy. Successful management of aseptic venous sinus thrombosis has been reported with surgical thrombectomy, catheter-directed urokinase therapy, and a combination of intrathrombus recombinant tissue plasminogen activator (rtPA) and intravenous heparin, but there are not enough data to recommend these therapies in septic venous sinus thrombosis.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 47

CHRONIC AND RECURRENT MENINGITIS

Walter J. Koroshetz ■ Avindra Nath

Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. Chronic meningitis is diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/μL). T e causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) autoimmune inflammatory disorders, (4) chemical meningitis, and (5) parameningeal infections.

CLINICAL PATHOPHYSIOLOGY

Neurologic manifestations of chronic meningitis **(Table 47-1)** are determined by the anatomic location of the inflammation and its consequences. Persistent headache with or without a stiff neck, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. T ese can occur alone or in combination. When they appear in combination, widespread dissemination of the inflammatory process along CSF pathways has occurred. In some cases, the presence of an underlying systemic illness points to a specific agent or class of agents as the probable cause. T e diagnosis of chronic meningitis is usually made when the clinical presentation prompts the physician to examine the CSF for signs of inflammation. CSF is produced by the choroid plexus of the cerebral ventricles, exits through narrow foramina into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus. CSF flow provides a pathway for rapid spread of infectious and other infiltrative processes over the brain, spinal cord, and cranial and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain tissue (Virchow-Robin spaces).

TABLE 47-1

SYMPTOMS AND SIGNS OF CHRONIC MENINGITIS

SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished Vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/ incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

Intracranial meningitis

Nociceptive nerve fibers of the meninges are stimulated by the inflammatory process, resulting in headache, neck pain, or back pain. Obstruction of CSF pathways at the foramina or arachnoid villi

www.ketabpezeshki.com (021) 66485457 - 66485438

may produce hydrocephalus and symptoms of raised intracranial pressure (ICP), including headache, vomiting, apathy or drowsiness, gait instability, papilledema, visual loss, impaired upgaze, or palsy of the sixth cranial nerve (CN). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage, which may similarly produce seizures, stroke, or myelopathy. Inflammatory deposits seeded via the CSF circulation are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed basal meningitis, often present as multiple cranial neuropathies, with decreased vision (CN II), facial weakness (CN VII), decreased hearing (CN VIII), diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or decreased facial sensation and masseter weakness (CN V).

Spinal meningitis

Injury may occur to motor and sensory roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radiculopathies with combinations of radicular pain, sensory loss, motor weakness, and urinary or fecal incontinence. Meningeal inflammation can encircle the cord, resulting in a myelopathy. Patients with slowly progressive involvement of multiple cranial nerves and/or spinal nerve roots are likely to have chronic meningitis. Electrophysiologic testing (electromyography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots.

Systemic manifestations

In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A complete history of travel, sexual practice, and exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infectious causes are of major concern in the immunosuppressed patient, especially in patients with AIDS, in whom chronic meningitis may present without headache or fever. Noninfectious inflammatory disorders often produce systemic manifestations, but meningitis may be the initial manifestation. Carcinomatous meningitis may or may not be accompanied by clinical evidence of the primary neoplasm.

APPROACH TO THE PATIENT: Chronic Meningitis

The occurrence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion, the diagnosis is made when an imaging study (CT or MRI) shows contrast enhancement of the meninges, which is always concerning with the exception of dural enhancement after lumbar puncture, neurosurgical procedures, or spontaneous CSF leakage. Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause **(Tables 47-2 and 47-3)** by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens.

Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes of illness. In the latter group, all symptoms, signs, and CSF parameters of meningeal inflammation resolve completely between episodes without specific therapy. In such patients, the likely etiologies include herpes simplex virus (HSV) type 2; chemical meningitis due to episodic leakage from an epidermoid tumor, craniopharyngioma, or cholesteatoma into CSF; primary autoimmune inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus (SLE), and Mollaret's meningitis; and drug hypersensitivity with repeated administration of the offending agent.

The epidemiologic history is of considerable importance and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure to a likely case; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (Brucella); time spent in wooded areas endemic for Lyme disease; exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (Cryptococcus); gardening (Sporothrix schenckii); ingestion of poorly cooked meat or contact with a household cat (Toxoplasma gondii); residence in Thailand or Japan (Gnathostoma spinigerum), Latin America (Paracoccidioides brasiliensis), or the South Pacific (Angiostrongylus cantonensis); rural residence and raccoon exposure (Baylisascaris procyonis); and residence in Latin America, the Philippines, or Southeast Asia (Taenia solium/cysticercosis).

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 47-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed polymorphonuclear-mononuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/μL); low CSF glucose, high protein	Tuberculin skin test may be negative; AFB culture of CSF (sputum, urine, gastric contents if indicated); tuberculostearic acid detection in CSF; identify tubercle bacillus on acid-fast stain of CSF or protein pellicle; PCR	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) Borrelia burgdorferi	Mononuclear cells; elevated protein	Serum Lyme antibody titer; Western blot confirmation; (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) Treponema pallidum	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Uncommon Bacterial Causes			
Actinomyces	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
Nocardia	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
Brucella	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease Tropheryma whipplei	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for T. whipplei; brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare Bacterial Causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 47-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS (CONTINUED)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes			
Cryptococcus neoformans	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum	Exposure history—southwestern U.S.; increased virulence in dark-skinned races
Candida sp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; post surgery; prolonged IV therapy; disseminated candidiasis
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern U.S.; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus sp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
Sporothrix schenckii	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare Fungal Causes			
Xylohypha (formerly Cladosporium) trichoides and other dark-walled (dematiaceous) fungi such as Curvularia, Drechslera; Mucor, and, after water aspiration, Pseudallescheria boydii, iatrogenic Exserohilum rostratum infection following spinal blocks			
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive patients
Trypanosomiasis Trypanosoma gambiense, T. rhodesiense	Mononuclear cells, elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder
Rare Protozoal Causes			
Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals. Balamuthia mandrillaris causing chronic meningoencephalitis in immunocompetent hosts.			
Helminthic Causes			
Cysticercosis (infection with cysts of Taenia solium)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Gnathostoma spinigerum	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
Angiostrongylus cantonensis	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 47-2

INFECTIOUS CAUSES OF CHRONIC MENINGITIS (CONTINUED)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Baylisascaris procyonis (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of B. procyonis eggs from raccoon feces; fatal meningoencephalitis
Rare Helminthic Causes			
Trichinella spiralis (trichinosis); Fasciola hepatica (liver fluke), Echinococcus cysts; Schistosoma sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (Echinococcus) or granulomatous lesions of brain or spinal cord			
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis	Mononuclear cells	Antibody in serum	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis
HIV (acute retroviral syndrome)	Mononuclear cells	p24 antigen in serum and CSF; high level of HIV viremia.	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV
Herpes simplex (HSV)	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Abbreviations: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–T. pallidum; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

The presence of focal cerebral signs in a patient with chronic meningitis suggests the possibility of a brain abscess or other parameningeal infection; identification of a potential source of infection (chronic draining ear, sinusitis, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behçet's syndrome, SLE, cryptococcosis, blastomycosis, Lyme disease, sporotrichosis, trypanosomiasis, IV drug use) or enlarged lymph nodes (lymphoma, sarcoid, tuberculosis, HIV, secondary syphilis, or Whipple's disease). A careful ophthalmologic examination may reveal uveitis (Vogt-Koyanagi-Harada syndrome, sarcoid, or central nervous system [CNS] lymphoma), keratoconjunctivitis sicca (Sjögren's syndrome), or iridocyclitis (Behçet's syndrome) and is essential to assess visual loss from papilledema. Aphthous oral lesions, genital ulcers, and hypopyon suggest Behçet's syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Herpetic lesions in the genital area or on the thighs suggest HSV-2 infection. A breast nodule, a suspicious pigmented skin

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 47-3

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Malignancy	Mononuclear cells, elevated protein, low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; meningeal sarcoma; cerebral dysgerminoma; meningeal melanoma or B cell lymphoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs, low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis"	Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary inf ammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/meningeal biopsy	CN palsy, especially of CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma
Isolated granulomatous angiitis of the nervous system	Mononuclear cells, elevated protein	Angiography or meningeal biopsy	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus
Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs, elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils	Complete blood count (eosinophilia)	Exposure to nonsteroidal anti-inf ammatory agents, sulfonamides, isoniazid, tolmetin, ciprof oxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 47-3

NONINFECTIOUS CAUSES OF CHRONIC MENINGITIS (CONTINUED)

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Granulomatosis with polyangiitis (Wegener's)	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Other: multiple sclerosis, Sjögren's syndrome, monogenic autoinflammatory disorders, and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells.

lesion, focal bone pain, or an abdominal mass directs attention to possible carcinomatous meningitis.

IMAGING Once the clinical syndrome is recognized as a potential manifestation of chronic meningitis, proper analysis of the CSF is essential. However, if the possibility of raised ICP exists, a brain imaging study should be performed before lumbar puncture. If ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage. In patients with open CSF flow pathways, elevated ICP can still occur due to impaired resorption of CSF by arachnoid villi. In such patients, lumbar puncture is usually safe, but repetitive or continuous lumbar drainage may be necessary to prevent abrupt deterioration and death from raised ICP. In some patients, especially those with cryptococcal meningitis, fatal levels of raised ICP can occur without enlarged ventricles.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy, inflammation or infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis) **(Fig. 47-1)**. Imaging studies are also useful to localize areas of meningeal disease prior to meningeal biopsy.

Angiographic studies can identify evidence of cerebral arteritis in patients with chronic meningitis and stroke.

CEREBROSPINAL FLUID ANALYSIS The CSF pressure should be measured and samples sent for bacterial, fungal, and tuberculous culture; Venereal Disease Research Laboratories (VDRL) test; cell count and differential; Gram's stain; and measurement of glucose and protein. Wet mount for fungus and parasites, india ink preparation and culture, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology should be performed. Other specific CSF tests (Tables 47-2 and 47-3) or blood tests and cultures should be ordered as indicated on the basis of the history, physical examination, or preliminary CSF results (i.e., eosinophilic, mononuclear, or polymorphonuclear meningitis). Rapid diagnosis may be facilitated by serologic tests and polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen. In patients with suspected fungal infections, when other tests are negative, assays for beta-glucans may be a useful adjunct in establishing the diagnosis.

In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are Nocardia asteroides, Actinomyces israelii, Brucella, Mycobacterium tuberculosis (5–10% of early cases only), various fungi (Blastomyces dermatitidis, Candida albicans, Histoplasma capsulatum, Aspergillus spp., Pseudallescheria boydii, Cladophialophora bantiana),

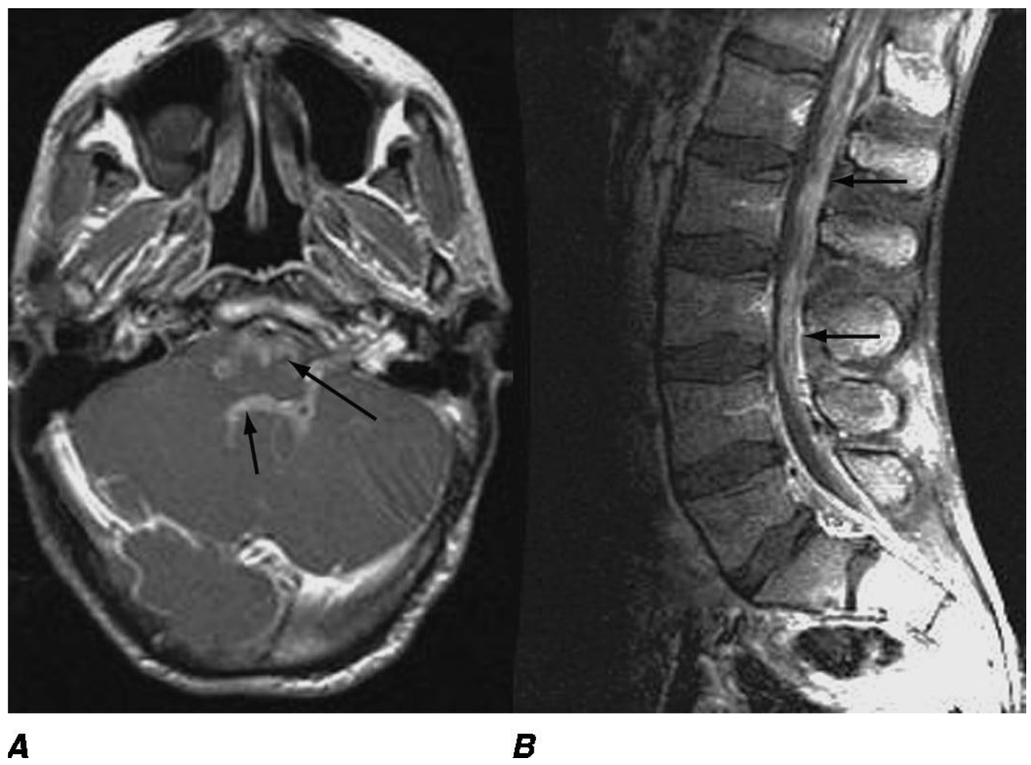


FIGURE 47-1
Primary central nervous system lymphoma. A 24-year-old man, immunosuppressed due to intestinal lymphangiectasia, developed multiple cranial neuropathies. CSF findings consisted of 100 lymphocytes/μL and a protein of 2.5 g/L (250 mg/dL); cytology and cultures were negative. Gadolinium-enhanced T1 MRI revealed diffuse, multifocal meningeal enhancement surrounding the brainstem (A), spinal cord, and cauda equina (B).

www.ketabpezeshki.com (021) 66485457 - 66485438

and noninfectious causes (SLE, exogenous chemical meningitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (A. cantonensis, G. spinigerum, B. procyonis, or Toxocara canis infection, cysticercosis, schistosomiasis, echinococcal disease, T. gondii infection), fungal infections (6–20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coccidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sarcoidosis, hypereosinophilic syndrome).

It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples of large volumes of CSF may be required to diagnose certain infectious and malignant causes of chronic meningitis. Flow cytometry for malignant cells may be useful in patients with suspected carcinomatous meningitis. Lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. T e diagnosis of fungal meningitis may require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful.

LABORATORY INVESTIGATION In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, alkaline phosphatase, sedimentation rate, antinuclear antibody, anti-Ro antibody, anti-La antibody, and serum angiotensin-converting enzyme level are often indicated. In some cases, a thorough search for a systemic site of infection is indicated. Pulmonary foci of infection may be present, particularly with fungal or tuberculous disease. Hence a CT or MRI of the chest and a sputum examination may be helpful. Abnormalities can be pursued by bronchoscopy or transthoracic needle biopsy. A tuberculin skin test is often placed, although the test has limited specificity and sensitivity for diagnosis of active disease. Liver or bone marrow biopsy may be diagnostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Positron emission tomography with fluorodeoxyglucose may be useful in identifying a systemic site for biopsy in patients with suspected carcinomatous meningitis or sarcoidosis when other tests are unrevealing. Genetic testing can identify mutations that cause rare monogenic autoinflammatory disorders.

MENINGEAL BIOPSY If CSF is not diagnostic then a meningeal biopsy should be strongly considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. T e activities of the surgeon, pathologist, microbiologist, and cytologist should be coordinated so that a large enough sample is obtained and the appropriate cultures and histologic and molecular studies, including electron-microscopic and PCR studies, are performed. T e diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT. With current microsurgical techniques, most areas of the basal meninges can be accessed for biopsy via a limited craniotomy. In a series from the Mayo Clinic reported by TM Cheng et al. (Neurosurgery 34:590, 1994), MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy. Biopsy of an enhancing region was diagnostic in 80% of cases; biopsy of nonenhancing regions was diagnostic in only 9%; sarcoid (31%) and metastatic adenocarcinoma (25%) were the most common conditions identified. Tuberculosis is the most common condition identified in many reports from outside the United States.

APPROACH TO THE ENIGMATIC CASE In approximately one-third of cases, the diagnosis is not known despite careful evaluation of CSF and potential extraneural sites of disease. A number of the organisms that cause chronic meningitis may take weeks to be identified by cultures. In enigmatic cases, several options are available, determined by the extent of the clinical deficits and rate of progression. It is prudent to wait until cultures are finalized if the patient is asymptomatic or symptoms are mild and not progressive. Unfortunately, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Ventricular-peritoneal shunts may be placed to relieve hydrocephalus, but the risk of disseminating the undiagnosed inflammatory process into the abdomen must be considered.

Empirical treatment Diagnosis of the causative agent is essential because effective therapies exist for many etiologies of chronic meningitis, but if the condition is left untreated, progressive damage to the CNS and cranial nerves and roots is likely to occur. Occasionally, empirical therapy must be initiated when all attempts at diagnosis fail. In general, empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection, or glucocorticoids for noninfectious inflammatory causes. It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with low CSF glucose and sixth and other CN palsies, since untreated disease can be devastating within weeks. Patients on prolonged anti–tumor necrosis factor therapy who develop chronic meningitis also should be treated empirically with antituberculous therapy if the etiology is uncertain. In the Mayo Clinic series, the most useful empirical therapy was administration of glucocorticoids rather than antituberculous therapy. Carcinomatous or lymphomatous meningitis may be dif cult to diagnose initially, but the diagnosis becomes evident with time.

www.ketabpezeshki.com (021) 66485457 - 66485438

Chronic meningitis is not uncommon in the course of HIV infection. Pleocytosis and mild meningeal signs often occur at the onset of HIV infection, and occasionally low-grade meningitis persists. Toxoplasmosis commonly presents as intracranial abscesses and also may be associated with meningitis. Other important causes of chronic meningitis in AIDS include infection with Cryptococcus, Nocardia, Candida, or other fungi; syphilis; and lymphoma (Fig. 47-1). Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiologic considerations in individuals with immunodeficiency states other than AIDS, including those due to immunosuppressive medications. Because of the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal irritation in immunosuppressed individuals, CSF examination should be performed for any persistent headache or unexplained change in mental state.

Acknowledgment

Morton N. Swartz contributed to earlier editions of this chapter.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 48

HIV NEUROLOGY

Anthony S. Fauci ■ H. Clifford Lane

Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with HIV infection **(Table 48-1)**. The neurologic problems that occur in HIV-infected individuals may be either primary to the pathogenic processes of HIV infection or secondary to opportunistic infections or neoplasms. Among the more frequent opportunistic diseases that involve the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Other less common problems include mycobacterial infections; syphilis; and infection with CMV, HTLV-1, Trypanosoma cruzi, or Acanthamoeba. Overall, secondary diseases of the CNS have been reported to occur in approximately one-third of patients with AIDS. These data antedate the widespread use of cART, and this frequency is considerably lower in patients receiving effective antiretroviral drugs. Primary processes related to HIV infection of the nervous system are reminiscent of those seen with other lentiviruses, such as the Visna-Maedi virus of sheep.

TABLE 48-1

NEUROLOGIC DISEASES IN PATIENTS WITH HIV INFECTION

- Opportunistic infections
  - Toxoplasmosis
  - Cryptococcosis
  - Progressive multifocal leukoencephalopathy
  - Cytomegalovirus
  - Syphilis
  - Mycobacterium tuberculosis
  - HTLV-1 infection
  - Amebiasis
- Neoplasms
  - Primary CNS lymphoma
  - Kaposi's sarcoma
- HIV-1 infection
  - Aseptic meningitis
  - HIV-associated neurocognitive disorders (HAND), including HIV encephalopathy/AIDS dementia complex
- Myelopathy
  - Vacuolar myelopathy
  - Pure sensory ataxia
  - Paresthesia/dysesthesia
- Peripheral neuropathy
  - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Mononeuritis multiplex
  - Distal symmetric polyneuropathy
- Myopathy

AIDS CLASSIFICATION

The current U.S. CDC classification system for HIV infection and AIDS categorizes people on the basis of clinical conditions associated with HIV infection and CD4+ T lymphocyte measurement. A confirmed HIV case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown). If there was a negative HIV test within 6 months of the first HIV infection diagnosis, the stage is 0, and remains 0 until 6 months after diagnosis. Advanced HIV disease (AIDS) is classified as stage 3 if one or more specific opportunistic illness has been diagnosed **(Table 48-2)**. Otherwise, the stage is determined by CD4 test results and immunologic criteria **(Table 48-3)**. If none of these criteria apply (e.g., because of missing information on CD4 test results), the stage is U (unknown).

The definition and staging criteria of AIDS are complex and comprehensive and were established for surveillance purposes rather than for the practical care of patients. Thus, the clinician should not focus on whether the patient fulfills the strict definition of AIDS, but should view HIV disease as a spectrum ranging from primary infection, with or without the acute syndrome, to the asymptomatic stage, to advanced stages associated with opportunistic diseases (see "Pathophysiology and Pathogenesis," below).

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 48-2

CDC STAGE 3 (AIDS)-DEFINING OPPORTUNISTIC ILLNESSES IN HIV INFECTION
Bacterial infections, multiple or recurrent[a]
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive[b]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
M. avium complex or M. kansasii, disseminated or extrapulmonary
M. tuberculosis of any site, pulmonary,[b] disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV

[a]Only among children age <6 years.
[b]Only among adults, adolescents, and children age ≥6 years.
Source: MMWR 63(No. RR-03), April 11, 2014.

ETIOLOGIC AGENT

HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. Nononcogenic lentiviruses cause disease in other animal species, including sheep, horses, goats, cattle, cats, and monkeys. T e four retroviruses known to cause human disease belong to two distinct groups: the human T lymphotropic viruses (HTLV)-1 and HTLV-2, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which cause cytopathic ef ects either directly or indirectly. T e most common cause of HIV disease throughout the world, and certainly in the United States, is HIV-1, which comprises several subtypes with dif erent geographic distributions (see "Molecular Heterogeneity of HIV-1," below). HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa. However, a number of cases that generally can be traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. T e currently defined groups of HIV-1 (M, N, O, P) and the HIV-2 groups A through H each are likely derived from a separate transfer to humans from a nonhuman primate reservoir. HIV-1 viruses likely came from chimpanzees and/or gorillas, and HIV-2 from sooty mangabeys. T e AIDS pandemic is primarily caused by the HIV-1 M group viruses. Although HIV-1 group O and HIV-2 viruses have been found in numerous countries, including those in the developed world, they have caused much more localized epidemics. T e taxonomic relationship between primate lentiviruses is shown in **Fig. 48-1**.

MORPHOLOGY OF HIV

Electron microscopy shows that the HIV virion is an icosahedral structure **(Fig. 48-2)** containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. T e HIV envelope exists as a trimeric heterodimer.

TABLE 48-3

CDC HIV INFECTION STAGES 1–3 BASED ON AGE-SPECIFIC CD4+ T LYMPHOCYTE COUNT OR CD4+ T LYMPHOCYTE PERCENTAGE OF TOTAL LYMPHOCYTES[a]

	AGE ON DATE OF CD4 T+ LYMPHOCYTE TEST					
	<1 YEAR		1–5 YEARS		6 YEARS THROUGH ADULT	
STAGE[a]	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a]The stage is based primarily on the CD4+ T-lymphocyte count; the CD4+ T-lymphocyte count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.
Source: MMWR 63(No. RR-03), April 11, 2014.

www.ketabpezeshki.com (021) 66485457 - 66485438

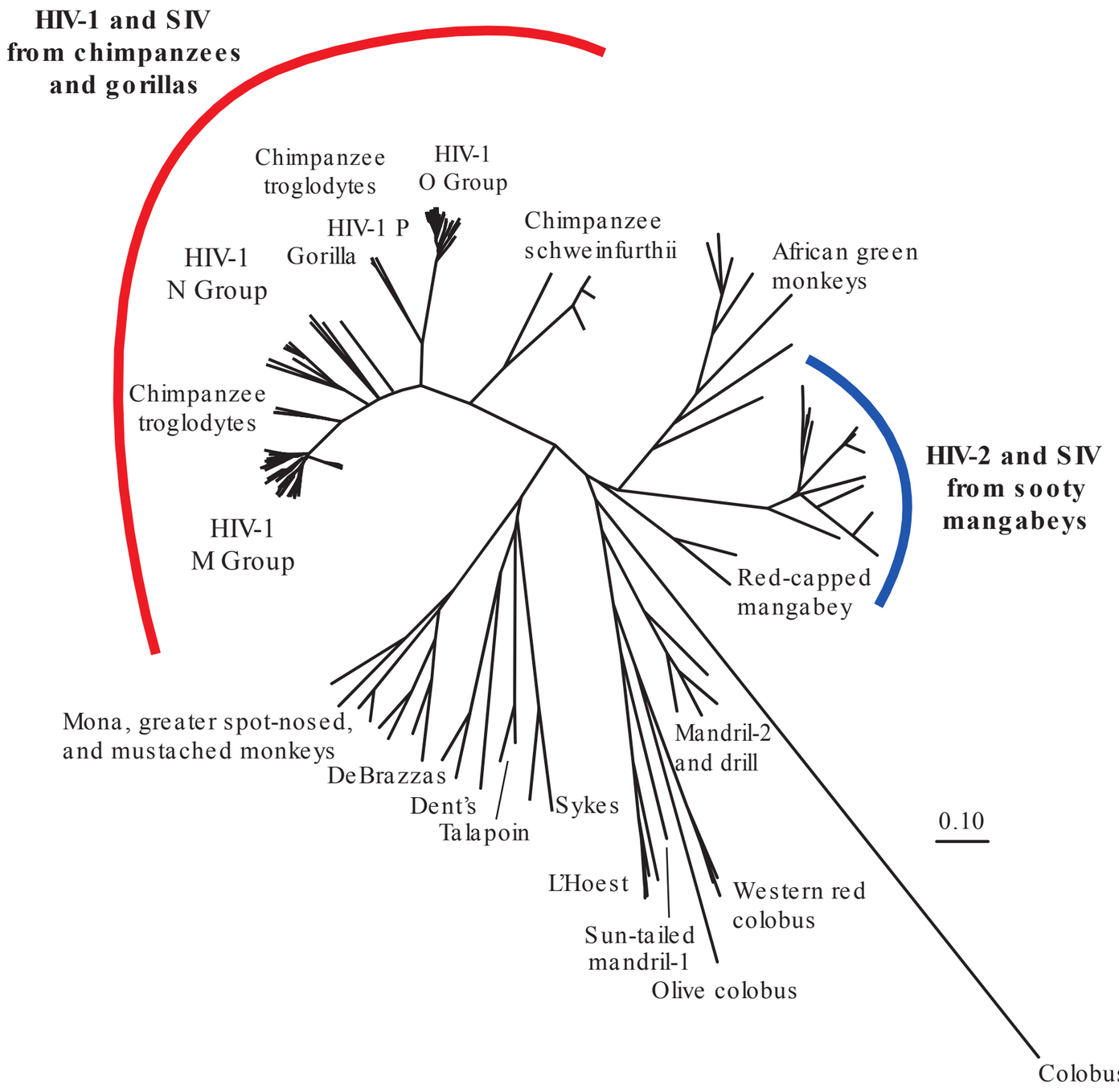


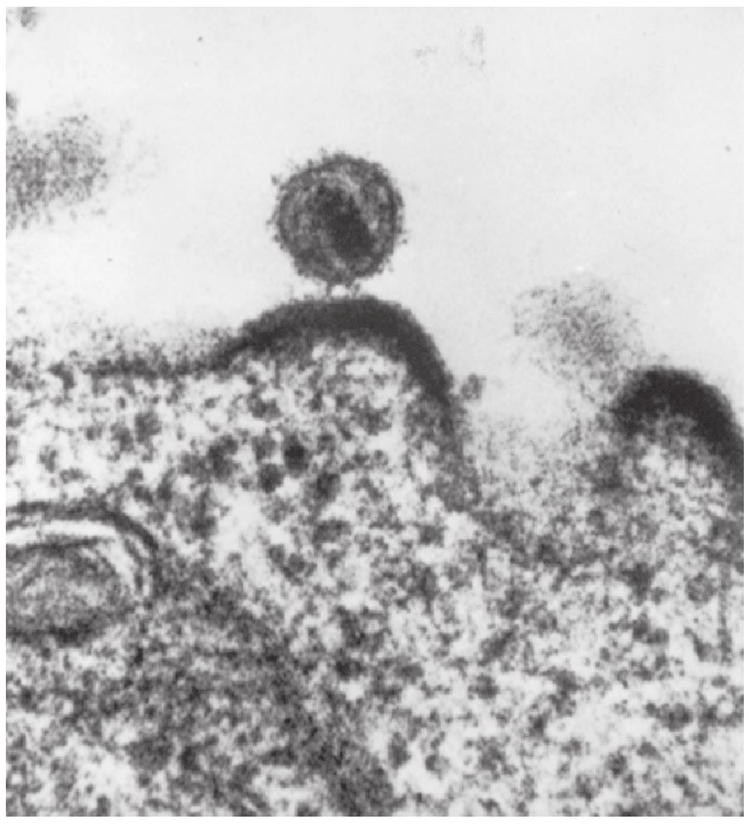
FIGURE 48-1
A phylogenetic tree based on the complete genomes of primate immunodeficiency viruses. The scale (0.10) indicates a 10% difference at the nucleotide level. (Prepared by Brian Foley, PhD, of the HIV Sequence Database, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory; additional information at www.hiv.lanl.gov/content/sequence/HelpDocs/subtypes.html.)

The virion buds from the surface of the infected cell and incorporates a variety of host proteins into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in **Fig. 48-2**B.

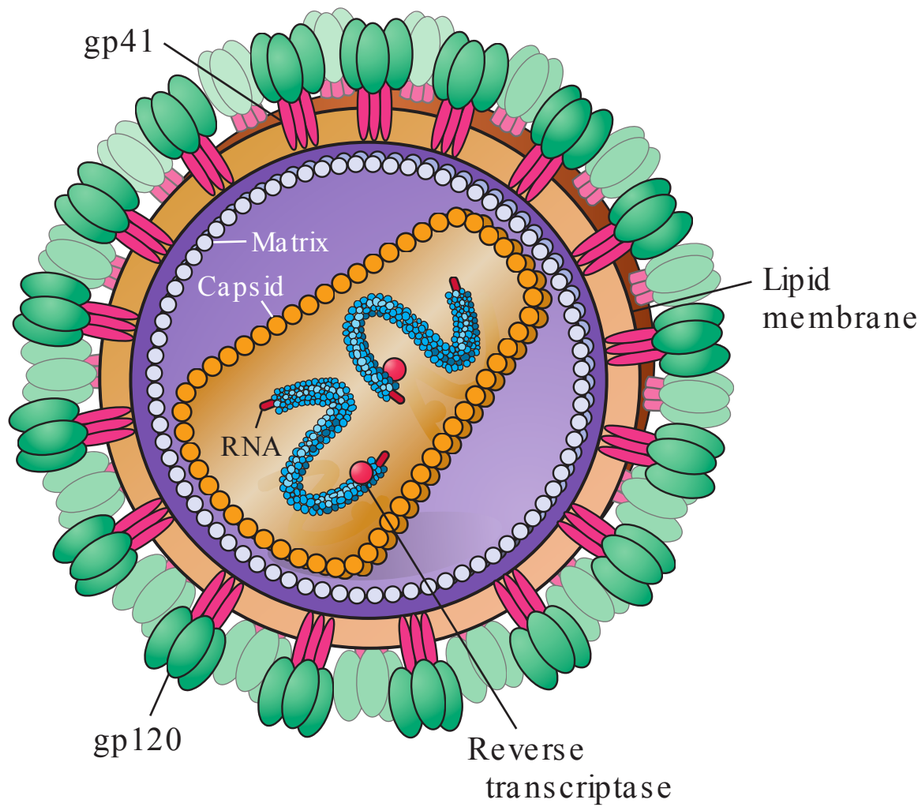
REPLICATION CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme reverse transcriptase. The replication cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the CD4 molecule **(Fig. 48-3)**. The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. Once it binds to CD4, the gp120 protein undergoes a conformational change that facilitates binding to one of two major co-receptors. The two major co-receptors for HIV-1 are CCR5 and CXCR4. Both receptors belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors, and the use of one or the other or both receptors by the virus for entry into the cell is an important determinant of the cellular tropism of the virus. Certain dendritic cells (DCs) express a diversity of C-type lectin receptors on their surface—one of which is called DC-SIGN—that also bind with high affinity to the HIV gp120 envelope protein, allowing DCs to facilitate virus spread to CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the above-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together **(Fig. 48-4)**. Following fusion, uncoating of the capsid protein shell is initiated—a step that facilitates reverse transcription and leads to formation of the preintegration complex, composed of viral RNA, enzymes, and accessory proteins and surrounded by capsid and matrix proteins (Fig. 48-3). As the preintegration complex traverses the cytoplasm to reach the nucleus, the viral reverse transcriptase enzyme catalyzes the reverse

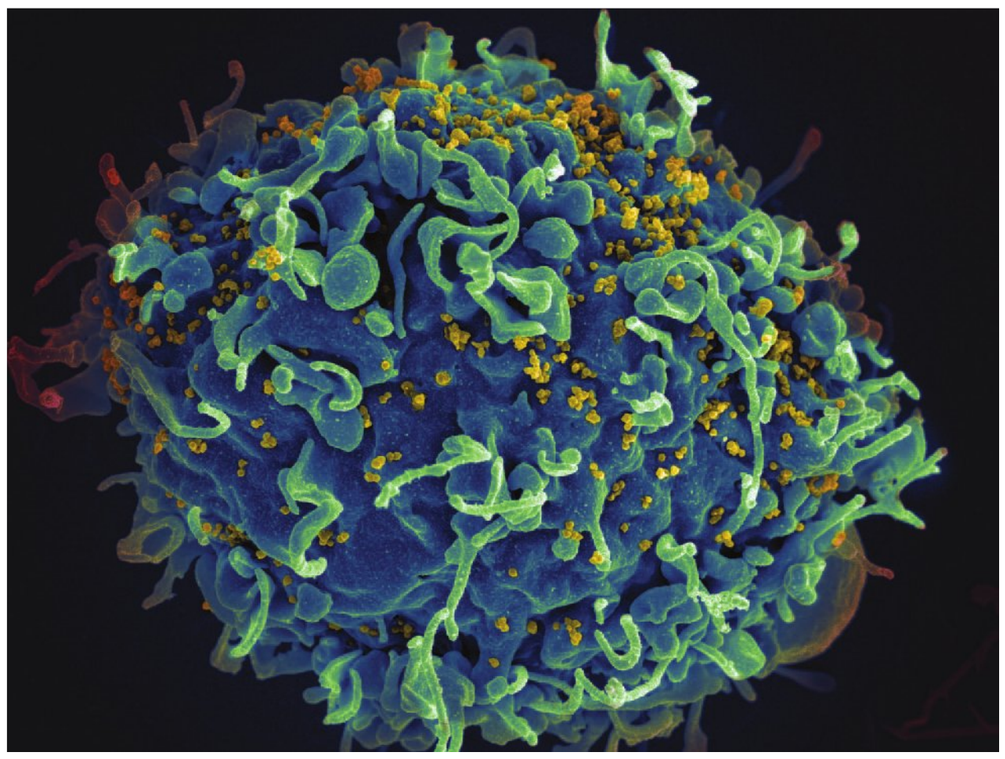
www.ketabpezeshki.com (021) 66485457 - 66485438



A



B



C

FIGURE 48-2

A. Electron micrograph of HIV. Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. B. Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). (Copyright by George V. Kelvin.) (Adapted *f*rom RC Gallo: Sci Am 256:46, 1987.) C. Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 8000× magnification. (Courtesy o*f* Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute o*f* Allergy and In*f*ectious Diseases; with permission.)

transcription of the genomic RNA into DNA, resulting in the formation of double-stranded proviral HIV-DNA. At the preintegration steps of the replication cycle, the viral genome is vulnerable to cellular factors that can block the progression of infection. In particular, the cytoplasmic tripartite motif-containing protein 5-α (TRIM5-α) is a host restriction factor that interacts with retroviral capsids (Fig. 48-3). Although the exact mechanisms of action of TRIM5-α remain unclear, the HIV-1 capsid is not recognized by the human form of TRIM5-α. T us this host factor is not effective in restricting HIV-1 replication in human cells. T e apolipoprotein B mRNA editing enzyme (catalytic polypeptide-like 3 [APOBEC3]) family of cellular proteins also inhibits progression of virus infection after virus has entered the cell and prior to entering the nucleus (Fig. 48-3). APOBEC3 proteins, which are incorporated into virions and released into the cytoplasm of a newly infected cell, bind to the single minus-strand DNA intermediate and deaminate viral cytidine, causing hypermutation of retroviral genomes. HIV has evolved a powerful strategy to protect itself from APOBEC. T e viral protein Vif targets APOBEC3 for proteasomal degradation.

www.ketabpezeshki.com (021) 66485457 - 66485438

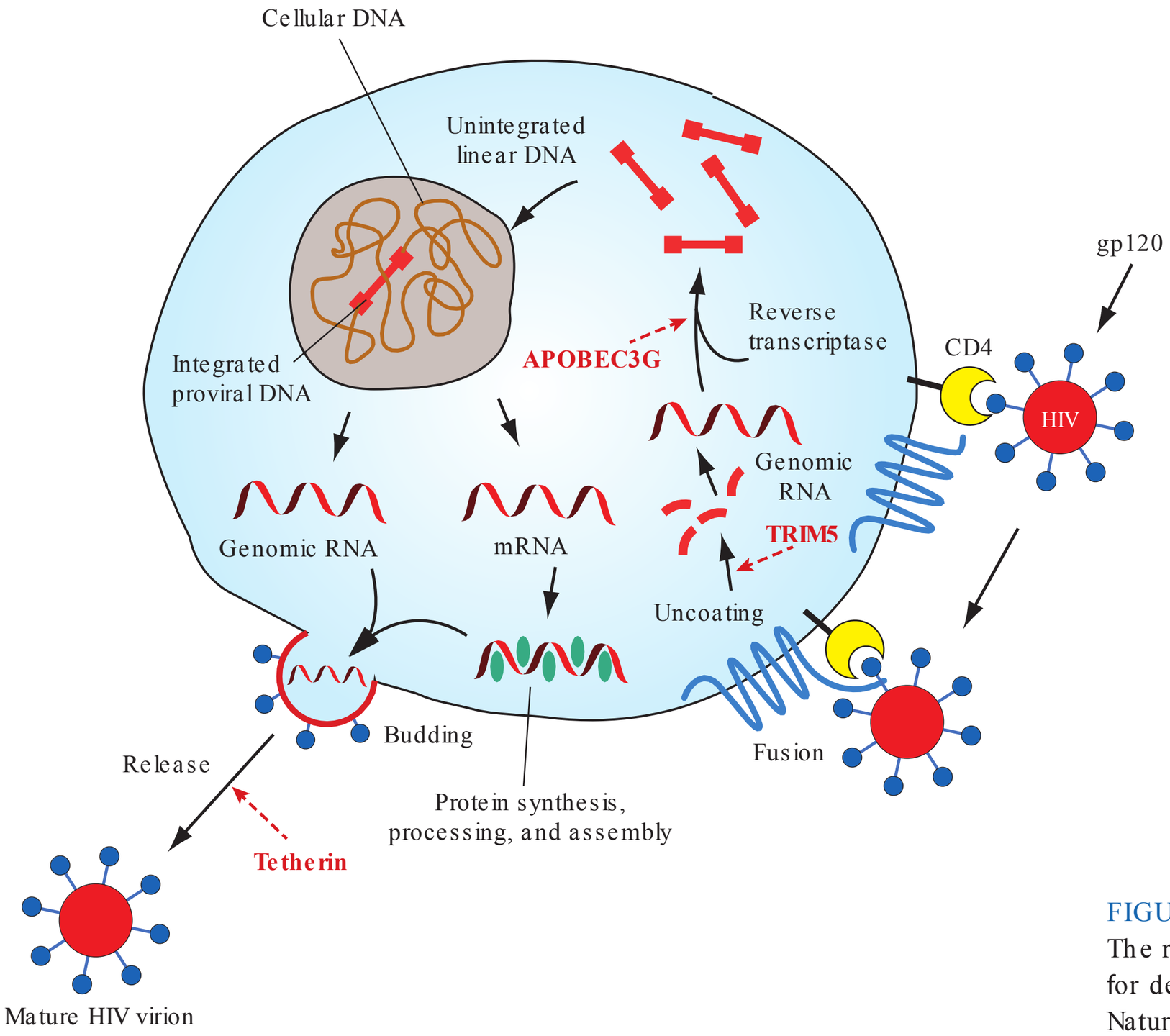


FIGURE 48-3
The replication cycle of HIV. See text for description. (Adapted from AS Fauci: Nature 384:529, 1996.)

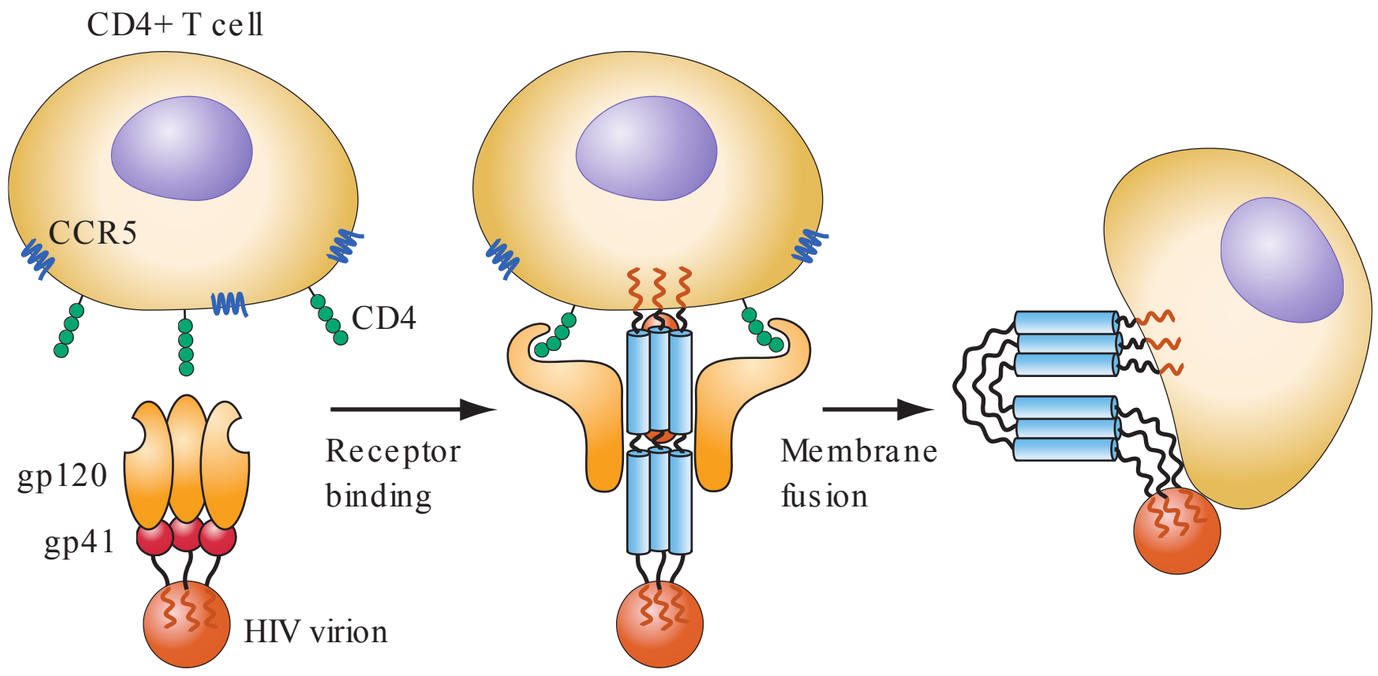


FIGURE 48-4
Binding and fusion of HIV-1 with its target cell. HIV-1 binds to its target cell via the CD4 molecule, leading to a conformational change in the gp120 molecule that allows it to bind to the co-receptor CCR5 (for R5-using viruses). The virus then firmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule. Virus-cell fusion occurs as the transitional intermediate of gp41 undergoes further changes to form a hairpin structure that draws the two membranes into close proximity (see text for details). (Adapted from D Montefori, JP Moore: Science 283:336, 1999; with permission.)

With activation of the cell, the viral DNA accesses the nuclear pore and is exported from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, integrase (Fig. 48-3). HIV provirus (DNA) integrates into the nuclear DNA preferentially within introns of active genes and regional hotspots. T is provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the

www.ketabpezeshki.com (021) 66485457 - 66485438

pathogenesis of HIV disease (see "Pathogenesis and Pathophysiology," below). Following initial binding, fusion, and internalization of the nucleic acid contents of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and do not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, some degree of activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. T is latter process may not necessarily be associated with the detectable expression of the classic cell-surface markers of activation. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristoylation, phosphorylation, and cleavage. T e viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion through the lipid bilayer of the host cell membrane is the point at which the core acquires its external envelope and where the host restriction factor tetherin can inhibit the release of budding particles (Fig. 48-3). Tetherin is an interferon (IFN)-induced type II transmembrane protein that interferes with virion detachment, although the HIV accessory protein Vpu counteracts the effect through direct interactions with tetherin. During or soon after budding, the virally encoded protease catalyzes the cleavage of the gag-pol precursor to yield the mature virion. Progression through the virus replication cycle is profoundly inf u-enced by a variety of viral regulatory gene products. Likewise, each point in the replication cycle of HIV is a real or potential target for therapeutic intervention. T us far, the reverse transcriptase, protease, and integrase enzymes as well as the process of virus–target cell binding and fusion have proved clinically to be susceptible to pharmacologic disruption.

HIV GENOME

Figure 48-5 illustrates schematically the arrangement of the HIV genome. Like other retroviruses, HIV-1 has genes that encode the structural proteins of the virus: gag encodes the proteins that form the core of the virion (including p24 antigen); pol encodes the enzymes

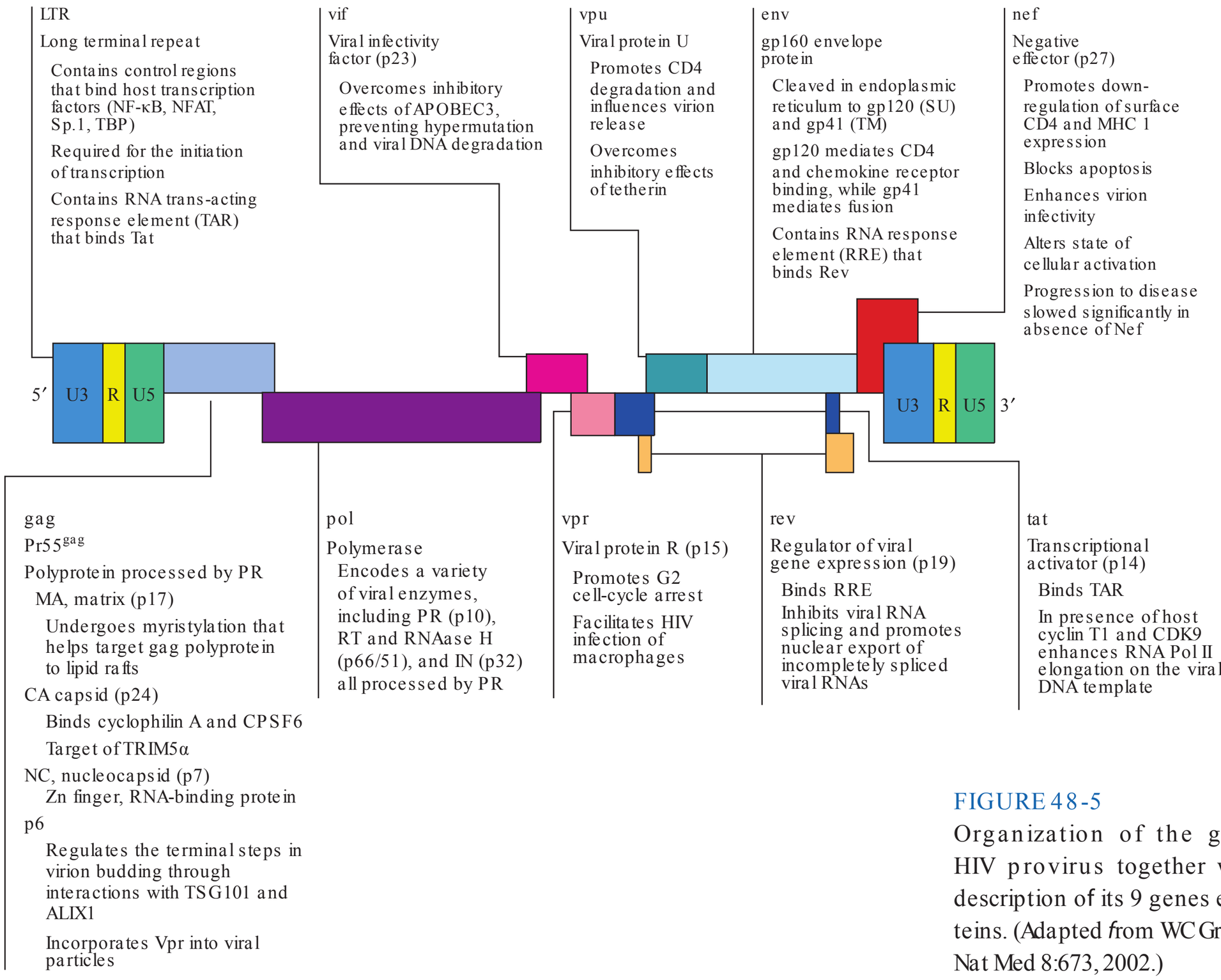


FIGURE 48-5
Organization of the genome of the HIV provirus together with a summary description of its 9 genes encoding 15 proteins. (Adapted from WC Greene, BM Peterlin: Nat Med 8:673, 2002.)

www.ketabpezeshki.com (021) 66485457 - 66485438

responsible for protease processing of viral proteins, reverse transcription, and integration; and env encodes the envelope glycoproteins. However, HIV-1 is more complex than other retroviruses, particularly those of the nonprimate group, in that it also contains at least six other genes (tat, rev, ne*f*, vi*f*, vpr, and vpu), which code for proteins involved in the modification of the host cell to enhance virus growth and the regulation of viral gene expression. Several of these proteins are thought to play a role in the pathogenesis of HIV disease; their various functions are listed in Fig. 48-5. Flanking these genes are the long terminal repeats (LTRs), which contain regulatory elements involved in gene expression (Fig. 48-5). T e major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the vpu gene and has a vpx gene not contained in HIV-1.

PATHOPHYSIOLOGY AND PATHOGENESIS

T e hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as helper T cells occurring in a setting of polyclonal immune activation. T e helper subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule, which serves as the primary cellular receptor for HIV. A co-receptor must also be present together with CD4 for efficient binding, fusion, and entry of HIV-1 into its target cells (Figs. 48-3 and 48-4). HIV uses two major co-receptors, CCR5 and CXCR4, for fusion and entry; these co-receptors are also the primary receptors for certain chemoattractive cytokines termed chemokines and belong to the seven-transmembrane-domain G protein–coupled family of receptors. A number of mechanisms responsible for cellular depletion and/or immune dysfunction of CD4+ T cells have been demonstrated in vitro; these include direct infection and destruction of these cells by HIV, as well as indirect effects such as immune clearance of infected cells, cell death associated with aberrant immune activation, and immune exhaustion due to aberrant cellular activation with resulting cellular dysfunction. Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi's sarcoma and certain neurologic abnormalities, cannot be explained completely by the immunodeficiency caused by HIV infection, since these complications may occur prior to the development of severe immunologic impairment.

T e combination of viral pathogenic and immunopathogenic events that occurs during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied. It is important to appreciate that the pathogenic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease. T erefore, it is essential to consider the typical clinical course of an untreated HIV-infected individual in order to more fully appreciate these pathogenic events **(Fig. 48-6)**.

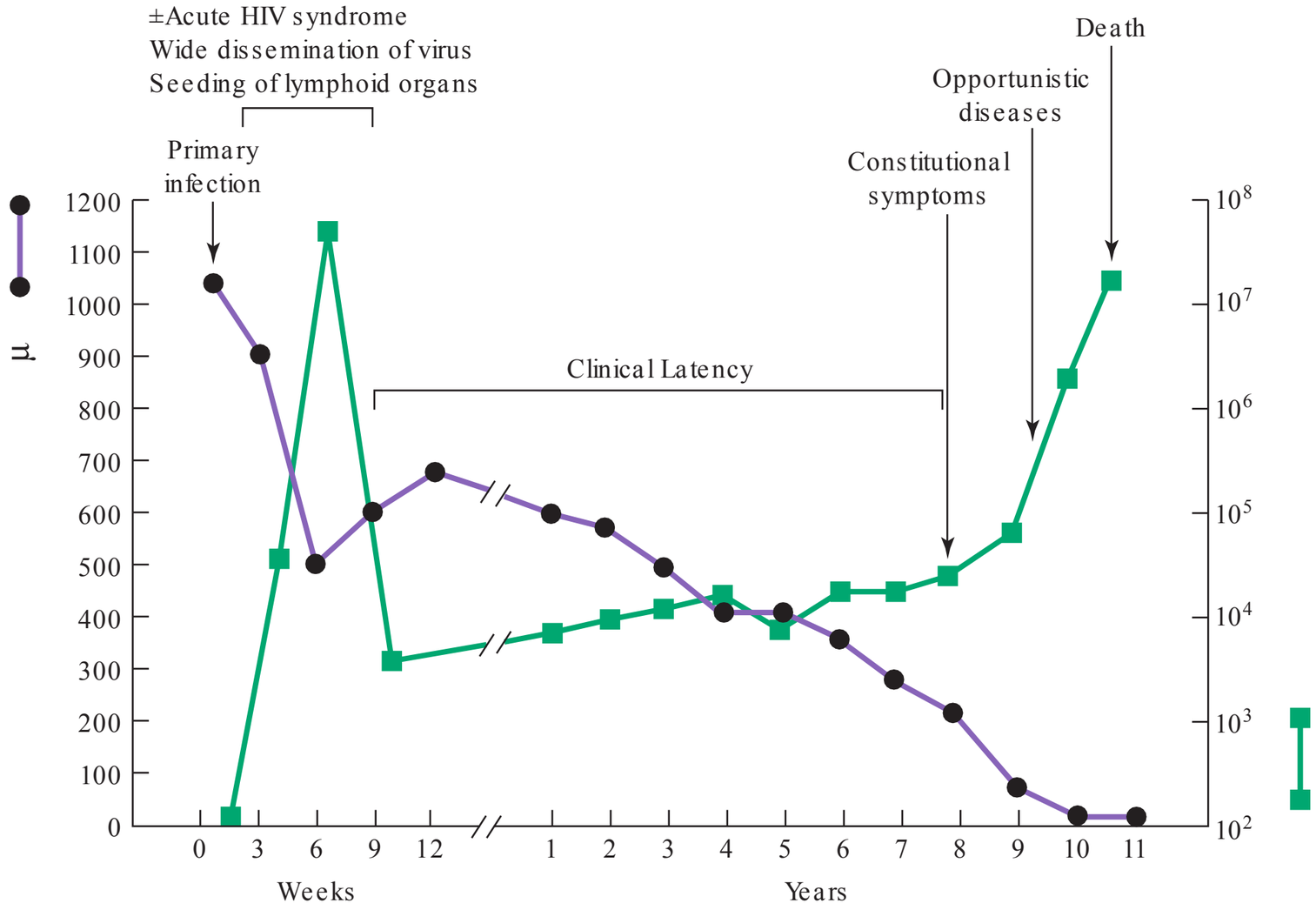


FIGURE 48-6
Typical course of an untreated HIV-infected individual. See text for detailed description. (From G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.)

www.ketabpezeshki.com (021) 66485457 - 66485438

NEUROPATHOGENESIS IN HIV DISEASE

While there has been a remarkable decrease in the incidence in the severe forms of HIV encephalopathy among those with access to treatment in the era of effective cART, HIV-infected individuals can still experience milder forms of neurocognitive impairment despite adequate cART. A variety of factors may contribute to the neurocognitive decline, which includes lack of complete control of HIV replication in the brain, production of HIV proteins that may be neurotoxic, low CD4+ T cell nadir, chronic immune activation, comorbidities such as drug abuse, and the potential for neurotoxicity of certain of the antiretroviral drugs. HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. As opposed to lymphoid tissues, there are no resident lymphocytes in the brain. T e main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells; low-level viral replication is also seen in perivascular astrocytes. Monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected within the brain. T e precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhesion molecule 1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule 1 (ICAM-1) in glial cells; this effect may facilitate entry of HIV-infected cells into the CNS. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, HIV-infected individuals who are heterozygous for CCR5-Δ32 appear to be relatively protected against the development of HIV encephalopathy. Once HIV enters the brain due to pressures of the local environment, it evolves to develop distinct sequences in the env, tat, and LTR genes. T ese unique sequences have been associated with neurocognitive dysfunction; however, it is unclear if they are causal (see below).

HIV-infected individuals may manifest white matter lesions as well as neuronal loss. T e white matter lesions are due to axonal injury and a disruption of the blood-brain barrier and not due to demyelination. Given the absence of evidence of HIV infection of neurons either in vivo or in vitro, it is highly unlikely that direct infection of these cells accounts for their loss. Rather, the HIV-mediated effects on neurons are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via the N-methyl-D-aspartate (NMDA) receptor. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracellular calcium levels, and by decreasing nerve growth factor levels in the cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein-1 (MCP-1 or CCL-2) in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy. In addition, infection and/or activation of monocyte-lineage cells can result in increased production of eicosanoids, quinolinic acid, nitric oxide, excitatory amino acids such as L-cysteine and glutamate, arachidonic acid, platelet activating factor, free radicals, TNF-α, and TGF-β, which may contribute to neurotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of HIV-infected individuals, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been suggested that astrocytes may downregulate macrophage-produced neurotoxins. Treatment with cART leads to improvement in neuropsychiatric manifestations and a decrease in these cytokine levels in CSF, suggesting that they are driven by the virus or by its products. However, even in patients on long-term cART, there may be evidence of persistently activated lymphocytes in the CSF. It is unclear if these lymphocytes may contribute to neuronal injury in the brain or are critical for controlling the CNS viral reservoir. T e contribution of host genetic factors to development of neuropsychiatric manifestations of HIV infection has not been well studied. However, evidence supports the role of the E4 allele for apoE in an increased risk of HIV-associated neurocognitive disorders and peripheral neuropathy.

It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells that might be a barrier for the eradication of virus by cART.

Neurologic problems directly attributable to HIV occur throughout the course of infection and may be inf ammatory, demyelinating, or degenerative in nature. T e term HIV-associated neurocognitive disorders (HAND) is used to describe a spectrum of disorders

www.ketabpezeshki.com (021) 66485457 - 66485438

that range from asymptomatic neurocognitive impairment (ANI) to minor neurocognitive disorder (MND) to clinically severe dementia. T e most severe form, HIV-associated dementia (HAD), also referred to as the AIDS dementia complex, or HIV encephalopathy, is considered an AIDS-defining illness. Most HIV-infected patients have some neurologic problem during the course of their disease. Even in the setting of suppressive cART, approximately 50% of HIV-infected individuals can be shown to have mild to moderate neurocognitive impairment using sensitive neuropsychiatric testing. As noted in the section on pathogenesis, damage to the CNS may be a direct result of viral infection of the CNS macrophages or glial cells or may be secondary to the release of neurotoxins and potentially toxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. It has been reported that HIV-infected individuals with the E4 allele for apoE are at increased risk for AIDS encephalopathy and peripheral neuropathy. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. T is is evidenced by the fact that CSF findings are abnormal in ~90% of patients, even during the asymptomatic phase of HIV infection. CSF abnormalities include pleocytosis (50–65% of patients), detection of viral RNA (~75%), elevated CSF protein (35%), and evidence of intrathecal synthesis of anti-HIV antibodies (90%). It is important to point out that evidence of infection of the CNS with HIV does not imply impairment of cognitive function. T e neurologic function of an HIV-infected individual should be considered normal unless clinical signs and symptoms suggest otherwise.

Aseptic meningitis may be seen in any but the very late stages of HIV infection. In the setting of acute primary infection, patients may experience a syndrome of headache, photophobia, and meningismus. Rarely, an acute encephalopathy due to encephalitis may occur. Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII. CSF findings include a lymphocytic pleocytosis, elevated protein level, and normal glucose level. T is syndrome, which cannot be clinically differentiated from other viral meningitides **(Chap. 47)**, usually resolves spontaneously within 2–4 weeks; however, in some patients, signs and symptoms may become chronic. Aseptic meningitis may occur any time in the course of HIV infection; however, it is rare following the development of AIDS. T is suggests that clinical aseptic meningitis in the context of HIV infection is an immune-mediated disease.

Cryptococcus is the leading infectious cause of meningitis in patients with AIDS. While the vast majority of these are due to C. neo*f*ormans, up to 12% may be due to C. gattii. Cryptococcal meningitis is the initial AIDS-defining illness in ~2% of patients and generally occurs in patients with CD4+ T cell counts <100/μL. Cryptococcal meningitis is particularly common in untreated patients with AIDS in Africa, occurring in ~5% of patients. Most patients present with a picture of subacute meningoencephalitis with fever, nausea, vomiting, altered mental status, headache, and meningeal signs. T e incidence of seizures and focal neurologic deficits is low. T e CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose. T e opening pressure in the CSF is usually elevated. In addition to meningitis, patients may develop cryptococcomas and cranial nerve involvement. Approximately one-third of patients also have pulmonary disease. Uncommon manifestations of cryptococcal infection include skin lesions that resemble molluscum contagiosum, lymphadenopathy, palatal and glossal ulcers, arthritis, gastroenteritis, myocarditis, and prostatitis. T e prostate gland may serve as a reservoir for smoldering cryptococcal infection. T e diagnosis of cryptococcal meningitis is made by identification of organisms in spinal f uid with india ink examination or by the detection of cryptococcal antigen. Blood cultures for fungus are often positive. A biopsy may be needed to make a diagnosis of CNS cryptococcoma. Treatment is with IV amphotericin B 0.7 mg/kg daily, or liposomal amphotericin 4–6 mg/kg daily, with f ucytosine 25 mg/kg qid for at least 2 weeks if possible, continuing with amphotericin alone ideally until the CSF culture turns negative. Decreases in renal function in association with amphotericin can lead to increases in f ucytosine levels and subsequent bone marrow suppression. Amphotericin is followed by f uconazole 400 mg/d PO for 8 weeks, and then f uconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/μL for 6 months in response to cART. Repeated lumbar puncture may be required to manage increased intracranial pressure. Symptoms may recur with initiation of cART as an immune reconstitution syndrome (see above). Other fungi that may cause meningitis in patients with HIV infection are C. immitis and H. capsulatum. Meningoencephalitis has also been reported due to Acanthamoeba or Naegleria.

HIV-associated dementia consists of a constellation of signs and symptoms of CNS disease. While this is generally a late complication of HIV infection that progresses slowly over months, it can be seen in patients with CD4+ T cell counts >350 cells/μL. A major feature of this entity is the development of dementia, defined as a decline in cognitive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty reading, or increased difficulty performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue. In contrast to "cortical" dementia (such as Alzheimer's

www.ketabpezeshki.com (021) 66485457 - 66485438

disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a "subcortical dementia" characterized by defects in short-term memory and executive function (see below). In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence. Behavioral problems include apathy, irritability, and lack of initiative, with progression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This is in contrast to the finding of somnolence in patients with dementia due to toxic/metabolic encephalopathies.

HIV-associated dementia is the initial AIDS-defining illness in ~3% of patients with HIV infection and thus only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy eventually develops in ~25% of untreated patients with AIDS. As immunologic function declines, the risk and severity of HIV-associated dementia increases. Autopsy series suggest that 80–90% of patients with HIV infection have histologic evidence of CNS involvement. Several classification schemes have been developed for grading HIV encephalopathy; a commonly used clinical staging system is outlined in **Table 48-4**.

The precise cause of HIV-associated dementia remains unclear, although the condition is thought to be a result of a combination of direct effects of HIV on the CNS and associated immune activation. HIV has been found in the brains of patients with HIV encephalopathy by Southern blot, in situ hybridization, PCR, and electron microscopy. Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harboring virus in the CNS. Histologically, the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor function, language, and judgment are most severely affected.

There are no specific criteria for a diagnosis of HIV-associated dementia, and this syndrome must be differentiated from a number of other diseases that affect the CNS of HIV-infected patients (Table 48-1). The diagnosis of dementia depends on demonstrating a decline in cognitive function. This can be accomplished objectively with the use of a Mini-Mental Status Examination (MMSE) in patients for whom prior scores are available.

TABLE 48-4

CLINICAL STAGING OF HAND ACCORDING TO FRASCATI CRITERIA

STAGE	NEUROCOGNITIVE STATUS[a]	FUNCTIONAL STATUS[b]
Asymptomatic	1 SD below mean in 2 cognitive domains	No impairments in activities of daily living
Mild neurocognitive disorder	1 SD below mean in 2 cognitive domains	Impairments in activities of daily living
HIV-associated dementia	2 SD below mean in 2 cognitive domains	Notable impairments in activities of daily living

[a]Neurocognitive testing should include assessment of at least 5 domains, including attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory (including learning and recall), simple motor skills, or sensory perceptual skills. Appropriate norms must be available to establish the number of domains in which performance is below 1 SD. [b]Functional status is typically assessed by self-reporting but might be corroborated by a collateral source. No agreed measures exist for HIV-associated neurocognitive disorder criteria. Note that, for diagnosis of HIV-associated neurocognitive disorder, other causes of dementia must be ruled out and potential confounding effects of substance use or psychiatric illness should be considered.
Source: Adapted from A Antinori et al: Neurology 69:1789, 2007.

For this reason, it is advisable for all patients with a diagnosis of HIV infection to have a baseline MMSE. However, changes in MMSE scores may be absent in patients with mild HIV encephalopathy. Imaging studies of the CNS, by either MRI or CT, often demonstrate evidence of cerebral atrophy **(Fig. 48-7)**. MRI may also reveal small areas of increased density on T2-weighted images. Lumbar puncture is an important element of the evaluation of patients with HIV infection and neurologic abnormalities. It is generally most helpful in ruling out or making a diagnosis of opportunistic infections. In HIV encephalopathy, patients may have the nonspecific findings of an increase in CSF cells and protein level. While HIV RNA can often be detected in the spinal fluid and HIV can be cultured from the CSF, this finding is not specific for HIV encephalopathy. There appears to be no correlation between the presence of HIV in the CSF and the presence of HIV encephalopathy. Elevated levels of macrophage chemoattractant protein (MCP-1), β_2-microglobulin, neopterin, and quinolinic acid (a metabolite of tryptophan reported to cause CNS injury) have been noted in the CSF of patients with HIV encephalopathy. These findings suggest that these factors as well as inflammatory cytokines may be involved in the pathogenesis of this syndrome.

Combination antiretroviral therapy is of benefit in patients with HIV-associated dementia. Improvement in neuropsychiatric test scores has been noted for both

www.ketabpezeshki.com (021) 66485457 - 66485438

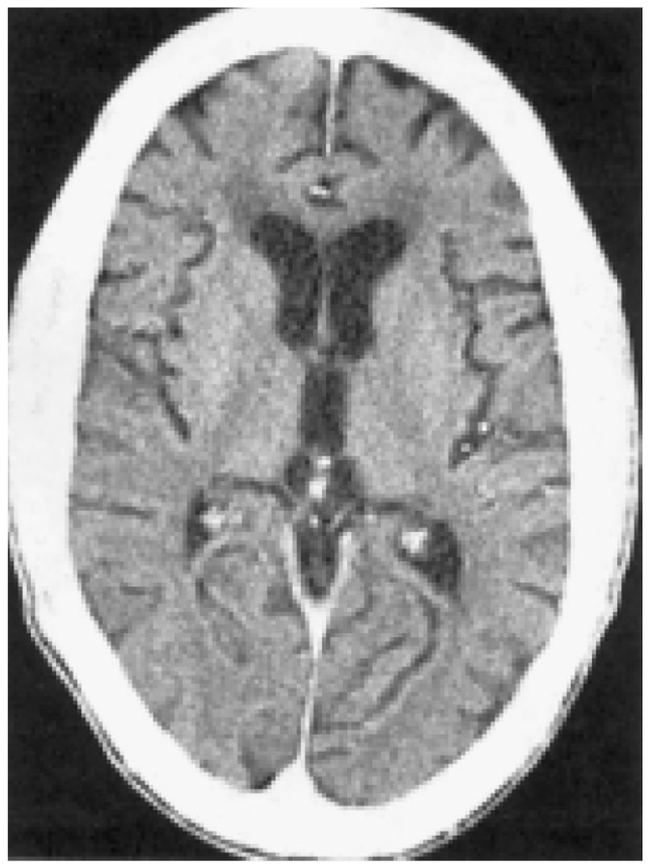


FIGURE 48-7
AIDS dementia complex. Postcontrast CT scan through the lateral ventricles of a 47-year-old man with AIDS, altered mental status, and dementia. The lateral and third ventricles and the cerebral sulci are abnormally prominent. Mild white matter hypodensity is seen adjacent to the frontal horns of the lateral ventricles.

adult and pediatric patients treated with antiretrovirals. The rapid improvement in cognitive function noted with the initiation of cART suggests that at least some component of this problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects; therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully. It is felt by many physicians that the decrease in the prevalence of severe cases of HAND brought about by cART has resulted in an increase in the prevalence of milder forms of this disorder.

Seizures may be a consequence of opportunistic infections, neoplasms, or HIV encephalopathy **(Table 48-5)**. The seizure threshold is often lower than normal in patients with advanced HIV infection due in part to the frequent presence of electrolyte abnormalities. Seizures are seen in 15–40% of patients with cerebral toxoplasmosis, 15–35% of patients with primary CNS lymphoma, 8% of patients with cryptococcal meningitis, and 7–50% of patients with HIV encephalopathy. Seizures may also be seen in patients with CNS tuberculosis, aseptic meningitis, and progressive multifocal leukoencephalopathy. Seizures may be the presenting clinical symptom of HIV disease. In one study of 100 patients with HIV infection presenting with a

TABLE 48-5

CAUSES OF SEIZURES IN PATIENTS WITH HIV INFECTION

DISEASE	OVERALL CONTRIBUTION TO FIRST SEIZURE, %	FRACTION OF PATIENTS WHO HAVE SEIZURES, %
HIV encephalopathy	24–47	7–50
Cerebral toxoplasmosis	28	15–40
Cryptococcal meningitis	13	8
Primary central nervous system lymphoma	4	15–30
Progressive multifocal leukoencephalopathy	1	20

Source: From DM Holtzman et al: Am J Med 87:173, 1989.

first seizure, cerebral mass lesions were the most common cause, responsible for 32 of the 100 new-onset seizures. Of these 32 cases, 28 were due to toxoplasmosis and 4 to lymphoma. HIV encephalopathy accounted for an additional 24 new-onset seizures. Cryptococcal meningitis was the third most common diagnosis, responsible for 13 of the 100 seizures. In 23 cases, no cause could be found, and it is possible that these cases represent a subcategory of HIV encephalopathy. Of these 23 cases, 16 (70%) had 2 or more seizures, suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rapidly correctable cause is found. While phenytoin remains the initial treatment of choice, hypersensitivity reactions to this drug have been reported in >10% of patients with AIDS, and therefore the use of phenobarbital or valproic acid should be considered as alternatives. Due to a variety of drug-drug interactions between antiseizure medications and antiretrovirals, drug levels need to be monitored carefully.

Patients with HIV infection may present with *f*ocal neurologic deficits from a variety of causes. The most common causes are toxoplasmosis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Other causes include cryptococcal infections (discussed above), stroke, and reactivation of Chagas' disease.

Toxoplasmosis has been one of the most common causes of secondary CNS infections in patients with AIDS, but its incidence is decreasing in the era of cART. It is most common in patients from the Caribbean and from France, where the seroprevalence of T. gondii is around 50%. This figure is closer to 15% in the United States. Toxoplasmosis is generally a late complication

www.ketabpezeshki.com (021) 66485457 - 66485438

of HIV infection and usually occurs in patients with CD4+ T cell counts <200/μL. Cerebral toxoplasmosis is thought to represent a reactivation of latent tissue cysts. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. Patients diagnosed with HIV infection should be screened for IgG antibodies to T. gondii during the time of their initial workup. T ose who are seronegative should be counseled about ways to minimize the risk of primary infection including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box. T e most common clinical presentation of cerebral toxoplasmosis in patients with HIV infection is fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal deficits or with a picture more inf uenced by the accompanying cerebral edema and characterized by confusion, dementia, and lethargy, which can progress to coma. T e diagnosis is usually suspected on the basis of MRI findings of multiple lesions in multiple locations, although in some cases only a single lesion is seen. Pathologically, these lesions generally exhibit inf ammation and central necrosis and, as a result, demonstrate ring enhancement on contrast MRI **(Fig. 48-8)** or, if MRI is unavailable or contraindicated, on double-dose contrast CT. T ere is usually evidence of surrounding edema. In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the HIV-infected patient includes primary CNS lymphoma and, less commonly, TB or fungal or bacterial abscesses. T e definitive diagnostic procedure is brain biopsy. However, given the morbidity rate that can accompany this procedure, it is usually reserved for the patient who has failed 2–4 weeks of empiric therapy for toxoplasmosis. If the patient is seronegative for T. gondii, the likelihood that a mass lesion is due to toxoplasmosis is <10%. In that setting, one may choose to be more aggressive and perform a brain biopsy sooner. Standard treatment is sulfadiazine and pyrimethamine with leucovorin as needed for a minimum of 4–6 weeks. Alternative therapeutic regimens include clindamycin in combination with pyrimethamine; atovaquone plus pyrimethamine; and azithromycin plus pyrimethamine plus rifabutin. Relapses are common, and it is recommended that patients with a history of prior toxoplasmic encephalitis receive maintenance therapy with sulfadiazine, pyrimethamine, and leucovorin as long as their CD4+ T cell counts remain <200 cells/μL. Patients with CD4+ T cell counts <100/μL and IgG antibody to Toxoplasma should receive primary prophylaxis for toxoplasmosis. Fortunately, the same daily regimen of a single double-strength tablet of TMP/SMX used for P. jiroveci prophylaxis provides adequate primary protection against toxoplasmosis.

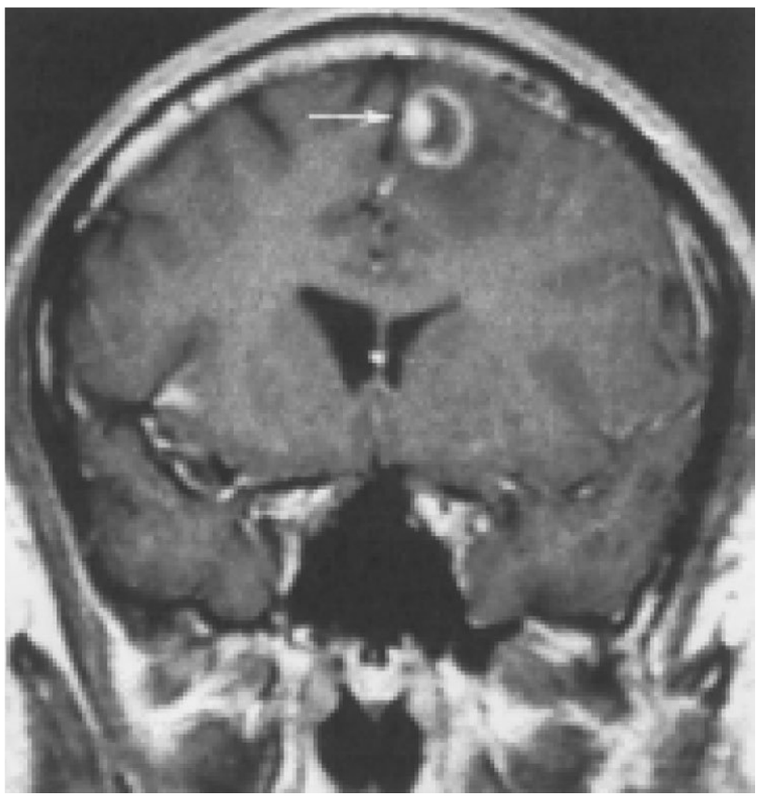


FIGURE 48-8
Central nervous system toxoplasmosis. A coronal postcontrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (arrow); this so-called eccentric target sign is typical of toxoplasmosis.

Secondary prophylaxis/maintenance therapy for toxoplasmosis may be discontinued in the setting of effective cART and increases in CD4+ T cell counts to >200/μL for 6 months.

JC virus, a human polyomavirus that is the etiologic agent of progressive multi*f*ocal leukoencephalopathy (PML), is an important opportunistic pathogen in patients with AIDS **(Chap. 46)**. While ~80% of the general adult population has antibodies to JC virus, indicative of prior infection, <10% of healthy adults show any evidence of ongoing viral replication. PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~1–4% of patients with AIDS. T e lesions of PML begin as small foci of demyelination in subcortical white matter that eventually coalesce. T e cerebral hemispheres, cerebellum, and brainstem may all be involved. Patients typically have a protracted course with multifocal neurologic deficits, with or without changes in mental status. Approximately 20% of patients experience seizures. Ataxia, hemiparesis, visual field defects, aphasia, and sensory defects may occur. Headache, fever, nausea, and vomiting are rarely seen. T eir presence should suggest another diagnosis. MRI typically reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. T e lesions show signal hyperintensity on T2-weighted images and diminished signal on T1-weighted images. T e measurement of JC virus DNA levels in CSF has a diagnostic sensitivity of 76% and a specificity of close to 100%. Prior to the availability of cART, the majority of patients with PML died within 3–6 months of the

www.ketabpezeshki.com (021) 66485457 - 66485438

onset of symptoms. Paradoxical worsening of PML has been seen with initiation of cART as an immune reconstitution syndrome. There is no specific treatment for PML; however, a median survival of 2 years and survival of >15 years have been reported in patients with PML treated with cART for their HIV disease. Despite having a significant impact on survival, only ~50% of patients with HIV infection and PML show neurologic improvement with cART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit. Factors influencing a favorable prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/μL at baseline and the ability to maintain an HIV viral load of <500 copies/mL. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few opportunistic infections that continues to occur with some frequency despite the widespread use of cART.

Reactivation American trypanosomiasis may present as acute meningoencephalitis with focal neurologic signs, fever, headache, vomiting, and seizures. Accompanying cardiac disease in the form of arrhythmias or heart failure should increase the index of suspicion. The presence of antibodies to T. cruzi supports the diagnosis. In South America, reactivation of Chagas' disease is considered to be an AIDS-defining condition and may be the initial AIDS-defining condition. The majority of cases occur in patients with CD4+ T cell counts <200 cells/μL. Lesions appear radiographically as single or multiple hypodense areas, typically with ring enhancement and edema. They are found predominantly in the subcortical areas, a feature that differentiates them from the deeper lesions of toxoplasmosis. T. cruzi amastigotes, or trypanosomes, can be identified from biopsy specimens or CSF. Other CSF findings include elevated protein and a mild (<100 cells/μL) lymphocytic pleocytosis. Organisms can also be identified by direct examination of the blood. Treatment consists of benznimidazole (2.5 mg/kg bid) or nifurtimox (2 mg/kg qid) for at least 60 days, followed by maintenance therapy for the duration of immunodeficiency with either drug at a dose of 5 mg/kg three times a week. As is the case with cerebral toxoplasmosis, successful therapy with antiretrovirals may allow discontinuation of therapy for Chagas' disease.

Stroke may occur in patients with HIV infection. In contrast to the other causes of focal neurologic deficits in patients with HIV infection, the symptoms of a stroke are sudden in onset. Patients with HIV infection have an increased prevalence of many classic risk factors associated with stroke, including smoking and diabetes. It has been reported that HIV infection itself can lead to an increase in carotid artery stiffness. The relative increase in risk for stroke as a consequence of HIV infection is more pronounced in women and in individuals between the ages of 18 and 29. Among the secondary infectious diseases in patients with HIV infection that may be associated with stroke are vasculitis due to cerebral varicella zoster or neurosyphilis and septic embolism in association with fungal infection. Other elements of the differential diagnosis of stroke in the patient with HIV infection include atherosclerotic cerebral vascular disease, thrombotic thrombocytopenic purpura, and cocaine or amphetamine use.

Primary CNS lymphoma is discussed below in the section on neoplastic diseases.

Spinal cord disease, or myelopathy, is present in ~20% of patients with AIDS, often as part of HIV-associated neurocognitive disorder. In fact, 90% of the patients with HIV-associated myelopathy have some evidence of dementia, suggesting that similar pathologic processes may be responsible for both conditions. Three main types of spinal cord disease are seen in patients with AIDS. The first of these is a vacuolar myelopathy, as mentioned above. This condition is pathologically similar to subacute combined degeneration of the cord, such as that occurring with pernicious anemia. Although vitamin B_{12} deficiency can be seen in patients with AIDS as a primary complication of HIV infection, it does not appear to be responsible for the myelopathy seen in the majority of patients. Vacuolar myelopathy is characterized by a subacute onset and often presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction. Physical findings include evidence of increased deep tendon reflexes and extensor plantar responses. The second form of spinal cord disease involves the dorsal columns and presents as a pure sensory ataxia. The third form is also sensory in nature and presents with paresthesias and dysesthesias of the lower extremities. In contrast to the cognitive problems seen in patients with HIV encephalopathy, these spinal cord syndromes do not respond well to antiretroviral drugs, and therapy is mainly supportive.

One important disease of the spinal cord that also involves the peripheral nerves is a myelopathy and polyradiculopathy seen in association with CMV infection. This entity is generally seen late in the course of HIV infection and is fulminant in onset, with lower extremity and sacral paresthesias, difficulty in walking, areflexia, ascending sensory loss, and urinary retention. The clinical course is rapidly progressive over a period of weeks. CSF examination reveals a predominantly neutrophilic pleocytosis, and CMV DNA can be detected by CSF PCR. Therapy with ganciclovir or foscarnet can lead to rapid improvement, and prompt initiation of foscarnet or ganciclovir therapy is important in minimizing the degree of permanent neurologic damage. Combination therapy with both drugs should be considered in patients who have been previously

www.ketabpezeshki.com (021) 66485457 - 66485438

treated for CMV disease. Other diseases involving the spinal cord in patients with HIV infection include HTLV-1-associated myelopathy (HAM), neurosyphilis, infection with herpes simplex or varicella-zoster, TB, and lymphoma.

Peripheral neuropathies are common in patients with HIV infection. T ey occur at all stages of illness and take a variety of forms. Early in the course of HIV infection, an acute inf ammatory demyelinating polyneuropathy resembling Guillain-Barré syndrome may occur **(Chap. 54)**. In other patients, a progressive or relapsing-remitting inf ammatory neuropathy resembling chronic inf ammatory demyelinating polyneuropathy (CIDP) has been noted. Patients commonly present with progressive weakness, aref exia, and minimal sensory changes. CSF examination often reveals a mononuclear pleocytosis, and peripheral nerve biopsy demonstrates a perivascular infiltrate suggesting an autoimmune etiology. Plasma exchange or IVIg has been tried with variable success. Because of the immunosuppressive effects of glucocorticoids, they should be reserved for severe cases of CIDP refractory to other measures. Another autoimmune peripheral neuropathy seen in patients with AIDS is mononeuritis multiplex **(Chap. 54)** due to a necrotizing arteritis of peripheral nerves. T e most common peripheral neuropathy in patients with HIV infection is a distal sensory polyneuropathy (DSPN) also referred to as painful sensory neuropathy (HIV-SN), predominantly sensory neuropathy, or distal symmetric peripheral neuropathy. T is condition may be a direct consequence of HIV infection or a side effect of dideoxynucleoside therapy. It is more common in taller individuals, older individuals, and those with lower CD4 counts. Two-thirds of patients with AIDS may be shown by electrophysiologic studies to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensation and a loss of ankle ref exes. Motor changes are mild and are usually limited to weakness of the intrinsic foot muscles. Response of this condition to antiretrovirals has been variable, perhaps because antiretrovirals are responsible for the problem in some instances. When due to dideoxynucleoside therapy, patients with lower extremity peripheral neuropathy may complain of a sensation that they are walking on ice. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B_{12} deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or analgesics may be effective for dysesthesias. Treatment-naïve patients may respond to cART.

Myopathy may complicate the course of HIV infection; causes include HIV infection itself, zidovudine, and the generalized wasting syndrome. HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. Quite pronounced elevations in creatine kinase may occur in asymptomatic patients, particularly after exercise. T e clinical significance of this as an isolated laboratory finding is unclear. A variety of both inf ammatory and noninf ammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inf ammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine therapy. T is toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymerases. It is reversible following discontinuation of the drug. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 49

PRIMARY AND METASTATIC TUMORS OF THE NERVOUS SYSTEM

Lisa M. DeAngelis ■ Patrick Y. Wen

Primary brain tumors are diagnosed in approximately 52,000 people each year in the United States. At least one-half of these tumors are malignant and associated with a high mortality. Glial tumors account for about 30% of all primary brain tumors, and 80% of those are malignant. Meningiomas account for 35%, vestibular schwannomas 10%, and central nervous system (CNS) lymphomas about 2%. Brain metastases are three times more common than all primary brain tumors combined and are diagnosed in approximately 150,000 people each year. Metastases to the leptomeninges and epidural space of the spinal cord each occur in approximately 3–5% of patients with systemic cancer and are also a major cause of neurologic disability.

APPROACH TO THE PATIENT: Primary and Metastatic Tumors of the Nervous System

CLINICAL FEATURES Brain tumors of any type can present with a variety of symptoms and signs that fall into two categories: general and focal; patients often have a combination of the two **(Table 49-1)**. General or nonspecific symptoms include headache, with or without nausea or vomiting, cognitive difficulties, personality change, and gait disorder. Generalized symptoms arise when the enlarging tumor and its surrounding edema cause an increase in intracranial pressure or direct compression of cerebrospinal fluid (CSF) circulation leading to hydrocephalus. The classic headache associated with a brain tumor is most evident in the morning and improves during the day, but this particular pattern is actually seen in a minority of patients. Headaches are often holocephalic but can be ipsilateral to the side of a tumor. Occasionally, headaches have features of a typical migraine with unilateral throbbing pain associated with visual scotoma. Personality changes may include apathy and withdrawal from social circumstances, mimicking depression. Focal or lateralizing findings include hemiparesis, aphasia, or visual field defect. Lateralizing symptoms are typically subacute and progressive. A visual field defect is often unnoticed by the patient; its presence may only be revealed after it leads to an injury such as an automobile accident occurring in the blind visual field. Language difficulties may be mistaken for confusion. Seizures are a common presentation of brain tumors, occurring in about 25% of patients with brain metastases or malignant gliomas but can be the presenting symptom in up to 90% of patients with a low-grade glioma. All seizures that arise

TABLE 49-1

SYMPTOMS AND SIGNS AT PRESENTATION OF BRAIN TUMORS

	HIGH-GRADE GLIOMA (%)	LOW-GRADE GLIOMA (%)	MENINGIOMA (%)	METASTASES (%)
Generalized				
Impaired cognitive function	50	10	30	60
Hemiparesis	40	10	36	60
Headache	50	40	37	50
Lateralizing				
Seizures	20	70+	17	18
Aphasia	20	<5	—	18
Visual field deficit	—	—	—	7

www.ketabpezeshki.com (021) 66485457 - 66485438

from a brain tumor will have a focal onset whether or not it is apparent clinically.

NEUROIMAGING Cranial MRI is the preferred diagnostic test for any patient suspected of having a brain tumor and should be performed with gadolinium contrast administration. Computed tomography (CT) scan should be reserved for those patients unable to undergo magnetic resonance imaging (MRI; e.g., pacemaker). Malignant brain tumors—whether primary or metastatic—typically enhance with gadolinium and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas usually do not enhance with gadolinium and are best appreciated on fluid-attenuated inversion recovery (FLAIR) MRIs. Meningiomas have a characteristic appearance on MRI because they are dural-based with a dural tail and compress but do not invade the brain. Dural metastases or a dural lymphoma can have a similar appearance. Imaging is characteristic for many primary and metastatic tumors and sometimes will suffice to establish a diagnosis when the location precludes surgical intervention (e.g., brainstem glioma). Functional MRI is useful in presurgical planning to define eloquent sensory, motor, or language cortex. Positron emission tomography (PET) is useful in determining the metabolic activity of the lesions seen on MRI; MR perfusion and spectroscopy can provide information on blood flow or tissue composition. T ese techniques may help distinguish tumor progression from necrotic tissue as a consequence of treatment with radiation and chemotherapy or identify foci of high-grade tumor in an otherwise low-grade-appearing glioma.

Neuroimaging is the only test necessary to diagnose a brain tumor. Laboratory tests are rarely useful, although patients with metastatic disease may have elevation of a tumor marker in their serum that reflects the presence of brain metastases (e.g., β human chorionic gonadotropin [β-hCG] from testicular cancer). Additional testing such as cerebral angiogram, electroencephalogram (EEG), or lumbar puncture is rarely indicated or helpful.

TREATMENT Brain Tumors

T erapy of any intracranial malignancy requires both symptomatic and definitive treatments. Definitive treatment is based on the specific tumor type and includes surgery, radiotherapy, and chemotherapy. However, symptomatic treatments apply to brain tumors of any type. Most high-grade malignancies are accompanied by substantial surrounding edema, which contributes to neurologic disability and raised intracranial pressure. Glucocorticoids are highly ef ective at reducing perilesional edema and improving neurologic function, often within hours of administration. Dexamethasone has been the glucocorticoid of choice because of its relatively low mineralocorticoid activity. Initial doses are typically 12–16 mg/d in divided doses given orally or IV (both are equivalent). Although glucocorticoids rapidly ameliorate symptoms and signs, their long-term use causes substantial toxicity including insomnia, weight gain, diabetes mellitus, steroid myopathy, and personality changes. Consequently, a taper is indicated as definitive treatment is administered and the patient improves.

Patients with brain tumors who present with seizures require antiepileptic drug therapy. T ere is no role for prophylactic antiepileptic drugs in patients who have not had a seizure. T e agents of choice are those drugs that do not induce the hepatic microsomal enzyme system. T ese include levetiracetam, topiramate, lamotrigine, valproic acid, and lacosamide **(Chap. 31)**. Other drugs, such as phenytoin and carbamazepine, are used less frequently because they are potent enzyme inducers that can interfere with both glucocorticoid metabolism and the metabolism of chemotherapeutic agents needed to treat the underlying systemic malignancy or the primary brain tumor. Venous thromboembolic disease occurs in 20–30% of patients with high-grade gliomas and brain metastases. T erefore, prophylactic anticoagulants should be used during hospitalization and in nonambulatory patients. T ose who have had either a deep vein thrombosis or pulmonary embolus can receive therapeutic doses of anticoagulation safely and without increasing the risk for hemorrhage into the tumor. Inferior vena cava filters are reserved for patients with absolute contraindications to anticoagulation such as recent craniotomy.

PRIMARY BRAIN TUMORS

PATHOGENESIS

No underlying cause has been identified for the majority of primary brain tumors. T e only established risk factors are exposure to ionizing radiation (meningiomas, gliomas, and schwannomas) and immunosuppression (primary CNS lymphoma). Evidence for an association with exposure to electromagnetic fields including cellular telephones, head injury, foods containing N-nitroso compounds, or occupational risk factors are unproven. A small minority of patients have a family history of brain tumors. Some of these familial cases are associated with genetic syndromes **(Table 49-2)**.

As with other neoplasms, brain tumors arise as a result of a multistep process driven by the sequential acquisition of genetic alterations. T ese include loss of tumor-suppressor genes (e.g., p53 and phosphatase and tensin homolog on chromosome 10 [PTEN]) and amplification and overexpression of protooncogenes

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 49-2

GENETIC SYNDROMES ASSOCIATED WITH PRIMARY BRAIN TUMORS

SYNDROME	INHERITANCE	GENE/PROTEIN	ASSOCIATED TUMORS
Cowden's syndrome	AD	Mutations of PTEN (ch10p23)	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), meningioma, astrocytoma
			Breast, endometrial, thyroid cancer, trichilemmomas
Familial schwannomatosis	Sporadic	Mutations in INI1/SNF5 (ch22q11)	Schwannomas, gliomas
	Hereditary		
Gardner's syndrome	AD	Mutations in APC (ch5q21)	Medulloblastoma, glioblastoma, craniopharyngioma
			Familial polyposis, multiple osteomas, skin and soft tissue tumors
Gorlin syndrome (basal cell nevus syndrome)	AD	Mutations in Patched 1 gene (ch9q22.3)	Medulloblastomas Basal cell carcinoma
Li-Fraumeni syndrome	AD	Mutations in p53 (ch17p13.1)	Gliomas, medulloblastomas
			Sarcomas, breast cancer, leukemias, others
Multiple endocrine neoplasia 1 (Werner's syndrome)	AD	Mutations in Menin (ch11q13)	Pituitary adenoma, malignant schwannomas Parathyroid and pancreatic islet cell tumors
Neurofibromatosis type 1 (NF1)	AD	Mutations in NF1/neurofibromin (ch17q12-22)	Schwannomas, astrocytomas, optic nerve gliomas, meningiomas
			Neurofibromas, neurofibrosarcomas, others
Neurofibromatosis type 2 (NF2)	AD	Mutations in NF2/merlin (ch22q12)	Bilateral vestibular schwannomas, astrocytomas, multiple meningiomas, ependymomas
Tuberous sclerosis (TSC) (Bourneville disease)	AD	Mutations in TSC1/TSC2 (ch9q34/16)	Subependymal giant-cell astrocytoma, ependymomas, glioma, ganglioneuroma, hamartoma
Turcot syndrome	AD	Mutations in APC[a] (ch5)	Gliomas, medulloblastomas
	AR	hMLH1 (ch3p21)	Adenomatous colon polyps, adenocarcinoma
von Hippel–Lindau (VHL)	AD	Mutations in VHL gene (ch3p25)	Hemangioblastomas
			Retinal angiomas, renal cell carcinoma, pheochromocytoma, pancreatic tumors and cysts, endolymphatic sac tumors of the middle ear

[a]Various DNA mismatch repair gene mutations may cause a similar clinical phenotype, also referred to as Turcot syndrome, in which there is a predisposition to nonpolyposis colon cancer and brain tumors.

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; ch, chromosome; PTEN, phosphatase and tensin homologue; TSC, tuberous sclerosis complex.

such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptors (PDGFR). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation.

Important progress has been made in understanding the molecular pathogenesis of several types of brain tumors, including glioblastoma and medulloblastoma. Morphologically indistinguishable glioblastomas can be separated into four subtypes defined by molecular profiling: (1) classical, characterized by overactivation of the EGFR pathway; (2) proneural, characterized by overexpression of PDGFRA, mutations of the isocitrate dehydrogenase (IDH) 1 and 2 genes, and expression of neural markers; (3) mesenchymal, defined by expression of mesenchymal markers and loss of NF1; and (4) neural, characterized by overactivity of EGFR and expression of neural markers. The clinical implications of these subtypes are under study. Medulloblastoma is the other primary brain tumor that has been highly analyzed, and four molecular subtypes have also been identified: (1) the Wnt subtype is defined by a mutation in β-catenin and has an excellent prognosis; (2) the SHH subtype has mutations in PTCH1, SMO, GLI2, or SUFU and has an intermediate prognosis; (3) group 3 has elevated MYC expression and has the worst prognosis; and (4) group 4 is characterized by isochromosome 17q. Targeted therapeutics are under development for some of the medulloblastoma subtypes, especially the SHH group.

www.ketabpezeshki.com (021) 66485457 - 66485438

INTRINSIC "MALIGNANT" TUMORS

ASTROCYTOMAS

T ese are infiltrative tumors with a presumptive glial cell of origin. T e World Health Organization (WHO) classifies astrocytomas into four prognostic grades based on histologic features: grade I (pilocytic astrocytoma, subependymal giant cell astrocytoma); grade II (dif use astrocytoma); grade III (anaplastic astrocytoma); and grade IV (glioblastoma). Grades I and II are considered low-grade astrocytomas, and grades III and IV are considered high-grade astrocytomas.

Low-grade astrocytoma

T ese tumors occur predominantly in children and young adults.

Grade I astrocytomas

Pilocytic astrocytomas (WHO grade I) are the most common tumor of childhood. T ey occur typically in the cerebellum but may also be found elsewhere in the neuraxis, including the optic nerves and brainstem. Frequently they appear as cystic lesions with an enhancing mural nodule. T ese are well-demarcated lesions that are potentially curable if they can be resected completely. Giant-cell subependymal astrocytomas are usually found in the ventricular wall of patients with tuberous sclerosis. T ey often do not require intervention but can be treated surgically or with inhibitors of the mammalian target of rapamycin (mTOR).

Grade II astrocytomas

T ese are infiltrative tumors that usually present with seizures in young adults. T ey appear as nonenhancing tumors with increased T2/FLAIR signal **(Fig. 49-1)**. If feasible, patients should undergo maximal surgical resection, although complete resection is rarely possible because of the invasive nature of the tumor. Radiation therapy (RT) is helpful, but there is no dif erence in overall survival between RT administered postoperatively or delayed until the time of tumor progression. A recent large trial demonstrated the benefit of chemotherapy plus RT compared to RT alone following surgical resection. T e tumor transforms to a malignant astrocytoma in the majority of patients, leading to variable survival with a median of about 5 years.

High-grade astrocytoma

Grade III (anaplastic) astrocytoma

T ese account for approximately 15–20% of high-grade astrocytomas. T ey generally present in the fourth and fifth decades of life as variably enhancing tumors. Treatment is the same as for glioblastoma, consisting of maximal safe surgical resection followed by RT with concurrent and adjuvant temozolomide or by RT and adjuvant temozolomide alone.

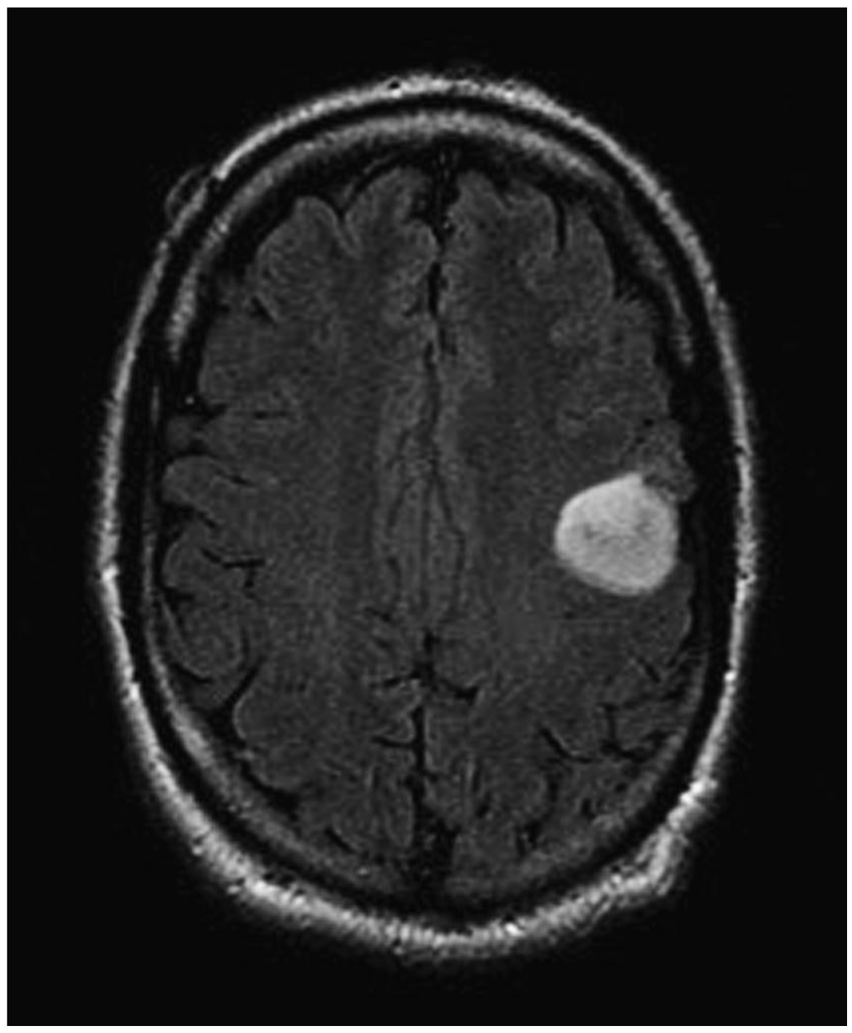


FIGURE 49-1
Fluid-attenuated inversion recovery (FLAIR) MRI of a left frontal low-grade astrocytoma. This lesion did not enhance.

Grade IV astrocytoma (glioblastoma)

Glioblastoma accounts for the majority of high-grade astrocytomas. T ey are the most common malignant primary brain tumor, with over 10,000 cases diagnosed each year in the United States. Patients usually present in the sixth and seventh decades of life with headache, seizures, or focal neurologic deficits. T e tumors appear as ring-enhancing masses with central necrosis and surrounding edema **(Fig. 49-2)**. T ese are highly infiltrative tumors, and the areas of increased T2/FLAIR signal surrounding the main tumor mass contain invading tumor cells. Treatment involves maximal surgical resection followed by partial-field external-beam RT (6000 cGy in thirty 200-cGy fractions) with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. With this regimen, median survival is increased to 14.6 months compared to only 12 months with RT alone, and 2-year survival is increased to 27%, compared to 10% with RT alone. Patients whose tumor contains the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) are relatively resistant to temozolomide and have a worse prognosis compared to those whose tumors contain low levels of MGMT as a result of silencing of the MGMT gene by promoter hypermethylation. Implantation of biodegradable polymers containing the chemotherapeutic agent carmustine into the tumor bed after resection of the tumor also produces a modest improvement in survival.

www.ketabpezeshki.com (021) 66485457 - 66485438

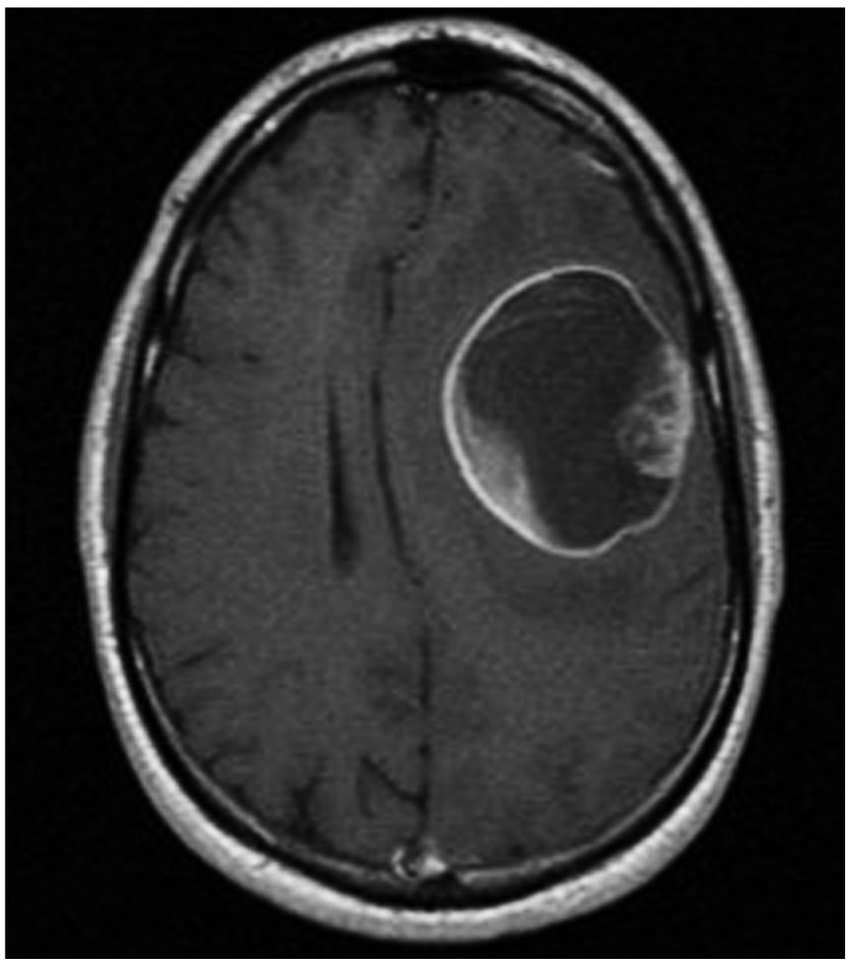
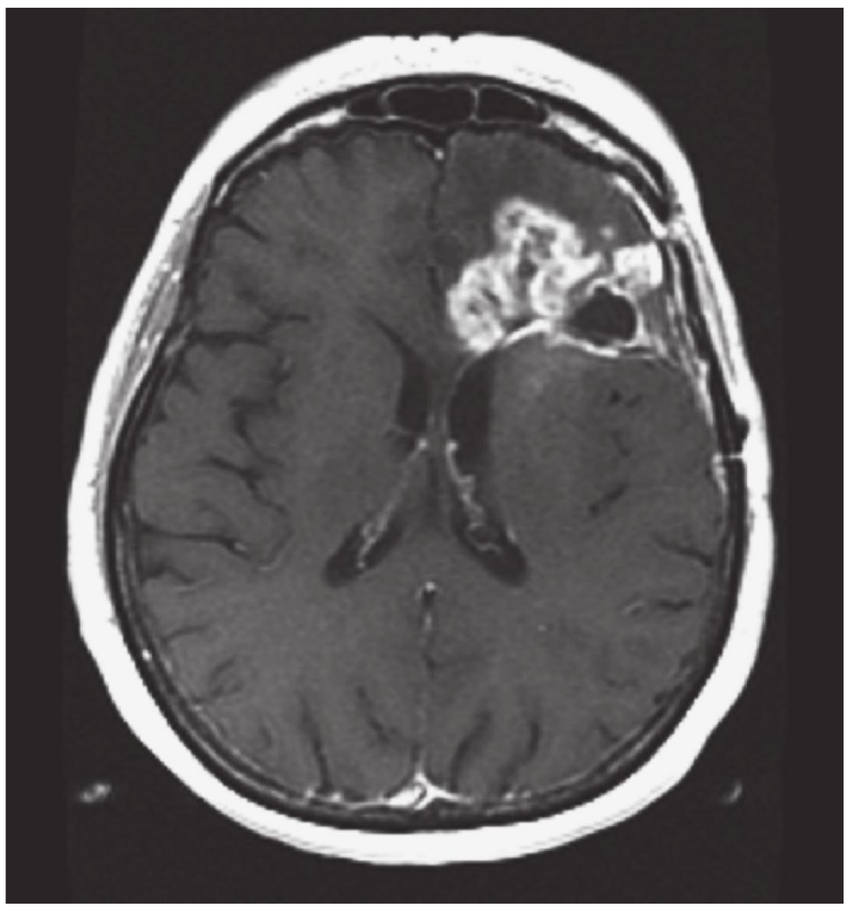


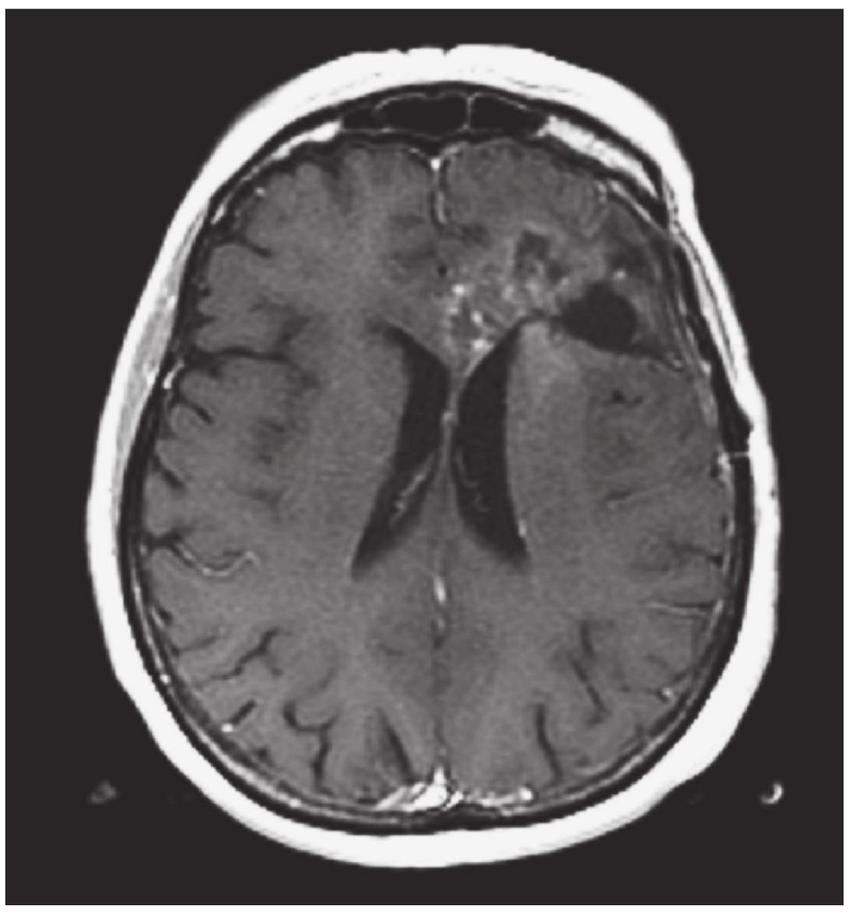
FIGURE 49-2
Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.

Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, carmustine wafers, and alternate chemotherapeutic regimens. Reirradiation is rarely helpful. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, has activity in recurrent glioblastoma, increasing progression-free survival and reducing peritumoral edema and glucocorticoid use **(Fig. 49-3)**. Treatment decisions for patients with recurrent glioblastoma must be made on an individual basis, taking into consideration such factors as previous therapy, time to relapse, performance status, and quality of life. Whenever feasible, patients with recurrent disease should be enrolled in clinical trials. Novel therapies undergoing evaluation in patients with glioblastoma include targeted molecular agents directed at receptor tyrosine kinases and signal transduction pathways; antiangiogenic agents, especially those directed at the VEGF receptors; chemotherapeutic agents that cross the blood-brain barrier more effectively than currently available drugs; gene therapy; immunotherapy; tumor-treating fields delivered by electrodes on the scalp; and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convection-enhanced delivery.

The most important adverse prognostic factors in patients with high-grade astrocytomas are older age, histologic features of glioblastoma, poor Karnofsky performance status, and unresectable tumor. Patients whose tumor contains an unmethylated MGMT promoter resulting in the presence of the repair enzyme in tumor cells and resistance to temozolomide also have a worse prognosis.



A



B

FIGURE 49-3
Postgadolinium T1 MRI of a recurrent glioblastoma before (A) and after (B) administration of bevacizumab. Note the decreased enhancement and mass effect.

Gliomatosis cerebri

Rarely, patients may present with a highly infiltrating, nonenhancing tumor of variable histologic grade involving more than two lobes of the brain. These tumors may be indolent initially, but will eventually behave aggressively and have a poor outcome. Treatment involves RT and temozolomide chemotherapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

OLIGODENDROGLIOMA

Oligodendrogliomas account for approximately 15–20% of gliomas. They are classified by the WHO into well-differentiated oligodendrogliomas (grade II) or anaplastic oligodendrogliomas (AOs) (grade III). Tumors with oligodendroglial components have distinctive pathologic features such as perinuclear clearing—giving rise to a "fried-egg" appearance—and a reticular pattern of blood vessel growth. Some tumors have both an oligodendroglial as well as an astrocytic component. These mixed tumors, or oligoastrocytomas (OAs), are also classified into well-differentiated OA (grade II) or anaplastic oligoastrocytomas (AOAs) (grade III).

Grade II oligodendrogliomas and OAs are generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. These tumors present similarly to grade II astrocytomas in young adults. The tumors are nonenhancing and often partially calcified. They should be treated with surgery and, if necessary, RT and chemotherapy. Patients with oligodendrogliomas have a median survival in excess of 10 years.

AOs and AOAs present in the fourth and fifth decades as variably enhancing tumors. They are more responsive to therapy than grade III astrocytomas. Co-deletion of chromosomes 1p and 19q, mediated by an unbalanced translocation of 19p to 1q, occurs in 61–89% of patients with AO and 14–20% of patients with AOA. Tumors with the 1p and 19q co-deletion are particularly sensitive to chemotherapy with procarbazine, lomustine (cyclohexylchloroethylnitrosourea [CCNU]), and vincristine (PCV) or temozolomide, as well as to RT. Median survival of patients with AO or AOA is approximately 3–6 years, but those with co-deleted tumors can have a median survival of 10–14 years if treated with RT and chemotherapy.

EPENDYMOMAS

Ependymomas are tumors derived from ependymal cells that line the ventricular surface. They account for approximately 5% of childhood tumors and frequently arise from the wall of the fourth ventricle in the posterior fossa. Although adults can have intracranial ependymomas, they occur more commonly in the spine, especially in the filum terminale of the spinal cord where they have a myxopapillary histology. Ependymomas that can be completely resected are potentially curable. Partially resected ependymomas will recur and require irradiation. The less common anaplastic ependymoma is more aggressive and is treated with resection and RT; chemotherapy has limited efficacy. Subependymomas are slow-growing benign lesions arising in the wall of ventricles that often do not require treatment.

OTHER LESS COMMON GLIOMAS

Gangliogliomas and pleomorphic xanthoastrocytomas occur in young adults. They behave as more indolent forms of grade II gliomas and are treated in the same way. Brainstem gliomas usually occur in children or young adults. Despite treatment with RT and chemotherapy, the prognosis is poor, with a median survival of only 1 year. Gliosarcomas contain both an astrocytic as well as a sarcomatous component and are treated in the same way as glioblastomas.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma accounting for less than 3% of primary brain tumors. For unclear reasons, its incidence is increasing, particularly in immunocompetent individuals.

PCNSL in immunocompetent patients usually consists of a diffuse large B cell lymphoma. PCNSL may also occur in immunocompromised patients, usually those infected with the human immunodeficiency virus (HIV) or organ transplant recipients on immunosuppressive therapy. PCNSL in immunocompromised patients is typically large cell with immunoblastic and more aggressive features. These patients are usually severely immunocompromised, with CD4 counts of less than 50/mL. The Epstein-Barr virus (EBV) frequently plays an important role in the pathogenesis of HIV-related PCNSL.

Immunocompetent patients with PCNSL are older (median 60 years) compared to patients with HIV-related PCNSL (median 31 years). PCNSL usually presents as a mass lesion, with neuropsychiatric symptoms, symptoms of increased intracranial pressure, lateralizing signs, or seizures.

On contrast-enhanced MRI, PCNSL usually appears as a densely enhancing tumor **(Fig. 49-4)**. Immunocompetent patients have solitary lesions more often than immunosuppressed patients. Frequently there is involvement of the basal ganglia, corpus callosum, or periventricular region. Although the imaging features are often characteristic, PCNSL can sometimes be difficult to differentiate from high-grade gliomas, infections, or demyelination. Stereotactic biopsy is necessary to obtain a histologic diagnosis. Whenever possible, glucocorticoids should be withheld until after the biopsy has been obtained because they have a cytolytic effect on lymphoma cells and may lead to nondiagnostic tissue. In addition, patients should be tested for HIV and the extent of disease should be assessed by performing PET or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. Bone marrow biopsy and testicular ultrasound are occasionally performed.

www.ketabpezeshki.com (021) 66485457 - 66485438

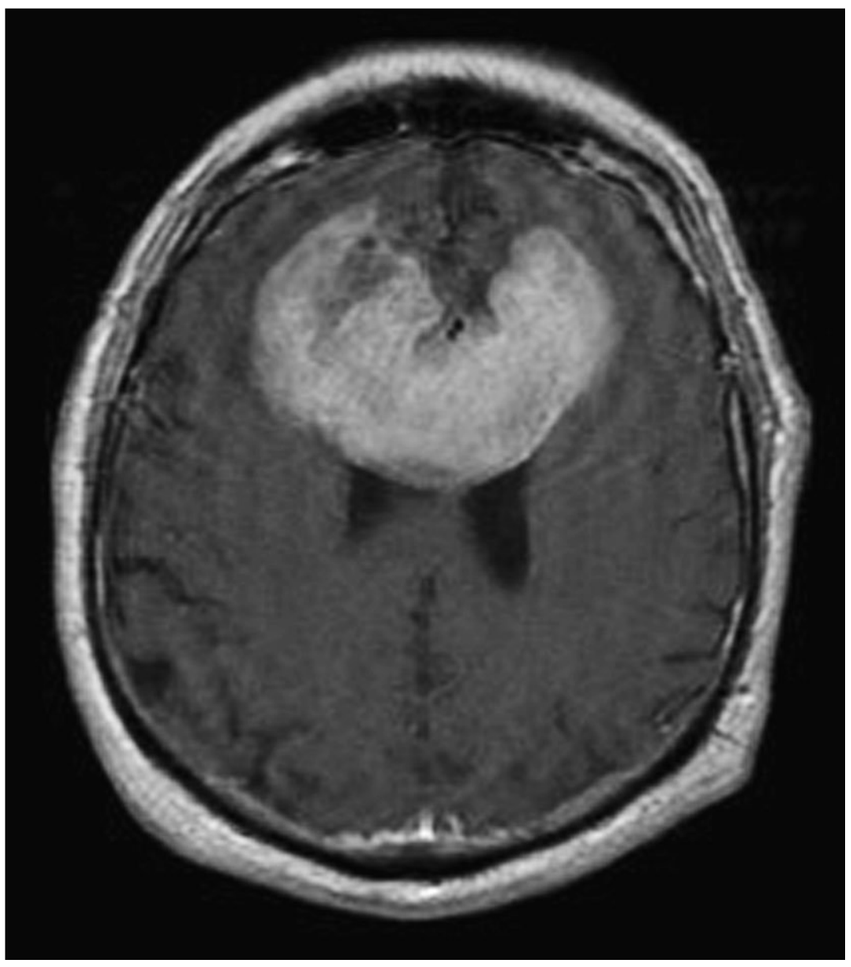


FIGURE 49-4
Postgadolinium T1 MRI demonstrating a large bifrontal primary central nervous system lymphoma (PCNSL). The periventricular location and diffuse enhancement pattern are characteristic of lymphoma.

TREATMENT Primary Central Nervous System Lymphoma

PCNSL is more sensitive to glucocorticoids, chemotherapy, and RT than other primary brain tumors. Durable complete responses and long-term survival are possible with these treatments. High-dose methotrexate, a folate antagonist that interrupts DNA synthesis, produces response rates ranging from 35–80% and median survival of up to 50 months. The combination of methotrexate with other chemotherapeutic agents such as cytarabine increases the response rate to 70–100%. The addition of whole-brain RT to methotrexate-based chemotherapy prolongs progression-free survival but not overall survival. Furthermore, RT is associated with delayed neurotoxicity, especially in patients over the age of 60 years. As a result, full-dose RT is frequently omitted, but there may be a role for reduced-dose RT. The anti-CD20 monoclonal antibody rituximab has activity in PCNSL and is often incorporated into the chemotherapy regimen. For some patients, high-dose chemotherapy with autologous stem cell rescue may offer the best chance of preventing relapse. At least 50% of patients will eventually develop recurrent disease. Treatment options include RT for patients who have not had prior irradiation, re-treatment with methotrexate, as well as other agents such as temozolomide, rituximab, procarbazine, topotecan, and pemetrexed. High-dose chemotherapy with autologous stem cell rescue may have a role in selected patients with relapsed disease.

PCNSL IN IMMUNOCOMPROMISED PATIENTS PCNSL in immunocompromised patients often produces multiple ring-enhancing lesions that can be difficult to differentiate from metastases and infections such as toxoplasmosis. The diagnosis is usually established by examination of the CSF for cytology and EBV DNA, toxoplasmosis serologic testing, brain PET imaging for hypermetabolism of the lesions consistent with tumor instead of infection, and, if necessary, brain biopsy. Since the advent of highly active antiretroviral drugs, the incidence of HIV-related PCNSL has declined. These patients may be treated with whole-brain RT, high-dose methotrexate, and initiation of highly active antiretroviral therapy. In organ transplant recipients, reduction of immunosuppression may improve outcome.

MEDULLOBLASTOMAS

Medulloblastomas are the most common malignant brain tumor of childhood, accounting for approximately 20% of all primary CNS tumors among children. They arise from granule cell progenitors or from multipotent progenitors from the ventricular zone. Approximately 5% of children have inherited disorders with germline mutations of genes that predispose to the development of medulloblastoma. Gorlin syndrome, the most common of these inherited disorders, is due to mutations in the patched-1 (PTCH-1) gene, a key component in the sonic hedgehog pathway. Turcot syndrome, caused by mutations in the adenomatous polyposis coli (APC) gene and familial adenomatous polyposis, has also been associated with an increased incidence of medulloblastoma. Histologically, medulloblastomas are highly cellular tumors with abundant dark staining, round nuclei, and rosette formation (Homer-Wright rosettes). They present with headache, ataxia, and signs of brainstem involvement. On MRI they appear as densely enhancing tumors in the posterior fossa, sometimes associated with hydrocephalus. Seeding of the CSF is common. Treatment involves maximal surgical resection, craniospinal irradiation, and chemotherapy with agents such as cisplatin, lomustine, cyclophosphamide, and vincristine. Approximately 70% of patients have long-term survival but usually at the cost of significant neurocognitive impairment. A major goal of current research is to improve survival while minimizing long-term complications.

PINEAL REGION TUMORS

A large number of tumors can arise in the region of the pineal gland. These typically present with headache, visual symptoms, and hydrocephalus. Patients may have Parinaud syndrome characterized by impaired upgaze and accommodation. Some pineal tumors such as pineocytomas and benign teratomas can be treated simply by surgical resection. Germinomas respond to irradiation, whereas pineoblastomas and malignant germ cell tumors require craniospinal radiation and chemotherapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

EXTRINSIC "BENIGN" TUMORS

MENINGIOMAS

Meningiomas are diagnosed with increasing frequency as more people undergo neuroimaging for various indications. T ey are now the most common primary brain tumor, accounting for approximately 35% of the total. T eir incidence increases with age. T ey tend to be more common in women and in patients with neurofibromatosis type 2. T ey also occur more commonly in patients with a past history of cranial irradiation.

Meningiomas arise from the dura mater and are composed of neoplastic meningothelial (arachnoidal cap) cells. T ey are most commonly located over the cerebral convexities, especially adjacent to the sagittal sinus, but can also occur in the skull base and along the dorsum of the spinal cord. Meningiomas are classified by the WHO into three histologic grades of increasing aggressiveness: grade I (benign), grade II (atypical), and grade III (malignant).

Many meningiomas are found incidentally following neuroimaging for unrelated reasons. T ey can also present with headaches, seizures, or focal neurologic deficits. On imaging studies they have a characteristic appearance usually consisting of a partially calcified, densely enhancing extraaxial tumor arising from the dura **(Fig. 49-5)**. Occasionally they may have a dural tail, consisting of thickened, enhanced dura extending like a tail from the mass. T e main dif erential diagnosis of meningioma is a dural metastasis.

If the meningioma is small and asymptomatic, no intervention is necessary and the lesion can be observed with serial MRI studies. Larger, symptomatic lesions should be resected. If complete resection is achieved, the patient is cured. Incompletely resected tumors tend to recur, although the rate of recurrence can be very slow with grade I tumors. Tumors that cannot be resected, or can only be partially removed, may benefit from treatment with external-beam RT or stereotactic radiosurgery (SRS). T ese treatments may also be helpful in patients whose tumor has recurred after surgery. Hormonal therapy and chemotherapy are currently unproven.

Rarer tumors that resemble meningiomas include hemangiopericytomas and solitary fibrous tumors. T ese are treated with surgery and RT but have a higher propensity to recur locally or metastasize systemically.

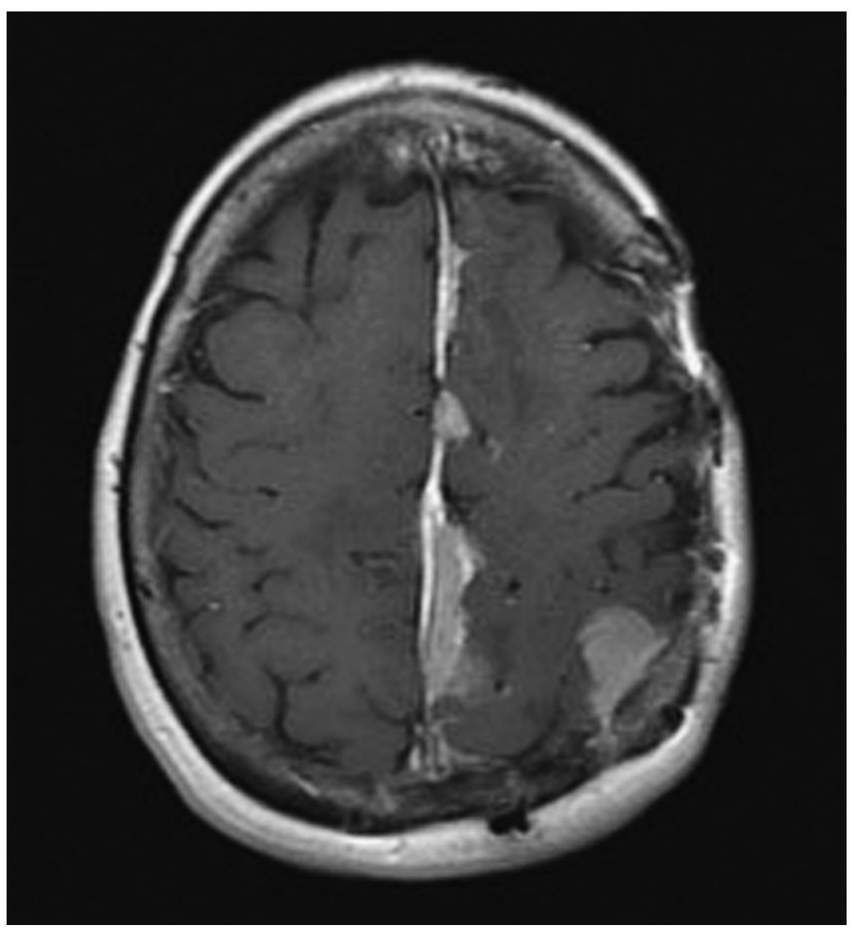


FIGURE 49-5
Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

SCHWANNOMAS

T ese are generally benign tumors arising from the Schwann cells of cranial and spinal nerve roots. T e most common schwannomas, termed vestibular schwannomas or acoustic neuromas, arise from the vestibular portion of the eighth cranial nerve and account for approximately 9% of primary brain tumors. Patients with neurofibromatosis type 2 have a high incidence of vestibular schwannomas that are frequently bilateral. Schwannomas arising from other cranial nerves, such as the trigeminal nerve (cranial nerve V), occur with much lower frequency. Neurofibromatosis type 1 is associated with an increased incidence of schwannomas of the spinal nerve roots.

Vestibular schwannomas may be found incidentally on neuroimaging or present with progressive unilateral hearing loss, dizziness, tinnitus, or less commonly, symptoms resulting from compression of the brainstem and cerebellum. On MRI they appear as densely enhancing lesions, enlarging the internal auditory canal and often extending into the cerebellopontine angle **(Fig. 49-6)**. T e dif erential diagnosis includes meningioma. Very small, asymptomatic lesions can be observed with serial MRIs. Larger lesions should be treated with surgery or SRS. T e optimal treatment will depend on the size of the tumor, symptoms, and the patient's preference. In patients with small vestibular schwannomas and relatively intact hearing, early surgical intervention increases the chance of preserving hearing.

PITUITARY TUMORS

T ese account for approximately 9% of primary brain tumors. T ey can be divided into functioning and nonfunctioning tumors. Functioning tumors are usually microadenomas (<1 cm in diameter) that secrete hormones and produce specific endocrine syndromes (e.g., acromegaly for growth hormone–secreting tumors, Cushing syndrome for adrenocorticotropic hormone [ACTH]-secreting tumors, and galactorrhea,

www.ketabpezeshki.com (021) 66485457 - 66485438

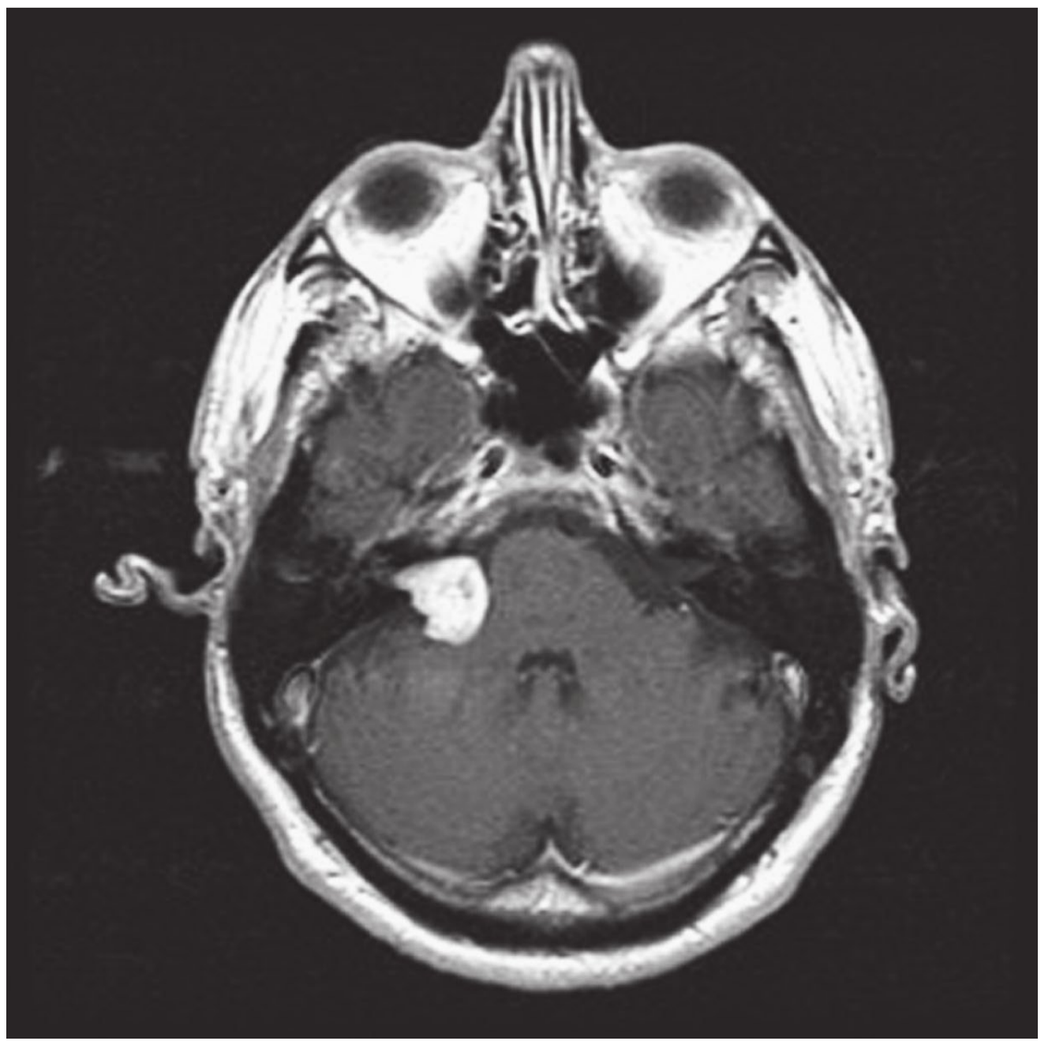


FIGURE 49-6
Postgadolinium MRI of a right vestibular schwannoma. The tumor can be seen to involve the internal auditory canal.

amenorrhea, and infertility for prolactin-secreting tumors). Nonfunctioning pituitary tumors tend to be macroadenomas (>1 cm) that produce symptoms by mass effect, giving rise to headaches, visual impairment (such as bitemporal hemianopia), and hypopituitarism. Prolactin-secreting tumors respond well to dopamine agonists such as bromocriptine and cabergoline. Other pituitary tumors usually require treatment with surgery and sometimes RT or radiosurgery and hormonal therapy.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are rare, usually suprasellar, partially calcified, solid, or mixed solid-cystic benign tumors that arise from remnants of Rathke's pouch. They have a bimodal distribution, occurring predominantly in children but also between the ages of 55 and 65 years. They present with headaches, visual impairment, and impaired growth in children and hypopituitarism in adults. Treatment involves surgery, RT, or a combination of the two.

OTHER BENIGN TUMORS

Dysembryoplastic neuroepithelial tumors (DNTs)

These are benign, supratentorial tumors, usually in the temporal lobe. They typically occur in children and young adults with a long-standing history of seizures. Surgical resection is curative.

Epidermoid cysts

These consist of squamous epithelium surrounding a keratin-filled cyst. They are usually found in the cerebellopontine angle and the intrasellar and suprasellar regions. They may present with headaches, cranial nerve abnormalities, seizures, or hydrocephalus. Imaging studies demonstrate extraaxial lesions with characteristics that are similar to CSF but have restricted diffusion. Treatment involves surgical resection.

Dermoid cysts

Like epidermoid cysts, dermoid cysts arise from epithelial cells that are retained during closure of the neural tube. They contain both epidermal and dermal structures such as hair follicles, sweat glands, and sebaceous glands. Unlike epidermoid cysts, these tumors usually have a midline location. They occur most frequently in the posterior fossa, especially the vermis, fourth ventricle, and suprasellar cistern. Radiographically, dermoid cysts resemble lipomas, demonstrating T1 hyperintensity and variable signal on T2. Symptomatic dermoid cysts can be treated with surgery.

Colloid cysts

These usually arise in the anterior third ventricle and may present with headaches, hydrocephalus, and, very rarely, sudden death. Surgical resection is curative, or a third ventriculostomy may relieve the obstructive hydrocephalus and be sufficient therapy.

NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES)

A number of genetic disorders are characterized by cutaneous lesions and an increased risk of brain tumors. Most of these disorders have an autosomal dominant inheritance with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (NF1) (VON RECKLINGHAUSEN'S DISEASE)

NF1 is an autosomal dominant disorder with an incidence of approximately 1 in 2600–3000. Approximately one-half the cases are familial; the remainder are caused by new mutations arising in patients with un-affected parents. The NF1 gene on chromosome 17q11.2 encodes a protein, neurofibromin, a guanosine triphosphatase (GTPase)-activating protein (GAP) that modulates signaling through the ras pathway. Mutations of NF1 result in a large number of nervous system tumors including neurofibromas, plexiform neurofibromas, optic nerve gliomas, astrocytomas, and meningiomas. In addition to

www.ketabpezeshki.com (021) 66485457 - 66485438

neurofibromas, which appear as multiple, soft, rubbery cutaneous tumors, other cutaneous manifestations of NF1 include café-au-lait spots and axillary freckling. NF1 is also associated with hamartomas of the iris termed Lisch nodules, pheochromocytomas, pseudoarthrosis of the tibia, scoliosis, epilepsy, and mental retardation.

NEUROFIBROMATOSIS TYPE 2 (NF2)

NF2 is less common than NF1, with an incidence of 1 in 25,000–40,000. It is an autosomal dominant disorder with full penetrance. As with NF1, approximately one-half the cases arise from new mutations. T e NF2 gene on 22q encodes a cytoskeletal protein, merlin (moesin, ezrin, radixin-like protein) that functions as a tumor suppressor. NF2 is characterized by bilateral vestibular schwannomas in over 90% of patients, multiple meningiomas, and spinal ependymomas and astrocytomas. Treatment of bilateral vestibular schwannomas can be challenging because the goal is to preserve hearing for as long as possible. T ese patients may also have dif use schwannomatosis that may af ect the cranial, spinal, or peripheral nerves; posterior subcapsular lens opacities; and retinal hamartomas.

TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE)

T is is an autosomal dominant disorder with an incidence of approximately 1 in 5000–10,000 live births. It is caused by mutations in either the TSC1 gene, which maps to chromosome 9q34 and encodes a protein termed hamartin, or the TSC2 gene, which maps to chromosome 16p13.3 and encodes the protein tuberin. Hamartin forms a complex with tuberin, which inhibits cellular signaling through the mTOR, and acts as a negative regulator of the cell cycle. Patients with tuberous sclerosis may have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periungual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. T ese patients have an increased incidence of subependymal nodules, cortical tubers, and subependymal giant-cell astrocytomas (SEGA). Patients frequently require anticonvulsants for seizures. SEGAs do not always require therapeutic intervention, but the most ef ective therapy is with the mTOR inhibitors sirolimus or everolimus, which often decrease seizures as well as SEGA size.

TUMORS METASTATIC TO THE BRAIN

Brain metastases arise from hematogenous spread and frequently either arise from a lung primary or are associated with pulmonary metastases. Most metastases develop at the gray matter–white matter junction in the watershed distribution of the brain where intravascular tumor cells lodge in terminal arterioles. T e distribution of metastases in the brain approximates the proportion of blood flow such that about 85% of all metastases are supratentorial and 15% occur in the posterior fossa. T e most common sources of brain metastases are lung and breast carcinomas; melanoma has the greatest propensity to metastasize to the brain, being found in 80% of patients at autopsy **Table 49-3**). Other tumor types such as ovarian and esophageal carcinoma rarely metastasize to the brain. Prostate and breast cancer also have a propensity to metastasize to the dura and can mimic meningioma. Leptomeningeal metastases are common from hematologic malignancies and also breast and lung cancers. Spinal cord compression primarily arises in patients with prostate and breast cancer, tumors with a strong propensity to metastasize to the axial skeleton.

DIAGNOSIS OF METASTASES

Brain metastases are best visualized on MRI, where they usually appear as well-circumscribed lesions **(Fig. 49-7)**. T e amount of perilesional edema can be highly variable, with large lesions causing minimal edema and sometimes very small lesions causing extensive edema. Enhancement may be in a ring pattern or dif use. Occasionally, intracranial metastases will hemorrhage; although melanoma, thyroid, and kidney cancer have the greatest propensity to hemorrhage, the most common cause of a hemorrhagic metastasis is lung cancer because it accounts for the majority of brain metastases. T e radiographic appearance of brain metastasis is nonspecific, and similar-appearing lesions

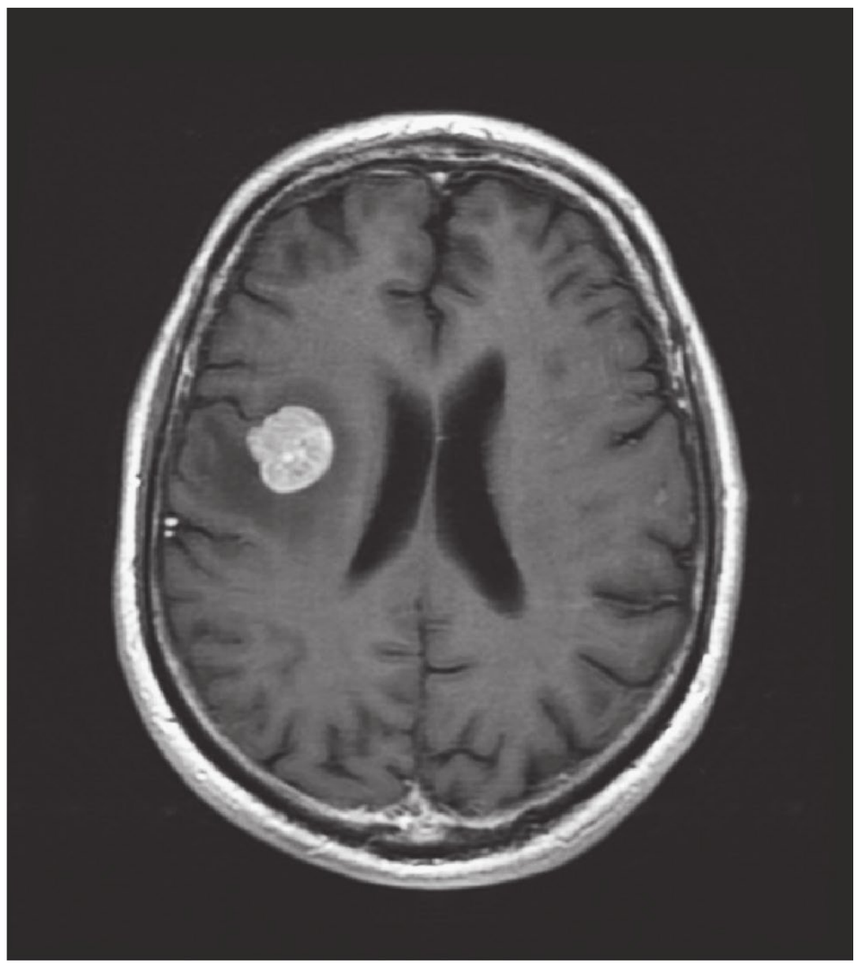
TABLE 49-3

FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS

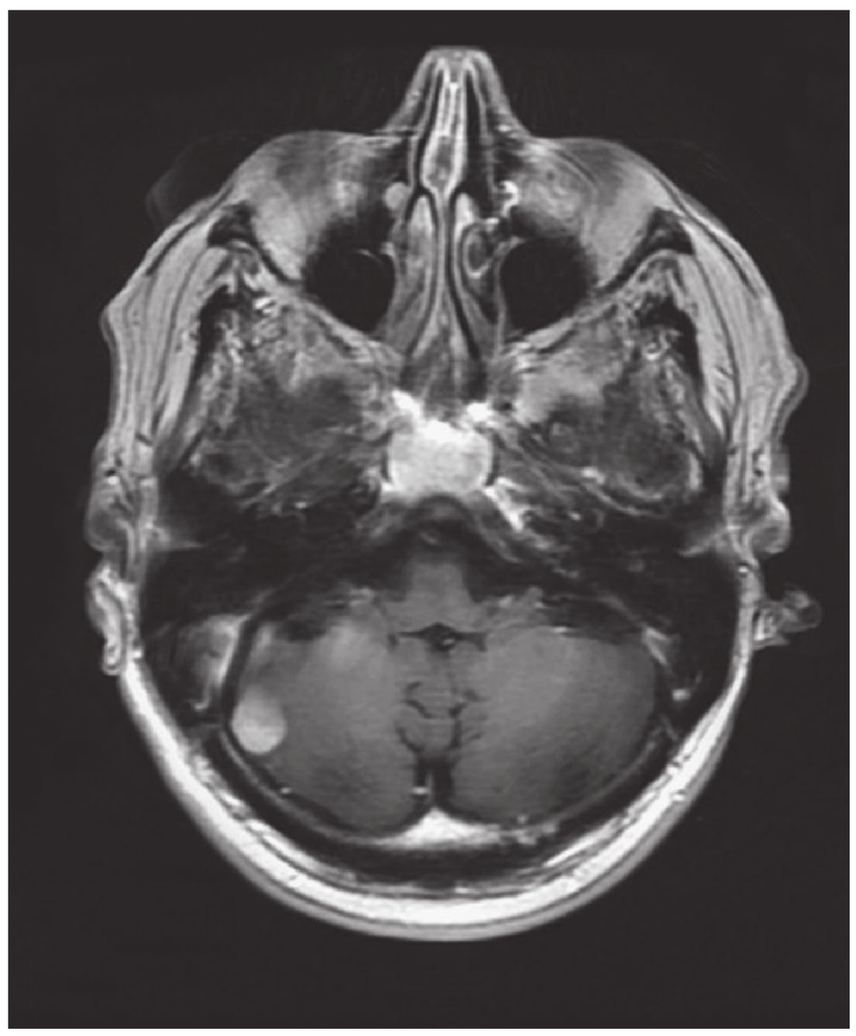
	BRAIN %	LM %	ESCC %
Lung	41	17	15
Breast	19	57	22
Melanoma	10	12	4
Prostate	1	1	10
GIT	7	—	5
Renal	3	2	7
Lymphoma	<1	10	10
Sarcoma	7	1	9
Other	11	—	18

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.

www.ketabpezeshki.com (021) 66485457 - 66485438



A



B

FIGURE 49-7
Postgadolinium T1 MRI of multiple brain metastases from non-small-cell lung cancer involving the right frontal (A) and right cerebellar (B) hemispheres. Note the diffuse enhancement pattern and absence of central necrosis.

can occur with infection including brain abscesses and also with demyelinating lesions, sarcoidosis, radiation necrosis in a previously treated patient, or a primary brain tumor that may be a second malignancy in a patient with systemic cancer. However, biopsy is rarely necessary for diagnosis in most patients because imaging alone in the appropriate clinical situation usually suffices. This is straightforward for the majority of patients with brain metastases because they have a known systemic cancer. However, in approximately 10% of patients, a systemic cancer may present with a brain metastasis, and if there is not an easily accessible systemic site to biopsy, then a brain lesion must be removed for diagnostic purposes.

TREATMENT Tumors Metastatic to the Brain

DEFINITIVE TREATMENT The number and location of brain metastases often determine the therapeutic options. The patient's overall condition and the current or potential control of the systemic disease are also major determinants. Brain metastases are single in approximately one-half of patients and multiple in the other half.

RADIATION THERAPY The standard treatment for brain metastases has been whole-brain radiotherapy (WBRT) usually administered to a total dose of 3000 cGy in 10 fractions. This affords rapid palliation, and approximately 80% of patients improve with glucocorticoids and RT. However, it is not curative. Median survival is only 4–6 months. More recently, SRS delivered through a variety of techniques including the gamma knife, linear accelerator, proton beam, and CyberKnife all can deliver highly focused doses of RT, usually in a single fraction. SRS can effectively sterilize the visible lesions and afford local disease control in 80–90% of patients. In addition, there are some patients who have clearly been cured of their brain metastases using SRS, whereas this is distinctly rare with WBRT. However, SRS can be used only for lesions 3 cm or less in diameter and should be confined to patients with only one to three metastases. The addition of WBRT to SRS improves disease control in the nervous system but does not prolong survival.

SURGERY Randomized controlled trials have demonstrated that surgical extirpation of a single brain metastasis followed by WBRT is superior to WBRT alone. Removal of two lesions or a single symptomatic mass, particularly if compressing the ventricular system, can also be useful. This is particularly useful in patients who have highly radioresistant lesions such as renal carcinoma. Surgical resection can afford rapid symptomatic improvement and prolonged survival. WBRT administered after complete resection of a brain metastasis improves disease control but does not prolong survival.

CHEMOTHERAPY Chemotherapy is rarely useful for brain metastases. Metastases from certain tumor types that are highly chemosensitive, such as germ cell tumors or small-cell lung cancer, may respond to chemotherapeutic regimens chosen according to the underlying malignancy. Increasingly, there are data demonstrating responsiveness of brain metastases to chemotherapy including small molecule–targeted therapy when the lesion possesses the target. This has been

www.ketabpezeshki.com (021) 66485457 - 66485438

best illustrated in patients with lung cancer harboring EGFR mutations that sensitize them to EGFR inhibitors. Antiangiogenic agents such as bevacizumab may also prove efficacious in the treatment of CNS metastases.

LEPTOMENINGEAL METASTASES

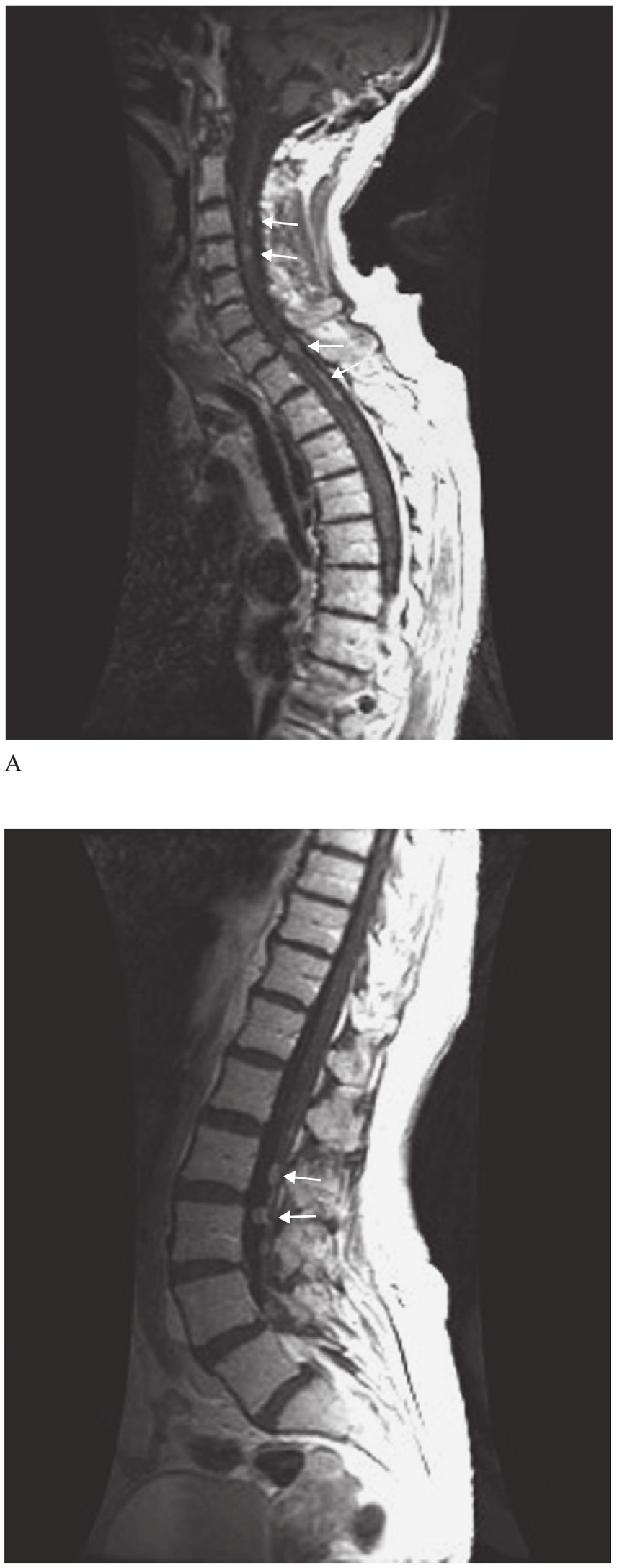
Leptomeningeal metastases are also identified as carcinomatous meningitis, meningeal carcinomatosis, or in the case of specific tumors, leukemic or lymphomatous meningitis. Among the hematologic malignancies, acute leukemia is the most common to metastasize to the subarachnoid space, and in lymphomas the aggressive diffuse lymphomas can metastasize to the subarachnoid space frequently as well. Among solid tumors, breast and lung carcinomas and melanoma most frequently spread in this fashion. Tumor cells reach the subarachnoid space via the arterial circulation or occasionally through retrograde flow in venous systems that drain metastases along the bony spine or cranium. In addition, leptomeningeal metastases may develop as a direct consequence of prior brain metastases and can develop in almost 40% of patients who have a metastasis resected from the cerebellum.

CLINICAL FEATURES

Leptomeningeal metastases are characterized clinically by multilevel symptoms and signs along the neuraxis. Combinations of lumbar and cervical radiculopathies, cranial neuropathies, seizures, confusion, and encephalopathy from hydrocephalus or raised intracranial pressure can be present. Focal deficits such as hemiparesis or aphasia are rarely due to leptomeningeal metastases unless there is direct brain infiltration, and they are more often associated with coexisting brain lesions. New-onset limb pain in patients with breast cancer, lung cancer, or melanoma should prompt consideration of leptomeningeal spread.

LABORATORY AND IMAGING DIAGNOSIS

Leptomeningeal metastases are particularly challenging to diagnose because identification of tumor cells in the subarachnoid compartment may be elusive. MRI can be definitive in patients when there are clear tumor nodules adherent to the cauda equina or spinal cord, enhancing cranial nerves, or subarachnoid enhancement on brain imaging **(Fig. 49-8)**. Imaging is diagnostic in approximately 75% of patients and is more often positive in patients with solid tumors. Demonstration of tumor cells in the CSF is definitive and often considered the gold standard. However, CSF cytologic examination is positive in only 50% of patients on the first lumbar puncture and still misses 10% after three CSF samples. CSF cytologic examination is most useful in hematologic malignancies. Accompanying CSF abnormalities include an elevated protein concentration and an elevated white count. Hypoglycorrhachia is noted in less than 25% of patients but is useful when



A

B

FIGURE 49-8
Postgadolinium MRI images of extensive leptomeningeal metastases from breast cancer. Nodules along the dorsal surface of the spinal cord (A) and cauda equina (B) are seen.

www.ketabpezeshki.com (021) 66485457 - 66485438

present. Identification of tumor markers or molecular confirmation of clonal proliferation with techniques such as flow cytometry within the CSF can also be definitive when present. Tumor markers are usually specific to solid tumors, and chromosomal or molecular markers are most useful in patients with hematologic malignancies. New technologies, such as rare cell capture, may enhance identification of tumor cells in the CSF.

TREATMENT Leptomeningeal Metastases

The treatment of leptomeningeal metastasis is palliative because there is no curative therapy. RT to the symptomatically involved areas, such as skull base for cranial neuropathy, can relieve pain and sometimes improve function. Whole-neuraxis RT has extensive toxicity with myelosuppression and gastrointestinal irritation as well as limited effectiveness. Systemic chemotherapy with agents that can penetrate the blood-CSF barrier may be helpful. Alternatively, intrathecal chemotherapy can be effective, particularly in hematologic malignancies. This is optimally delivered through an intraventricular cannula (Ommaya reservoir) rather than by lumbar puncture. Few drugs can be delivered safely into the subarachnoid space, and they have a limited spectrum of antitumor activity, perhaps accounting for the relatively poor response to this approach. In addition, impaired CSF flow dynamics can compromise intrathecal drug delivery. Surgery has a limited role in the treatment of leptomeningeal metastasis, but placement of a ventriculoperitoneal shunt can relieve raised intracranial pressure. However, it compromises delivery of chemotherapy into the CSF.

EPIDURAL METASTASIS

Epidural metastasis occurs in 3–5% of patients with a systemic malignancy and causes neurologic compromise by compressing the spinal cord or cauda equina. The most common cancers that metastasize to the epidural space are those malignancies that spread to bone, such as breast and prostate. Lymphoma can cause bone involvement and compression, but it can also invade the intervertebral foramens and cause spinal cord compression without bone destruction. The thoracic spine is affected most commonly, followed by the lumbar and then cervical spine.

CLINICAL FEATURES

Back pain is the presenting symptom of epidural metastasis in virtually all patients; the pain may precede neurologic findings by weeks or months. The pain is usually exacerbated by lying down; by contrast, arthritic pain is often relieved by recumbency. Leg weakness is seen in about 50% of patients, as is sensory dysfunction. Sphincter problems are present in about 25% of patients at diagnosis.

DIAGNOSIS

Diagnosis is established by imaging, with MRI of the complete spine being the best test **(Fig. 49-9)**. Contrast is not needed to identify spinal or epidural lesions. Any patient with cancer who has severe back pain should undergo an MRI. Plain films, bone scans, or even CT scans may show bone metastases, but only MRI can reliably delineate epidural tumor. For patients unable to have an MRI, CT myelography should be performed to outline the epidural space. The differential diagnosis of epidural tumor includes epidural abscess, acute or chronic hematomas, and rarely, extramedullary hematopoiesis.

TREATMENT Epidural Metastasis

Epidural metastasis requires immediate treatment. A randomized controlled trial demonstrated the superiority of surgical resection followed by RT compared to RT alone. However, patients must be able to tolerate surgery, and the surgical procedure of choice is a complete removal of the mass, which is typically anterior to the spinal canal, necessitating an extensive approach and resection. Otherwise, RT is

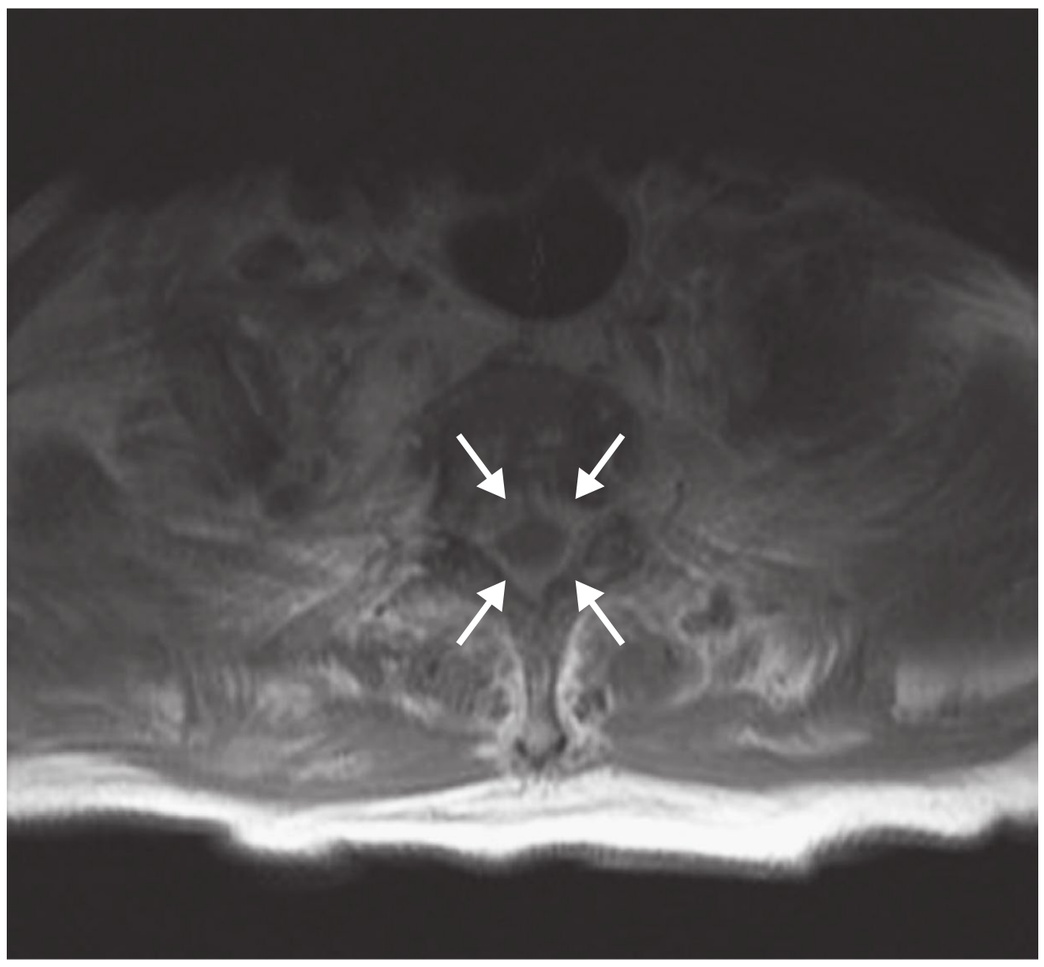


FIGURE 49-9
Postgadolinium T1 MRI showing circumferential epidural tumor around the thoracic spinal cord from esophageal cancer.

www.ketabpezeshki.com (021) 66485457 - 66485438

the mainstay of treatment and can be used for patients with radiosensitive tumors, such as lymphoma, or for those unable to undergo surgery. Chemotherapy is rarely used for epidural metastasis unless the patient has minimal to no neurologic deficit and a highly chemosensitive tumor such as lymphoma or germinoma. Patients generally fare well if treated before there is severe neurologic deficit. Recovery after paraparesis is better after surgery than with RT alone, but survival is often short due to widespread metastatic tumor.

NEUROLOGIC TOXICITY OF THERAPY

TOXICITY FROM RADIOTHERAPY

RT can cause a variety of toxicities in the CNS. T ese are usually described based on their relationship in time to the administration of RT: acute (occurring within days of RT), early delayed (months), or late delayed (years). In general, the acute and early delayed syndromes resolve and do not result in persistent deficits, whereas the late delayed toxicities are usually permanent and sometimes progressive.

Acute toxicity

Acute cerebral toxicity usually occurs during RT to the brain. RT can cause a transient disruption of the blood-brain barrier, resulting in increased edema and elevated intracranial pressure. T is is usually manifest as headache, lethargy, nausea, and vomiting and can be both prevented and treated with the administration of glucocorticoids. T ere is no acute RT toxicity that af ects the spinal cord.

Early delayed toxicity

Early delayed toxicity is usually apparent weeks to months after completion of cranial irradiation and is likely due to focal demyelination. Clinically it may be asymptomatic or take the form of worsening or reappearance of a preexisting neurologic deficit. At times a contrast-enhancing lesion can be seen on MRI/CT that can mimic the tumor for which the patient received the RT. For patients with a malignant glioma, this has been described as "pseudoprogression" because it mimics tumor recurrence on MRI but actually represents inflammation and necrotic debris engendered by ef ective therapy. T is is seen with increased frequency when chemotherapy, particularly temozolomide, is given concurrently with RT. Pseudoprogression can resolve on its own or, if very symptomatic, may require resection. A rare form of early delayed toxicity is the somnolence syndrome that occurs primarily in children and is characterized by marked sleepiness.

In the spinal cord, early delayed RT toxicity is manifest as a Lhermitte symptom with paresthesias of the limbs or along the spine when the patient flexes the neck. Although frightening, it is benign, resolves on its own, and does not portend more serious problems.

Late delayed toxicity

Late delayed toxicities are the most serious because they are often irreversible and cause severe neurologic deficits. In the brain, late toxicities can take several forms, the most common of which include radiation necrosis and leukoencephalopathy. Radiation necrosis is a focal mass of necrotic tissue that is contrast enhancing on CT/MRI and may be associated with significant edema. T is may appear identical to pseudoprogression but is seen months to years after RT and is always symptomatic. Clinical symptoms and signs include seizure and lateralizing findings referable to the location of the necrotic mass. T e necrosis is caused by the ef ect of RT on cerebral vasculature with resultant fibrinoid necrosis and occlusion of the blood vessels. It can mimic tumor radiographically, but unlike tumor, it is typically hypometabolic on a PET scan and has reduced perfusion on perfusion MR sequences. It may require resection for diagnosis and treatment unless it can be managed with glucocorticoids. T ere are rare reports of improvement with hyperbaric oxygen or anticoagulation, but the usefulness of these approaches is questionable.

Leukoencephalopathy is seen most commonly after WBRT as opposed to focal RT. On T2 or FLAIR MR sequences, there is dif use increased signal seen throughout the hemispheric white matter, often bilaterally and symmetrically. T ere tends to be a periventricular predominance that may be associated with atrophy and ventricular enlargement. Clinically, patients develop cognitive impairment, gait disorder, and later urinary incontinence, all of which can progress over time. T ese symptoms mimic those of normal pressure hydrocephalus, and placement of a ventriculoperitoneal shunt can improve function in some patients but does not reverse the deficits completely. Increased age is a risk factor for leukoencephalopathy but not for radiation necrosis. Necrosis appears to depend on an as yet unidentified predisposition.

Other late neurologic toxicities include endocrine dysfunction if the pituitary or hypothalamus was included in the RT port. An RT-induced neoplasm can occur many years after therapeutic RT for either a prior CNS tumor or a head and neck cancer; accurate diagnosis requires surgical resection or biopsy. In addition, RT causes accelerated atherosclerosis, which can cause stroke either from intracranial vascular disease or carotid plaque from neck irradiation.

www.ketabpezeshki.com (021) 66485457 - 66485438

T e peripheral nervous system is relatively resistant to RT toxicities. Peripheral nerves are rarely af ected by RT, but the plexus is more vulnerable. Plexopathy develops more commonly in the brachial distribution than in the lumbosacral distribution. It must be dif erentiated from tumor progression in the plexus, which is usually accomplished with CT/MR imaging of the area or PET scan demonstrating tumor infiltrating the region. Clinically, tumor progression is usually painful, whereas RT-induced plexopathy is painless. Radiation plexopathy is also more commonly associated with lymphedema of the af ected limb. Sensory loss and weakness are seen in both.

TOXICITY FROM CHEMOTHERAPY

Neurotoxicity is second to myelosuppression as the dose-limiting toxicity of chemotherapeutic agents **(Table 49-4)**. Chemotherapy causes peripheral neuropathy from a number of commonly used agents, and the type of neuropathy can dif er, depending on the drug. Vincristine causes paresthesias but little sensory loss and is associated with motor dysfunction, autonomic impairment (frequently ileus), and rarely cranial nerve compromise. Cisplatin causes large fiber sensory loss resulting in sensory ataxia but little cutaneous sensory loss and no weakness. T e taxanes also cause a predominately sensory neuropathy. Agents such as bortezomib and thalidomide also cause neuropathy.

Encephalopathy and seizures are common toxicities from chemotherapeutic drugs. Ifosfamide can cause a severe encephalopathy, which is reversible with discontinuation of the drug and the use of methylene blue for severely af ected patients. Fludarabine also causes a severe global encephalopathy that may be permanent. Bevacizumab and other anti-VEGF agents can cause posterior reversible encephalopathy syndrome. Cisplatin can cause hearing loss and less frequently vestibular dysfunction. Immunotherapy with anti-CTLA-4 monoclonal antibodies, such as ipilimumab, can cause an autoimmune hypophysitis.

TABLE 49-4

NEUROLOGIC SIGNS CAUSED BY AGENTS COMMONLY USED IN PATIENTS WITH CANCER

Acute encephalopathy (delirium)	Seizures
Methotrexate (high-dose IV, IT)	Methotrexate
Cisplatin	Etoposide (high-dose)
Vincristine	Cisplatin
Asparaginase	Vincristine
Procarbazine	Asparaginase
5-Fluorouracil (± levamisole)	Nitrogen mustard
Cytarabine (high-dose)	Carmustine
Nitrosoureas (high-dose or arterial)	Dacarbazine (intraarterial or high-dose)
Ifosfamide	Busulfan (high-dose)
Etoposide (high-dose)	Myelopathy (intrathecal drugs)
Bevacizumab (PRES)	Methotrexate
Chronic encephalopathy (dementia)	Cytarabine
Methotrexate	Thiotepa
Carmustine	Peripheral neuropathy
Cytarabine	Vinca alkaloids
Fludarabine	Cisplatin
Visual loss	Procarbazine
Tamoxifen	Etoposide
Gallium nitrate	Teniposide
Cisplatin	Cytarabine
Fludarabine	Taxanes
Cerebellar dysfunction/ataxia	Suramin
5-Fluorouracil (± levamisole)	Bortezomib
Cytarabine	
Procarbazine	

Abbreviations: IT, intrathecal; IV, intravenous; PRES, posterior reversible encephalopathy syndrome.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 50

PARANEOPLASTIC NEUROLOGIC SYNDROMES AND AUTOIMMUNE ENCEPHALITIS

Josep Dalmau ■ Myrna R. Rosenfeld

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system **(Table 50-1)**. T ey are caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of patients, the neurologic symptoms precede the cancer diagnosis. Clinically disabling PNDs occur in 0.5–1% of all cancer patients, but they affect 2–3% of patients with neuroblastoma or small-cell lung cancer (SCLC) and 30–50% of patients with thymoma or sclerotic myeloma.

TABLE 50-1

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

CLASSIC SYNDROMES: USUALLY OCCUR WITH CANCER ASSOCIATION	NONCLASSIC SYNDROMES: MAY OCCUR WITH AND WITHOUT CANCER ASSOCIATION
Encephalomyelitis	Brainstem encephalitis
Limbic encephalitis	Stiff-person syndrome
Cerebellar degeneration (adults)	Necrotizing myelopathy
Opsoclonus-myoclonus	Motor neuron disease
Subacute sensory neuronopathy	Guillain-Barré syndrome
Gastrointestinal paresis or pseudo-obstruction	Subacute and chronic mixed sensory-motor neuropathies
Dermatomyositis (adults)	Neuropathy associated with plasma cell dyscrasias and lymphoma
Lambert-Eaton myasthenic syndrome	Vasculitis of nerve
Cancer- or melanoma-associated retinopathy	Pure autonomic neuropathy
	Acute necrotizing myopathy
	Polymyositis
	Vasculitis of muscle
	Optic neuropathy
	BDUMP

Abbreviation: BDUMP, bilateral diffuse uveal melanocytic proliferation.

PATHOGENESIS

Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumors. In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified **(Table 50-2)**. T ese antibodies react with the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) usually predicts the presence of cancer. When the antigens are intracellular, most syndromes are associated with extensive infiltrates of CD4+ and CD8+ T cells, microglial activation, gliosis, and variable neuronal loss. T e infiltrating T cells are often in close contact with neurons undergoing degeneration, suggesting a primary pathogenic role. T cell–mediated cytotoxicity may contribute directly to cell death in these PNDs. T us both humoral and cellular immune mechanisms participate in the pathogenesis of many PNDs. T is complex immunopathogenesis may underlie the resistance of many of these conditions to therapy.

In contrast to the disorders associated with immune responses against intracellular antigens, those associated with antibodies to antigens expressed on the neuronal cell surface of the CNS or at the neuromuscular junction are more responsive to immunotherapy **(Table 50-3, Fig. 50-1)**. T ese disorders occur with and without a cancer association and may affect children and young adults, and there is increasing evidence that they are mediated by the antibodies.

Other PNDs are likely immune-mediated, although their antigens are unknown. T ese include several syndromes of inflammatory neuropathies and myopathies. In addition, many patients with typical PND syndromes are antibody-negative.

For still other PNDs, the cause remains quite obscure. T ese include, among others, several neuropathies that

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 50-2

ANTIBODIES TO INTRACELLULAR ANTIGENS, SYNDROMES, AND ASSOCIATED CANCERS

ANTIBODY	ASSOCIATED NEUROLOGIC SYNDROME(S)	TUMORS
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin, bipolar cell antibodies, others[a]	Cancer-associated retinopathy (CAR) Melanoma-associated retinopathy (MAR)	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndromes, limbic encephalitis	Infrequent tumor association (thymoma)

[a]A variety of target antigens have been identified.
Abbreviations: CRMP, collapsing response-mediator protein; SCLC, small-cell lung cancer.

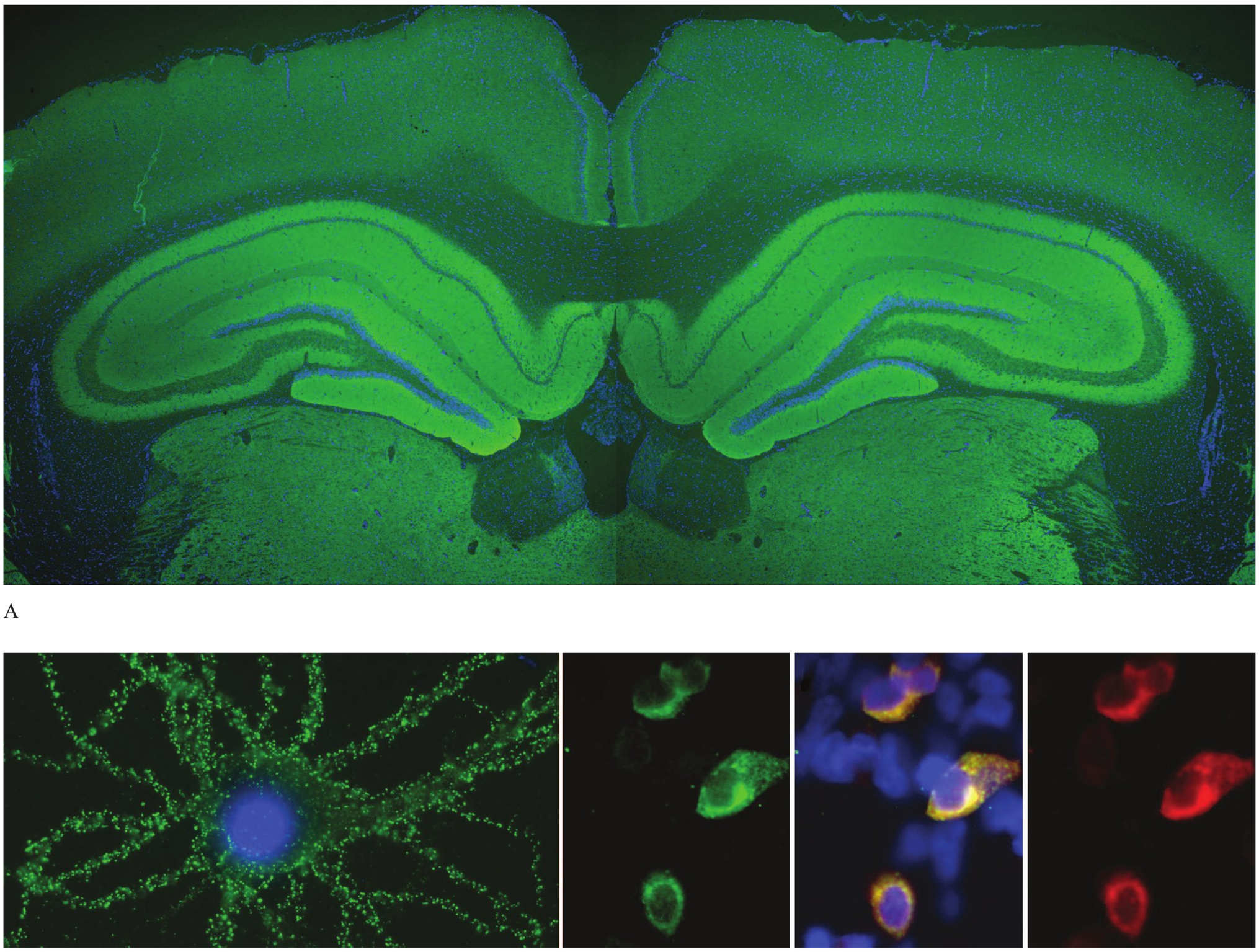
TABLE 50-3

ANTIBODIES TO CELL SURFACE OR SYNAPTIC ANTIGENS, SYNDROMES, AND ASSOCIATED TUMORS

ANTIBODY	NEUROLOGIC SYNDROME	TUMOR TYPE WHEN ASSOCIATED
Anti-AChR (muscle)[a]	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)[a]	Autonomic ganglionopathy	SCLC
Anti-VGCC[b]	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR[a]	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1[c]	Limbic encephalitis, hyponatremia, faciobrachial tonic or dystonic seizures	Rarely thymoma
Anti-Caspr2[c]	Morvan's syndrome, neuromyotonia	Thymoma, prostate cancer
Anti-$GABA_BR$[d]	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-$GABA_AR$[d]	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Rarely thymoma
Anti-AMPAR[d]	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor[d]	Encephalomyelitis with rigidity, stiff-person syndrome	Rarely, thymoma, lung cancer
Anti-DPPX[d]	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia

[a]A direct pathogenic role of these antibodies has been demonstrated.
[b]Anti-VGCC antibodies are pathogenic for LEMS.
[c]Previously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable)
[d]These antibodies are strongly suspected to be pathogenic.
Abbreviations: AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, N-methyl-d-aspartate receptor; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.

www.ketabpezeshki.com (021) 66485457 - 66485438



A

B C D E

FIGURE 50-1
Antibodies to the GluN1 subunit of the N-methyl-d-aspartate (NMDA) receptor in a patient with anti-NMDA receptor encephalitis and ovarian teratoma. (A) Coronal section of rat brain immunolabeled (green fluorescence) with the patient's antibodies. The reactivity predominates in the hippocampus, which is highly enriched in NMDA receptors. (B) This image shows the antibody reactivity with cultures of rat hippocampal neurons; the intense green immunolabeling is due to the antibodies against the GluN1 subunit of NMDA receptors. (C–E) Images of HEK cells (a human kidney cell line) transfected to express NMDA receptors, showing reactivity with patient's antibodies (C) and with a commercial monoclonal antibody against NMDA receptors (E); the patient's antibody reactivity co-labels only the cells that express NMDA receptors (D). (From J Dalmau et al: Lancet Neurol 7:1091, 2008; with permission.)

occur in the terminal stages of cancer and a number of neuropathies associated with plasma cell dyscrasias or lymphoma without evidence of inflammatory infiltrates or deposits of immunoglobulin, cryoglobulin, or amyloid.

APPROACH TO THE PATIENT: Paraneoplastic Neurologic Disorders

Three key concepts are important for the diagnosis and management of PNDs. First, it is common for symptoms to appear before the presence of a tumor is known; second, the neurologic syndrome usually develops rapidly, producing severe deficits in a short period of time; and third, there is evidence that prompt tumor control improves the neurologic outcome. Therefore, the major concern of the physician is to recognize a disorder promptly as paraneoplastic and to identify and treat the tumor.

PND OF THE CENTRAL NERVOUS SYSTEM AND DORSAL ROOT GANGLIA

When symptoms involve brain, spinal cord, or dorsal root ganglia, the suspicion of PND is usually based on a combination of clinical, radiologic, and CSF findings. Presence of antineuronal antibodies (Tables 50-2 and 50-3) may help in the diagnosis, but only 60–70% of PNDs of the CNS and less than 20% of those involving the peripheral

www.ketabpezeshki.com (021) 66485457 - 66485438

nervous system have neuronal or neuromuscular junction antibodies that can be used as diagnostic tests.

Magnetic resonance imaging (MRI) and CSF studies are important to rule out neurologic complications due to the direct spread of cancer, particularly metastatic and leptomeningeal disease. In most PNDs, the MRI findings are nonspecific. Paraneoplastic limbic encephalitis is usually associated with characteristic MRI abnormalities in the mesial temporal lobes (see below), but similar findings can occur with other disorders (e.g., nonparaneoplastic autoimmune limbic encephalitis and human herpesvirus type 6 [HHV-6] encephalitis) **(Fig. 50-2)**. The CSF profile of patients with PND of the CNS or dorsal root ganglia typically consists of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands. There are no specific electrophysiologic tests that are diagnostic of PND. Moreover, a biopsy of the affected tissue is often difficult to obtain, and although useful to rule out other disorders (e.g., metastasis) the pathologic findings are not specific for PND.

PND OF NERVE AND MUSCLE If symptoms involve peripheral nerve, neuromuscular junction, or muscle, the diagnosis of a specific PND is usually established on clinical, electrophysiologic, and pathologic grounds. The clinical history, accompanying symptoms (e.g., anorexia, weight loss), and type of syndrome dictate the studies and degree of effort needed to demonstrate a neoplasm. For example, the frequent association of Lambert-Eaton myasthenic syndrome (LEMS) with SCLC should lead to a chest and abdomen computed tomography (CT) or body positron emission tomography (PET) scan and, if negative, periodic tumor screening for at least 3 years after the neurologic diagnosis. In contrast, the weak association of polymyositis with cancer calls into question the need for repeated cancer screenings in this situation. Serum and urine immunofixation studies should be considered in patients with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to anti-CV_2/CRMP5 and anti-Hu.

For any type of PND, if antineuronal antibodies are negative, the diagnosis relies on the demonstration of cancer and the exclusion of other cancer-related or independent neurologic disorders. Combined CT and PET scans often uncover tumors undetected by other tests. For germ cell tumors of the testis and teratomas of the ovary, ultrasound and CT or MRI of the abdomen and pelvis may reveal tumors undetectable by PET.

FIGURE 50-2
Fluid-attenuated inversion recovery sequence magnetic resonance imaging of a patient with limbic encephalitis and LGI1 antibodies. Note the abnormal hyperintensity involving the medial aspect of the temporal lobes.

SPECIFIC PARANEOPLASTIC NEUROLOGIC SYNDROMES

PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS

The term encephalomyelitis describes an inflammatory process with multifocal involvement of the nervous system, including brain, brainstem, cerebellum, and spinal cord. It is often associated with dorsal root ganglia and autonomic dysfunction. For any given patient, the clinical manifestations are determined by the areas predominantly involved, but pathologic studies almost always reveal abnormalities beyond the symptomatic regions. Several clinicopathologic syndromes may occur alone or in combination: (1) cortical encephalitis, which may present as "epilepsia partialis continua"; (2) limbic encephalitis, characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities, best seen with T2 and fluid-attenuated inversion recovery sequences); (3) brainstem encephalitis, resulting in eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction; (4) cerebellar gait and limb ataxia; (5) myelitis, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms; and (6) autonomic dysfunction as a result of involvement of the neuraxis at multiple levels, including hypothalamus,

www.ketabpezeshki.com (021) 66485457 - 66485438

brainstem, and autonomic nerves (see "Paraneoplastic Peripheral Neuropathies," below). Cardiac arrhythmias, postural hypotension, and central hypoventilation are frequent causes of death in patients with encephalomyelitis.

Paraneoplastic encephalomyelitis and focal encephalitis are usually associated with SCLC, but many other cancers have been implicated. Patients with SCLC and these syndromes usually have anti-Hu antibodies in serum and CSF. Anti-CRMP5 antibodies occur less frequently; some of these patients may develop chorea, uveitis, or optic neuritis. Antibodies to Ma proteins are associated with limbic, hypothalamic, and brainstem encephalitis and occasionally with cerebellar symptoms **(Fig. 50-3)**; some patients develop hypersomnia, cataplexy, and severe hypokinesia. MRI abnormalities are frequent, including those described with limbic encephalitis and variable involvement of the hypothalamus, basal ganglia, or upper brainstem. T e oncologic associations of these antibodies are shown in Table 50-2.

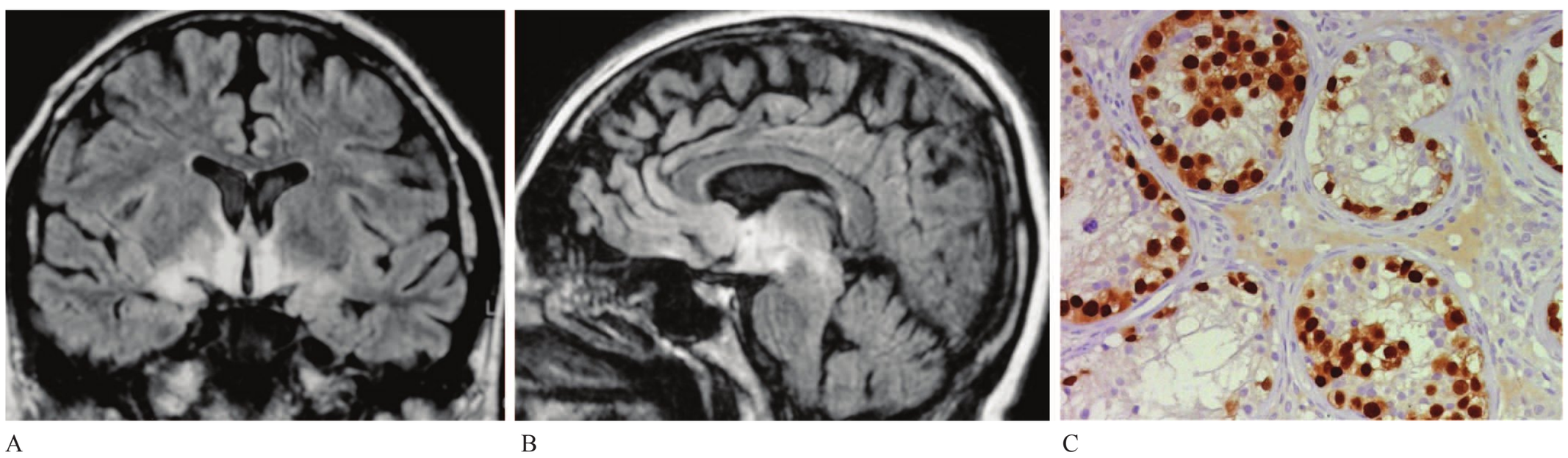
TREATMENT Encephalomyelitis and Focal Encephalitis

Most types of paraneoplastic encephalitis and encephalomyelitis respond poorly to treatment. Stabilization of symptoms or partial neurologic improvement may occasionally occur, particularly if there is a satisfactory response of the tumor to treatment. Controlled trials of therapy are lacking, but many experts recommend treatment initially with glucocorticoids. If there is no response within several days, one can advance to intravenous immunoglobulin (IVIg) or plasma exchange, and then to immunosuppression with either rituximab or cyclophosphamide. Approximately 30% of patients with anti-Ma2-associated encephalitis respond to treatment of the tumor (usually a germ cell neoplasm of the testis) and immunotherapy.

ENCEPHALITIDES WITH ANTIBODIES TO CELL-SURFACE OR SYNAPTIC PROTEINS

T ese disorders are important for three reasons: (1) they can occur with and without tumor association, (2) some syndromes predominate in young individuals and children, and (3) despite the severity of the symptoms patients usually respond to treatment of the tumor, if found, and immunotherapy (e.g., glucocorticoids, IVIg, plasma exchange, rituximab, or cyclophosphamide). (Table 50-3)

Encephalitis with N-methyl-d-aspartate (NMDA) receptor antibodies (Fig. 50-1) usually occurs in young women and children, but men and older patients of both sexes can be affected. T e disorder has a characteristic pattern of symptom progression that includes a prodrome resembling a viral process, followed in a few days by the onset of severe psychiatric symptoms, memory loss, seizures, decreased level of consciousness, abnormal movements (orofacial, limb, and trunk dyskinesias, dystonic postures), autonomic instability, and frequent hypoventilation. Monosymptomatic episodes, such as pure psychosis, occur in 4% of the patients. Clinical relapses occur in 12–24% of patients (12% during the first 2 years after initial presentation). Most patients have intrathecal synthesis of antibodies, likely by infiltrating plasma cells in brain and meninges **(Fig. 50-4A)**. T e syndrome is often misdiagnosed as a viral or idiopathic encephalitis, neuroleptic malignant syndrome, or encephalitis lethargica, and many patients are initially evaluated by psychiatrists with the suspicion of acute psychosis. T e detection of an associated teratoma is dependent on age and gender: 46% of female patients 12 years or older have uni- or bilateral ovarian teratomas, whereas less than 7% of girls younger than 12 have a teratoma **(Fig. 50-4B)**. In male patients, the detection of a tumor is rare. Patients older

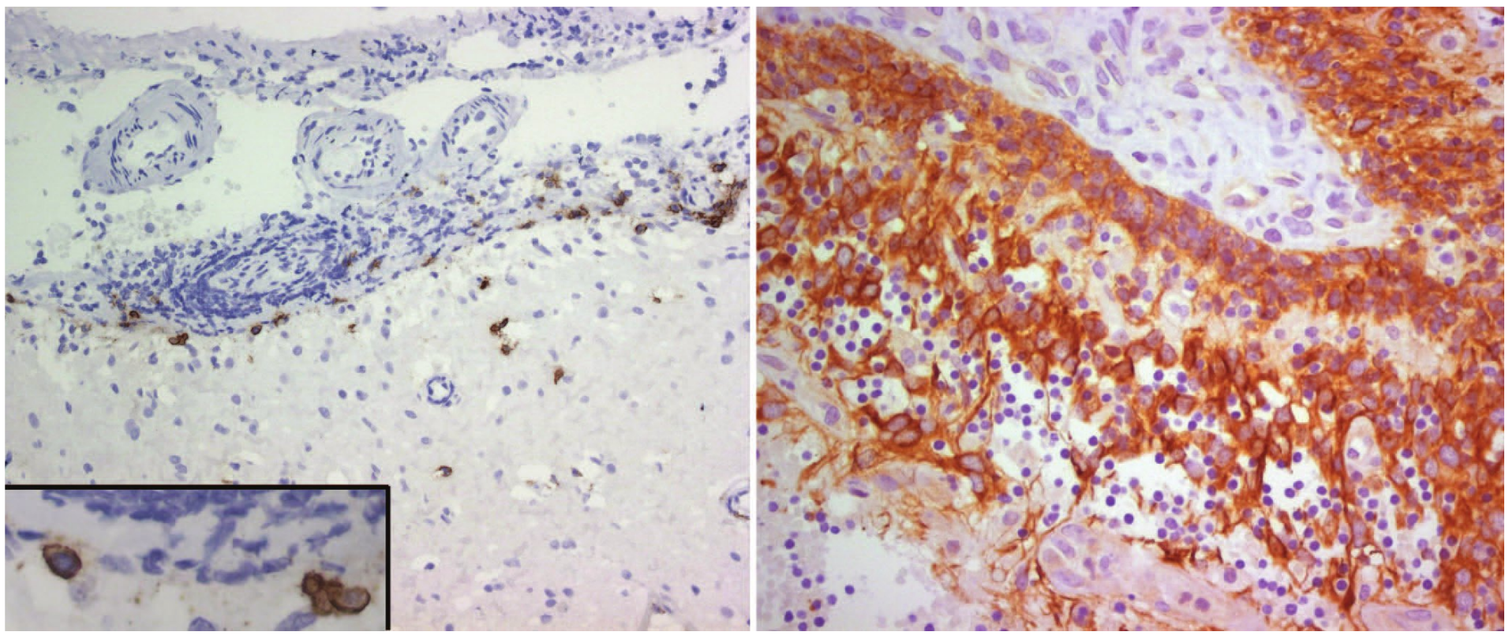


A B C

FIGURE 50-3

Magnetic resonance imaging (MRI) and tumor of a patient with anti-Ma2-associated encephalitis. A and B. Fluid-attenuated inversion recovery MRI sequences showing abnormal hyperintensities in the medial temporal lobes, hypothalamus, and upper brainstem. C. This image corresponds to a section of the patient's orchiectomy incubated with a specif c marker (Oct4) of germ cell tumors. The positive (brown) cells correspond to an intratubular germ cell neoplasm.

www.ketabpezeshki.com (021) 66485457 - 66485438



A B

FIGURE 50-4
Pathologic findings in anti–N-methyl-d-aspartate (NMDA) receptor encephalitis. A. Infiltrates of plasma cells (brown cells; stained for CD138) in the meninges and brain of a patient; the inset is a magnification of some plasma cells. B. Neurons and neuronal processes in the teratoma of a patient (brown cells; stained with MAP2); these neurons express NMDA receptors (not shown). (From E Martinez-Hernandez et al: Neurology 77:589, 2011, with permission.)

than 45 years are more frequently male; about 20% of these patients have tumors (e.g., cancer of the breast, ovary, or lung).

Encephalitis with leucine-rich glioma-inactivated 1 (LGI1) antibodies predominates in patients older than 50 years (65% male) and frequently presents with memory loss and seizures (limbic encephalopathy), along with hyponatremia and sleep dysfunction. In a small number of patients, the encephalitis is preceded by or occurs with myoclonic-like movements called faciobrachial dystonic or tonic seizures. Less than 10% of patients have thymoma.

Encephalitis with contactin-associated protein-like 2 (Caspr2) antibodies predominates in patients older than 50 years and is associated with Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia) and, less frequently, with limbic encephalitis, neuromyotonia, and neuropathic pain. About 30–40% of patients have thymoma.

Encephalitis with γ-aminobutyric acid type B ($GABA_B$) receptor antibodies is usually associated with limbic encephalitis and seizures. In rare instances, patients develop cerebellar symptoms and opsoclonus. Fifty percent of patients have SCLC or a neuroendocrine tumor of the lung. Patients may have additional antibodies to glutamic acid decarboxylase (GAD), which are of unclear significance. Other antibodies to nonneuronal proteins are often found in these patients as well as in patients with α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antibodies, indicating a general tendency to autoimmunity.

Encephalitis with GABAA receptor antibodies may affect children and adults. When antibodies are present at high titer in serum and CSF, the disorder associates with prominent seizures and status epilepticus, often requiring pharmacologically induced coma. Low titer antibodies in serum are often associated with other autoimmune conditions, and the spectrum of symptoms is wider, including encephalitis, seizures, opsoclonus, or stiff-person syndrome. Most patients do not have an underlying tumor, but some may have thymoma.

Encephalitis with AMPA receptor antibodies affects middle-aged women, who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms; 70% of the patients have an underlying tumor in the lung, breast, or thymus. Neurologic relapses may occur; these also respond to immunotherapy and are not necessarily associated with tumor recurrence.

Encephalitis with glycine receptor (GlyR) antibodies has been described in adults with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff-person spectrum of symptoms (with or without GAD antibodies). The disorder usually occurs without tumor association, although some patients have lung cancer, thymoma, or Hodgkin's lymphoma.

Encephalitis with dipeptidyl-peptidase-like protein-6 (DPPX) antibodies results in symptoms of CNS hyperexcitability including agitation, hallucinations, paranoid delusions, tremor, myoclonus, nystagmus, seizures, and sometimes hyperekplexia. Some patients develop progressive encephalomyelitis with rigidity and myoclonus. Diarrhea, other gastrointestinal symptoms, and substantial loss of weight often suggest the presence of an underlying tumor, but no tumor association has been identified. The disorder responds to immunotherapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

PARANEOPLASTIC CEREBELLAR DEGENERATION

T is disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting. A few days or weeks later, patients develop dysarthria, gait and limb ataxia, and variable dysphagia. T e examination usually shows downbeating nystagmus and, rarely, opsoclonus. Brainstem dysfunction, upgoing toes, or a mild neuropathy may occur. Early in the course, MRI studies are usually normal; later, the MRI reveals cerebellar atrophy. T e disorder results from extensive degeneration of Purkinje cells, with variable involvement of other cerebellar cortical neurons, deep cerebellar nuclei, and spinocerebellar tracts. T e tumors more frequently involved are SCLC, cancer of the breast and ovary, and Hodgkin's lymphoma.

Anti-Yo antibodies in patients with breast and gynecologic cancers and anti-Tr antibodies in patients with Hodgkin's lymphoma are the two immune responses typically associated with prominent or pure cerebellar degeneration. Antibodies to P/Q-type voltage-gated calcium channels (VGCC) occur in some patients with SCLC and cerebellar dysfunction; only some of these patients develop LEMS. A variable degree of cerebellar dysfunction can be associated with virtually any of the antibodies and PND of the CNS shown in Table 50-2.

A number of single case reports have described neurologic improvement after tumor removal, plasma exchange, IVIg, cyclophosphamide, rituximab, or glucocorticoids. However, most patients with paraneoplastic cerebellar degeneration do not improve with treatment.

PARANEOPLASTIC OPSOCLONUS-MYOCLONUS SYNDROME

Opsoclonus is a disorder of eye movement characterized by involuntary, chaotic saccades that occur in all directions of gaze; it is frequently associated with myoclonus and ataxia. Opsoclonus-myoclonus may be cancer-related or idiopathic. When the cause is paraneoplastic, the tumors involved are usually cancer of the lung and breast in adults, neuroblastoma in children, and ovarian teratoma in adolescents and young women. T e pathologic substrate of opsoclonus-myoclonus is unclear, but studies suggest that disinhibition of the fastigial nucleus of the cerebellum is involved. Most patients do not have antineuronal antibodies. A small subset of patients with ataxia, opsoclonus, and other eye-movement disorders develop anti-Ri antibodies; in rare instances, muscle rigidity, laryngeal spasms, autonomic dysfunction, and dementia also occur. T e tumors most frequently involved in anti-Ri-associated syndromes are breast and ovarian cancer. If the tumor is not successfully treated, the syndrome in adults often progresses to encephalopathy, coma, and death. In addition to treating the tumor, symptoms may respond to immunotherapy (glucocorticoids, plasma exchange, and/or IVIg).

At least 50% of children with opsoclonus-myoclonus have an underlying neuroblastoma. Hypotonia, ataxia, behavioral changes, and irritability are frequent accompanying symptoms. Neurologic symptoms often improve with treatment of the tumor and glucocorticoids, adrenocorticotropic hormone (ACTH), plasma exchange, IVIg, and rituximab. Many patients are left with psychomotor retardation and behavioral and sleep problems.

PARANEOPLASTIC SYNDROMES OF THE SPINAL CORD

T e number of reports of paraneoplastic spinal cord syndromes, such as subacute motor neuronopathy and acute necrotizing myelopathy, has decreased in recent years. T is may represent a true decrease in incidence, due to improved and prompt oncologic interventions, or the identification of nonparaneoplastic etiologies. Some patients with cancer develop upper or lower motor neuron dys*f*unction or both, resembling amyotrophic lateral sclerosis. It is unclear whether these disorders have a paraneoplastic etiology or simply coincide with the presence of cancer. T ere are isolated case reports of cancer patients with motor neuron dysfunction who had neurologic improvement after tumor treatment. A search for lymphoma should be undertaken in patients with a rapidly progressive motor neuron syndrome and a monoclonal protein in serum or CSF.

Paraneoplastic myelitis may present with upper or lower motor neuron symptoms, segmental myoclonus, and rigidity, and can be the first manifestation of encephalomyelitis. Neuromyelitis optica (NMO) with aquaporin 4 antibodies may occur in rare instances as a paraneoplastic manifestation of a cancer.

PARANEOPLASTIC STIFF-PERSON SYNDROME

T is disorder is characterized by progressive muscle rigidity, stiffness, and painful spasms triggered by auditory, sensory, or emotional stimuli. Rigidity mainly involves the lower trunk and legs, but it can affect the upper extremities and neck. Sometimes, only one extremity is affected (stif -limb syndrome). Symptoms improve with sleep and general anesthetics. Electrophysiologic studies demonstrate continuous motor unit activity. T e associated antibodies target proteins (GAD, amphiphysin) involved in the function of inhibitory synapses using γ-aminobutyric acid (GABA) or glycine as neurotransmitters. T e presence of amphiphysin antibodies usually indicates a paraneoplastic etiology related to SCLC and

www.ketabpezeshki.com (021) 66485457 - 66485438

breast cancer. By contrast, GAD antibodies may occur in some cancer patients but are much more frequently present in the nonparaneoplastic disorder. GlyR antibodies may occur in some patients with stiff-person syndrome; these antibodies are also detectable in patients with PERM.

Optimal treatment of stiff-person syndrome requires therapy of the underlying tumor, glucocorticoids, and symptomatic use of drugs that enhance GABA-ergic transmission (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin). IVIg and plasma exchange are transiently effective in some patients.

PARANEOPLASTIC SENSORY NEURONOPATHY OR DORSAL ROOT GANGLIONOPATHY

T is syndrome is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes. All modalities of sensation and any part of the body including face and trunk can be involved. Specialized sensations such as taste and hearing can also be affected. Electrophysiologic studies show decreased or absent sensory nerve potentials with normal or near-normal motor conduction velocities. Symptoms result from an inflammatory, likely immune-mediated, process that targets the dorsal root ganglia, causing neuronal loss and secondary degeneration of the posterior columns of the spinal cord. T e dorsal and, less frequently, the anterior nerve roots and peripheral nerves may also be involved. T is disorder often precedes or is associated with encephalomyelitis and autonomic dysfunction and has the same immunologic and oncologic associations (Hu antibodies, SCLC).

As with anti-Hu-associated encephalomyelitis, the therapeutic approach focuses on prompt treatment of the tumor. Glucocorticoids occasionally produce clinical stabilization or improvement. T e benefit of IVIg and plasma exchange is not proven.

PARANEOPLASTIC PERIPHERAL NEUROPATHIES

T ese disorders may develop any time during the course of the neoplastic disease. Neuropathies occurring at late stages of cancer or lymphoma usually cause mild to moderate sensorimotor deficits due to axonal degeneration of unclear etiology. T ese neuropathies are often masked by concurrent neurotoxicity from chemotherapy and other cancer therapies. In contrast, the neuropathies that develop in the early stages of cancer frequently show a rapid progression, sometimes with a relapsing and remitting course, and evidence of inflammatory infiltrates and axonal loss or demyelination. If demyelinating features predominate **(Chaps. 53 and 54)**, IVIg, plasma exchange, or glucocorticoids may improve symptoms. Occasionally anti-CRMP5 antibodies are present; detection of anti-Hu suggests concurrent dorsal root ganglionitis.

Guillain-Barré syndrome and brachial plexitis have occasionally been reported in patients with lymphoma, but there is no clear evidence of a paraneoplastic association **(Chap. 54)**.

Malignant monoclonal gammopathies include: (1) multiple myeloma and sclerotic myeloma associated with IgG or IgA monoclonal proteins; and (2) Waldenström's macroglobulinemia, B cell lymphoma, and chronic B cell lymphocytic leukemia associated with IgM monoclonal proteins. T ese disorders may cause neuropathy by a variety of mechanisms, including compression of roots and plexuses by metastasis to vertebral bodies and pelvis, deposits of amyloid in peripheral nerves, and paraneoplastic mechanisms. T e paraneoplastic variety has several distinctive features. Approximately half of patients with sclerotic myeloma develop a sensorimotor neuropathy with predominantly motor deficits, resembling a chronic inflammatory demyelinating neuropathy **(Chap. 54)**; some patients develop elements of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes). Treatment of the plasmacytoma or sclerotic lesions usually improves the neuropathy. In contrast, the sensorimotor or sensory neuropathy associated with multiple myeloma is more refractory to treatment. Between 5 and 10% of patients with Waldenström's macroglobulinemia develop a distal symmetric sensorimotor neuropathy with predominant involvement of large sensory fibers. T ese patients may have IgM antibodies in their serum against myelin-associated glycoprotein and various gangliosides **(Chap. 54)**. In addition to treating the Waldenström's macroglobulinemia, other therapies may improve the neuropathy, including plasma exchange, IVIg, chlorambucil, cyclophosphamide, fludarabine, or rituximab.

Vasculitis *of* the nerve and muscle causes a painful symmetric or asymmetric distal axonal sensorimotor neuropathy with variable proximal weakness. It predominantly affects elderly men and is associated with an elevated erythrocyte sedimentation rate and increased CSF protein concentration. SCLC and lymphoma are the primary tumors involved. Glucocorticoids and cyclophosphamide often result in neurologic improvement.

Peripheral nerve hyperexcitability (neuromyotonia, or Isaacs' syndrome) is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin. Clinical features include cramps, muscle twitching (fasciculations or myokymia), stiffness, delayed muscle relaxation (pseudomyotonia), and spontaneous or

www.ketabpezeshki.com (021) 66485457 - 66485438

evoked carpal or pedal spasms. T e involved muscles may be hypertrophic, and some patients develop paresthesias and hyperhidrosis. CNS dysfunction, including mood changes, sleep disorder, hallucinations, and autonomic symptoms may occur. T e electromyogram (EMG) shows fibrillations; fasciculations; and doublet, triplet, or multiplet single-unit (myokymic) discharges that have a high intraburst frequency. Some patients have Caspr2 antibodies in the context of Morvan's syndrome, but most cases of isolated neuromyotonia are antibody negative. T e disorder often occurs without cancer; if paraneoplastic, benign and malignant thymomas and SCLC are the usual tumors. Phenytoin, carbamazepine, and plasma exchange improve symptoms.

Paraneoplastic autonomic neuropathy usually develops as a component of other disorders, such as LEMS and encephalomyelitis. It may rarely occur as a pure or predominantly autonomic neuropathy with cholinergic or adrenergic dysfunction at the pre- or postganglionic levels. Patients can develop several life-threatening complications, such as gastrointestinal paresis with pseudo-obstruction, cardiac dysrhythmias, and postural hypotension. Other clinical features include abnormal pupillary responses, dry mouth, anhidrosis, erectile dysfunction, and problems in sphincter control. T e disorder occurs in association with several tumors, including SCLC, cancer of the pancreas or testis, carcinoid tumors, and lymphoma. Because autonomic symptoms can be the presenting feature of encephalomyelitis, serum anti-Hu and anti-CRMP5 antibodies should be sought. Antibodies to ganglionic (alpha3-type) neuronal acetylcholine receptors are the cause of autoimmune autonomic ganglionopathy, a disorder that frequently occurs without cancer association **(Chap. 41)**.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is discussed in Chap. 55.

MYASTHENIA GRAVIS

Myasthenia gravis is discussed in Chap. 55.

POLYMYOSITIS-DERMATOMYOSITIS

Polymyositis and dermatomyositis are discussed in detail in Chap. 57.

ACUTE NECROTIZING MYOPATHY

Patients with this syndrome develop myalgias and rapid progression of weakness involving the extremities and the pharyngeal and respiratory muscles, often resulting in death. Serum muscle enzymes are elevated, and muscle biopsy shows extensive necrosis with minimal or absent inflammation and sometimes deposits of complement. T e disorder occurs as a paraneoplastic manifestation of a variety of cancers including SCLC and cancer of the gastrointestinal tract, breast, kidney, and prostate, among others. Glucocorticoids and treatment of the underlying tumor rarely control the disorder.

PARANEOPLASTIC VISUAL SYNDROMES

T is group of disorders involves the retina and, less frequently, the uvea and optic nerves. T e term cancer-associated retinopathy is used to describe paraneoplastic cone and rod dysfunction characterized by photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG). T e most commonly associated tumor is SCLC. Melanoma-associated retinopathy affects patients with metastatic cutaneous melanoma. Patients develop acute onset of night blindness and shimmering, flickering, or pulsating photopsias that often progress to visual loss. T e ERG shows reduced b waves with normal dark adapted a waves. Paraneoplastic optic neuritis and uveitis are very uncommon and can develop in association with encephalomyelitis. Some patients with paraneoplastic uveitis and optic neuritis have anti-CRMP5 antibodies.

Some paraneoplastic retinopathies are associated with serum antibodies that specifically react with the subset of retinal cells undergoing degeneration, supporting an immune-mediated pathogenesis (Table 50-2). Paraneoplastic retinopathies usually fail to improve with treatment, although rare responses to glucocorticoids, plasma exchange, and IVIg have been reported.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 51

ANTERIOR PITUITARY TUMOR SYNDROMES

Shlomo Melmed ■ J. Larry Jameson

HYPOTHALAMIC, PITUITARY, AND OTHER SELLAR MASSES

EVALUATION OF SELLAR MASSES

Local mass effects

Clinical manifestations of sellar lesions vary, depending on the anatomic location of the mass and the direction of its extension **(Table 51-1)**. The dorsal sellar diaphragm presents the least resistance to soft tissue expansion from the sella; consequently, pituitary adenomas frequently extend in a suprasellar direction. Bony invasion may occur as well.

Headaches are common features of small intrasellar tumors, even with no demonstrable suprasellar extension. Because of the confined nature of the pituitary, small changes in intrasellar pressure stretch the dural plate; however, headache severity correlates poorly with adenoma size or extension.

Suprasellar extension can lead to visual loss by several mechanisms, the most common being compression of the optic chiasm, but rarely, direct invasion of the optic nerves or obstruction of cerebrospinal fluid (CSF) flow leading to secondary visual disturbances can occur. Pituitary stalk compression by a hormonally active or inactive intrasellar mass may compress the portal vessels, disrupting pituitary access to hypothalamic hormones and dopamine; this results in early hyperprolactinemia and later concurrent loss of other pituitary hormones. This "stalk section" phenomenon may also be caused by trauma, whiplash injury with posterior clinoid stalk compression, or skull base fractures. Lateral mass invasion may impinge on the cavernous sinus and compress its neural contents, leading to cranial nerve III, IV, and VI palsies as well as effects on the ophthalmic and maxillary branches of the fifth cranial nerve **(Chap. 42)**. Patients may present with diplopia, ptosis, ophthalmoplegia, and decreased facial sensation, depending on the extent of neural damage. Extension into the sphenoid sinus indicates that the pituitary mass has eroded through the sellar floor. Aggressive tumors rarely invade the palate roof and cause nasopharyngeal obstruction, infection, and CSF leakage. Temporal and

TABLE 51-1

FEATURES OF SELLAR MASS LESIONS[a]

IMPACTED STRUCTURE	CLINICAL IMPACT
Pituitary	Hypogonadism Hypothyroidism Growth failure and adult hyposomatotropism Hypoadrenalism
Optic chiasm	Loss of red perception Bitemporal hemianopia Superior or bitemporal field defect Scotoma Blindness
Hypothalamus	Temperature dysregulation Appetite and thirst disorders Obesity Diabetes insipidus Sleep disorders Behavioral dysfunction Autonomic dysfunction
Cavernous sinus	Ophthalmoplegia with or without ptosis or diplopia Facial numbness
Frontal lobe	Personality disorder Anosmia
Brain	Headache Hydrocephalus Psychosis Dementia Laughing seizures

[a]As the intrasellar mass expands, it first compresses intrasellar pituitary tissue, then usually invades dorsally through the dura to lift the optic chiasm or laterally to the cavernous sinuses. Bony erosion is rare, as is direct brain compression. Microadenomas may present with headache.

www.ketabpezeshki.com (021) 66485457 - 66485438

frontal lobe involvement may rarely lead to uncinate seizures, personality disorders, and anosmia. Direct hypothalamic encroachment by an invasive pituitary mass may cause important metabolic sequelae, including precocious puberty or hypogonadism, diabetes insipidus, sleep disturbances, dysthermia, and appetite disorders.

Magnetic resonance imaging

Sagittal and coronal T1-weighted magnetic resonance imaging (MRI) before and after administration of gadolinium allows precise visualization of the pituitary gland with clear delineation of the hypothalamus, pituitary stalk, pituitary tissue and surrounding suprasellar cisterns, cavernous sinuses, sphenoid sinus, and optic chiasm. Pituitary gland height ranges from 6 mm in children to 8 mm in adults; during pregnancy and puberty, the height may reach 10–12 mm. The upper aspect of the adult pituitary is flat or slightly concave, but in adolescent and pregnant individuals, this surface may be convex, reflecting physiologic pituitary enlargement. The stalk should be midline and vertical. Computed tomography (CT) scan is reserved to define the extent of bony erosion or the presence of calcification.

Anterior pituitary gland soft tissue consistency is slightly heterogeneous on MRI, and signal intensity resembles that of brain matter on T1-weighted imaging **(Fig. 51-1)**. Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. The high phospholipid content of the posterior pituitary results in a "pituitary bright spot."

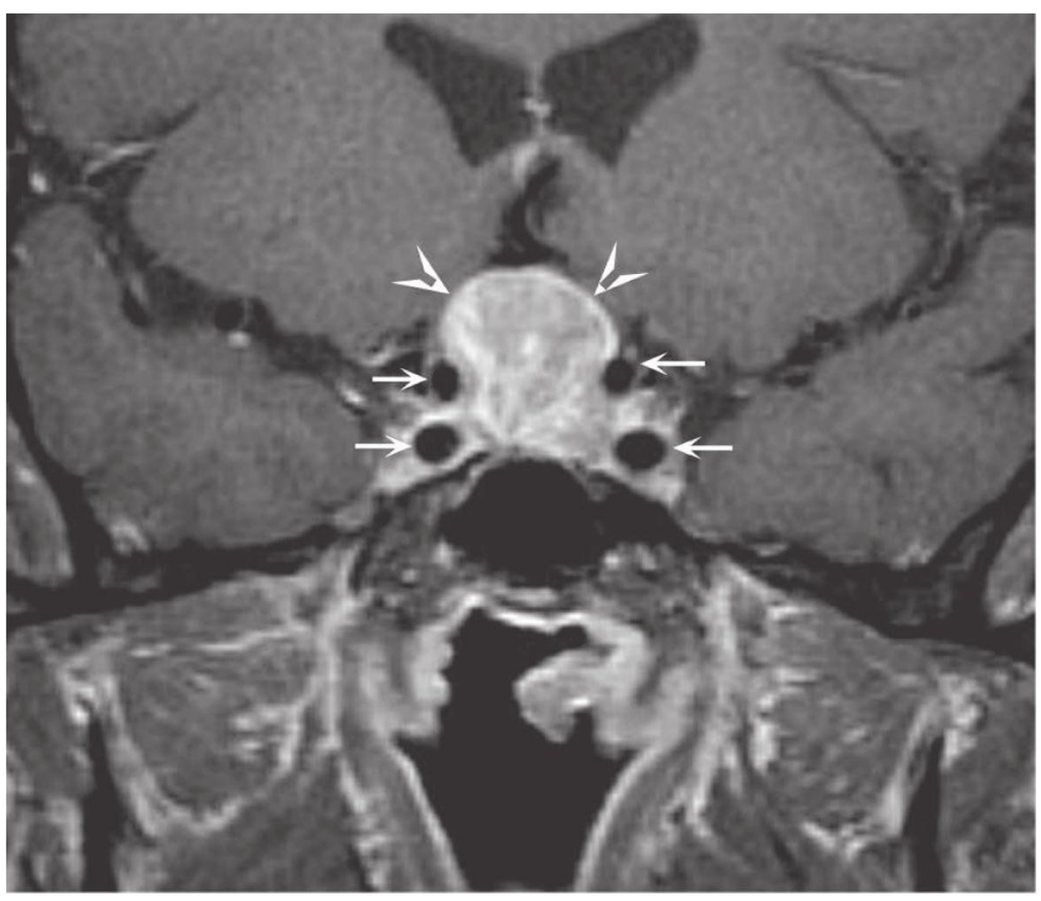


FIGURE 51-1
Pituitary adenoma. Coronal T1-weighted postcontrast magnetic resonance image shows a homogeneously enhancing mass (arrowheads) in the sella turcica and suprasellar region compatible with a pituitary adenoma; the small arrows outline the carotid arteries.

Sellar masses are encountered commonly as incidental findings on MRI, and most of them are pituitary adenomas (incidentalomas). In the absence of hormone hypersecretion, these small intrasellar lesions can be monitored safely with MRI, which is performed annually and then less often if there is no evidence of further growth. Resection should be considered for incidentally discovered larger macroadenomas, because about one-third become invasive or cause local pressure effects. If hormone hypersecretion is evident, specific therapies are indicated as described below. When larger masses (>1 cm) are encountered, they should also be distinguished from nonadenomatous lesions. Meningiomas often are associated with bony hyperostosis; craniopharyngiomas may be calcified and are usually hypodense, whereas gliomas are hyperdense on T2-weighted images.

Ophthalmologic evaluation

Because optic tracts may be contiguous to an expanding pituitary mass, reproducible visual field assessment using perimetry techniques should be performed on all patients with sellar mass lesions that impinge the optic chiasm **(Chap. 25)**. Bitemporal hemianopia, often more pronounced superiorly, is observed classically. It occurs because nasal ganglion cell fibers, which cross in the optic chiasm, are especially vulnerable to compression of the ventral optic chiasm. Occasionally, homonymous hemianopia occurs from postchiasmal compression or monocular temporal field loss from prechiasmal compression. Invasion of the cavernous sinus can produce diplopia from ocular motor nerve palsy. Early diagnosis reduces the risk of optic atrophy, vision loss, or eye misalignment.

Laboratory investigation

The presenting clinical features of functional pituitary adenomas (e.g., acromegaly, prolactinomas, or Cushing's syndrome) should guide the laboratory studies **(Table 51-2)**. However, for a sellar mass with no obvious clinical features of hormone excess, laboratory studies are geared toward determining the nature of the tumor and assessing the possible presence of hypopituitarism. When a pituitary adenoma is suspected based on MRI, initial hormonal evaluation usually includes (1) basal prolactin (PRL); (2) insulin-like growth factor (IGF) I; (3) 24-h urinary free cortisol (UFC) and/or overnight oral dexamethasone (1 mg) suppression test; (4) α subunit, follicle-stimulating hormone (FSH), and luteinizing hormone (LH); and (5) thyroid function tests. Additional hormonal evaluation may be

www.ketabpezeshki.com (021) 66485457 - 66485438

indicated based on the results of these tests. Pending more detailed assessment of hypopituitarism, a menstrual history, measurement of testosterone and 8 A.M. cortisol levels, and thyroid function tests usually identify patients with pituitary hormone deficiencies that require hormone replacement before further testing or surgery.

Histologic evaluation

Immunohistochemical staining of pituitary tumor specimens obtained at transsphenoidal surgery confirms clinical and laboratory studies and provides a histologic diagnosis when hormone studies are equivocal and in cases of clinically nonfunctioning tumors. Occasionally, ultrastructural assessment by electron microscopy is required for diagnosis.

TREATMENT Hypothalamic, Pituitary, and Other Sellar Masses

OVERVIEW Successful management of sellar masses requires accurate diagnosis as well as selection of optimal therapeutic modalities. Most pituitary tumors are benign and slow-growing. Clinical features result from local mass effects and hormonal hyper- or hyposecretion syndromes caused directly by the adenoma or occurring as a consequence of treatment. T us, lifelong management and follow-up are necessary for these patients.

MRI with gadolinium enhancement for pituitary visualization, new advances in transsphenoidal surgery and in stereotactic radiotherapy (including gamma-knife radiotherapy), and novel therapeutic agents have improved pituitary tumor management. T e goals of pituitary tumor treatment include normalization of excess pituitary secretion, amelioration of symptoms and signs of hormonal hypersecretion syndromes, and shrinkage or ablation of large tumor masses with relief of adjacent structure compression. Residual anterior pituitary function should be preserved during treatment and sometimes can be restored by removing the tumor mass. Ideally, adenoma recurrence should be prevented.

TRANSSPHENOIDAL SURGERY Transsphenoidal rather than transfrontal resection is the desired surgical approach for pituitary tumors, except for the rare invasive suprasellar mass surrounding the frontal or middle fossa or the optic nerves or invading posteriorly behind the clivus. Intraoperative microscopy facilitates visual distinction between adenomatous and normal pituitary tissue as well as microdissection of small tumors that may not be visible by MRI **(Fig. 51-2)**. Transsphenoidal surgery also avoids the cranial invasion and manipulation of brain tissue required by subfrontal surgical approaches. Endoscopic techniques with three-dimensional intraoperative localization have also improved visualization and access to tumor tissue. Individual surgical experience is a major determinant of outcome ef cacy with these techniques.

TABLE 51-2

SCREENING TESTS FOR FUNCTIONAL PITUITARY ADENOMAS

	TEST	COMMENTS
Acromegaly	Serum IGF-I Oral glucose tolerance test with GH obtained at 0, 30, and 60 min	Interpret IGF-I relative to age- and sex-matched controls Normal subjects should suppress growth hormone to <1 g/L
Prolactinoma	Serum PRL	Exclude medications MRI of the sella should be ordered if PRL is elevated
Cushing's disease	24-h urinary free cortisol Dexamethasone (1 mg) at 11 p.m. and fasting plasma cortisol measured at 8 a.m. ACTH assay	Ensure urine collection is total and accurate Normal subjects suppress to <5 g/dL Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated)

Abbreviations: ACTH, adrenocorticotropin hormone; GH, growth hormone; IGF-I, insulin-like growth factor I; MRI, magnetic resonance imaging; PRL, prolactin.

In addition to correction of hormonal hypersecretion, pituitary surgery is indicated for mass lesions that impinge on surrounding structures. Surgical decompression and resection are required for an expanding pituitary mass accompanied by persistent headache, progressive visual field defects, cranial nerve palsies, hydrocephalus, and, occasionally, intrapituitary hemorrhage and apoplexy. Transsphenoidal surgery sometimes is used for pituitary tissue biopsy to establish a histologic diagnosis.Whenever possible, the pituitary mass lesion should be selectively excised; normal pituitary tissue should be manipulated or resected only when critical for effective mass dissection. Nonselective hemihypophysectomy or total hypophysectomy may be indicated if no hypersecreting mass lesion is clearly discernible, multifocal lesions are present, or the remaining nontumorous pituitary tissue is obviously necrotic. T is strategy, however, increases the likelihood of hypopituitarism and the need for lifelong hormone replacement.

Preoperative mass effects, including visual field defects and compromised pituitary function, may be reversed by surgery, particularly when the deficits are not long-standing. For large and invasive tumors, it is necessary to determine the optimal balance between maximal tumor resection and preservation of anterior pituitary function, especially for preserving growth and reproductive function in younger

www.ketabpezeshki.com (021) 66485457 - 66485438

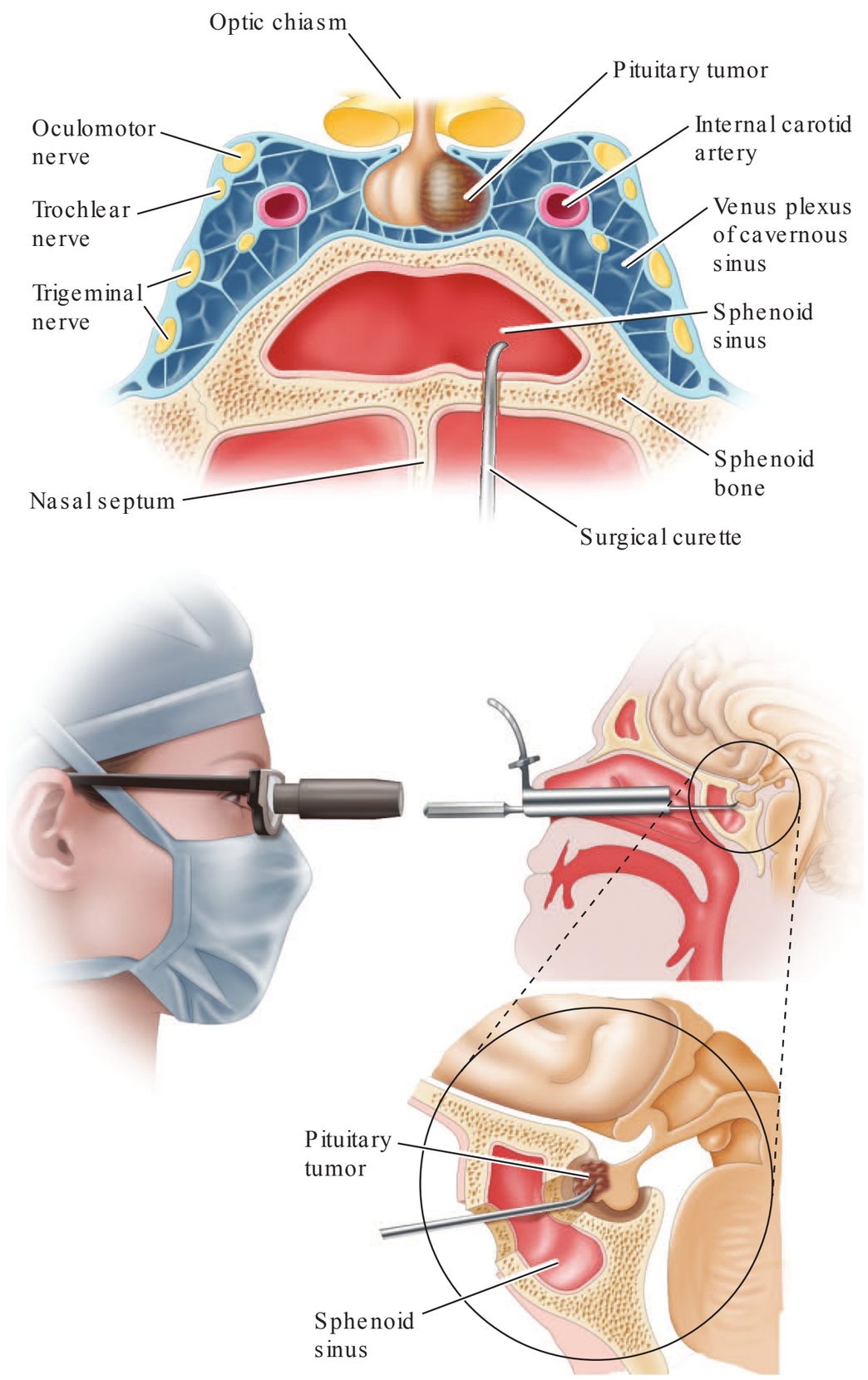


FIGURE 51-2
Transsphenoidal resection of pituitary mass via the endonasal approach. (Adapted from R Fahlbusch: Endocrinol Metab Clin 21:669, 1992.)

patients. Similarly, tumor invasion outside the sella is rarely amenable to surgical cure; the surgeon must judge the risk-versus-benefit ratio of extensive tumor resection.

Side effects Tumor size, the degree of invasiveness, and experience of the surgeon largely determine the incidence of surgical complications. Operative mortality rate is about 1%. Transient diabetes insipidus and hypopituitarism occur in up to 20% of patients. Permanent diabetes insipidus, cranial nerve damage, nasal septal perforation, or visual disturbances may be encountered in up to 10% of patients. CSF leaks occur in 4% of patients. Less common complications include carotid artery injury, loss of vision, hypothalamic damage, and meningitis. Permanent side effects are rare after surgery for microadenomas.

RADIATION Radiation is used either as a primary therapy for pituitary or parasellar masses or, more commonly, as an adjunct to surgery or medical therapy. Focused megavoltage irradiation is achieved by precise MRI localization, using a high-voltage linear accelerator and accurate isocentric rotational arcing. A major determinant of accurate irradiation is reproduction of the patient's head position during multiple visits and maintenance of absolute head immobility. A total of <50 Gy (5000 rad) is given as 180-cGy (180-rad) fractions divided over about 6 weeks. Stereotactic radiosurgery delivers a large single high-energy dose from a cobalt-60 source (gamma knife), linear accelerator, or cyclotron. Long-term effects of gamma-knife surgery are unclear but appear to be similar to those encountered with conventional radiation. Proton beam therapy is available in some centers and provides concentrated radiation doses within a localized region.

The role of radiation therapy in pituitary tumor management depends on multiple factors, including the nature of the tumor, the age of the patient, and the availability of surgical and radiation expertise. Because of its relatively slow onset of action, radiation therapy is usually reserved for postsurgical management. As an adjuvant to surgery, radiation is used to treat residual tumor and in an attempt to prevent regrowth. Irradiation offers the only means for potentially ablating significant postoperative residual nonfunctioning tumor tissue. In contrast, PRL- and growth hormone (GH)-secreting tumor tissues are amenable to medical therapy.

Side effects In the short term, radiation may cause transient nausea and weakness. Alopecia and loss of taste and smell may be more long-lasting. Failure of pituitary hormone synthesis is common in patients who have undergone head and neck or pituitary-directed irradiation. More than 50% of patients develop loss of GH, adrenocorticotropin hormone (ACTH), thyroid-stimulating hormone (TSH), and/or gonadotropin secretion within 10 years, usually due to hypothalamic damage. Lifelong follow-up with testing of anterior pituitary hormone reserve is therefore required after radiation treatment. Optic nerve damage with impaired vision due to optic neuritis is reported in about 2% of patients who undergo pituitary irradiation. Cranial nerve damage is uncommon now that radiation doses are ≤2 Gy (200 rad) at any one treatment session and the maximum dose is <50 Gy (5000 rad). The use of stereotactic radiotherapy may reduce damage to adjacent structures. Radiotherapy for pituitary tumors has been associated with adverse mortality rates, mainly from cerebrovascular disease. The cumulative risk of developing a secondary tumor after conventional radiation is 1.3% after 10 years and 1.9% after 20 years.

MEDICAL Medical therapy for pituitary tumors is highly specific and depends on tumor type. For prolactinomas, dopamine agonists are the treatment of choice. For acromegaly, somatostatin analogues and GH receptor antagonists are indicated. For TSH-secreting tumors, somatostatin analogues and occasionally dopamine agonists are indicated. ACTH-secreting tumors and nonfunctioning tumors are generally not responsive to medications and require surgery and/or irradiation.

www.ketabpezeshki.com (021) 66485457 - 66485438

SELLAR MASSES

Sellar masses other than pituitary adenomas may arise from brain, hypothalamic, or pituitary tissues. Each exhibit features related to the lesion location but also unique to the specific etiology.

Hypothalamic lesions

Lesions involving the anterior and preoptic hypothalamic regions cause paradoxical vasoconstriction, tachycardia, and hyperthermia. Acute hyperthermia usually is due to a hemorrhagic insult, but poikilothermia may also occur. Central disorders of thermoregulation result from posterior hypothalamic damage. The periodic hypothermia syndrome is characterized by episodic attacks of rectal temperatures <30°C (86°F), sweating, vasodilation, vomiting, and bradycardia. Damage to the ventromedial hypothalamic nuclei by craniopharyngiomas, hypothalamic trauma, or inflammatory disorders may be associated with hyperphagia and obesity. This region appears to contain an energy-satiety center where melanocortin receptors are influenced by leptin, insulin, pro-opiomelanocortin (POMC) products, and gastrointestinal peptides. Polydipsia and hypodipsia are associated with damage to central osmoreceptors located in preoptic nuclei **(Chap. 52)**. Slow-growing hypothalamic lesions can cause increased somnolence and disturbed sleep cycles as well as obesity, hypothermia, and emotional outbursts. Lesions of the central hypothalamus may stimulate sympathetic neurons, leading to elevated serum catecholamine and cortisol levels. These patients are predisposed to cardiac arrhythmias, hypertension, and gastric erosions.

Craniopharyngiomas are benign, suprasellar cystic masses that present with headaches, visual field deficits, and variable degrees of hypopituitarism. They are derived from Rathke's pouch and arise near the pituitary stalk, commonly extending into the suprasellar cistern. Craniopharyngiomas are often large, cystic, and locally invasive. Many are partially calcified, exhibiting a characteristic appearance on skull x-ray and CT images. More than half of all patients present before age 20, usually with signs of increased intracranial pressure, including headache, vomiting, papilledema, and hydrocephalus. Associated symptoms include visual field abnormalities, personality changes and cognitive deterioration, cranial nerve damage, sleep difficulties, and weight gain. Hypopituitarism can be documented in about 90%, and diabetes insipidus occurs in about 10% of patients. About half of affected children present with growth retardation. MRI is generally superior to CT for evaluating cystic structure and tissue components of craniopharyngiomas. CT is useful to define calcifications and evaluate invasion into surrounding bony structures and sinuses.

Treatment usually involves transcranial or transsphenoidal surgical resection followed by postoperative radiation of residual tumor. Surgery alone is curative in less than half of patients because of recurrences due to adherence to vital structures or because of small tumor deposits in the hypothalamus or brain parenchyma. The goal of surgery is to remove as much tumor as possible without risking complications associated with efforts to remove firmly adherent or inaccessible tissue. In the absence of radiotherapy, about 75% of craniopharyngiomas recur, and 10-year survival is less than 50%. In patients with incomplete resection, radiotherapy improves 10-year survival to 70–90% but is associated with increased risk of secondary malignancies. Most patients require lifelong pituitary hormone replacement.

Developmental failure of Rathke's pouch obliteration may lead to Rathke's cysts, which are small (<5 mm) cysts entrapped by squamous epithelium and are found in about 20% of individuals at autopsy. Although Rathke's cleft cysts do not usually grow and are often diagnosed incidentally, about a third present in adulthood with compressive symptoms, diabetes insipidus, and hyperprolactinemia due to stalk compression. Rarely, hydrocephalus develops. The diagnosis is suggested preoperatively by visualizing the cyst wall on MRI, which distinguishes these lesions from craniopharyngiomas. Cyst contents range from CSF-like fluid to mucoid material. Arachnoid cysts are rare and generate an MRI image that is isointense with CSF.

Sella chordomas usually present with bony clival erosion, local invasiveness, and, on occasion, calcification. Normal pituitary tissue may be visible on MRI, distinguishing chordomas from aggressive pituitary adenomas. Mucinous material may be obtained by fine-needle aspiration.

Meningiomas arising in the sellar region may be difficult to distinguish from nonfunctioning pituitary adenomas. Meningiomas typically enhance on MRI and may show evidence of calcification or bony erosion. Meningiomas may cause compressive symptoms.

Histiocytosis X includes a variety of syndromes associated with foci of eosinophilic granulomas. Diabetes insipidus, exophthalmos, and punched-out lytic bone lesions (Hand-Schüller-Christian disease) are associated with granulomatous lesions visible on MRI, as well as a characteristic axillary skin rash. Rarely, the pituitary stalk may be involved.

Pituitary metastases occur in ~3% of cancer patients. Bloodborne metastatic deposits are found almost exclusively in the posterior pituitary. Accordingly, diabetes insipidus can be a presenting feature of lung, gastrointestinal, breast, and other pituitary metastases. About half of pituitary metastases originate from breast cancer; about 25% of patients with metastatic breast cancer have such deposits. Rarely, pituitary

www.ketabpezeshki.com (021) 66485457 - 66485438

stalk involvement results in anterior pituitary insufficiency. The MRI diagnosis of a metastatic lesion may be difficult to distinguish from an aggressive pituitary adenoma; the diagnosis may require histologic examination of excised tumor tissue. Primary or metastatic lymphoma, leukemias, and plasmacytomas also occur within the sella.

Hypothalamic hamartomas and gangliocytomas may arise from astrocytes, oligodendrocytes, and neurons with varying degrees of differentiation. These tumors may overexpress hypothalamic neuropeptides, including gonadotropin-releasing hormone (GnRH), growth hormone–releasing hormone (GHRH), and corticotropin-releasing hormone (CRH). With GnRH-producing tumors, children present with precocious puberty, psychomotor delay, and laughing-associated seizures. Medical treatment of GnRH-producing hamartomas with long-acting GnRH analogues effectively suppresses gonadotropin secretion and controls premature pubertal development. Rarely, hamartomas also are associated with craniofacial abnormalities; imperforate anus; cardiac, renal, and lung disorders; and pituitary failure as features of Pallister-Hall syndrome, which is caused by mutations in the carboxy terminus of the GLI3 gene. Hypothalamic hamartomas are often contiguous with the pituitary, and preoperative MRI diagnosis may not be possible. Histologic evidence of hypothalamic neurons in tissue resected at transsphenoidal surgery may be the first indication of a primary hypothalamic lesion.

Hypothalamic gliomas and optic gliomas occur mainly in childhood and usually present with visual loss. Adults have more aggressive tumors; about a third are associated with neurofibromatosis.

Brain germ cell tumors may arise within the sellar region. They include dysgerminomas, which frequently are associated with diabetes insipidus and visual loss. They rarely metastasize. Germinomas, embryonal carcinomas, teratomas, and choriocarcinomas may arise in the parasellar region and produce hCG. These germ cell tumors present with precocious puberty, diabetes insipidus, visual field defects, and thirst disorders. Many patients are GH-deficient with short stature.

PITUITARY ADENOMAS AND HYPERSECRETION SYNDROMES

Pituitary adenomas are the most common cause of pituitary hormone hypersecretion and hyposecretion syndromes in adults. They account for ~15% of all intracranial neoplasms and have been identified with a population prevalence of ~80/100,000. At autopsy, up to one-quarter of all pituitary glands harbor an unsuspected microadenoma (<10 mm diameter). Similarly, pituitary imaging detects small clinically inapparent pituitary lesions in at least 10% of individuals.

Pathogenesis

Pituitary adenomas are benign neoplasms that arise from one of the five anterior pituitary cell types. The clinical and biochemical phenotypes of pituitary adenomas depend on the cell type from which they are derived. Thus, tumors arising from lactotrope (PRL), somatotrope (GH), corticotrope (ACTH), thyrotrope (TSH), or gonadotrope (LH, FSH) cells hypersecrete their respective hormones **(Table 51-3)**. Plurihormonal tumors express various combinations of GH, PRL, TSH, ACTH, or the glycoprotein hormone α or β subunits. They may be diagnosed by careful immunocytochemistry or may manifest as clinical syndromes that combine features of these hormonal hypersecretory syndromes. Morphologically, these tumors may arise from a single polysecreting cell type or include cells with mixed function within the same tumor.

Hormonally active tumors are characterized by autonomous hormone secretion with diminished feedback responsiveness to physiologic inhibitory pathways. Hormone production does not always correlate with

TABLE 51-3

CLASSIFICATION OF PITUITARY ADENOMAS[a]

ADENOMA CELL ORIGIN	HORMONE PRODUCT	CLINICAL SYNDROME
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH, subunits	Silent or hypogonadism
Somatotrope	GH	Acromegaly/ gigantism
Corticotrope	ACTH	Cushing's disease
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurihormonal cell	Any	Mixed
Acidophil stem cell	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Mammosomatotrope	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Thyrotrope	TSH	Thyrotoxicosis
Null cell	None	Pituitary failure
Oncocytoma	None	Pituitary failure

[a]Hormone-secreting tumors are listed in decreasing order of frequency. All tumors may cause local pressure effects, including visual disturbances, cranial nerve palsy, and headache.
Note: For abbreviations, see text.
Source: Adapted from S Melmed, in JL Jameson (ed): Principles of Molecular Medicine. Totowa, NJ, Humana Press, 1998.

www.ketabpezeshki.com (021) 66485457 - 66485438

tumor size. Small hormone-secreting adenomas may cause significant clinical perturbations, whereas larger adenomas that produce less hormone may be clinically silent and remain undiagnosed (if no central compressive effects occur). About one-third of all adenomas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. Most of them arise from gonadotrope cells and may secrete small amounts of α- and β-glycoprotein hormone subunits or, very rarely, intact circulating gonadotropins. True pituitary carcinomas with documented extracranial metastases are exceedingly rare.

Almost all pituitary adenomas are monoclonal in origin, implying the acquisition of one or more somatic mutations that confer a selective growth advantage. Consistent with their clonal origin, complete surgical resection of small pituitary adenomas usually cures hormone hypersecretion. Nevertheless, hypothalamic hormones such as GHRH and CRH also enhance mitotic activity of their respective pituitary target cells in addition to their role in pituitary hormone regulation. T us, patients who harbor rare abdominal or chest tumors that elaborate ectopic GHRH or CRH may present with somatotrope or corticotrope hyperplasia with GH or ACTH hypersecretion.

Several etiologic genetic events have been implicated in the development of pituitary tumors. T e pathogenesis of sporadic forms of acromegaly has been particularly informative as a model of tumorigenesis. GHRH, after binding to its G protein–coupled somatotrope receptor, uses cyclic adenosine monophosphate (AMP) as a second messenger to stimulate GH secretion and somatotrope proliferation. A subset (~35%) of GH-secreting pituitary tumors contains sporadic mutations in Gsα (Arg 201 →Cys or His; Gln 227 →Arg). T ese mutations attenuate intrinsic GTPase activity, resulting in constitutive elevation of cyclic AMP, Pit-1 induction, and activation of cyclic AMP response element binding protein (CREB), thereby promoting somatotrope cell proliferation and GH secretion.

Characteristic loss of heterozygosity (LOH) in various chromosomes has been documented in large or invasive macroadenomas, suggesting the presence of putative tumor suppressor genes at these loci in up to 20% of sporadic pituitary tumors, including GH-, PRL-, and ACTH-producing adenomas and some nonfunctioning tumors. Lineage-specific cell cycle disruptions with elevated levels of CDK inhibitors are present in most of these adenomas.

Compelling evidence also favors growth factor promotion of pituitary tumor proliferation. Basic fibroblast growth factor (bFGF) is abundant in the pituitary and stimulates pituitary cell mitogenesis, whereas epithelial growth factor (EGF) receptor signaling induces both hormone synthesis and cell proliferation. Other factors involved in initiation and promotion of pituitary tumors include loss of negative-feedback inhibition (as seen with primary hypothyroidism or hypogonadism) and estrogen-mediated or paracrine angiogenesis. Growth characteristics and neoplastic behavior also may be influenced by several activated oncogenes, including RAS and pituitary tumor transforming gene (PTTG), or inactivation of growth suppressor genes, including MEG3.

Genetic syndromes associated with pituitary tumors

Several familial syndromes are associated with pituitary tumors, and the genetic mechanisms for some of them have been unraveled **(Table 51-4)**.

Multiple endocrine neoplasia (MEN) 1 is an autosomal dominant syndrome characterized primarily by a genetic predisposition to parathyroid, pancreatic islet, and pituitary adenomas. MEN1 is caused by inactivating germline mutations in MENIN, a constitutively expressed tumor-suppressor gene located on chromosome 11q13. Loss of heterozygosity or a somatic mutation of the remaining normal MENIN allele leads to tumorigenesis. About half of affected patients develop prolactinomas; acromegaly and Cushing's syndrome are less commonly encountered.

Carney's syndrome is characterized by spotty skin pigmentation, myxomas, and endocrine tumors, including

TABLE 51-4

FAMILIAL PITUITARY TUMOR SYNDROMES

	GENE MUTATED	CLINICAL FEATURES
Multiple endocrine neoplasia 1 (MEN 1)	MEN1 (11q13)	Hyperparathyroidism Pancreatic neuroendocrine tumors Foregut carcinoids Adrenal adenomas Skin lesions Pituitary adenomas (40%)
Multiple endocrine neoplasia 4 (MEN 4)	CDKNIB (12p13)	Hyperparathyroidism Pituitary adenomas Other tumors
Carney complex	PRKAR1 A (17q23-24)	Pituitary hyperplasia andadenomas (10%) Atrial myxomas Schwannomas Adrenal hyperplasia Lentigines
Familial pituitary adenomas	AIP (11q13.3)	Acromegaly/gigantism (~15% of af icted families)

www.ketabpezeshki.com (021) 66485457 - 66485438

testicular, adrenal, and pituitary adenomas. Acromegaly occurs in about 20% of these patients. A subset of patients have mutations in the R1α regulatory subunit of protein kinase A (PRKAR1A).

McCune-Albright syndrome consists of polyostotic fibrous dysplasia, pigmented skin patches, and a variety of endocrine disorders, including acromegaly, adrenal adenomas, and autonomous ovarian function. Hormonal hypersecretion results from constitutive cyclic AMP production caused by inactivation of the GTPase activity of Gsα. T e Gsα mutations occur postzygotically, leading to a mosaic pattern of mutant expression.

Familial acromegaly is a rare disorder in which family members may manifest either acromegaly or gigantism. A subset of families with a predisposition for familial pituitary tumors, especially acromegaly, have been found to harbor germline mutations in the AIP gene, which encodes the aryl hydrocarbon receptor interacting protein.

HYPERPROLACTINEMIA

Etiology

Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women. PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >200 μg/L (see below). Less pronounced PRL elevation can also be seen with microprolactinomas but is more commonly caused by drugs, pituitary stalk compression, hypothyroidism, or renal failure **(Table 51-5)**.

Pregnancy and lactation are the important physiologic causes of hyperprolactinemia. Sleep-associated hyperprolactinemia reverts to normal within an hour of awakening. Nipple stimulation and sexual orgasm also may increase PRL. Chest wall stimulation or trauma (including chest surgery and herpes zoster) invoke the ref ex suckling arc with resultant hyperprolactinemia. Chronic renal failure elevates PRL by decreasing peripheral clearance. Primary hypothyroidism is associated with mild hyperprolactinemia, probably because of compensatory TRH secretion.

Lesions of the hypothalamic-pituitary region that disrupt hypothalamic dopamine synthesis, portal vessel delivery, or lactotrope responses are associated with hyperprolactinemia. T us, hypothalamic tumors, cysts, infiltrative disorders, and radiation-induced damage cause elevated PRL levels, usually in the range of 30–100 μg/L. Plurihormonal adenomas (including GH and ACTH tumors) may hypersecrete PRL directly. Pituitary masses, including clinically nonfunctioning pituitary tumors, may compress the pituitary stalk to cause hyperprolactinemia.

TABLE 51-5

ETIOLOGY OF HYPERPROLACTINEMIA

- **I. Physiologic hypersecretion**
  - Pregnancy
  - Lactation
  - Chest wall stimulation
  - Sleep
  - Stress
- **II. Hypothalamic–pituitary stalk damage**
  - Tumors
    - Craniopharyngioma
    - Suprasellar pituitary mass
    - Meningioma
    - Dysgerminoma
    - Metastases
  - Empty sella
  - Lymphocytic hypophysitis
  - Adenoma with stalk
  - Compression
  - Granulomas
  - Rathke's cyst
  - Irradiation
  - Trauma
    - Pituitary stalk section
    - Suprasellar surgery
- **III. Pituitary hypersecretion**
  - Prolactinoma
  - Acromegaly
- **IV. Systemic disorders**
  - Chronic renal failure
  - Hypothyroidism
  - Cirrhosis
  - Pseudocyesis
  - Epileptic seizures
- **V. Drug-induced hypersecretion**
  - Dopamine receptor blockers
    - Atypical antipsychotics: risperidone
    - Phenothiazines: chlorpromazine, perphenazine
    - Butyrophenones: haloperidol
    - Thioxanthenes
    - Metoclopramide
  - Dopamine synthesis inhibitors
    - α-Methyldopa
  - Catecholamine depletors
    - Reserpine
  - Opiates
  - H_2 antagonists
    - Cimetidine, ranitidine
  - Imipramines
    - Amitriptyline, amoxapine
  - Serotonin reuptake inhibitors
    - Fluoxetine
  - Calcium channel blockers
    - Verapamil
    - Estrogens
    - Thyrotropin-releasing hormone

Note: Hyperprolactinemia >200 μg/L almost invariably is indicative of a prolactin-secreting pituitary adenoma. Physiologic causes, hypothyroidism, and drug-induced hyperprolactinemia should be excluded before extensive evaluation.

www.ketabpezeshki.com (021) 66485457 - 66485438

Drug-induced inhibition or disruption of dopaminergic receptor function is a common cause of hyperprolactinemia (Table 51-5). T us, antipsychotics and antidepressants are a relatively common cause of mild hyperprolactinemia. Most patients receiving risperidone have elevated prolactin levels, sometimes exceeding 200 μg/L. Methyldopa inhibits dopamine synthesis, and verapamil blocks dopamine release, also leading to hyperprolactinemia. Hormonal agents that induce PRL include estrogens and thyrotropin-releasing hormone (TRH).

Presentation and diagnosis

Amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia in women. If hyperprolactinemia develops before menarche, primary amenorrhea results. More commonly, hyperprolactinemia develops later in life and leads to oligomenorrhea and ultimately to amenorrhea. If hyperprolactinemia is sustained, vertebral bone mineral density can be reduced compared with age-matched controls, particularly when it is associated with pronounced hypoestrogenemia. Galactorrhea is present in up to 80% of hyperprolactinemic women. Although usually bilateral and spontaneous, it may be unilateral or expressed only manually. Patients also may complain of decreased libido, weight gain, and mild hirsutism.

In men with hyperprolactinemia, diminished libido, infertility, and visual loss (from optic nerve compression) are the usual presenting symptoms. Gonadotropin suppression leads to reduced testosterone, impotence, and oligospermia. True galactorrhea is uncommon in men with hyperprolactinemia. If the disorder is long-standing, secondary effects of hypogonadism are evident, including osteopenia, reduced muscle mass, and decreased beard growth.

T e diagnosis of idiopathic hyperprolactinemia is made by exclusion of known causes of hyperprolactinemia in the setting of a normal pituitary MRI. Some of these patients may harbor small microadenomas below visible MRI sensitivity (~2 mm).

GALACTORRHEA

Galactorrhea, the inappropriate discharge of milk-containing fluid from the breast, is considered abnormal if it persists longer than 6 months after childbirth or discontinuation of breast-feeding. Postpartum galactorrhea associated with amenorrhea is a self-limiting disorder usually associated with moderately elevated PRL levels. Galactorrhea may occur spontaneously, or it may be elicited by nipple pressure. In both men and women, galactorrhea may vary in color and consistency (transparent, milky, or bloody) and arise either unilaterally or bilaterally. Mammography or ultrasound is indicated for bloody discharges (particularly from a single nipple), which may be caused by breast cancer. Galactorrhea is commonly associated with hyperprolactinemia caused by any of the conditions listed in Table 51-5. Acromegaly is associated with galactorrhea in about one-third of patients. Treatment of galactorrhea usually involves managing the underlying disorder (e.g., replacing T_4 for hypothyroidism, discontinuing a medication, treating prolactinoma).

Laboratory investigation

Basal, fasting morning PRL levels (normally <20 μg/L) should be measured to assess hypersecretion. Both false-positive and false-negative results may be encountered. In patients with markedly elevated PRL levels (>1000 μg/L), reported results may be falsely lowered because of assay artifacts; sample dilution is required to measure these high values accurately. Falsely elevated values may be caused by aggregated forms of circulating PRL, which are usually biologically inactive (macroprolactinemia). Hypothyroidism should be excluded by measuring TSH and T_4 levels.

TREATMENT Hyperprolactinemia

Treatment of hyperprolactinemia depends on the cause of elevated PRL levels. Regardless of the etiology, however, treatment should be aimed at normalizing PRL levels to alleviate suppressive effects on gonadal function, halt galactorrhea, and preserve bone mineral density. Dopamine agonists are effective for most causes of hyperprolactinemia (see the treatment section for prolactinoma, below) regardless of the underlying cause.

If the patient is taking a medication known to cause hyperprolactinemia, the drug should be withdrawn, if possible. For psychiatric patients who require neuroleptic agents, supervised dose titration or the addition of a dopamine agonist can help restore normoprolactinemia and alleviate reproductive symptoms. However, dopamine agonists may worsen the underlying psychiatric condition, especially at high doses. Hyperprolactinemia usually resolves after adequate thyroid hormone replacement in hypothyroid patients or after renal transplantation in patients undergoing dialysis. Resection of hypothalamic or sellar mass lesions can reverse hyperprolactinemia caused by stalk compression and reduced dopamine tone. Granulomatous infiltrates occasionally respond to glucocorticoid administration. In patients with irreversible hypothalamic damage, no treatment may be warranted. In up to 30% of patients with hyperprolactinemia—usually without a visible pituitary microadenoma—the condition may resolve spontaneously.

www.ketabpezeshki.com (021) 66485457 - 66485438

PROLACTINOMA

Etiology and prevalence

Tumors arising from lactotrope cells account for about half of all functioning pituitary tumors, with a population prevalence of ~10/100,000 in men and ~30/100,000 in women. Mixed tumors that secrete combinations of GH and PRL, ACTH and PRL, and rarely TSH and PRL are also seen. T ese plurihormonal tumors are usually recognized by immunohistochemistry, sometimes without apparent clinical manifestations from the production of additional hormones. Microadenomas are classified as <1 cm in diameter and usually do not invade the parasellar region. Macroadenomas are >1 cm in diameter and may be locally invasive and impinge on adjacent structures. T e female-to-male ratio for microprolactinomas is 20:1, whereas the sex ratio is near 1:1 for macroadenomas. Tumor size generally correlates directly with PRL concentrations; values >250 μg/L usually are associated with macroadenomas. Men tend to present with larger tumors than women, possibly because the features of male hypogonadism are less readily evident. PRL levels remain stable in most patients, reflecting the slow growth of these tumors. About 5% of microadenomas progress in the long term to macroadenomas.

Presentation and diagnosis

Women usually present with amenorrhea, infertility, and galactorrhea. If the tumor extends outside the sella, visual field defects or other mass effects may be seen. Men often present with impotence, loss of libido, infertility, or signs of central nervous system (CNS) compression, including headaches and visual defects. Assuming that physiologic and medication-induced causes of hyperprolactinemia are excluded (Table 51-5), the diagnosis of prolactinoma is likely with a PRL level >200 μg/L. PRL levels <100 μg/L may be caused by microadenomas, other sellar lesions that decrease dopamine inhibition, or nonneoplastic causes of hyperprolactinemia. For this reason, an MRI should be performed in all patients with hyperprolactinemia. It is important to remember that hyperprolactinemia caused secondarily by the mass effects of nonlactotrope lesions is also corrected by treatment with dopamine agonists despite failure to shrink the underlying mass. Consequently, PRL suppression by dopamine agonists does not necessarily indicate that the underlying lesion is a prolactinoma.

TREATMENT Prolactinoma

Because microadenomas rarely progress to become macroadenomas, no treatment may be needed if patients are asymptomatic and fertility is not desired; these patients should be monitored by regular serial PRL measurements and MRI scans.For symptomatic microadenomas, therapeutic goals include control of hyperprolactinemia, reduction of tumor size, restoration of menses and fertility, and resolution of galactorrhea. Dopamine agonist doses should be titrated to achieve maximal PRL suppression and restoration of reproductive function **(Fig. 51-3)**. A normalized PRL level does

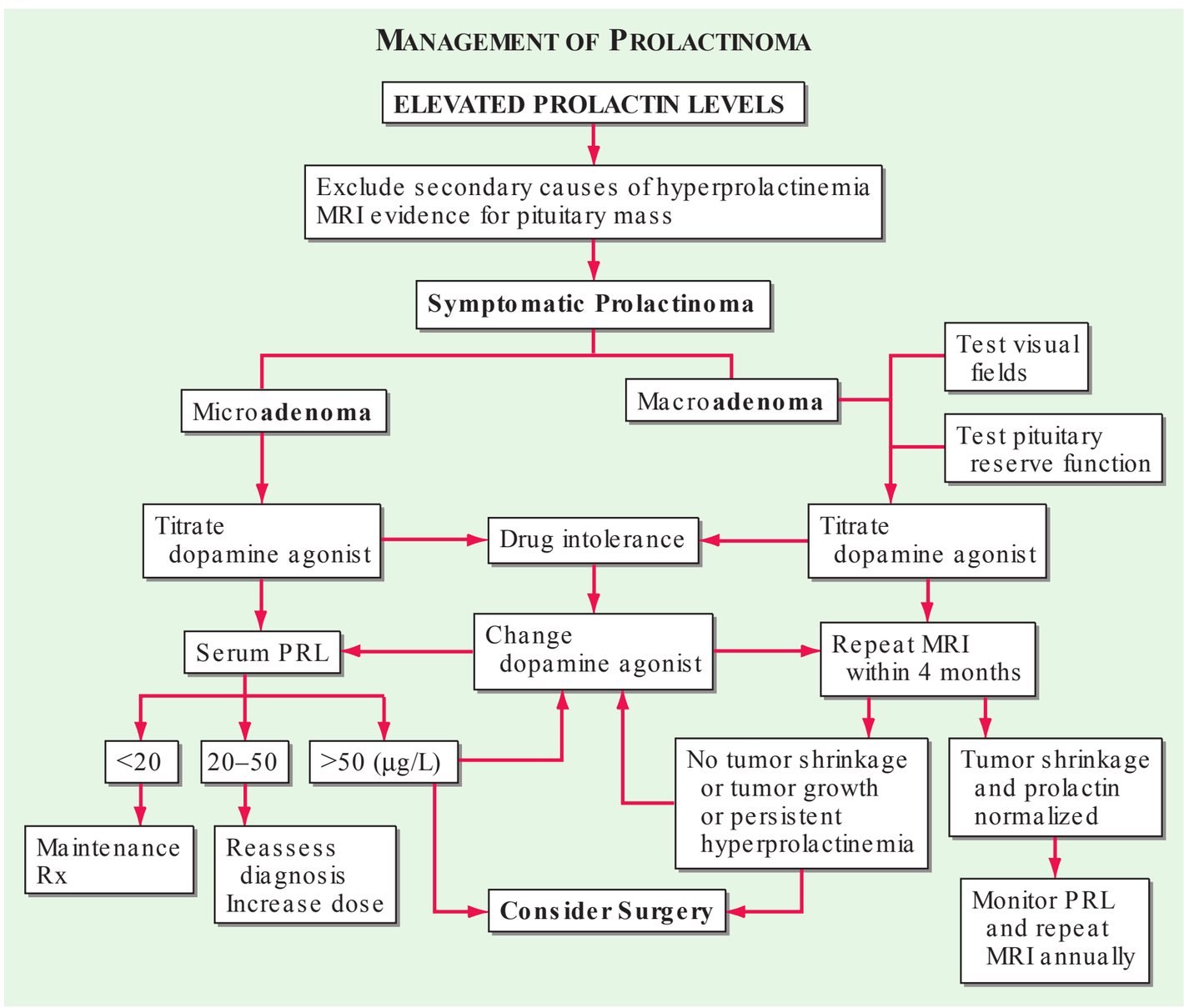


FIGURE 51-3
Management of prolactinoma. MRI, magnetic resonance imaging; PRL, prolactin.

www.ketabpezeshki.com (021) 66485457 - 66485438

not ensure reduced tumor size. However, tumor shrinkage usually is not seen in those who do not respond with lowered PRL levels. For macroadenomas, formal visual field testing should be performed before initiating dopamine agonists. MRI and visual fields should be assessed at 6- to 12-month intervals until the mass shrinks and annually thereafter until maximum size reduction has occurred.

MEDICAL Oral dopamine agonists (cabergoline and bromocriptine) are the mainstay of therapy for patients with micro- or macroprolactinomas. Dopamine agonists suppress PRL secretion and synthesis as well as lactotrope cell proliferation. In patients with microadenomas who have achieved normoprolactinemia and significant reduction of tumor mass, the dopamine agonist may be withdrawn after 2 years. T ese patients should be monitored carefully for evidence of prolactinoma recurrence. About 20% of patients (especially males) are resistant to dopaminergic treatment; these adenomas may exhibit decreased D_2 dopamine receptor numbers or a postreceptor defect. D_2 receptor gene mutations in the pituitary have not been reported.

Cabergoline An ergoline derivative, cabergoline is a long-acting dopamine agonist with high D_2 receptor af nity. T e drug effectively suppresses PRL for >14 days after a single oral dose and induces prolactinoma shrinkage in most patients. Cabergoline (0.5–1.0 mg twice weekly) achieves normoprolactinemia and resumption of normal gonadal function in ~80% of patients with microadenomas; galactorrhea improves or resolves in 90% of patients. Cabergoline normalizes PRL and shrinks ~70% of macroprolactinomas. Mass effect symptoms, including headaches and visual disorders, usually improve dramatically within days after cabergoline initiation; improvement of sexual function requires several weeks of treatment but may occur before complete normalization of prolactin levels. After initial control of PRL levels has been achieved, cabergoline should be reduced to the lowest effective maintenance dose. In ~5% of treated patients harboring a microadenoma, hyperprolactinemia may resolve and not recur when dopamine agonists are discontinued after long-term treatment. Cabergoline also may be effective in patients resistant to bromocriptine. Adverse effects and drug intolerance are encountered less commonly than with bromocriptine.

BROMOCRIPTINE T e ergot alkaloid bromocriptine mesylate is a dopamine receptor agonist that suppresses prolactin secretion. Because it is short-acting, the drug is preferred when pregnancy is desired. In microadenomas, bromocriptine rapidly lowers serum prolactin levels to normal in up to 70% of patients, decreases tumor size, and restores gonadal function. In patients with macroadenomas, prolactin levels are also normalized in 70% of patients, and tumor mass shrinkage (≥50%) is achieved in most patients.

T erapy is initiated by administering a low bromocriptine dose (0.625–1.25 mg) at bedtime with a snack, followed by gradually increasing the dose. Most patients are controlled with a daily dose of ≤7.5 mg (2.5 mg tid).

SIDE EFFECTS Side effects of dopamine agonists include constipation, nasal stuf ness, dry mouth, nightmares, insomnia, and vertigo; decreasing the dose usually alleviates these problems. Nausea, vomiting, and postural hypotension with faintness may occur in ~25% of patients after the initial dose. T ese symptoms may persist in some patients. In general, fewer side effects are reported with cabergoline. For the approximately 15% of patients who are intolerant of oral bromocriptine, cabergoline may be better tolerated. Intravaginal administration of bromocriptine is often ef cacious in patients with intractable gastrointestinal side effects. Auditory hallucinations, delusions, and mood swings have been reported in up to 5% of patients and may be due to the dopamine agonist properties or to the lysergic acid derivative of the compounds. Rare reports of leukopenia, thrombocytopenia, pleural fibrosis, cardiac arrhythmias, and hepatitis have been described. Patients with Parkinson's disease who receive at least 3 mg of cabergoline daily have been reported to be at risk for development of cardiac valve regurgitation. Studies analyzing over 500 prolactinoma patients receiving recommended doses of cabergoline (up to 2 mg weekly) have shown no evidence for an increased incidence of valvular disorders. Nevertheless, because no controlled prospective studies in pituitary tumor patients are available, it is prudent to perform echocardiograms before initiating standard-dose cabergoline therapy.

Surgery Indications for surgical adenoma debulking include dopamine resistance or intolerance and the presence of an invasive macroadenoma with compromised vision that fails to improve after drug treatment. Initial PRL normalization is achieved in about 70% of microprolactinomas after surgical resection, but only 30% of macroadenomas can be resected successfully. Follow-up studies have shown that hyperprolactinemia recurs in up to 20% of patients within the first year after surgery; long-term recurrence rates exceed 50% for macroadenomas. Radiotherapy for prolactinomas is reserved for patients with aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery.

PREGNANCY T e pituitary increases in size during pregnancy, reflecting the stimulatory effects of estrogen and perhaps other growth factors on pituitary vascularity and lactotrope cell hyperplasia. About 5% of microadenomas significantly increase in size, but 15–30% of macroadenomas grow during pregnancy. Bromocriptine has been used for more than 30 years to restore fertility in women with hyperprolactinemia, without evidence of teratogenic effects. Nonetheless, most authorities recommend strategies to minimize fetal exposure to the drug. For women taking bromocriptine who desire pregnancy, mechanical contraception should be used through three regular menstrual cycles to allow for conception timing. When pregnancy is confirmed, bromocriptine should be discontinued and PRL levels followed serially, especially if headaches or visual symptoms occur. For women harboring macroadenomas, regular visual field testing is recommended, and the drug should be reinstituted if tumor

www.ketabpezeshki.com (021) 66485457 - 66485438

growth is apparent. Although pituitary MRI may be safe during pregnancy, this procedure should be reserved for symptomatic patients with severe headache and/or visual field defects. Surgical decompression may be indicated if vision is threatened. Although comprehensive data support the efficacy and relative safety of bromocriptine-facilitated fertility, patients should be advised of potential unknown deleterious effects and the risk of tumor growth during pregnancy. Because cabergoline is long-acting with a high D_2-receptor affinity, it is not recommended for use in women when fertility is desired.

ACROMEGALY

Etiology

GH hypersecretion is usually the result of a somatotrope adenoma but may rarely be caused by extrapituitary lesions **(Table 51-6)**. In addition to the more common GH-secreting somatotrope adenomas, mixed mammosomatotrope tumors and acidophilic stem-cell adenomas secrete both GH and PRL. In patients with acidophilic stem-cell adenomas, features of hyperprolactinemia (hypogonadism and galactorrhea) predominate over the less clinically evident signs of acromegaly. Occasionally, mixed plurihormonal tumors are encountered that also secrete ACTH, the glycoprotein hormone α subunit, or TSH in addition to GH. Patients with partially empty sellas may present with GH hypersecretion due to a small GH-secreting adenoma within the compressed rim of pituitary tissue; some of these may reflect the spontaneous necrosis of tumors that were previously larger. GH-secreting tumors rarely arise from ectopic pituitary tissue remnants in the nasopharynx or midline sinuses.

T ere are case reports of ectopic GH secretion by tumors of pancreatic, ovarian, lung, or hematopoietic origin. Rarely, excess GHRH production may cause acromegaly because of chronic stimulation of somatotropes. T ese patients present with classic features of acromegaly, elevated GH levels, pituitary enlargement on MRI, and pathologic characteristics of pituitary hyperplasia. T e most common cause of GHRH-mediated acromegaly is a chest or abdominal carcinoid tumor. Although these tumors usually express positive GHRH immunoreactivity, clinical features of acromegaly are evident in only a minority of patients with carcinoid disease. Excessive GHRH also may be elaborated by hypothalamic tumors, usually choristomas or neuromas.

TABLE 51-6

CAUSES OF ACROMEGALY

	PREVALENCE, %
EXCESS GROWTH HORMONE SECRETION	
Pituitary	98
Densely or sparsely granulated GH cell adenoma	60
Mixed GH cell and PRL cell adenoma	25
Mammosomatotrope cell adenoma	10
Plurihormonal adenoma	
GH cell carcinoma or metastases	
Multiple endocrine neoplasia 1 (GH cell adenoma)	
McCune-Albright syndrome	
Ectopic sphenoid or parapharyngeal sinus pituitary adenoma	
Extrapituitary tumor	
Pancreatic islet cell tumor	<1
Lymphoma	
EXCESS GROWTH HORMONE–RELEASING HORMONE SECRETION	
Central	<1
Hypothalamic hamartoma, choristoma, ganglioneuroma	<1
Peripheral	<1
Bronchial carcinoid, pancreatic islet cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma	

Abbreviations: GH, growth hormone; PRL, prolactin.
Source: Adapted from S Melmed: N Engl J Med 355:2558–2573, 2006.

Presentation and diagnosis

Protean manifestations of GH and IGF-I hypersecretion are indolent and of en are not clinically diagnosed for 10 years or more. Acral bony overgrowth results in frontal bossing, increased hand and foot size, mandibular enlargement with prognathism, and widened space between the lower incisor teeth. In children and adolescents, initiation of GH hypersecretion before epiphyseal long bone closure is associated with development of pituitary gigantism **(Fig. 51-4)**. Sof tissue swelling results in increased heel pad thickness, increased shoe or glove size, ring tightening, characteristic coarse facial features, and a large fleshy nose. Other commonly encountered clinical features include hyperhidrosis, a deep and hollow-sounding voice, oily skin, arthropathy, kyphosis, carpal tunnel syndrome, proximal muscle weakness and fatigue, acanthosis nigricans, and skin tags. Generalized visceromegaly occurs, including cardiomegaly, macroglossia, and thyroid gland enlargement.

T e most significant clinical impact of GH excess occurs with respect to the cardiovascular system. Coronary heart disease, cardiomyopathy with arrhythmias, lef ventricular hypertrophy, decreased diastolic function, and hypertension ultimately occur in most patients if untreated. Upper airway obstruction with sleep apnea occurs in more than 60% of patients and

www.ketabpezeshki.com (021) 66485457 - 66485438

A

B

C

FIGURE 51-4
Features of acromegaly/gigantism. A 22-year-old man with gigantism due to excess growth hormone is shown to the left of his identical twin. The increased height and prognathism (A) and enlarged hand (B) and foot (C) of the affected twin are apparent. Their clinical features began to diverge at the age of approximately 13 years. (Reproduced from RGagel, IEMcCutcheon: N Engl J Med 324:524, 1999; with permission.)

is associated with both soft tissue laryngeal airway obstruction and central sleep dysfunction. Diabetes mellitus develops in 25% of patients with acromegaly, and most patients are intolerant of a glucose load (as GH counteracts the action of insulin). Acromegaly is associated with an increased risk of colon polyps and mortality from colonic malignancy; polyps are diagnosed in up to one-third of patients. Overall mortality is increased about threefold and is due primarily to cardiovascular and cerebrovascular disorders and respiratory disease. Unless GH levels are controlled, survival is reduced by an average of10 years compared with an age-matched control population.

Laboratory investigation

Age-matched serum IGF-I levels are elevated in acromegaly. Consequently, an IGF-I level provides a useful laboratory screening measure when clinical features raise the possibility of acromegaly. Due to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diagnosis or exclusion of acromegaly and does not correlate with disease severity. T e diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <0.4 μg/L within 1–2 h of an oral glucose load (75 g). When newer ultrasensitive GH assays are used, normal nadir GH levels are even lower (<0.05 μg/L). About 20% of patients exhibit a paradoxical GH rise after glucose. PRL should be measured, as it is elevated in ~25% of patients with acromegaly. T yroid function, gonadotropins, and sex steroids may be attenuated because of tumor mass effects. Because most patients will undergo surgery with glucocorticoid coverage, tests of ACTH reserve in asymptomatic patients are more ef ciently deferred until after surgery.

TREATMENT Acromegaly

T e goal of treatment is to control GH and IGF-I hypersecretion, ablate or arrest tumor growth, ameliorate comorbidities, restore mortality rates to normal, and preserve pituitary function.

Surgical resection of GH-secreting adenomas is the initial treatment for most patients **(Fig. 51-5)**. Somatostatin analogues are used as adjuvant treatment for preoperative shrinkage of large invasive macroadenomas, immediate relief of debilitating symptoms, and reduction of GH hypersecretion; in frail patients experiencing morbidity; and in patients who decline surgery or, when surgery fails, to achieve biochemical control. Irradiation or repeat surgery may be required for patients who cannot tolerate or do not respond to adjunctive medical therapy. T e high rate of late

www.ketabpezeshki.com (021) 66485457 - 66485438

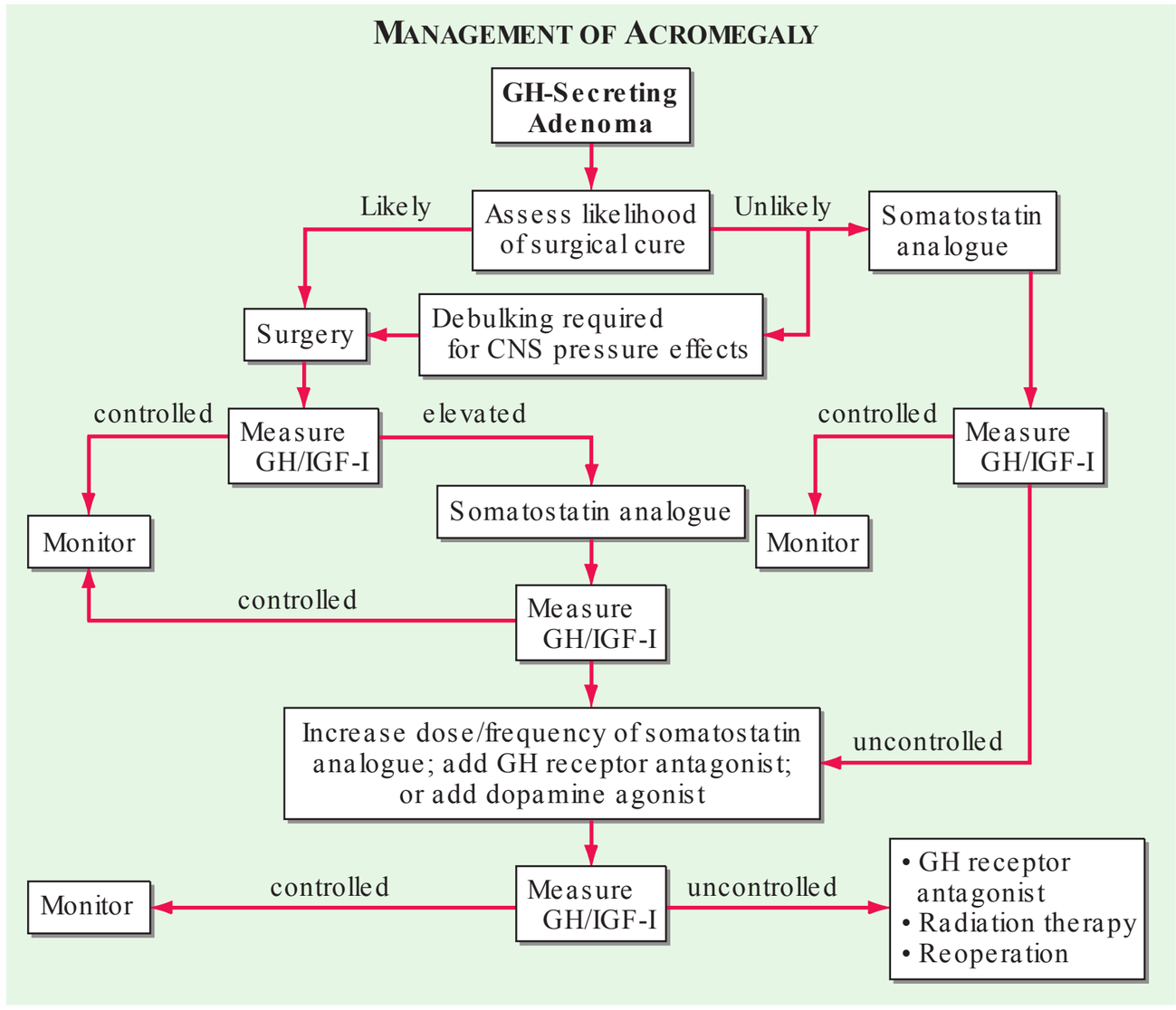


FIGURE 51-5

Management of acromegaly. GH, growth hormone; CNS, central nervous system; IGF, insulin-like growth factor. (Adapted fromS Melmed et al: J Clin Endocrinol Metab 94:1509–1517, 2009; © The Endocrine Society.)

hypopituitarism and the slow rate (5–15 years) of biochemical response are the main disadvantages of radiotherapy. Irradiation is also relatively ineffective in normalizing IGF-I levels. Stereotactic ablation of GH-secreting adenomas by gamma-knife radiotherapy is promising, but initial reports suggest that long-term results and side effects are similar to those observed with conventional radiation. Somatostatin analogues may be required while awaiting the full benefits of radiotherapy. Systemic co-morbid sequelae of acromegaly, including cardiovascular disease, diabetes, and arthritis, should be managed aggressively. Mandibular surgical repair may be indicated.

SURGERY Transsphenoidal surgical resection by an experienced surgeon is the preferred primary treatment for both microadenomas (remission rate ~70%) and macroadenomas (<50% in remission). Soft tissue swelling improves immediately after tumor resection. GH levels return to normal within an hour, and IGF-I levels are normalized within 3–4 days. In ~10% of patients, acromegaly may recur several years after apparently successful surgery; hypopituitarism develops in up to 15% of patients after surgery.

SOMATOSTATIN ANALOGUES Somatostatin analogues exert their therapeutic effects through SSTR2 and SSTR5 receptors, both of which are expressed by GH-secreting tumors. Octreotide acetate is an eight-amino-acid synthetic somatostatin analogue. In contrast to native somatostatin, the analogue is relatively resistant to plasma degradation. It has a 2-h serum half-life and possesses fortyfold greater potency than native somatostatin to suppress GH. Octreotide is administered by subcutaneous injection, beginning with 50 μg tid; the dose can be increased gradually up to 1500 μg/d. Fewer than 10% of patients do not respond to the analogue. Octreotide suppresses integrated GH levels and normalizes IGF-I levels in ~60% of treated patients.

The long-acting somatostatin depot formulations, octreotide and lanreotide, are the preferred medical treatment for patients with acromegaly. Sandostatin-LAR is a sustained-release, long-acting formulation of octreotide incorporated into microspheres that sustain drug levels for several weeks after intramuscular injection. GH suppression occurs for as long as 6 weeks after a 30-mg intramuscular injection; long-term monthly treatment sustains GH and IGF-I suppression and also reduces pituitary tumor size in ~50% of patients. Lanreotide autogel, a slow-release depot somatostatin preparation, is a cyclic somatostatin octapeptide analogue that suppresses GH and IGF-I hypersecretion after a 60-mg subcutaneous injection. Long-term (4–6 weeks) administration controls GH hypersecretion in about two-thirds of treated patients and improves patient compliance because of the long interval required between drug injections. Rapid relief of headache and soft tissue swelling occurs in ~75% of patients within days to weeks of somatostatin analogue initiation. Most patients report symptomatic improvement, including amelioration of headache, perspiration, obstructive apnea, and cardiac failure.

www.ketabpezeshki.com (021) 66485457 - 66485438

Side Effects Somatostatin analogues are well tolerated in most patients. Adverse effects are short-lived and mostly relate to drug-induced suppression of gastrointestinal motility and secretion. Transient nausea, abdominal discomfort, fat malabsorption, diarrhea, and flatulence occur in one-third of patients, and these symptoms usually remit within 2 weeks. Octreotide suppresses postprandial gallbladder contractility and delays gallbladder emptying; up to 30% of patients develop long-term echogenic sludge or asymptomatic cholesterol gallstones. Other side effects include mild glucose intolerance due to transient insulin suppression, asymptomatic bradycardia, hypothyroxinemia, and local injection site discomfort.

GH RECEPTOR ANTAGONIST Pegvisomant antagonizes endogenous GH action by blocking peripheral GH binding to its receptor. Consequently, serum IGF-I levels are suppressed, reducing the deleterious effects of excess endogenous GH. Pegvisomant is administered by daily subcutaneous injection (10–20 mg) and normalizes IGF-I in ~70% of patients. GH levels, however, remain elevated as the drug does not target the pituitary adenoma. Side effects include reversible liver enzyme elevation, lipodystrophy, and injection site pain. Tumor size should be monitored by MRI.

Combined treatment with monthly somatostatin analogues and weekly or biweekly pegvisomant injections has been used effectively in resistant patients.

DOPAMINE AGONISTS Bromocriptine and cabergoline may modestly suppress GH secretion in some patients. Very high doses of bromocriptine (≥20 mg/d) or cabergoline (0.5 mg/d) are usually required to achieve modest GH therapeutic efficacy. Combined treatment with octreotide and cabergoline may induce additive biochemical control compared with either drug alone.

RADIATION External radiation therapy or high-energy stereotactic techniques are used as adjuvant therapy for acromegaly. An advantage of radiation is that patient compliance with long-term treatment is not required. Tumor mass is reduced, and GH levels are attenuated over time. However, 50% of patients require at least 8 years for GH levels to be suppressed to <5 μg/L; this level of GH reduction is achieved in about 90% of patients after 18 years but represents suboptimal GH suppression. Patients may require interim medical therapy for several years before attaining maximal radiation benefits. Most patients also experience hypothalamic-pituitary damage, leading to gonadotropin, ACTH, and/or TSH deficiency within 10 years of therapy.

In summary, surgery is the preferred primary treatment for GH-secreting microadenomas (Fig. 51-5). The high frequency of GH hypersecretion after macroadenoma resection usually necessitates adjuvant or primary medical therapy for these larger tumors. Patients unable to receive or respond to unimodal medical treatment may benefit from combined treatments, or can be offered radiation.

CUSHING'S SYNDROME (ACTH-PRODUCING ADENOMA)

Etiology and prevalence

Pituitary corticotrope adenomas account for 70% of patients with endogenous causes of Cushing's syndrome. However, it should be emphasized that iatrogenic hypercortisolism is the most common cause of cushingoid features. Ectopic tumor ACTH production, cortisol-producing adrenal adenomas, adrenal carcinoma, and adrenal hyperplasia account for the other causes; rarely, ectopic tumor CRH production is encountered.

ACTH-producing adenomas account for about 10–15% of all pituitary tumors. Because the clinical features of Cushing's syndrome often lead to early diagnosis, most ACTH-producing pituitary tumors are relatively small microadenomas. However, macroadenomas also are seen and some ACTH-expressing adenomas are clinically silent. Cushing's disease is 5–10 times more common in women than in men. These pituitary adenomas exhibit unrestrained ACTH secretion, with resultant hypercortisolemia. However, they retain partial suppressibility in the presence of high doses of administered glucocorticoids, providing the basis for dynamic testing to distinguish pituitary from nonpituitary causes of Cushing's syndrome.

Presentation and diagnosis

The diagnosis of Cushing's syndrome presents two great challenges: (1) to distinguish patients with pathologic cortisol excess from those with physiologic or other disturbances of cortisol production and (2) to determine the etiology of pathologic cortisol excess.

Typical features of chronic cortisol excess include thin skin, central obesity, hypertension, plethoric moon facies, purple striae and easy bruisability, glucose intolerance or diabetes mellitus, gonadal dysfunction, osteoporosis, proximal muscle weakness, signs of hyperandrogenism (acne, hirsutism), and psychological disturbances (depression, mania, and psychoses) **(Table 51-7)**. Hematopoietic features of hypercortisolism include leukocytosis, lymphopenia, and eosinopenia. Immune suppression includes delayed hypersensitivity and infection propensity. These protean yet commonly encountered manifestations of hypercortisolism make it challenging to decide which patients mandate formal laboratory evaluation. Certain features make pathologic causes of hypercortisolism more likely; they include characteristic central redistribution of fat, thin skin with striae and bruising, and proximal muscle weakness. In children and young females, early osteoporosis may be particularly prominent. The primary cause of death is cardiovascular disease, but

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 51-7

CLINICAL FEATURES OF CUSHING'S SYNDROME (ALL AGES)	
SYMPTOMS/SIGNS	FREQUENCY, %
Obesity or weight gain (>115% ideal body weight)	80
Thin skin	80
Moon facies	75
Hypertension	75
Purple skin striae	65
Hirsutism	65
Menstrual disorders (usually amenorrhea)	60
Plethora	60
Abnormal glucose tolerance	55
Impotence	55
Proximal muscle weakness	50
Truncal obesity	50
Acne	45
Bruising	45
Mental changes	45
Osteoporosis	40
Edema of lower extremities	30
Hyperpigmentation	20
Hypokalemic alkalosis	15
Diabetes mellitus	15

Source: Adapted from MA Magiokou et al, in ME Wierman (ed): Diseases of the Pituitary. Totowa, NJ, Humana, 1997.

life-threatening infections and risk of suicide are also increased.

Rapid development of features of hypercortisolism associated with skin hyperpigmentation and severe myopathy suggests an ectopic tumor source of ACTH. Hypertension, hypokalemic alkalosis, glucose intolerance, and edema are also more pronounced in these patients. Serum potassium levels <3.3 mmol/L are evident in ~70% of patients with ectopic ACTH secretion but are seen in <10% of patients with pituitary-dependent Cushing's syndrome.

Laboratory investigation

The diagnosis of Cushing's syndrome is based on laboratory documentation of endogenous hypercortisolism. Measurement of 24-h urine free cortisol (UFC) is a precise and cost-effective screening test. Alternatively, the failure to suppress plasma cortisol after an overnight 1-mg dexamethasone suppression test can be used to identify patients with hypercortisolism. As nadir levels of cortisol occur at night, elevated midnight serum or salivary samples of cortisol are suggestive of Cushing's syndrome. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syndrome. Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion than in those with pituitary ACTH-secreting adenomas. However, extensive overlap of ACTH levels in these two disorders precludes using ACTH measurements to make the distinction. Preferably, dynamic testing based on differential sensitivity to glucocorticoid feedback or ACTH stimulation in response to CRH or cortisol reduction is used to distinguish ectopic from pituitary sources of excess ACTH **(Table 51-8)**. Very rarely, circulating CRH levels are elevated, reflecting ectopic tumor-derived secretion of CRH and often ACTH.

Most ACTH-secreting pituitary tumors are <5 mm in diameter, and about half are undetectable by sensitive MRI. The high prevalence of incidental pituitary microadenomas diminishes the ability to distinguish ACTH-secreting pituitary tumors accurately from nonsecreting incidentalomas.

Inferior petrosal venous sampling

Because pituitary MRI with gadolinium enhancement is insufficiently sensitive to detect small (<2 mm) pituitary ACTH-secreting adenomas, bilateral inferior petrosal sinus ACTH sampling before and after CRH administration may be required to distinguish these lesions from ectopic ACTH-secreting tumors that may have similar clinical and biochemical characteristics. Simultaneous assessment of ACTH in each inferior petrosal vein and in the diagnosis of peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at baseline and 2, 5, and 10 min after intravenous bovine CRH (1 μg/kg) injection. An increased ratio (>2) of inferior petrosal:peripheral vein ACTH confirms pituitary Cushing's syndrome. After CRH injection, peak petrosal:peripheral ACTH ratios ≥3 confirm the presence of a pituitary ACTH-secreting tumor. The sensitivity of this test is >95%, with very rare false-positive results. False-negative results may be encountered in patients with aberrant venous drainage. Petrosal sinus catheterizations are technically difficult, and about 0.05% of patients develop neurovascular complications. The procedure should not be performed in patients with hypertension, in patients with known cerebrovascular disease, or in the presence of a well-visualized pituitary adenoma on MRI.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 51-8

DIFFERENTIAL DIAGNOSIS OF ACTH-DEPENDENT CUSHING'S SYNDROME[a]

	ACTH-SECRETING PITUITARY TUMOR	ECTOPIC ACTH SECRETION
Etiology	Pituitary corticotrope adenoma Plurihormonal adenoma	Bronchial, abdominal carcinoid Small cell lung cancer Thymoma
Sex	F > M	M > F
Clinical features	Slow onset	Rapid onset Pigmentation Severe myopathy
Serum potassium <3.3μg/L	<10%	75%
24-h urinary free cortisol (UFC)	High	High
Basal ACTH level	Inappropriately high	Very high
Dexamethasone suppression 1 mg overnight		
Low-dose (0.5 mg q6h)	Cortisol >5 μg/dL	Cortisol >5 μg/dL
High-dose (2 mg q6h)	Cortisol <5 μg/dL	Cortisol >5 μg/dL
UFC >80% suppressed	Microadenomas: 90% Macroadenomas: 50%	10%
Inferior petrosal sinus sampling (IPSS)		
Basal IPSS: peripheral	>2	<2
CRH-induced IPSS: peripheral	>3	<3

[a]ACTH-independent causes of Cushing's syndrome are diagnosed by suppressed ACTH levels and an adrenal mass in the setting of hypercortisolism. Iatrogenic Cushing's syndrome is excluded by history.
Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; F, female; M, male.

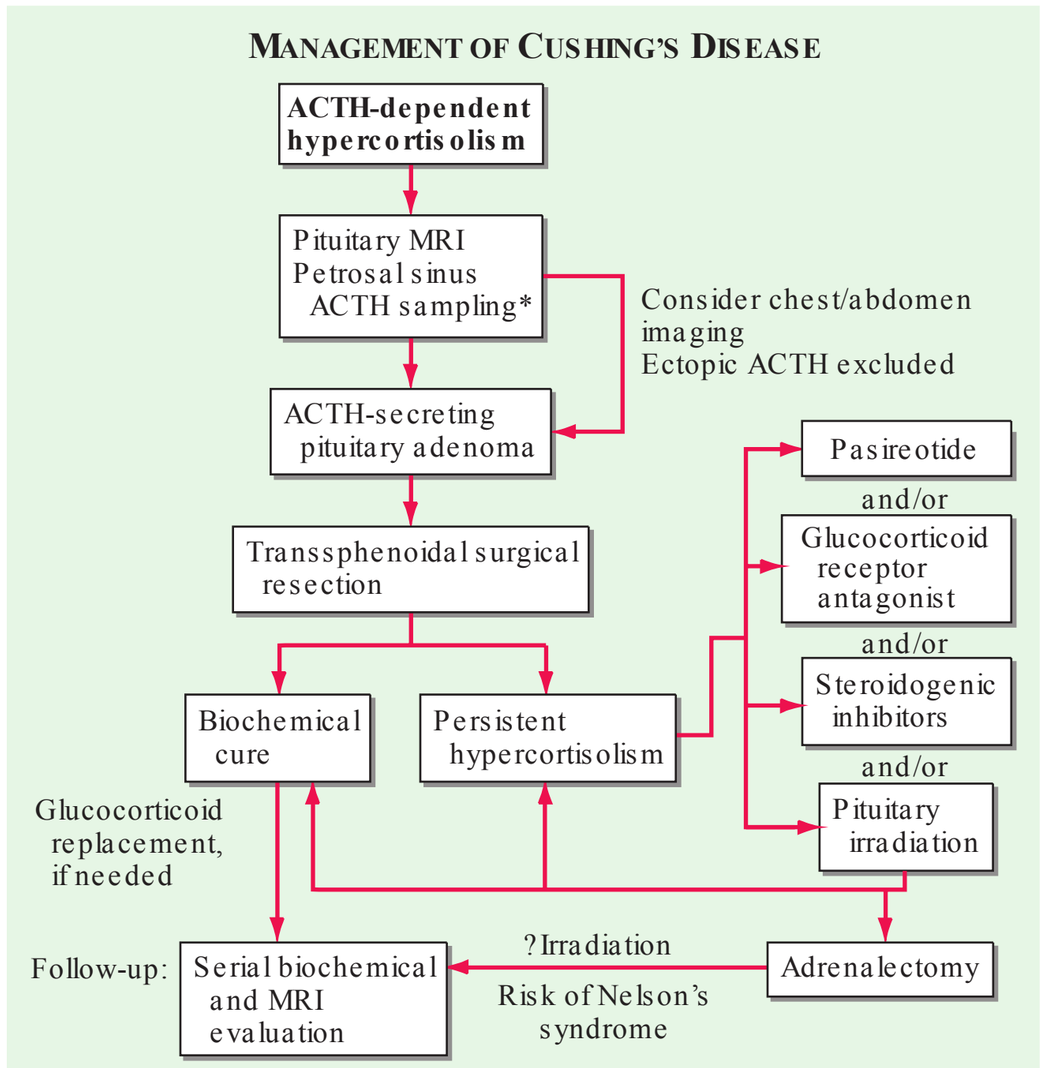


FIGURE 51-6
Management of Cushing's syndrome. ACTH, adrenocorticotropin hormone; MRI, magnetic resonance imaging. *, Not usually required.

TREATMENT Cushing's Syndrome

Selective transsphenoidal resection is the treatment of choice for Cushing's disease **(Fig. 51-6)**. The remission rate for this procedure is ~80% for microadenomas but <50% for macroadenomas. However, surgery is rarely successful when the adenoma is not visible on MRI. After successful tumor resection, most patients experience a postoperative period of symptomatic ACTH deficiency that may last up to 12 months. This usually requires low-dose cortisol replacement, as patients experience both steroid withdrawal symptoms and have a suppressed hypothalamic-pituitary-adrenal axis. Biochemical recurrence occurs in approximately 5% of patients in whom surgery was initially successful.

When initial surgery is unsuccessful, repeat surgery is sometimes indicated, particularly when a pituitary source for ACTH is well documented. In older patients, in whom issues of growth and fertility are less important, hemi- or total hypophysectomy may be necessary if a discrete pituitary adenoma is not recognized. Pituitary irradiation may be used after unsuccessful surgery, but it cures only about 15% of patients. Because the effects of radiation are slow and only partially effective in adults, steroidogenic inhibitors are used in combination with pituitary irradiation to block adrenal effects of persistently high ACTH levels.

Pasireotide (600 or 900 ug/day subcutaneously), a somatostatin analog with high affinity for SST5 > SST2 receptors, has been approved for treating patients with ACTH-secreting pituitary tumors when surgery is not an option or has been unsuccessful. In clinical trials, the drug lowered plasma ACTH levels, normalized 24-h urinary free cortisol levels in about 25% of patients, and resulted in up to 40% mean pituitary tumor shrinkage. Side effects include development of hyperglycemia and diabetes in about 70% of patients, likely due to suppressed pancreatic secretion of insulin and incretins. Because patients with hypercortisolism are

www.ketabpezeshki.com (021) 66485457 - 66485438

insulin-resistant, hyperglycemia should be rigorously managed. Other side effects are similar to those encountered for somatostatin analogs and include transient abdominal discomfort, diarrhea, nausea, and gallstones (20% of patients). T e drug requires consistent long-term administration.

Ketoconazole, an imidazole derivative antimycotic agent, inhibits several P450 enzymes and effectively lowers cortisol in most patients with Cushing's disease when administered twice daily (600–1200 mg/d). Elevated hepatic transaminases, gynecomastia, impotence, gastrointestinal upset, and edema are common side effects.

Mifepristone (300–1200 mg/d), a glucocorticoid receptor antagonist, blocks peripheral cortisol action and is approved to treat hyperglycemia in Cushing's disease. Because the drug does not target the pituitary tumor, both ACTH and cortisol levels remain elevated, thus obviating a reliable circulating biomarker. Side effects are largely due to general antagonism of other steroid hormones and include hypokalemia, endometrial hyperplasia, hypoadrenalism, and hypertension.

Metyrapone (2–4 g/d) inhibits 11β-hydroxylase activity and normalizes plasma cortisol in up to 75% of patients. Side effects include nausea and vomiting, rash, and exacerbation of acne or hirsutism. Mitotane (o,p '-DDD; 3–6 g/d orally in four divided doses) suppresses cortisol hypersecretion by inhibiting 11β-hydroxylase and cholesterol side-chain cleavage enzymes and by destroying adrenocortical cells. Side effects of mitotane include gastrointestinal symptoms, dizziness, gynecomastia, hyperlipidemia, skin rash, and hepatic enzyme elevation. It also may lead to hypoaldosteronism. Other agents include aminoglutethimide (250 mg tid), trilostane (200–1000 mg/d), cyproheptadine (24 mg/d), and IV etomidate (0.3 mg/kg per hour). Glucocorticoid insuf ciency is a potential side effect of agents used to block steroidogenesis.

T e use of steroidogenic inhibitors has decreased the need for bilateral adrenalectomy. Surgical removal of both adrenal glands corrects hypercortisolism but may be associated with significant morbidity rates and necessitates permanent glucocorticoid and mineralocorticoid replacement. Adrenalectomy in the setting of residual corticotrope adenoma tissue predisposes to the development of Nelson's syndrome, a disorder characterized by rapid pituitary tumor enlargement and increased pigmentation secondary to high ACTH levels. Prophylactic radiation therapy may be indicated to prevent the development of Nelson's syndrome after adrenalectomy.

NONFUNCTIONING AND GONADOTROPIN-PRODUCING PITUITARY ADENOMAS

Etiology and prevalence

Nonfunctioning pituitary adenomas include those that secrete little or no pituitary hormones as well as tumors that produce too little hormone to result in recognizable clinical features. T ey are the most common type of pituitary adenoma and are usually macroadenomas at the time of diagnosis because clinical features are not apparent until tumor mass effects occur. Based on immunohistochemistry, most clinically nonfunctioning adenomas can be shown to originate from gonadotrope cells. T ese tumors typically produce small amounts of intact gonadotropins (usually FSH) as well as uncombined α, LH β, and FSH β subunits. Tumor secretion may lead to elevated α and FSH β subunits and, rarely, to increased LH β subunit levels. Some adenomas express α subunits without FSH or LH. TRH administration often induces an atypical increase of tumor-derived gonadotropins or subunits.

Presentation and diagnosis

Clinically nonfunctioning tumors often present with optic chiasm pressure and other symptoms of local expansion or may be incidentally discovered on an MRI performed for another indication (incidentaloma). Rarely, menstrual disturbances or ovarian hyperstimulation occur in women with large tumors that produce FSH and LH. More commonly, adenoma compression of the pituitary stalk or surrounding pituitary tissue leads to attenuated LH and features of hypogonadism. PRL levels are usually slightly increased, also because of stalk compression. It is important to distinguish this circumstance from true prolactinomas, as nonfunctioning tumors do not shrink in response to treatment with dopamine agonists.

Laboratory investigation

T e goal of laboratory testing in clinically nonfunctioning tumors is to classify the type of the tumor, identify hormonal markers of tumor activity, and detect possible hypopituitarism. Free α subunit levels may be elevated in 10–15% of patients with nonfunctioning tumors. In female patients, peri- or postmenopausal basal FSH concentrations are dif cult to distinguish from tumor-derived FSH elevation. Premenopausal women have cycling FSH levels, also preventing clear-cut diagnostic distinction from tumor-derived FSH. In men, gonadotropin-secreting tumors may be diagnosed because of slightly increased gonadotropins (FSH > LH) in the setting of a pituitary mass. Testosterone levels are usually low despite the normal or increased LH level, perhaps reflecting reduced LH bioactivity or the loss of normal LH pulsatility. Because this pattern of hormone test results is also seen in primary gonadal failure and, to some extent, with aging, the finding of increased gonadotropins alone is insuf cient for the diagnosis of a gonadotropin-secreting tumor. In the majority of patients with gonadotrope adenomas, TRH administration stimulates LH β subunit secretion; this response is not seen in normal individuals. GnRH testing, however, is not helpful for making the diagnosis. For

www.ketabpezeshki.com (021) 66485457 - 66485438

nonfunctioning and gonadotropin-secreting tumors, the diagnosis usually rests on immunohistochemical analyses of surgically resected tumor tissue, as the mass effects of these tumors usually necessitate resection.

Although acromegaly or Cushing's syndrome usually presents with unique clinical features, clinically inapparent (silent) somatotrope or corticotrope adenomas may only be diagnosed by immunostaining of resected tumor tissue. If PRL levels are <100 μg/L in a patient harboring a pituitary mass, a nonfunctioning adenoma causing pituitary stalk compression should be considered.

TREATMENT Nonfunctioning and Gonadotropin-Producing Pituitary Adenomas

Asymptomatic small nonfunctioning microadenomas adenomas with no threat to vision may be followed with regular MRI and visual field testing without immediate intervention. However, for macroadenomas, transsphenoidal surgery is indicated to reduce tumor size and relieve mass effects **(Fig. 51-7)**. Although it is not usually possible to remove all adenoma tissue surgically, vision improves in 70% of patients with preoperative visual field defects. Preexisting hypopituitarism that results from tumor mass effects may improve or resolve completely. Beginning about 6 months postoperatively, MRI scans should be performed yearly to detect tumor regrowth. Within 5–6 years after successful surgical resection, ~15% of nonfunctioning tumors recur. When substantial tumor remains after transsphenoidal surgery, adjuvant radiotherapy may be indicated to prevent tumor regrowth. Radiotherapy may be deferred if no postoperative residual mass is evident. Nonfunctioning pituitary tumors respond poorly to dopamine agonist treatment and somatostatin analogues are largely ineffective for shrinking these tumors. T e selective GnRH antagonist Nal-Glu GnRH suppresses FSH hypersecretion but has no effect on adenoma size.

TSH-SECRETING ADENOMAS

TSH-producing macroadenomas are very rare but are often large and locally invasive when they occur. Patients usually present with thyroid goiter and hyperthyroidism, reflecting overproduction of TSH. Diagnosis is based on demonstrating elevated serum free T_4 levels, inappropriately normal or high TSH secretion, and MRI evidence of a pituitary adenoma. Elevated uncombined α subunits are seen in many patients.

It is important to exclude other causes of inappropriate TSH secretion, such as resistance to thyroid hormone, an autosomal dominant disorder caused by mutations in the thyroid hormone β receptor. T e presence of a pituitary mass and elevated β subunit levels are suggestive of a TSH-secreting tumor. Dysalbuminemic hyperthyroxinemia syndromes, caused by mutations in serum thyroid hormone binding proteins, are also characterized by

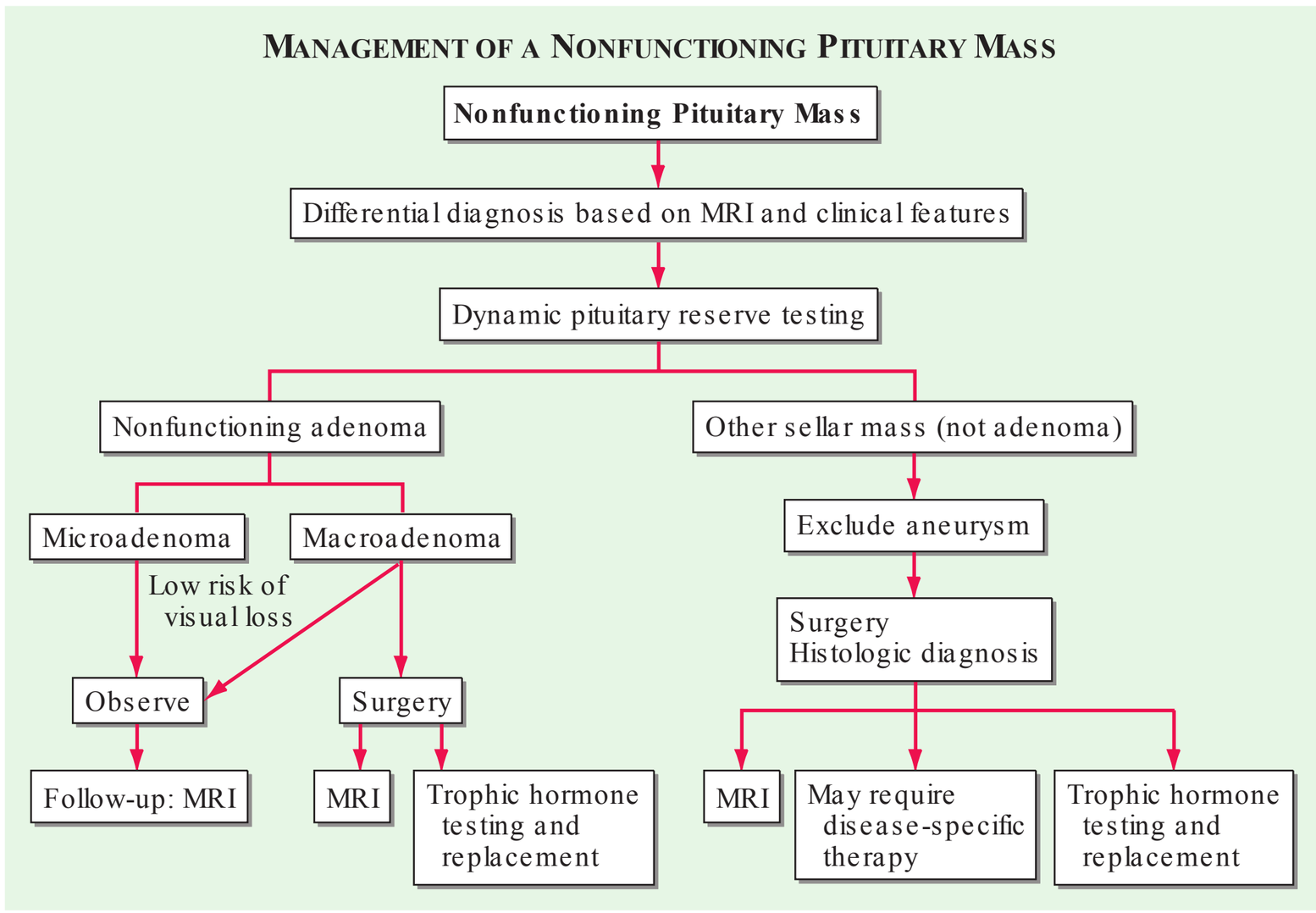


FIGURE 51-7
Management of a nonfunctioning pituitary mass. MRI, magnetic resonance imaging.

www.ketabpezeshki.com (021) 66485457 - 66485438

elevated thyroid hormone levels, but with normal rather than suppressed TSH levels. Moreover, free thyroid hormone levels are normal in these disorders, most of which are familial.

TREATMENT TSH-Secreting Adenomas

The initial therapeutic approach is to remove or debulk the tumor mass surgically, usually using a transsphenoidal approach. Total resection is not often achieved as most of these adenomas are large and locally invasive. Normal circulating thyroid hormone levels are achieved in about two-thirds of patients after surgery. Thyroid ablation or antithyroid drugs (methimazole and propylthiouracil) can be used to reduce thyroid hormone levels. Somatostatin analogue treatment effectively normalizes TSH and α subunit hypersecretion, shrinks the tumor mass in 50% of patients, and improves visual fields in 75% of patients; euthyroidism is restored in most patients. Because somatostatin analogues markedly suppress TSH, biochemical hypothyroidism often requires concomitant thyroid hormone replacement, which may also further control tumor growth.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 52

DISORDERS OF THE NEUROHYPOPHYSIS

Gary L. Robertson

The neurohypophysis, or posterior pituitary, is formed by axons that originate in large cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. It produces two hormones: (1) arginine vasopressin (AVP), also known as antidiuretic hormone, and (2) oxytocin. AVP acts on the renal tubules to reduce water loss by concentrating the urine. Oxytocin stimulates postpartum milk letdown in response to suckling. A deficiency of AVP secretion or action causes diabetes insipidus (DI), a syndrome characterized by the production of large amounts of dilute urine. Excessive or inappropriate AVP production impairs urinary water excretion and predisposes to hyponatremia if water intake is not reduced in parallel with urine output.

VASOPRESSIN

SYNTHESIS AND SECRETION

AVP is a nonapeptide composed of a six-member disulfide ring and a tripeptide tail **(Fig. 52-1)**. It is synthesized via a polypeptide precursor that includes AVP, neurophysin, and copeptin, all encoded by a single gene on chromosome 20. After preliminary processing and folding, the precursor is packaged in neurosecretory vesicles, where it is transported down the axon; further processed to AVP, neurophysin, and copeptin; and stored in neurosecretory vesicles until released by exocytosis into peripheral blood.

AVP secretion is regulated primarily by the "effective" osmotic pressure of body fluids. This control is mediated by specialized hypothalamic cells known as osmoreceptors, which are extremely sensitive to small changes in the plasma concentration of sodium and its anions but normally are insensitive to other solutes such as urea and glucose. The osmoreceptors appear to include inhibitory as well as stimulatory components that function in concert to form a threshold, or

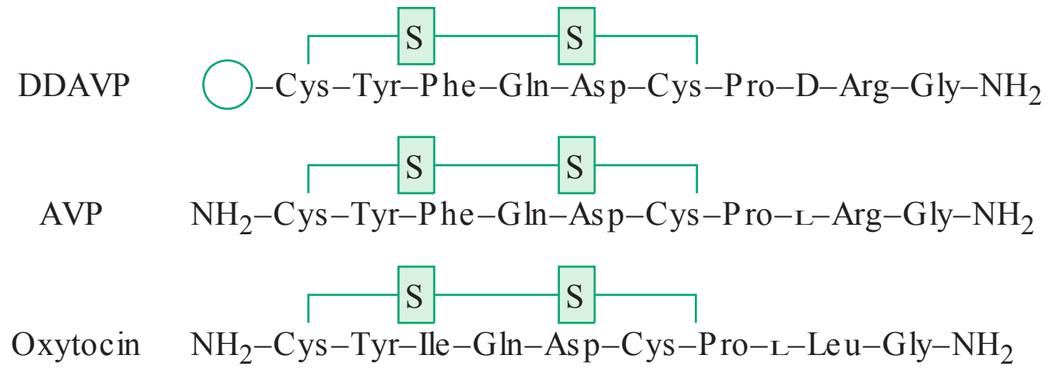


FIGURE 52-1
Primary structures of arginine vasopressin (AVP), oxytocin, and desmopressin (DDAVP).

set point, control system. Below this threshold, plasma AVP is suppressed to levels that permit the development of a maximum water diuresis. Above it, plasma AVP rises steeply in direct proportion to plasma osmolarity, quickly reaching levels sufficient to effect a maximum antidiuresis. The absolute levels of plasma osmolarity/sodium at which minimally and maximally effective levels of plasma AVP occur, vary appreciably from person to person, apparently due to genetic influences on the set and sensitivity of the system. However, the average threshold, or set point, for AVP release corresponds to a plasma osmolarity or sodium of about 280 mosmol/L or 135 meq/L, respectively; levels only 2–4% higher normally result in maximum antidiuresis.

Although it is relatively stable in a healthy adult, the set point of the osmoregulatory system can be lowered by pregnancy, the menstrual cycle, estrogen, and relatively large, acute reductions in blood pressure or volume. Those reductions are mediated largely by neuronal afferents that originate in transmural pressure receptors of the heart and large arteries and project via the vagus and glossopharyngeal nerves to the brainstem, from which postsynaptic projections ascend to the hypothalamus. These pathways maintain a tonic inhibitory tone that decreases when blood volume or pressure falls by >10–20%. This baroregulatory system is probably of minor importance in the physiology of AVP secretion

www.ketabpezeshki.com (021) 66485457 - 66485438

because the hemodynamic changes required to affect it usually do not occur during normal activities. However, the baroregulatory system undoubtedly plays an important role in AVP secretion in patients with disorders that produce large, acute disturbances of hemodynamic function. However, the baroregulatory system undoubtedly plays an important role in AVP secretion in patients with disorders that produce large, acute disturbances of hemodynamic function.

AVP secretion also can be stimulated by nausea, acute hypoglycemia, glucocorticoid deficiency, smoking, and, possibly, hyperangiotensinemia. T e emetic stimuli are extremely potent since they typically elicit immediate, 50- to 100-fold increases in plasma AVP even when the nausea is transient and is not associated with vomiting or other symptoms. T ey appear to act via the emetic center in the medulla and can be blocked completely by treatment with antiemetics such as fluphenazine. T ere is no evidence that pain or other noxious stresses have any effect on AVP unless they elicit a vasovagal reaction with its associated nausea and hypotension.

ACTION

T e most important, if not the only, physiologic action of AVP is to reduce water excretion by promoting concentration of urine. T is antidiuretic effect is achieved by increasing the hydroosmotic permeability of cells that line the distal tubule and medullary collecting ducts of the kidney **(Fig. 52-2)**. In the absence of AVP, these cells are impermeable to water and reabsorb little, if any, of the relatively large volume of dilute filtrate that enters from the proximal nephron. T e lack of reabsorption results in the excretion of very large volumes (as much as 0.2 mL/kg per min) of maximally dilute urine (specific gravity and osmolarity ~1.000 and 50 mosmol/L, respectively), a condition known as water

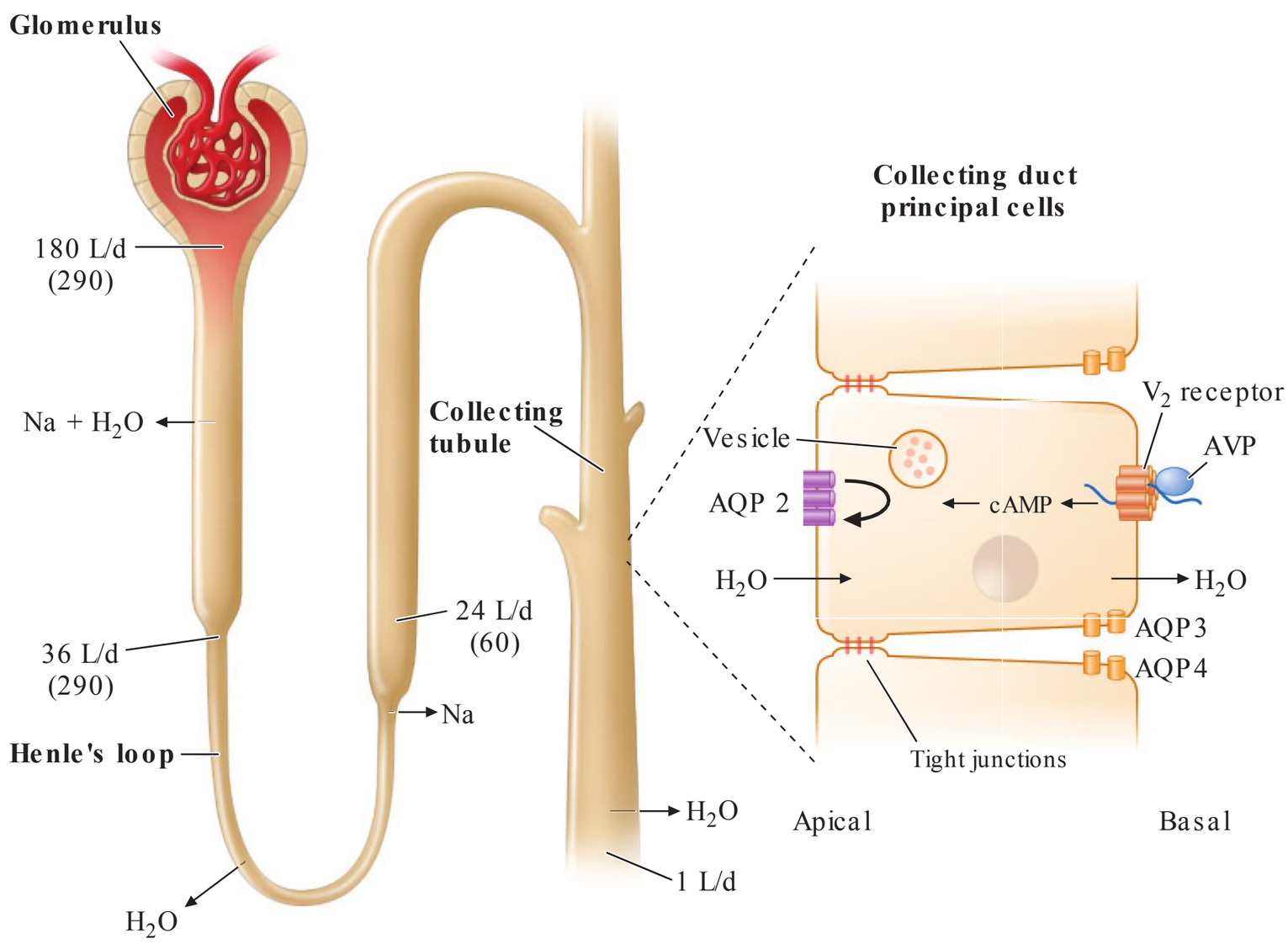


FIGURE 52-2

Antidiuretic effect of arginine vasopressin (AVP) in the regulation of urine volume. In a typical 70-kg adult, the kidney filters ~180 L/d of plasma. Of this, ~144 L (80%) is reabsorbed isosmotically in the proximal tubule and another 8 L (4–5%) is reabsorbed without solute in the descending limb of Henle's loop. The remainder is diluted to an osmolarity of ~60 mmol/kg by selective reabsorption of sodium and chloride in the ascending limb. In the absence of AVP, the urine issuing from the loop passes largely unmodified through the distal tubules and collecting ducts, resulting in a maximum water diuresis. In the presence of AVP, solute-free water is reabsorbed osmotically through the principal cells of the collecting ducts, resulting in the excretion of a much smaller volume of concentrated urine. This antidiuretic effect is mediated via a G protein–coupled V_2 receptor that increases intracellular cyclic AMP, thereby inducing translocation of aquaporin 2 (AQP 2) water channels into the apical membrane. The resultant increase in permeability permits an influx of water that diffuses out of the cell through AQP 3 and AQP 4 water channels on the basal-lateral surface. The net rate of flux across the cell is determined by the number of AQP 2 water channels in the apical membrane and the strength of the osmotic gradient between tubular fluid and the renal medulla. Tight junctions on the lateral surface of the cells serve to prevent unregulated water flow.

www.ketabpezeshki.com (021) 66485457 - 66485438

diuresis. In the presence of AVP, these cells become selectively permeable to water, allowing the water to diffuse back down the osmotic gradient created by the hypertonic renal medulla. As a result, the dilute fluid passing through the tubules is concentrated and the rate of urine flow decreases. T e magnitude of this effect varies in direct proportion to the plasma AVP concentration and the rate of solute excretion. At maximum levels of AVP and normal rates of solute excretion, it approximates a urine flow rate as low as 0.35 mL/min and a urine osmolarity as high as 1200 mosmol/L. T is effect is reduced by a solute diuresis such as glucosuria in diabetes mellitus. Antidiuresis is mediated via binding to G protein–coupled V_2 receptors on the serosal surface of the cell, activation of adenyl cyclase, and insertion into the luminal surface of water channels composed of a protein known as aquaporin 2 (AQP2). T e V_2 receptors and aquaporin 2 are encoded by genes on chromosomes Xq28 and 12q13, respectively.

At high concentrations, AVP also causes contraction of smooth muscle in blood vessels in the skin and gastrointestinal tract, induces glycogenolysis in the liver, and potentiates adrenocorticotropic hormone (ACTH) release by corticotropin-releasing factor. T ese effects are mediated by V_{1a} or V_{1b} receptors that are coupled to phospholipase C. T eir role, if any, in human physiology/pathophysiology is uncertain.

METABOLISM

AVP distributes rapidly into a space roughly equal to the extracellular fluid volume. It is cleared irreversibly with a half-life ($t_{1/2}$) of 10–30 min. Most AVP clearance is due to degradation in the liver and kidneys. During pregnancy, the metabolic clearance of AVP is increased three- to fourfold due to placental production of an N-terminal peptidase.

THIRST

Because AVP cannot reduce water loss below a certain minimum level obligated by urinary solute load and evaporation from skin and lungs, a mechanism for ensuring adequate intake is essential for preventing dehydration. T is vital function is performed by the thirst mechanism. Like AVP, thirst is regulated primarily by an osmostat that is situated in the anteromedial hypothalamus and is able to detect very small changes in the plasma concentration of sodium and its anions. T e thirst osmostat appears to be "set" about 3% higher than the AVP osmostat. T is arrangement ensures that thirst, polydipsia, and dilution of body fluids do not occur until plasma osmolarity/sodium starts to exceed the defensive capacity of the antidiuretic mechanism.

OXYTOCIN

Oxytocin is also a nonapeptide that differs from AVP only at positions 3 and 8 (Fig. 52-1). However, it has relatively little antidiuretic effect and seems to act mainly on mammary ducts to facilitate milk letdown during nursing. It also may help initiate or facilitate labor by stimulating contraction of uterine smooth muscle, but it is not clear if this action is physiologic or necessary for normal delivery.

DEFICIENCIES OF AVP SECRETION AND ACTION

DIABETES INSIPIDUS

Clinical characteristics

A decrease of 75% or more in the secretion or action of AVP usually results in DI, a syndrome characterized by the production of abnormally large volumes of dilute urine. T e 24-h urine volume exceeds 50 mL/kg body weight, and the osmolarity is less than 300 mosmol/L. T e polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence. It also results in a slight rise in plasma osmolarity that stimulates thirst and a commensurate increase in fluid intake (polydipsia). Overt clinical signs of dehydration are uncommon unless thirst and/or the compensatory increase of fluid intake are also impaired.

Etiology

A primary deficiency of AVP secretion usually results from agenesis or irreversible destruction of the neurohypophysis. It is referred to variously as neurohypophyseal DI, neurogenic DI, pituitary DI, cranial DI, or central DI. It can be caused by a variety of congenital, acquired, or genetic disorders, but in about one-half of all adult patients, it is idiopathic **(Table 52-1)**. Pituitary DI caused by surgery in or around the neurohypophysis usually appears within 24 h. After a few days, it may transition to a 2- to 3-week period of inappropriate antidiuresis, after which the DI may or may not recur permanently. Five genetic forms of pituitary DI are now known. By far, the most common is transmitted in an autosomal dominant mode and is caused by diverse mutations in the coding region of one allele of the AVP–neurophysin II (or AVP-NPII) gene. All the mutations alter one or more amino acids known to be critical for correct processing and/or folding of the prohormone, thus interfering with its traf cking through the endoplasmic reticulum. T e misfolded mutant precursor accumulates and interferes with production of AVP by the normal allele, eventually

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 52-1

CAUSES OF DIABETES INSIPIDUS

Pituitary diabetes insipidus
- Acquired
  - Head trauma (closed and penetrating) including pituitary surgery
  - Neoplasms
    - Primary
      - Craniopharyngioma
      - Pituitary adenoma (suprasellar)
      - Dysgerminoma
      - Meningioma
    - Metastatic (lung, breast)
    - Hematologic (lymphoma, leukemia)
  - Granulomas
    - Sarcoidosis
    - Histiocytosis
    - Xanthoma disseminatum
  - Infectious
    - Chronic meningitis
    - Viral encephalitis
    - Toxoplasmosis
  - Inflammatory
    - Lymphocytic infundibuloneurohypophysitis
    - Granulomatosis with polyangiitis (Wegener's)
    - Lupus erythematosus
    - Scleroderma
  - Chemical toxins
    - Tetrodotoxin
    - Snake venom
  - Vascular
    - Sheehan's syndrome
    - Aneurysm (internal carotid)
    - Aortocoronary bypass
    - Hypoxic encephalopathy
  - Idiopathic
- Congenital malformations
  - Septo-optic dysplasia
  - Midline craniofacial defects
  - Holoprosencephaly
  - Hypogenesis, ectopia of pituitary
- Genetic
  - Autosomal dominant (AVP-neurophysin gene)
  - Autosomal recessive
  - Type A (AVP-neurophysin gene)
  - Type B (AVP-neurophysin gene)
  - Type C (Wolfram's [4p-WFS 1] gene)
  - X-linked recessive (Xq28)

Gestational diabetes insipidus
- Pregnancy (second and third trimesters)

Nephrogenic diabetes insipidus
- Acquired
  - Drugs
    - Lithium
    - Demeclocycline
    - Methoxyflurane
    - Amphotericin B
    - Aminoglycosides
    - Cisplatin
    - Rifampin
    - Foscarnet
  - Metabolic
    - Hypercalcemia, hypercalciuria
    - Hypokalemia
  - Obstruction (ureter or urethra)
  - Vascular
    - Sickle cell disease and trait
    - Ischemia (acute tubular necrosis)
  - Granulomas
    - Sarcoidosis
  - Neoplasms
    - Sarcoma
  - Infiltration
    - Amyloidosis
  - Idiopathic
- Genetic
  - X-linked recessive (AVP receptor-2 gene)
  - Autosomal recessive (AQP2 gene)
  - Autosomal dominant (AQP2 gene)

Primary polydipsia
- Acquired
  - Psychogenic
    - Schizophrenia
    - Obsessive compulsive disorder
  - Dipsogenic (abnormal thirst)
    - Granulomas (sarcoidosis)
    - Infectious (tuberculous meningitis)
    - Head trauma (closed and penetrating)
    - Demyelination (multiple sclerosis)
    - Drugs
    - Idiopathic
    - Iatrogenic

destroying the magnocellular neurons in which it is produced. T e AVP deficiency and DI are usually not present at birth but develop gradually over a period of several months to years, progressing from partial to severe at different rates depending on the mutation. Once established, the deficiency of AVP is permanent, but for unknown reasons, the DI occasionally improves or remits spontaneously in late middle age. T e parvocellular neurons that make AVP and the magnocellular neurons that make oxytocin appear to be unaffected. T ere are also rare autosomal recessive forms of pituitary DI. One is due to an inactivating mutation in the AVP portion of the gene; another is due to a large deletion involving the majority of the AVP gene and regulatory sequences in the intergenic region. A third form is caused by mutations of the WFS 1 gene responsible for Wolfram's syndrome (DI, diabetes mellitus, optic atrophy, and neural deafness [DIDMOAD]). An X-linked recessive form linked to a region on Xq28 has also been described.

A primary deficiency of plasma AVP also can result from increased metabolism by an N-terminal aminopeptidase produced by the placenta. It is referred to as gestational DI because the signs and symptoms manifest during pregnancy and usually remit several weeks after delivery.

Secondary deficiencies of AVP secretion result from inhibition by excessive intake of fluids. T ey are referred to as primary polydipsia and can be divided into three subcategories. One of them, dipsogenic DI, is characterized by inappropriate thirst caused by a reduction in the set of the osmoregulatory mechanism. It sometimes occurs in association with multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, and multiple sclerosis but is often idiopathic. T e second subtype, psychogenic polydipsia, is not associated with thirst, and the polydipsia seems to be a feature of psychosis or obsessive compulsive disorder. T e third subtype, iatrogenic polydipsia, results from recommendations to increase fluid intake for its presumed health benefits.

Primary deficiencies in the antidiuretic action of AVP result in nephrogenic DI. T e causes can be genetic, acquired, or drug induced (Table 52-1). T e most common genetic form is transmitted in a semirecessive X-linked manner. It is caused by mutations in the coding region of the V_2 receptor gene that impair trafficking and/or ligand binding of the mutant receptor. T ere are also autosomal recessive or dominant forms of nephrogenic DI. T ey are caused by AQP2 gene mutations that result in complete or partial defects in traf cking and function of the water channels that mediate antidiuresis in the distal and collecting tubules of the kidney.

Secondary deficiencies in the antidiuretic response to AVP result from polyuria per se. T ey are caused by

www.ketabpezeshki.com (021) 66485457 - 66485438

washout of the medullary concentration gradient and/or suppression of aquaporin function. They usually resolve 24–48 h after the polyuria is corrected but can complicate interpretation of some acute tests used for differential diagnosis.

Pathophysiology

In pituitary, gestational, or nephrogenic DI, the polyuria results in a small (1–2%) decrease in body water and a commensurate increase in plasma osmolarity and sodium that stimulates thirst and a compensatory increase in water intake. As a result, hypernatremia and other overt physical or laboratory signs of dehydration do not develop unless the patient also has a defect in thirst or fails to increase fluid intake for some other reason.

In pituitary and nephrogenic DI, the severity of the defect in AVP secretion or action varies significantly from patient to patient. In some, the defect is so severe that it cannot be overcome by even an intense stimulus such as nausea or severe dehydration. In others, the defect in AVP secretion or action is incomplete, and a modest stimulus such as a few hours of fluid deprivation, smoking, or a vasovagal reaction can raise urine osmolarity as high as 800 mosmol/L. However, even when the defects are partial, the relation of urine osmolarity to plasma AVP in patients with nephrogenic DI **(Fig. 52-3A)** or of plasma AVP to plasma osmolarity and sodium in patients with pituitary DI **(Fig. 52-3B)** is subnormal.

In primary polydipsia, the pathogenesis of the polydipsia and polyuria is the reverse of that in pituitary, nephrogenic, and gestational DI. In primary polydipsia, an abnormality in cognition or thirst causes excessive intake of fluids and an increase in body water that reduces plasma osmolarity/sodium, AVP secretion, and urinary concentration. Dilution of the urine, in turn, results in a compensatory increase in urinary free-water excretion that usually offsets the increase in intake and stabilizes plasma osmolarity/sodium at a level only 1–2% below basal. Thus, hyponatremia or clinically appreciable overhydration is uncommon unless the polydipsia is very severe or the compensatory water diuresis is impaired by a drug or disease that stimulates or mimics the antiduretic effect of endogenous AVP. A rise in plasma osmolarity and sodium produced by fluid deprivation or hypertonic saline infusion increases plasma AVP normally. However, the resultant increase in urine concentration is often subnormal because polyuria per se temporarily reduces the capacity of the kidney to concentrate the urine. Thus, the maximum level of urine osmolarity achieved during fluid deprivation is often indistinguishable from that in patients with partial pituitary or partial nephrogenic DI.

Differential diagnosis

When symptoms of urinary frequency, enuresis, nocturia, and/or persistent thirst are present in the absence of glucosuria, the possibility of DI should be evaluated by collecting a 24-h urine on ad libitum fluid intake. If the volume exceeds 50 mL/kg per day (3500 mL in a 70-kg male) and the osmolarity is below 300 mosmol/L, DI is confirmed and the patient should be evaluated further to determine the type in order to select the appropriate therapy.

The type of DI can sometimes be inferred from the clinical setting or medical history. Often, however, such information is lacking, ambiguous, or misleading, and other approaches to differential diagnosis are needed. If basal plasma osmolarity and sodium are within normal limits, the traditional approach is to determine the

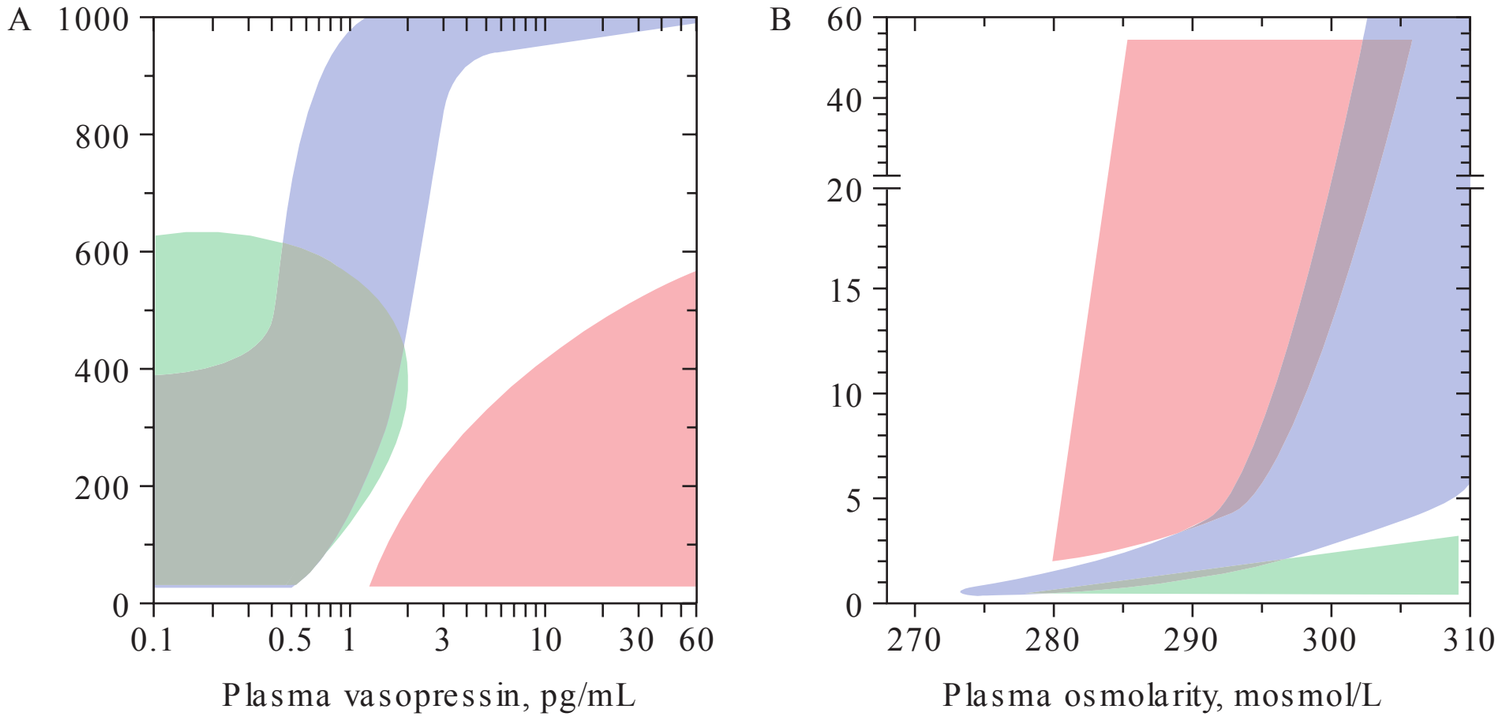


FIGURE 52-3

Relationship of plasma AVP to urine osmolarity (A) and plasma osmolarity (B) before and during fluid deprivation–hypertonic saline infusion test in patients who are normal or have primary polydipsia (blue zones), pituitary diabetes insipidus (green zones), or nephrogenic diabetes insipidus (pink zones).

www.ketabpezeshki.com (021) 66485457 - 66485438

effect of fluid deprivation and injection of antidiuretic hormone on urine osmolarity. T is approach suf ces for differential diagnosis *if* fluid deprivation raises plasma osmolarity and sodium above the normal range without inducing concentration of the urine. In that event, primary polydipsia and partial defects in AVP secretion and action are excluded, and the effect on urine osmolarity of injecting 2 μg of the AVP analogue, desmopressin, indicates whether the patient has severe pituitary DI or severe nephrogenic DI. However, this approach is of little or no diagnostic value if fluid deprivation results in concentration of the urine because the increases in urine osmolarity achieved both before and after the injection of desmopressin are similar in patients with partial pituitary DI, partial nephrogenic DI, and primary polydipsia. T ese disorders can be differentiated by measuring plasma AVP during fluid deprivation and relating it to the concurrent level of plasma and urine osmolarity (Fig. 52-3). However, this approach does not always differentiate clearly between partial pituitary DI and primary polydipsia unless the measurement is made when plasma osmolarity and sodium are at or above the normal range. T is level is dif cult to achieve by fluid deprivation alone once urinary concentration occurs. T erefore it is usually necessary to give a short infusion of 3% saline condition (0.1 mL/kg body weight per minute for 60 to 90 minutes) and repeat the measurement of plasma AVP.

A simpler but equally reliable way to differentiate between pituitary DI, nephrogenic DI, and primary polydipsia is to measure basal plasma AVP to determine if a brain magnetic resonance imaging (MRI) is needed and suf cient for diagnosis **(Fig. 52-4)**. If plasma AVP on ad libitum fuid intake is normal or elevated (>1 pg/mL) when measured by a sensitive and specific assay, both primary polydipsia and pituitary DI are excluded and the diagnosis of nephrogenic DI can be confirmed, if desired, by a 1- to 2-day outpatient trial of desmopressin therapy. If, however, basal plasma AVP is low or undetectable (<1 pg/mL), nephrogenic DI is very unlikely and MRI of the brain can be used to differentiate pituitary DI from primary polydipsia. In most healthy adults and children, the posterior pituitary emits a hyperintense signal visible in T1-weighted midsagittal images. T is "bright spot" is almost always present in patients with primary polydipsia but is always absent or abnormally small in patients with pituitary DI, even if their AVP deficiency is partial. T e MRI is also useful in searching for pathology responsible for pituitary DI or the dipsogenic form of primary polydipsia (Fig. 52-2). T e principal caveat is that MRI is not reliable for differential diagnosis of DI in patients with empty sella because they typically lack a bright spot even when their AVP secretion and action are normal. MRI also cannot be used to differentiate pituitary from nephrogenic DI because many patients with nephrogenic DI also lack a posterior pituitary bright spot, probably because they have an abnormally high rate of AVP secretion and turnover.

If MRI and/or AVP assays with the requisite sensitivity and specificity are unavailable and a fluid deprivation test is impractical or undesirable, a third way to differentiate between pituitary DI, nephrogenic DI, and primary polydipsia is a trial of desmopressin therapy. Such a trial should be conducted with very close monitoring of serum sodium as well as urine output, preferably in hospital, because desmopressin will produce hyponatremia in 8–24 h if the patient has primary polydipsia.

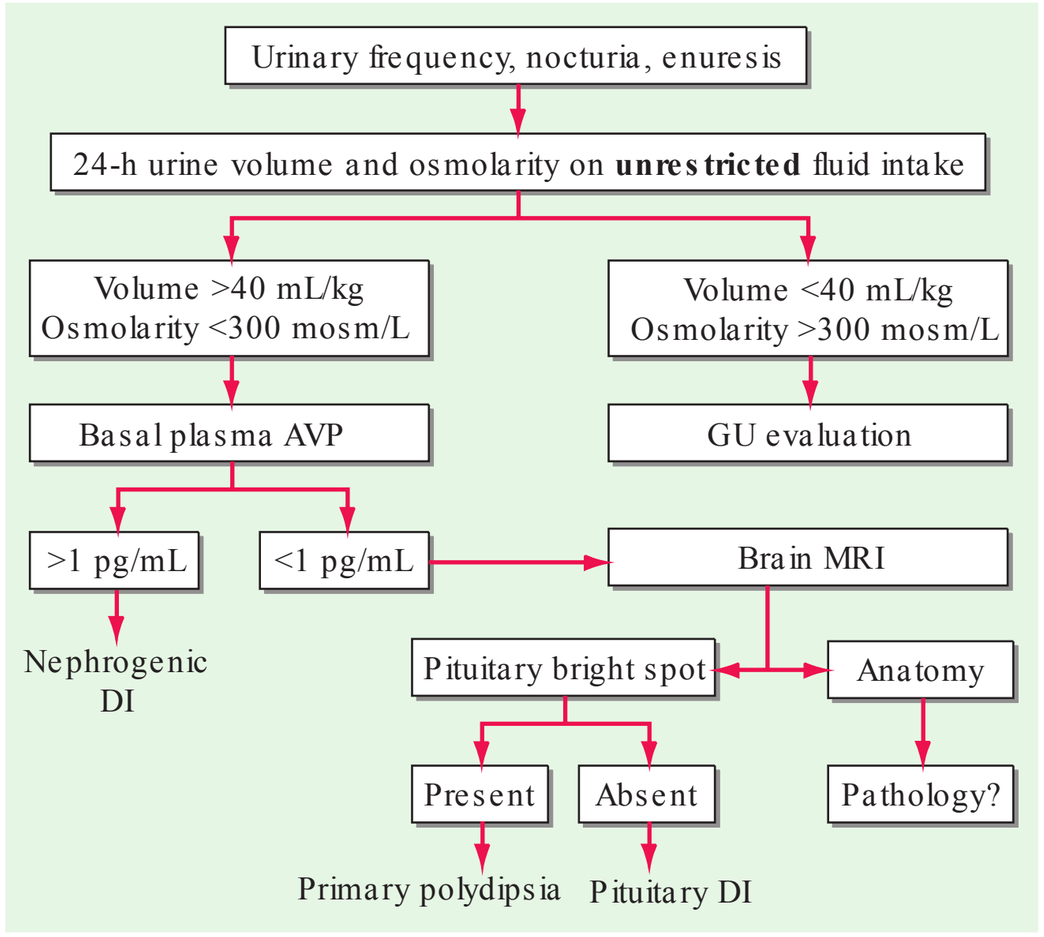


FIGURE 52-4
Simplified approach to the differential diagnosis of diabetes insipidus. When symptoms suggest diabetes insipidus (DI), the syndrome should be differentiated from a genitourinary (GU) abnormality by measuring the 24-h urine volume and osmolarity on unrestricted fluid intake. If DI is confirmed, basal plasma arginine vasopressin (AVP) should be measured on unrestricted fluid intake. If AVP is normal or elevated (>1 pg/mL), the patient probably has nephrogenic DI. However, if plasma AVP is low or undetectable, the patient has either pituitary DI or primary polydipsia. In that case, magnetic resonance imaging (MRI) of the brain can be performed to differentiate between these two conditions by determining whether or not the normal posterior pituitary bright spot is visible on T1-weighted midsagittal images. In addition, the MRI anatomy of the pituitary hypothalamic area can be examined to look for evidence of pathology that sometimes causes pituitary DI or the dipsogenic form of primary polydipsia. MRI is not reliable for differential diagnosis unless nephrogenic DI has been excluded because the bright spot is also absent, small, or faint in this condition.

www.ketabpezeshki.com (021) 66485457 - 66485438

TREATMENT Diabetes Insipidus

T e signs and symptoms of uncomplicated pituitary DI can be eliminated by treatment with desmopressin (DDAVP), a synthetic analogue of AVP (Fig. 52-1). DDAVP acts selectively at V_2 receptors to increase urine concentration and decrease urine flow in a dose-dependent manner. It is also more resistant to degradation than is AVP and has a three- to fourfold longer duration of action. DDAVP can be given by IV or SC injection, nasal inhalation, or orally by means of a tablet of melt. T e doses required to control pituitary DI completely vary widely, depending on the patient and the route of administration. However, among adults, they usually range from 1–2 μg qd or bid by injection, 10–20 μg bid or tid by nasal spray, or 100–400 μg bid or tid orally. T e onset of antidiuresis is rapid, ranging from as little as 15 min after injection to 60 min after oral administration. When given in a dose that normalizes 24-h urinary osmolarity (400–800 mosmol/L) and volume (15–30 mL/kg body weight), DDAVP produces a slight (1–3%) increase in total body water and a decrease in plasma osmolarity/sodium that rapidly eliminates thirst and polydipsia **(Fig. 52-5)**. Consequently, water balance is maintained within the normal range. Hyponatremia does not develop unless urine volume is reduced too far (to less than 10 mL/kg per day) or fluid intake is excessive due to an associated abnormality in thirst or cognition. Fortunately, thirst abnormalities are rare, and if the patient is taught to drink only when truly thirsty, DDAVP can be given safely in doses suf cient to normalize urine output (~15–30 mL/kg per day) without the need for allowing intermittent escape to prevent water intoxication.

Primary polydipsia cannot be treated safely with DDAVP or any other antidiuretic drug because eliminating the polyuria does not eliminate the urge to drink. T erefore, it invariably produces hyponatremia and/or other signs of water intoxication, usually within 8–24 h if urine output is normalized completely. T ere is no consistently effective way to correct dipsogenic or psychogenic polydipsia, but the iatrogenic form may respond to patient education. To minimize the risk of water intoxication, all patients should be warned about the use of other drugs such as thiazide diuretics or carbamazepine (Tegretol) that can impair urinary free-water excretion directly or indirectly.

T e polyuria and polydipsia of nephrogenic DI are not affected by treatment with standard doses of DDAVP. If resistance is partial, it may be overcome by tenfold higher doses, but this treatment is too expensive and inconvenient for long-term use. However, treatment with conventional doses of a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet and a prostaglandin synthesis inhibitor (e.g., indomethacin) usually reduces the polyuria and polydipsia by 30–70% and may eliminate them completely in some patients. Side effects such as hypokalemia and gastric irritation can be minimized by the use of amiloride or potassium supplements and by taking medications with meals.

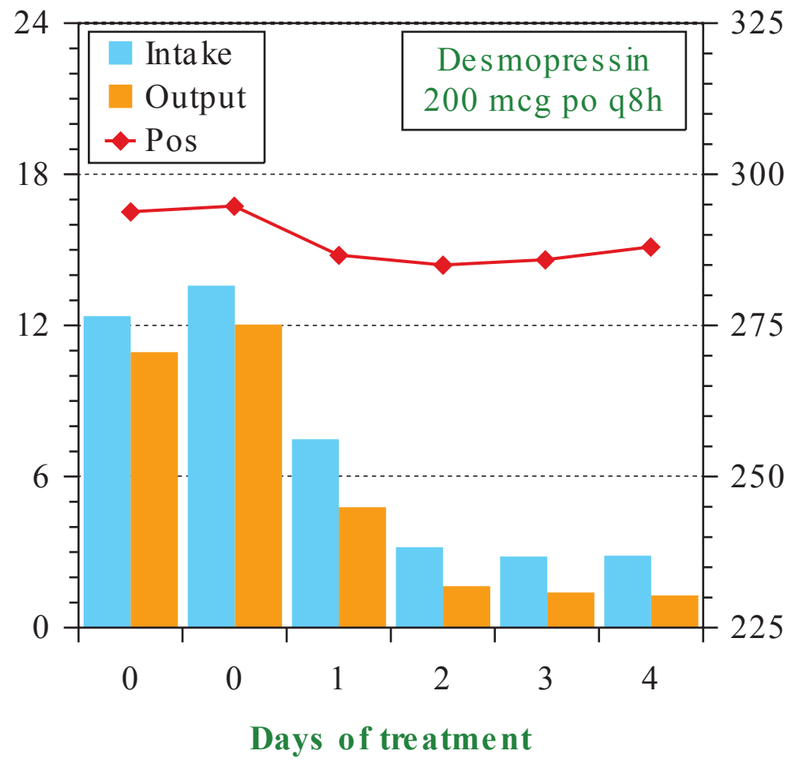


FIGURE 52-5
Effect of desmopressin therapy on fluid intake (blue bars), urine output (orange bars), and plasma osmolarity (red line)in a patient with uncomplicated pituitary diabetes insipidus. Notethat treatment rapidly reduces fluid intake and urine output tonormal, with only a slight increase in body water as evidenced by the slight decrease in plasma osmolarity.

HYPODIPSIC HYPERNATREMIA

An increase in plasma osmolarity/sodium above the normal range (hypertonic hypernatremia) can be caused by either a decrease in total body water or an increase in total body sodium. T e former results from a failure to drink enough to replace normal or increased urinary and insensible water loss. T e deficient intake can be due either to water deprivation or a lack of thirst (hypodipsia). T e most common cause of an increase in total body sodium is primary hyperaldosteronism. Rarely, it can also result from ingestion of hypertonic saline in the form of sea water or incorrectly prepared infant formula. However, even in these forms of hypernatremia, inadequate intake of water also contributes. T is chapter focuses on hypodipsic hypernatremia, the form of hypernatremia due to a primary defect in the thirst mechanism.

Clinical characteristics

Hypodipsic hypernatremia is a syndrome characterized by chronic or recurrent hypertonic dehydration. T e hypernatremia varies widely in severity and usually is associated with signs of hypovolemia such as tachycardia, postural hypotension, azotemia, hyperuricemia, and hypokalemia due to secondary hyperaldosteronism. Muscle weakness, pain, rhabdomyolysis, hyperglycemia, hyperlipidemia, and acute renal failure may also occur. Obtundation or coma may be present but are often absent. Despite inappropriately low levels of plasma AVP, DI usually is not evident at presentation

www.ketabpezeshki.com (021) 66485457 - 66485438

but may develop during rehydration as blood volume, blood pressure, and plasma osmolarity/sodium return toward normal, further reducing plasma AVP.

Etiology

Hypodipsia is usually due to hypogenesis or destruction of the osmoreceptors in the anterior hypothalamus that regulate thirst. T ese defects can result from various congenital malformations of midline brain structures or may be acquired due to diseases such as occlusions of the anterior communicating artery, primary or metastatic tumors in the hypothalamus, head trauma, surgery, granulomatous diseases such as sarcoidosis and histiocytosis, AIDS, and cytomegalovirus encephalitis. Because of their proximity, the osmoreceptors that regulate AVP secretion also are usually impaired. T us, AVP secretion responds poorly or not at all to hyperosmotic stimulation **(Fig. 52-6)** but, in most cases, increases normally to nonosmotic stimuli such as nausea or large reductions in blood volume or blood pressure, indicating that the neurohypophysis is intact.

Pathophysiology

Hypodipsia results in a failure to drink enough water to replenish obligatory renal and extrarenal losses. Consequently, plasma osmolarity and sodium rise often to extremely high levels before the disorder is recognized. In most cases, urinary loss of water contributes little, if any, to the dehydration because AVP continues to be secreted in the small amounts necessary to concentrate the urine. In some patients this appears to be due to hypovolemic stimulation and/or incomplete destruction of AVP osmoreceptors because plasma AVP declines and DI develops during rehydration (Fig. 52-6). In others, however, plasma AVP does not decline during rehydration even if they are overhydrated. Consequently, they develop a hyponatremic syndrome indistinguishable from inappropriate antidiuresis. T is suggests that the AVP osmoreceptors normally provide inhibitory and stimulatory input to the neurohypophysis and the patients can no longer osmotically stimulate or suppress tonic secretion of the hormone because both inputs have been totally eliminated by the same pathology that destroyed the osmoregulation of thirst. In a few patients, the neurohypophysis is also destroyed, resulting in a combination of chronic pituitary DI and hypodipsia that is particularly dif cult to manage.

Dif erential diagnosis

Hypodipsic hypernatremia usually can be distinguished from other causes of inadequate fluid intake (e.g., coma, paralysis, restraints, absence of fresh water) by the clinical history and setting. Previous episodes

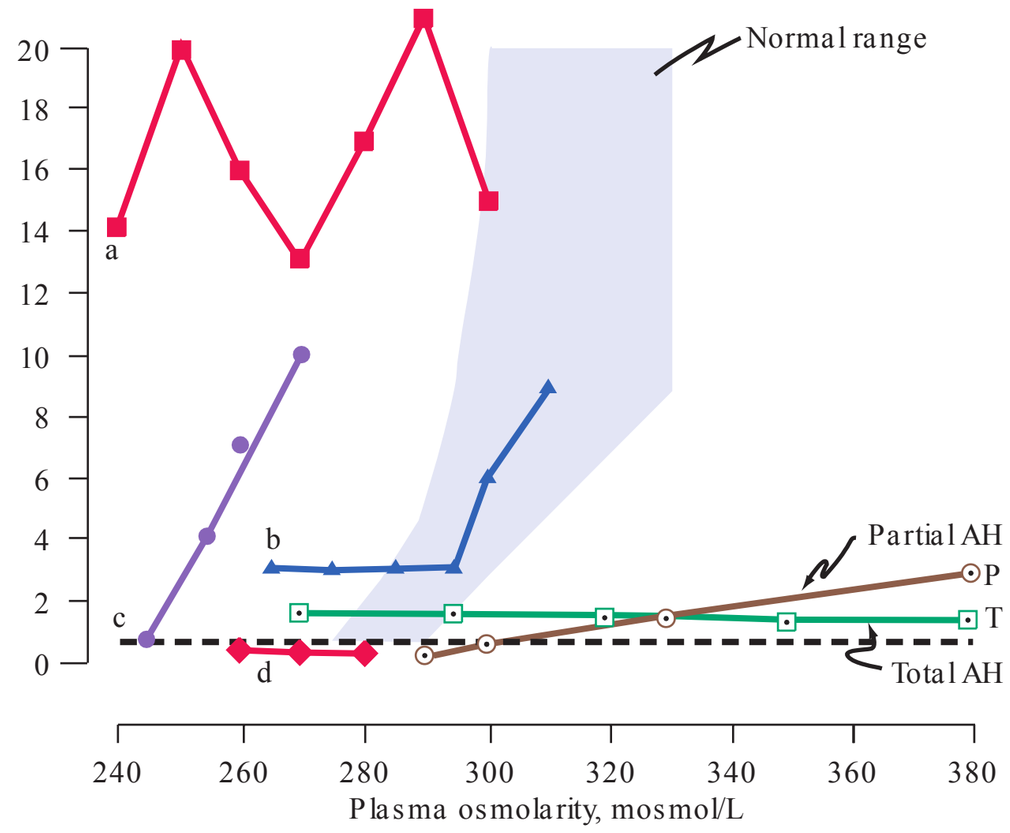


FIGURE 52-6
Heterogeneity of osmoregulatory dysfunction in adipsic hypernatremia (AH) and the syndrome of inappropriate antidiuresis (SIAD). Each line depicts schematically the relationship of plasma arginine vasopressin (AVP) to plasma osmolarity during water loading and/or infusion of 3% saline in a patient with either AH (open symbols) or SIAD (closed symbols). The shaded area indicates the normal range of the relationship. The horizontal broken line indicates the plasma AVP level below which the hormone is undetectable and urinary concentration usually does not occur. Lines P and T represent patients with a selective deficiency in the osmoregulation of thirst and AVP that is either partial (○) or total (□). In the latter, plasma AVP does not change in response to increases or decreases in plasma osmolarity but remains within a range suf cient to concentrate the urine even if overhydration produces hypotonic hyponatremia. In contrast, if the osmoregulatory deficiency is partial (○), rehydration of the patient suppresses plasma AVP to levels that result in urinary dilution and polyuria before plasma osmolarity and sodium are reduced to normal. Lines a –d represent different defects in the osmoregulation of plasma AVP observed in patients with SIADH or SIAD. In a (□), plasma AVP is markedly elevated and fluctuates widely without relation to changes in plasma osmolarity, indicating complete loss of osmoregulation. In b (▲), plasma AVP remains fixed at a slightly elevated level until plasma osmolarity reaches the normal range, at which point it begins to rise appropriately, indicating a selective defect in the inhibitory component of the osmoregulatory mechanism. In c (●), plasma AVP rises in close correlation with plasma osmolarity before the latter reaches the normal range, indicating downward resetting of the osmostat. In d (), plasma AVP appears to be osmoregulated normally, suggesting that the inappropriate antidiuresis is caused by some other abnormality.

and/or denial of thirst and failure to drink spontaneously when the patient is conscious, unrestrained, and hypernatremic are virtually diagnostic. T e hypernatremia caused by excessive retention or intake of sodium can be distinguished by the presence of thirst as well as the physical and laboratory signs of hypervolemia rather than hypovolemia.

www.ketabpezeshki.com (021) 66485457 - 66485438

TREATMENT Hypodipsic Hypernatremia

Hypodipsic hypernatremia should be treated by administering water orally if the patient is alert and cooperative or by infusing hypotonic fluids (0.45% saline or 5% dextrose and water) if the patient is not. The amount of free water in liters required to correct the deficit (ΔFW) can be estimated from body weight in kg (BW) and the serum sodium concentration in mmol/L (S_{Na}) by the formula $\Delta FW = 0.5BW \times ([S_{Na} - 140]/140)$. If serum glucose ($S_{Glu}$) is elevated, the measured S_{Na} should be corrected (S_{Na}^*) by the formula $S_{Na}^* = S_{Na} + ([S_{Glu} - 90]/36)$. This amount plus an allowance for continuing insensible and urinary losses should be given over a 24- to 48-h period. Close monitoring of serum sodium as well as fluid intake and urinary output is essential because, depending on the extent of osmoreceptor deficiency, some patients will develop AVP-deficient DI, requiring DDAVP therapy to complete rehydration; others will develop hyponatremia and a syndrome of inappropriate antidiuresis (SIAD)-like picture if overhydrated. If hyperglycemia and/or hypokalemia are present, insulin and/or potassium supplements should be given with the expectation that both can be discontinued soon after rehydration is complete. Plasma urea/creatinine should be monitored closely for signs of acute renal failure caused by rhabdomyolysis, hypovolemia, and hypotension.

Once the patient has been rehydrated, an MRI of the brain and tests of anterior pituitary function should be performed to look for the cause and collateral defects in other hypothalamic functions. A long-term management plan to prevent or minimize recurrence of the fluid and electrolyte imbalance also should be developed. This should include a practical method to regulate fluid intake in accordance with variations in water balance as indicated by changes in body weight or serum sodium determined by home monitoring analyzers. Prescribing a constant fluid intake is ineffective and potentially dangerous because it does not take into account the large, uncontrolled variations in insensible loss that inevitably result from changes in ambient temperature and physical activity.

HYPONATREMIA DUE TO INAPPROPRIATE ANTIDIURESIS

A decrease in plasma osmolarity/sodium below the normal range (hypotonic hyponatremia) can be due to any of three different types of salt and water imbalance: (1) an increase in total body water that exceeds the increase in total body sodium (hypervolemic hyponatremia); (2) a decrease in body sodium greater than the decrease in body water (hypovolemic hyponatremia); or (3) an increase in body water with little or no change in body sodium (euvolemic hyponatremia) **(Chap. 63)**. All three forms are associated with a failure to fully dilute the urine and mount a water diuresis in the face of hypotonic hyponatremia. The hypervolemic form typically occurs in disorders like severe congestive heart failure or cirrhosis. The hypovolemic form typically occurs in disorders such as severe diarrhea, diuretic abuse, or mineralocorticoid deficiency. Euvolemic hyponatremia, however, is due mainly to expansion of total body water caused by excessive intake in the face of a defect in urinary dilution. The impaired dilution is usually caused by a defect in the osmotic suppression of AVP that can have either of two causes. One is a nonhemodynamic stimulus such as nausea or a cortisol deficiency, which can be corrected quickly by treatment with antiemetics or cortisol. The other is a primary defect in osmoregulation caused by another disorder such as malignancy, stroke, or pneumonia that cannot be easily or quickly corrected. The latter is commonly known as the syndrome of inappropriate antidiuretic hormone (SIADH). Much less often, euvolemic hyponatremia can also result from AVP-independent activation of renal V_2 receptors, a variant known as nephrogenic inappropriate antidiuresis or NSIAD. Both of the latter will be discussed in this chapter.

Clinical characteristics

Antidiuresis of any cause decreases the volume and increases the concentration of urine. If not accompanied by a commensurate reduction in fluid intake or an increase in insensible loss, the reduction in urine output results in excess water retention which expands and dilutes body fluids. If the hyponatremia develops gradually or has been present for more than a few days, it may be largely asymptomatic. However, if it develops acutely, it is usually accompanied by symptoms and signs of water intoxication that may include mild headache, confusion, anorexia, nausea, vomiting, coma, and convulsions. Severe acute hyponatremia may be lethal. Other clinical signs and symptoms vary greatly, depending on the type of hyponatremia. The hypervolemic form is characterized by generalized edema and other signs of marked volume expansion. The opposite is evident in the hypovolemic form. However, overt signs of volume expansion or contraction are absent in SIADH, SIAD, and other forms of euvolemic hyponatremia.

Etiology

In SIADH, the inappropriate secretion of AVP can have many different causes. They include ectopic production of AVP by lung cancer or other neoplasms; eutopic release induced by various diseases or drugs; and exogenous administration of AVP, DDAVP, or large doses of oxytocin **(Table 52-2)**. The ectopic forms result from abnormal expression of the AVP-NPII gene by primary or metastatic malignancies. The eutopic forms occur most often in patients with acute infections or strokes

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 52-2

CAUSES OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

- Neoplasms
  - Carcinomas
    - Lung
    - Duodenum
    - Pancreas
    - Ovary
    - Bladder, ureter
  - Other neoplasms
    - Thymoma
    - Mesothelioma
    - Bronchial adenoma
    - Carcinoid
    - Gangliocytoma
    - Ewing's sarcoma
- Head trauma (closed and penetrating)
- Infections
  - Pneumonia, bacterial or viral
  - Abscess, lung or brain
  - Cavitation (aspergillosis)
  - Tuberculosis, lung or brain
  - Meningitis, bacterial or viral
  - Encephalitis
  - AIDS
- Vascular
  - Cerebrovascular occlusions, hemorrhage
  - Cavernous sinus thrombosis
- Neurologic
  - Guillain-Barré syndrome
  - Multiple sclerosis
  - Delirium tremens
  - Amyotrophic lateral sclerosis
  - Hydrocephalus
  - Psychosis
  - Peripheral neuropathy
- Congenital malformations
  - Agenesis corpus callosum
  - Cleft lip/palate
  - Other midline defects
- Metabolic
  - Acute intermittent porphyria
- Pulmonary
  - Asthma
  - Pneumothorax
  - Positive-pressure respiration
- Drugs
  - Vasopressin or desmopressin
  - Serotonin reuptake inhibitors
  - Oxytocin, high dose
  - Vincristine
  - Carbamazepine
  - Nicotine
  - Phenothiazines
  - Cyclophosphamide
  - Tricyclic antidepressants
  - Monoamine oxidase inhibitors

but have also been associated with many other neurologic diseases and injuries. The mechanisms by which these diseases interfere with osmotic suppression of AVP are not known. The defect in osmoregulation can take any of four distinct forms (Fig. 52-6). In one of the most common (reset osmostat), AVP secretion remains fully responsive to changes in plasma osmolarity/sodium, but the threshold, or set point, of the osmoregulatory system is abnormally low. These patients differ from those with the other types of SIADH in that they are able to maximally suppress plasma AVP and dilute their urine if their fluid intake is high enough to reduce their plasma osmolarity and/or sodium to the new set point. In most patients, SIADH is self-limited and remits spontaneously within 2–3 weeks, but about 10% of cases are chronic. Another, smaller subgroup (~10% of the total) has inappropriate antidiuresis without a demonstrable defect in the osmoregulation of plasma AVP (Fig. 52-6). In some of them, all young boys, the inappropriate antidiuresis has been traced to a constitutively activating mutation of the V_2 receptor gene. This unusual variant may be referred to as familial nephrogenic SIAD (NSIAD) to distinguish it from other possible causes of the syndrome. The inappropriate antidiuresis in these patients appears to be permanent, although the hyponatremia is variable owing presumably to individual differences in fluid intake.

Pathophysiology

Impaired osmotic suppression of antidiuresis results in excessive retention of water and dilution of body fluids only if water intake exceeds insensible and urinary losses. The excess intake is sometimes due to an associated defect in the osmoregulation of thirst (dipsogenic) but can also be psychogenic or iatrogenic, including excessive IV administration of hypotonic fluids. In SIADH and other forms of euvolemic hyponatremia, the decrease in plasma osmolarity/sodium and the increase in extracellular and intracellular volume are proportional to the amount of water retained. Thus, an increase in body water of 10% (~4 L in a 70-kg adult) reduces plasma osmolarity and sodium by approximately 10% (~28 mosmol/L or 14 meq/L). An increase in body water of this magnitude is rarely detectable on physical examination but will be reflected in a weight gain of about 4 kg. It also increases glomerular filtration and atrial natriuretic hormone and suppresses plasma renin activity, thereby increasing urinary sodium excretion. The resultant reduction in total body sodium decreases the expansion of extracellular volume but aggravates the hyponatremia and further expands intracellular volume. The latter further increases brain swelling and intracranial pressure, which probably produces most of the symptoms of acute water intoxication. Within a few days, this swelling may be counteracted by inactivation or elimination of intracellular solutes, resulting in the remission of symptoms even though the hyponatremia persists.

In type I (hypervolemic) or type II (hypovolemic) hyponatremia, osmotic suppression of AVP secretion appears to be counteracted by a hemodynamic stimulus resulting from a large reduction in cardiac output and/or effective blood volume. The resultant antidiuresis is enhanced by decreased distal delivery of glomerular filtrate that results from increased reabsorption of sodium in proximal nephron. If the reduction in urine output is not associated with a commensurate reduction in water intake or an increase in insensible loss, body fluids are expanded and diluted, resulting in hyponatremia despite an increase in body sodium. Unlike SIADH and other forms of euvolemic hyponatremia, however, glomerular filtration is reduced and plasma renin activity and aldosterone are elevated. Thus, the rate of urinary sodium excretion is low (unless sodium reabsorption is

www.ketabpezeshki.com (021) 66485457 - 66485438

impaired by a diuretic), and the hyponatremia is usually accompanied by edema, hypokalemia, azotemia, and hyperuricemia. In type II (hypovolemic) hyponatremia, sodium and water are also retained as an appropriate compensatory response to the severe depletion.

Differential diagnosis

SIADH is a diagnosis of exclusion that usually can be made from the history, physical examination, and basic laboratory data. If hyperglycemia is present, its contribution to the reduction in plasma sodium can be estimated either by measuring plasma osmolarity for a more accurate estimate of the true "effective" tonicity of body fluids or by correcting the measured plasma sodium for the reduction caused by the hyperglycemia using the simplified formula

$$\text{Corrected } P_{na} = \text{measured } P_{na} + (P_{glu} - 90)/36$$

If the plasma osmolarity and/or corrected plasma sodium are below normal limits, hypotonic hyponatremia is present and further evaluation to determine the type should be undertaken in order to administer safe and effective treatment. T is differentiation is usually possible by evaluating standard clinical indicators of the extracellular fluid volume **(Table 52-3)**. If these findings are ambiguous or contradictory, measuring plasma renin activity or the rate of urinary sodium excretion may be helpful provided that the hyponatremia is not in the recovery phase or is due to a primary defect in renal conservation of sodium, diuretic abuse, or hyporeninemic hypoaldosteronism. T e latter may be suspected if serum potassium is elevated instead of low, as it usually is in types I and II hyponatremia. Measurements of plasma AVP are currently of no value in differentiating SIADH from the other types of hyponatremia since the

TABLE 52-3

DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA BASED ON CLINICAL ASSESSMENT OF EXTRACELLULAR FLUID VOLUME (ECFV)

CLINICAL FINDINGS	TYPE I, HYPERVOLEMIC	TYPE II, HYPOVOLEMIC	TYPE III, EUVOLEMIC	SIADH AND SIAD EUVOLEMIC
History				
CHF, cirrhosis, or nephrosis	Yes	No	No	No
Salt and water loss	No	Yes	No	No
ACTH–cortisol deficiency and/or nausea and vomiting	No	No	Yes	No
Physical examination				
Generalized edema, ascites	Yes	No	No	No
Postural hypotension	Maybe	Maybe	Maybe[a]	No
Laboratory				
BUN, creatinine	High-normal	High-normal	Low-normal	Low-normal
Uric acid	High-normal	High-normal	Low-normal	Low-normal
Serum potassium	Low-normal	Low-normal[b]	Normal[c]	Normal
Serum urate	High	High	Low	Low
Serum albumin	Low-normal	High-normal	Normal	Normal
Serum cortisol	Normal-high	Normal-high[d]	Low[e]	Normal
Plasma renin activity	High	High	Low[f]	Low
Urinary sodium (meq per unit of time)[g]	Low	Low[h]	High[i]	High[i]

[a]Postural hypotension may occur in secondary (ACTH-dependent) adrenal insuf ciency even though extracellular fluid volume and aldosterone are usually normal.
[b]Serum potassium may be high if hypovolemia is due to aldosterone deficiency.
[c]Serum potassium may be low if vomiting causes alkalosis.
[d]Serum cortisol is low if hypovolemia is due to primary adrenal insuf ciency (Addison's disease).
[e]Serum cortisol will be normal or high if the cause is nausea and vomiting rather than secondary (ACTH-dependent) adrenal insuf ciency.
[f]Plasma renin activity may be high if the cause is secondary (ACTH) adrenal insuf ciency.
[g]Urinary sodium should be expressed as the rate of excretion rather than the concentration. In a hyponatremic adult, an excretion rate >25 meq/d (or 25 μeq/mg of creatinine) could be considered high.
[h]The rate of urinary sodium excretion may be high if the hypovolemia is due to diuretic abuse, primary adrenal insuf ciency, or other causes of renal sodium wasting.
[i]The rate of urinary sodium excretion may be low if intake is curtailed by symptoms or treatment.
Abbreviations: ACTH, adrenocorticotropic hormone; BUN, blood urea nitrogen; CHF, congestive heart failure; SIAD, syndrome of inappropriate antidiuresis.

www.ketabpezeshki.com (021) 66485457 - 66485438

plasma levels are elevated similarly in all. In patients who fulfill the clinical criteria for type III (euvolemic) hyponatremia, morning plasma cortisol should also be measured to exclude secondary adrenal insuf ciency. If it is normal and there is no history of nausea/vomiting, the diagnosis of SIADH is confirmed, and a careful search for occult lung cancer or other common causes of the syndrome (Table 52-2) should be undertaken.

SIAD due to an activating mutation of the V_2 receptor gene should be suspected if the hyponatremia occurs in a child or several members of the family or is refractory to treatment with a vaptan (see below). In that case, plasma AVP should be measured to confirm that it is appropriately suppressed while the hyponatremia and antidiuresis are present, and the V_2 receptor gene should be sequenced, if possible.

TREATMENT Hyponatremia

T e management of hyponatremia differs depending on the type and the severity and duration of symptoms. In acute symptomatic SIADH, the aim should be to raise plasma osmolarity and/or plasma sodium at a rate approximating 1% an hour until they reach levels of about 270 mosmol/L or 130 meq/L, respectively. T is can be accomplished in either of two ways. One is to infuse hypertonic (3%) saline at a rate of about 0.05 mL/kg body weight per minute. T is treatment also has the advantage of correcting the sodium deficiency that is partly responsible for the hyponatremia and often produces a solute diuresis that serves to remove some of the excess water. T e other treatment is to reduce body water by giving an AVP receptor-2 antagonist (vaptan) to block the antidiuretic effect of AVP and increase urine output **(Fig. 52-7)**. One of the vaptans, a combined V_2/V_{1a} antagonist (Conivaptan), has been approved for short-term, in-hospital IV treatment of SIADH, and others are in various stages of development. With either approach, fluid intake should be restricted to less than urine output, and serum sodium should be checked at least once every2h to ensure it is not raised too fast or too far. Doing so may result in central pontine myelinolysis, an acute, potentially fatal neurologic syndrome characterized by quadriparesis, ataxia, and abnormal extraocular movements.

In chronic and/or minimally symptomatic SIADH, the hyponatremia can and should be corrected more gradually. T is can be achieved by restricting total fluid intake to less than the sum of urinary and insensible losses. Because the water derived from food (300–700 mL/d) usually approximates basal insensible losses in adults, the aim should be to reduce total discretionary intake (all liquids) to approximately 500 mL less than urinary output. Adherence to this regimen is often problematic and, even if achieved, usually reduces body water and increases serum sodium by only about 1–2% per day. Hence, additional approaches are

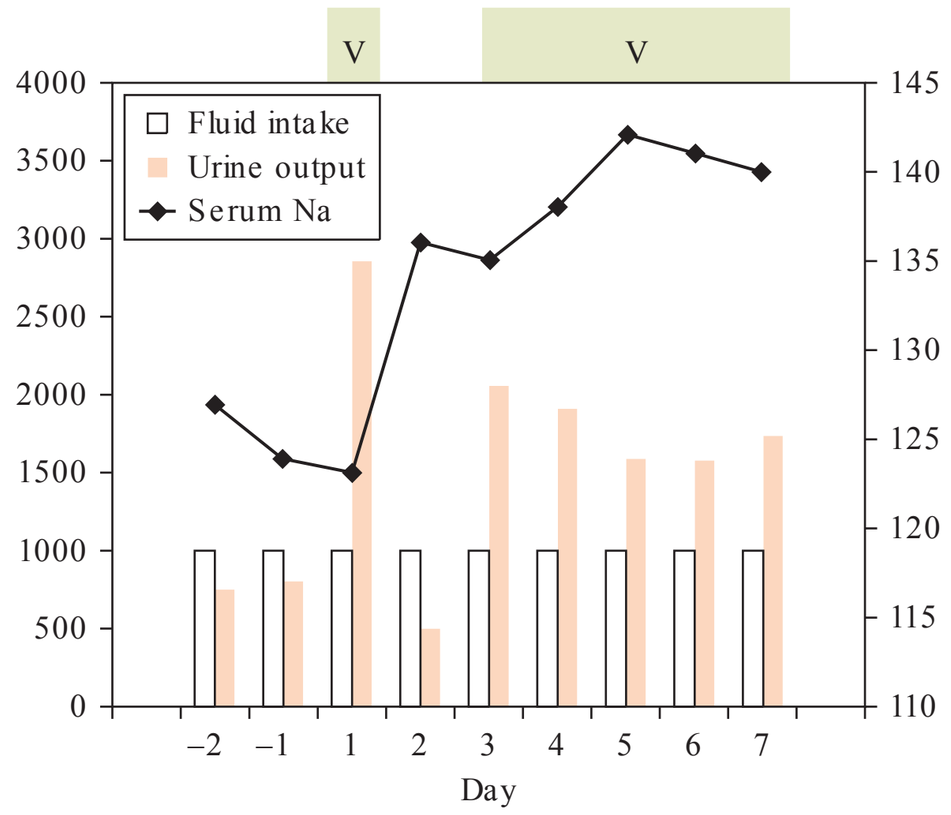


FIGURE 52-7
The effect of vaptan therapy on water balance in a patient with chronic syndrome of inappropriate antidiuretic hormone (SIADH). The periods of vaptan (V) therapy are indicated by the green shaded boxes at the top. Urine output is indicated by orange bars. Fluid intake is shown by the open bars. Intake was restricted to 1 L/d throughout. Serum sodium is indicated by the black line. Note that sodium increased progressively when vaptan increased urine output to levels that clearly exceeded fluid intake.

usually desirable if not necessary. T e best approach for treatment of chronic SIADH is the administration of an oral vaptan, tolvaptan, a selective V_2 antagonist that also increases urinary water excretion by blocking the antidiuretic effect of AVP. Some restriction of fluid intake may also be necessary to achieve satisfactory control of the hyponatremia. It is approved for treatment of nonemergent SIADH with initial in-hospital dosing. Other approaches include demeclocycline, 150–300 mg PO tid or qid, or fludrocortisone, 0.05–0.2 mg PO bid. T e effect of the demeclocycline manifests in 7–14 days and is due to induction of a reversible form of nephrogenic DI. Potential side effects include phototoxicity and azotemia. T e effect of fludrocortisone also requires 1–2 weeks and is partly due to increased retention of sodium and possibly inhibition of thirst. It also increases urinary potassium excretion, which may require replacement through dietary adjustments or supplements and may induce hypertension, occasionally necessitating discontinuation of the treatment.

In euvolemic hyponatremia caused by protracted nausea and vomiting or isolated glucocorticoid deficiency (type III), all abnormalities can be corrected quickly and completely by giving an antiemetic or stress doses of hydrocortisone (for glucocorticoid deficiency). As with other treatments, care must be taken to ensure that serum sodium does not rise too quickly or too far.

In SIAD due to an activating mutation of the V_2 receptor, the V_2 antagonists usually do not block the antidiuresis

www.ketabpezeshki.com (021) 66485457 - 66485438

or raise plasma osmolarity/sodium. In that condition, use of an osmotic diuretic such as urea is reported to be effective in preventing or correcting hyponatremia. However, some vaptans may be effective in patients with a different type of activating mutation so the response to this therapy may be neither predictable nor diagnostic.

In hypervolemic hyponatremia, fluid restriction is also appropriate and somewhat effective if it can be maintained. However, infusion of hypertonic saline is contraindicated because it further increases total body sodium and edema and may precipitate cardiovascular decompensation. However, as in SIADH, the V_2 receptor antagonists are also safe and effective in the treatment of hypervolemic hyponatremia caused by congestive heart failure. Tolvaptan is approved by the Food and Drug Administration for this indication with the caveat that treatment should be initiated or reinitiated in hospital. Its use should also be limited to 30 days at a time because of reports that longer periods may be associated with abnormal liver chemistries.

In hypovolemic hyponatremia, the defect in AVP secretion and water balance usually can be corrected easily and quickly by stopping the loss of sodium and water and/or replacing the deficits by mouth or IV infusion of normal or hypertonic saline. As with the treatment of other forms of hyponatremia, care must be taken to ensure that plasma sodium does not increase too rapidly or too far. Fluid restriction and administration of AVP antagonists are contraindicated in type II hyponatremia because they would only aggravate the underlying volume depletion and could result in hemodynamic collapse.

GLOBAL PERSPECTIVES

The incidence, clinical characteristics, etiology, pathophysiology, differential diagnosis, and treatments of fluid and electrolyte disorders in tropical and nonindustrialized countries differ in some respects from those in the United States and other industrialized parts of the world. Hyponatremia, for example, appears to be more common and is more likely to be due to infectious diseases such as cholera, shigellosis, and other diarrheal disorders. In these circumstances, hyponatremia is probably due to gastrointestinal losses of salt and water (hypovolemia type II), but other abnormalities, including undefined infectious toxins, also may contribute. The causes of DI are similar worldwide except that malaria and venoms from snake or insect bites are much more common.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 53

PERIPHERAL NEUROPATHY

Anthony A. Amato ■ Richard J. Barohn

Peripheral nerves are composed of sensory, motor, and autonomic elements. Diseases can affect the cell body of a neuron or its peripheral processes, namely the axons or the encasing myelin sheaths. Most peripheral nerves are mixed and contain sensory and motor as well as autonomic fibers. Nerves can be subdivided into three major classes: large myelinated, small myelinated, and small unmyelinated. Motor axons are usually large myelinated fibers that conduct rapidly (approximately 50 m/s). Sensory fibers may be any of the three types. Large-diameter sensory fibers conduct proprioception and vibratory sensation to the brain, while the smaller-diameter myelinated and unmyelinated fibers transmit pain and temperature sensation. Autonomic nerves are also small in diameter. T us, peripheral neuropathies can impair sensory, motor, or autonomic function, either singly or in combination. Peripheral neuropathies are further classified into those that primarily affect the cell body (e.g., neuronopathy or ganglionopathy), myelin (myelinopathy), and the axon (axonopathy). T ese different classes of peripheral neuropathies have distinct clinical and electrophysiologic features. T is chapter discusses the clinical approach to a patient suspected of having a peripheral neuropathy, as well as specific neuropathies, including hereditary and acquired neuropathies. **T e inf ammatory neuropathies are discussed in Chap. 54.**

GENERAL APPROACH

In approaching a patient with a neuropathy, the clinician has three main goals: (1) identify where the lesion is, (2) identify the cause, and (3) determine the proper treatment. T e first goal is accomplished by obtaining a thorough history, neurologic examination, and electrodiagnostic and other laboratory studies **(Fig. 53-1)**. While gathering this information, seven key questions are asked **(Table 53-1)**, the answers to which can usually identify the category of pathology that is present **(Table 53-2)**. Despite an extensive evaluation, in approximately half of patients, no etiology is ever found; these patients typically have a predominately sensory polyneuropathy and have been labeled as having idiopathic or cryptogenic sensory polyneuropathy (CSPN).

INFORMATION FROM THE HISTORY AND PHYSICAL EXAMINATION: SEVEN KEY QUESTIONS

1. What systems are involved?

It is important to determine if the patient's symptoms and signs are motor, sensory, autonomic, or a combination of these (Table 53-1). If the patient has only weakness without any evidence of sensory or autonomic dysfunction, a motor neuropathy, neuromuscular junction abnormality, or myopathy should be considered. Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction. Symptoms of autonomic involvement include fainting spells or orthostatic lightheadedness; heat intolerance; or any bowel, bladder, or sexual dysfunction **(Chap. 41)**. T ere will typically be an orthostatic fall in blood pressure without an appropriate increase in heart rate. Autonomic dysfunction in the absence of diabetes should alert the clinician to the possibility of amyloid polyneuropathy. Rarely, a pandysautonomic syndrome can be the only manifestation of a peripheral neuropathy without other motor or sensory findings. T e majority of neuropathies are predominantly sensory in nature.

2. What is the distribution of weakness?

Delineating the pattern of weakness, if present, is essential for diagnosis, and in this regard two additional questions should be answered: (1) Does the weakness only involve the distal extremity, or is it both proximal and distal? and (2) Is the weakness focal and asymmetric, or is it symmetric? Symmetric proximal and distal weakness

www.ketabpezeshki.com (021) 66485457 - 66485438

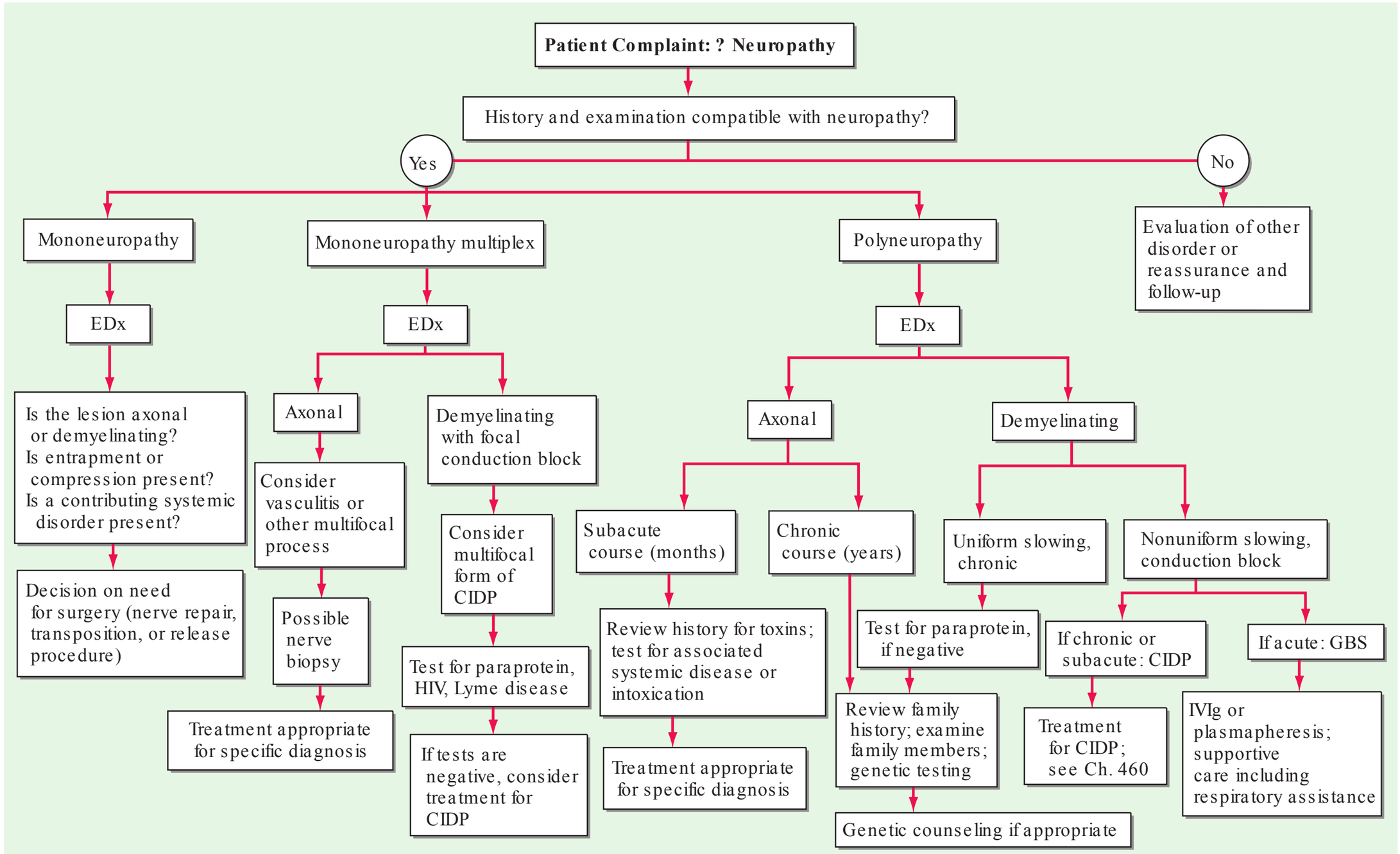


FIGURE 53-1
Approach to the evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

is the hallmark of acquired immune demyelinating polyneuropathies, both the acute form (acute inflammatory demyelinating polyneuropathy [AIDP], also known as Guillain-Barré syndrome [GBS]) and the chronic form (chronic inflammatory demyelinating polyneuropathy [CIDP]). The importance of finding symmetric proximal and distal weakness in a patient who presents with both motor and sensory symptoms cannot be overemphasized because this identifies the important subset of patients who may have a treatable acquired demyelinating neuropathic disorder (i.e., AIDP or CIDP).

Findings of an asymmetric or multifocal pattern of weakness narrow the differential diagnosis. Some neuropathic disorders may present with unilateral extremity weakness. In the absence of sensory symptoms and signs, such weakness evolving over weeks or months would be worrisome for motor neuron disease (e.g., amyotrophic lateral sclerosis [ALS]), but it would be important to exclude multifocal motor neuropathy that may be treatable **(Chap. 39)**. In a patient presenting with asymmetric subacute or acute sensory and motor symptoms and signs, radiculopathies, plexopathies, compressive mononeuropathies, or multiple mononeuropathies (e.g., mononeuropathy multiplex) must be considered.

3. What is the nature of the sensory involvement?

The patient may have loss of sensation (numbness), altered sensation to touch (hyperpathia or allodynia), or uncomfortable spontaneous sensations (tingling, burning, or aching) **(Chap. 15)**. Neuropathic pain can be burning, dull, and poorly localized (protopathic pain), presumably transmitted by polymodal C nociceptor fibers, or sharp and lancinating (epicritic pain), relayed by A-delta fibers. If pain and temperature perception are lost, while vibratory and position sense are preserved along with muscle strength, deep tendon reflexes, and normal nerve conduction studies, a small-fiber neuropathy is likely. This is important, because the most likely cause of small-fiber neuropathies, when one is identified, is diabetes mellitus or glucose intolerance. Amyloid neuropathy should be considered as well in such cases, but most of these small-fiber neuropathies remain idiopathic in nature despite extensive evaluation.

Severe proprioceptive loss also narrows the differential diagnosis. Affected patients will note imbalance, especially in the dark. A neurologic examination revealing a dramatic loss of proprioception with vibration loss and normal strength should alert the clinician to consider a sensory neuronopathy/ganglionopathy

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-1

APPROACH TO NEUROPATHIC DISORDERS: SEVEN KEY QUESTIONS
1. What systems are involved?
– Motor, sensory, autonomic, or combinations
2. What is the distribution of weakness?
– Only distal versus proximal and distal
– Focal/asymmetric versus symmetric
3. What is the nature of the sensory involvement?
– Temperature loss or burning or stabbing pain (e.g., small fiber)
– Vibratory or proprioceptive loss (e.g., large fiber)
4. Is there evidence of upper motor neuron involvement?
– Without sensory loss
– With sensory loss
5. What is the temporal evolution?
– Acute (days to 4 weeks)
– Subacute (4–8 weeks)
– Chronic (>8 weeks)
– Monophasic, progressive, or relapsing-remitting
6. Is there evidence for a hereditary neuropathy?
– Family history of neuropathy
– Lack of sensory symptoms despite sensory signs
7. Are there any associated medical conditions?
– Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy)
– Medications including over-the-counter drugs that may cause a toxic neuropathy
– Preceding events, drugs, toxins

(Table 53-2, Pattern 8). In particular, if this loss is asymmetric or affects the arms more than the legs, this pattern suggests a non-length-dependent process as seen in sensory neuronopathies.

4. Is there evidence of upper motor neuron involvement?

If the patient presents with symmetric distal sensory symptoms and signs suggestive of a distal sensory neuropathy, but there is additional evidence of symmetric upper motor neuron involvement **(Chap. 14)**, the physician should consider a disorder such as combined system degeneration with neuropathy. The most common cause for this pattern is vitamin B_{12} deficiency, but other causes of combined system degeneration with neuropathy should be considered (e.g., copper deficiency, HIV infection, severe hepatic disease, adrenomyeloneuropathy).

5. What is the temporal evolution?

It is important to determine the onset, duration, and evolution of symptoms and signs. Does the disease have an acute (days to 4 weeks), subacute (4–8 weeks), or chronic (>8 weeks) course? Is the course monophasic, progressive, or relapsing? Most neuropathies are insidious and slowly progressive in nature. Neuropathies with acute and subacute presentations include GBS, vasculitis, and radiculopathies related to diabetes or Lyme disease. A relapsing course can be present in CIDP and porphyria.

6. Is there evidence for a hereditary neuropathy?

In patients with slowly progressive distal weakness over many years with very little in the way of sensory symptoms yet with significant sensory deficits on clinical examination, the clinician should consider a hereditary neuropathy (e.g., Charcot-Marie-Tooth disease [CMT]). On examination, the feet may show arch and toe abnormalities (high or flat arches, hammertoes); scoliosis may be present. In suspected cases, it may be necessary to perform both neurologic and electrophysiologic studies on family members in addition to the patient.

7. Does the patient have any other medical conditions?

It is important to inquire about associated medical conditions (e.g., diabetes mellitus, systemic lupus erythematosus); preceding or concurrent infections (e.g. diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy), including over-the-counter vitamin preparations (B_6); alcohol; dietary habits; and use of dentures (e.g., fixatives contain zinc that can lead to copper deficiency).

PATTERN RECOGNITION APPROACH TO NEUROPATHIC DISORDERS

Based on the answers to the seven key questions, neuropathic disorders can be classified into several patterns based on the distribution or pattern of sensory, motor, and autonomic involvement (Table 53-2). Each pattern has a limited differential diagnosis. A final diagnosis is established by using other clues such as the temporal course, presence of other disease states, family history, and information from laboratory studies.

ELECTRODIAGNOSTIC STUDIES

The electrodiagnostic (EDx) evaluation of patients with a suspected peripheral neuropathy consists of nerve conduction studies (NCS) and needle electromyography

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-2

PATTERNS OF NEUROPATHIC DISORDERS
Pattern 1: Symmetric proximal and distal weakness with sensory loss
Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP)
Pattern 2: Symmetric distal sensory loss with or without distal weakness
Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, and others
Pattern 3: Asymmetric distal weakness with sensory loss
With involvement of multiple nerves Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration With involvement of single nerves/regions Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy
Pattern 4: Asymmetric proximal and distal weakness with sensory loss
Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, hereditary plexopathy (HNPP, HNA), idiopathic
Pattern 5: Asymmetric distal weakness without sensory loss
With upper motor neuron findings Consider: motor neuron disease Without upper motor neuron findings Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy
Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings
Consider: Vitamin B_{12}, vitamin E, and copper deficiency with combined system degeneration with peripheral neuropathy, hereditary leukodystrophies (e.g., adrenomyeloneuropathy)
Pattern 7: Symmetric weakness without sensory loss
With proximal and distal weakness Consider: SMA With distal weakness Consider: hereditary motor neuropathy ("distal" SMA) or atypical CMT
Pattern 8: Asymmetric proprioceptive sensory loss without weakness
Consider causes of a sensory neuronopathy (ganglionopathy): Cancer (paraneoplastic) Sjögren's syndrome Idiopathic sensory neuronopathy (possible GBS variant) Cisplatin and other chemotherapeutic agents Vitamin B_6 toxicity HIV-related sensory neuronopathy
Pattern 9: Autonomic symptoms and signs
Consider neuropathies associated with prominent autonomic dysfunction: Hereditary sensory and autonomic neuropathy Amyloidosis (familial and acquired) Diabetes mellitus Idiopathic pandysautonomia (may be a variant of Guillain-Barré syndrome) Porphyria HIV-related autonomic neuropathy Vincristine and other chemotherapeutic agents

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; CMV, cytomegalovirus; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency virus; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; SMA, spinal muscular atrophy.

(EMG). In addition, studies of autonomic function can be valuable. The electrophysiologic data provide additional information about the distribution of the neuropathy that will support or refute the findings from the history and physical examination; they can confirm whether the neuropathic disorder is a mononeuropathy, multiple mononeuropathy (mononeuropathy multiplex), radiculopathy, plexopathy, or generalized

www.ketabpezeshki.com (021) 66485457 - 66485438

polyneuropathy. Similarly, EDx evaluation can ascertain whether the process involves only sensory fibers, motor fibers, autonomic fibers, or a combination of these. Finally, the electrophysiologic data can help distinguish axonopathies from myelinopathies as well as axonal degeneration secondary to ganglionopathies from the more common length-dependent axonopathies.

NCS are most helpful in classifying a neuropathy as being due to axonal degeneration or segmental demyelination **(Table 53-3)**. In general, low-amplitude potentials with relatively preserved distal latencies, conduction velocities, and late potentials, along with fibrillations on needle EMG, suggest an axonal neuropathy. On the other hand, slow conduction velocities, prolonged distal latencies and late potentials, relatively preserved amplitudes, and the absence of fibrillations on needle EMG imply a primary demyelinating neuropathy. T e presence of nonuniform slowing of conduction velocity, conduction block, or temporal dispersion further suggests an acquired demyelinating neuropathy (e.g., GBS or CIDP) as opposed to a hereditary demyelinating neuropathy (e.g., CMT type 1).

Autonomic studies are used to assess small myelinated (A-delta) or unmyelinated (C) nerve fiber involvement. Such testing includes heart rate response to deep breathing, heart rate, and blood pressure response to both the Valsalva maneuver and tilt-table testing and quantitative sudomotor axon reflex testing **(Chap. 41)**. T ese studies are particularly useful in patients who have pure small-fiber neuropathy or autonomic neuropathy in which routine NCS are normal.

OTHER IMPORTANT LABORATORY INFORMATION

In patients with generalized symmetric peripheral neuropathy, a standard laboratory evaluation should include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose (FBS), HbA_{1c}, urinalysis, thyroid function tests, B_{12}, folate, erythrocyte sedimentation rate (ESR), rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixation, and urine for Bence Jones protein. Quantification of the concentration of serum free light chains and the kappa/lambda ratio is more sensitive than SPEP, immunoelectrophoresis, or immunofixation in looking for a monoclonal gammopathy and therefore should be done if one suspects amyloidosis. A skeletal survey should be performed in patients with acquired demyelinating

TABLE 53-3

ELECTROPHYSIOLOGIC FEATURES: AXONAL DEGENERATION VERSUS SEGMENTAL DEMYELINATION

	AXONAL DEGENERATION	SEGMENTAL DEMYELINATION
Motor Nerve Conduction Studies		
CMAP amplitude	Decreased	Normal (except with CB or distal dispersion)
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Conduction block	Absent	Present
Temporal dispersion	Absent	Present
F wave	Normal or absent	Prolonged or absent
H reflex	Normal or absent	Prolonged or absent
Sensory Nerve Conduction Studies		
SNAP amplitude	Decreased	Normal or decreased
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Needle EMG		
Spontaneous activity		
Fibrillations	Present	Absent
Fasciculations	Present	Absent
Motor unit potentials		
Recruitment	Decreased	Decreased
Morphology	Long duration/polyphasic	Normal

Abbreviations: CB, conduction block; CMAP, compound motor action potential; EMG, electromyography; SNAP, sensory nerve action potential.

www.ketabpezeshki.com (021) 66485457 - 66485438

neuropathies and M-spikes to look for osteosclerotic or lytic lesions. Patients with monoclonal gammopathy should also be referred to a hematologist for consideration of a bone marrow biopsy. An oral glucose tolerance test is indicated in patients with painful sensory neuropathies even if FBS and HbA_{1c} are normal, as the test is abnormal in about one-third of such patients. In addition to the above tests, patients with a mononeuropathy multiplex pattern of involvement should have a vasculitis workup, including antineutrophil cytoplasmic antibodies (ANCA), cryoglobulins, hepatitis serology, Western blot for Lyme disease, HIV, and occasionally a cytomegalovirus (CMV) titer.

T ere are many autoantibody panels (various antiganglioside antibodies) marketed for screening routine neuropathy patients for a treatable condition. T ese autoantibodies have no proven clinical utility or added benefit beyond the information obtained from a complete clinical examination and detailed EDx. A heavy metal screen is also not necessary as a screening procedure, unless there is a history of possible exposure or suggestive features on examination (e.g., severe painful sensorimotor and autonomic neuropathy and alopecia—thallium; severe painful sensorimotor neuropathy with or without gastrointestinal [GI] disturbance and Mee's lines—arsenic; wrist or finger extensor weakness and anemia with basophilic stippling of red blood cells—lead).

In patients with suspected GBS or CIDP, a lumbar puncture is indicated to look for an elevated cerebral spinal fluid (CSF) protein. In idiopathic cases of GBS and CIDP, there should not be pleocytosis in the CSF. If cells are present, one should consider HIV infection, Lyme disease, sarcoidosis, or lymphomatous or leukemic infiltration of nerve roots. Some patients with GBS and CIDP have abnormal liver function tests. In these cases, it is important to also check for hepatitis B and C, HIV, CMV, and Epstein-Barr virus (EBV) infection. In patients with an axonal GBS (by EMG/NCS) or those with a suspicious coinciding history (e.g., unexplained abdominal pain, psychiatric illness, significant autonomic dysfunction), it is reasonable to screen for porphyria.

In patients with a severe sensory ataxia, a sensory ganglionopathy or neuronopathy should be considered. T e most common causes of sensory ganglionopathies are Sjögren's syndrome and a paraneoplastic neuropathy. Neuropathy can be the initial manifestation of Sjögren's syndrome. T us, one should always inquire about dry eyes and mouth in patients with sensory signs and symptoms. Further, some patients can manifest sicca complex without full-blown Sjögren's syndrome. T us, patients with sensory ataxia should have a senile systemic amyloidosis (SSA) and single strand binding (SSB) in addition to the routine ANA. To work up a possible paraneoplastic sensory ganglionopathy, antineuronal nuclear antibodies (e.g., anti-Hu antibodies) should be obtained **(Chap. 50)**. T ese antibodies are most commonly seen in patients with small-cell carcinoma of the lung but are seen also in breast, ovarian, lymphoma, and other cancers. Importantly, the paraneoplastic neuropathy can precede the detection of the cancer, and detection of these autoantibodies should lead to a search for malignancy.

NERVE BIOPSIES

Nerve biopsies are now rarely indicated for evaluation of neuropathies. T e primary indication for nerve biopsy is suspicion for amyloid neuropathy or vasculitis. In most instances, the abnormalities present on biopsies do not help distinguish one form of peripheral neuropathy from another (beyond what is already apparent by clinical examination and the NCS). Nerve biopsies should only be done if the NCS are abnormal. T e sural nerve is most commonly biopsied because it is a pure sensory nerve and biopsy will not result in loss of motor function. In suspected vasculitis, a combination biopsy of a superficial peroneal nerve (pure sensory) and the underlying peroneus brevis muscle obtained from a single small incision increases the diagnostic yield. Tissue can be analyzed by frozen section and paraffin section to assess the supporting structures for evidence of inflammation, vasculitis, or amyloid deposition. Semithin plastic sections, teased fiber preparations, and electron microscopy are used to assess the morphology of the nerve fibers and to distinguish axonopathies from myelinopathies.

SKIN BIOPSIES

Skin biopsies are sometimes used to diagnose a small-fiber neuropathy. Following a punch biopsy of the skin in the distal lower extremity, immunologic staining can be used to measure the density of small unmyelinated fibers. T e density of these nerve fibers is reduced in patients with small-fiber neuropathies in whom NCS and routine nerve biopsies are of en normal. T is technique may allow for an objective measurement in patients with mainly subjective symptoms. However, it adds little to what one already knows from the clinical examination and EDx.

SPECIFIC DISORDERS

HEREDITARY NEUROPATHIES

Charcot-Marie-Tooth (CMT) disease is the most common type of hereditary neuropathy. Rather than one disease, CMT is a syndrome of several genetically distinct disorders **(Table 53-4)**. T e various subtypes of CMT are classified according to the nerve conduction

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-4

CLASSIFICATION OF CHARCOT-MARIE-TOOTH DISEASE AND RELATED NEUROPATHIES

NAME	INHERITANCE	GENE LOCATION	GENE PRODUCT
CMT1			
CMT1A	AD	17p11.2	PMP-22 (usually duplication of gene)
CMT1B	AD	1q21-23	MPZ
CMT1C	AD	16p13.1-p12.3	LITAF
CMT1D	AD	10q21.1-22.1	ERG2
CMT1E (with deafness)	AD	17p11.2	Point mutations in PMP 22 gene
CMT1F	AD	8p13-21	Neurofilament light chain
CMT1G	AD	14q32.33	INF2
CMT1X	X-linked dominant	Xq13	Connexin-32
HNPP	AD	17p11.2	PMP-22
		1q21-23	MPZ
CMT dominant-intermediate (CMTD1)			
CMTD1A	AD	10q24.1-25.1	?
CMTD1B	AD	19.p12-13.2	Dynamin 2
CMTD1C	AD	1p35	YARS
CMTD1D	AD	1q22	MPZ
CMT2			
CMT2A2 (allelic to HMSN VI with optic atrophy)	AD	1p36.2	MFN2
CMT2B	AD	3q13-q22	RAB7
CMT2B1 (allelic to LGMD 1B)	AR	1q21.2	Lamin A/C
CMT2B2	AR and AD	19q13	MED25 for AR Unknown for AD
CMT2C (with vocal cord and diaphragm paralysis)	AD	12q23-24	TRPV4
CMT2D (allelic to distal SMA5)	AD	7p14	Glycine tRNA synthetase
CMT2E (allelic to CMT 1F)	AD	8p21	Neurofilament light chain
CMT2F	AD	7q11-q21	Heat-shock 27-kDa protein-1
CMT2G	AD	12q23	Unknown
CMT2I (allelic to CMT1B)	AD	1q22	MPZ
CMT2J	AD	1q22	MPZ
CMT2H, CMT2K (allelic to CMT4A)	AD	8q13-q21	GDAP1
CMT2L (allelic to distal hereditary motor neuropathy type 2)	AD	12q24	Heat-shock protein 8
CMT2M	AD	16q22	Dynamin-2
CMT2N	AD	16q22.1	AARS
CMT2O	AD	14q32.31	DYNC1H1
CMT2P	AD	9q34.13	LRSAM1
CMT2P-Okinawa (HSMN2P)	AD	3q13-q14	TFG
CMT2X	X-linked	Xq22-24	PRPS1
CMT3	AD	17p11.2	PMP-22
(Dejerine-Sottas disease, congenital hypomyelinating neuropathy)	AD	1q21-23	MPZ
	AR	10q21.1-22.1	ERG2

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-4

CLASSIFICATION OF CHARCOT-MARIE-TOOTH DISEASE AND RELATED NEUROPATHIES (CONTINUED)

NAME	INHERITANCE	GENE LOCATION	GENE PRODUCT
	AR	19q13	Periaxon
CMT4			
CMT4A	AR	8q13-21.1	GDAP1
CMT4B1	AR	11q23	MTMR2
CMT4B2	AR	11p15	MTMR13
CMT4C	AR	5q23-33	SH3TC2
CMT4D (HMSN-Lom)	AR	8q24	NDRG1
CMT4E (congenital hypomyelinating neuropathy)	AR	Multiple	Includes PMP22, MPZ, and ERG-2
CMT4F	AR	19q13.1-13.3	Periaxin
CMT4G	AR	10q23.2	HKI
CMT4H	AR	12q12-q13	Frabin
CMT4J	AR	6q21	FIG4
HNA	AD	17q24	SEPT9
HSAN1A	AD	9q22	SPTLC1
HSAN1B	AD	3q21	RAB7
HSAN1C	AD	14q24.3	SPTLC2
HSAN1D	AD	14q21.3	ATL1
HSAN1E	AD	19p13.2	DNMT1
HSAN2A	AR	12p13.33	PRKWNK1
HSAN2B	AR	5p15.1	FAM134B
HSAN2C	AR	12q13.13	KIF1A
HSAN3	AR	9q21	IKAP
HSAN4	AR	3q	trkA/NGF receptor
HSAN5	AD or AR	1p11.2-p13.2	NGFb
HSAN6	AR	6p12.1	Dystonin

Abbreviations: AARS, alanyl-tRNA synthetase; AD, autosomal dominant; AR, autosomal recessive; ATL, atlastin; CMT, Charcot-Marie-Tooth; DNMT1, DNA methyltransferase 1; DYNC1HI, cytoplasmic dynein 1 heavy chain 1; ERG2, early growth response-2 protein; FAM134B, family with sequence similarity 134, member B; FIG4, FDG1-related F actin-binding protein; GDAP1, ganglioside-induced differentiation-associated protein-1; HK1, hexokinase 1; HMSN-P, hereditary motor and sensory neuropathyproximal; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN; hereditary sensory and autonomic neuropathy; IFN2, inverted formin-2; IKAP, $_{k}$B kinase complex-associated protein; LGMD, limb girdle muscular dystrophy; LITAF, lipopolysaccharide-induced tumor necrosis factor α factor; LRSAM1, E3 ubiquitin-protein ligase; MED25, mediator 25; MFN2, mitochondrial fusion protein mitofusin 2 gene; MPZ, myelin protein zero protein; MTMR2, myotubularin-related protein-2; NDRG1, N-myc downstream regulated 1; PMP-22, peripheral myelin protein-22; PRKWNK1, protein kinase, lysine deficient 1; PRPS1, phosphoribosylpyrophosphate synthetase 1; RAB7, Ras-related protein 7; SEPT9, Septin 9; SH3TC2, SH3 domain and tetratricopeptide repeats 2; SMA, spinal muscular atrophy; SPTLC, serine palmitoyltransferase long-chain base; TFG, TRK-fused gene; TrkA/NGF, tyrosine kinase A/nerve growth factor; tRNA, transfer ribonucleic acid; TRPV4, transient receptor potential cation channel, subfamily V, member 4; WNK1, WNK lysine deficient; YARS, tyrosyl-tRNA synthetase.
Source: Modified from AA Amato, J Russell: Neuromuscular Disease. New York, McGraw-Hill, 2008.

velocities and predominant pathology (e.g., demyelination or axonal degeneration), inheritance pattern (autosomal dominant, recessive, or X-linked), and the specific mutated genes. Type 1 CMT (or CMT1) refers to inherited demyelinating sensorimotor neuropathies, whereas the axonal sensory neuropathies are classified as CMT2. By definition, motor conduction velocities in the arms are slowed to less than 38 m/s in CMT1 and are greater than 38 m/s in CMT2. However, most cases of CMT1 actually have motor nerve conduction velocities (NCVs) between 20 and 25 m/s. CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are associated with autosomal dominant inheritance, with a few exceptions. CMT3 is an autosomal dominant neuropathy that appears in infancy and is associated with severe demyelination or hypomyelination. CMT4 is an autosomal recessive neuropathy that typically begins in childhood

www.ketabpezeshki.com (021) 66485457 - 66485438

or early adult life. T ere are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial, as can bracing (e.g., ankle-foot orthotics for footdrop) and other orthotic devices.

CMT1

CMT1 is the most common form of hereditary neuropathy, with the ratio of CMT1:CMT2 being approximately 2:1. Affected individuals usually present in the first to third decade of life with distal leg weakness (e.g., footdrop), although patients may remain asymptomatic even late in life. People with CMT generally do not complain of numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy in which sensory symptoms usually predominate. Although usually asymptomatic in this regard, reduced sensation to all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout. T ere is of en atrophy of the muscles below the knee (particularly the anterior compartment), leading to so-called inverted champagne bottle legs.

Motor NCVs are usually in the 20–25 m/s range. Nerve biopsies usually are not performed on patients suspected of having CMT1, because the diagnosis usually can be made by less invasive testing (e.g., NCS and genetic studies). However, when done, the biopsies reveal reduction of myelinated nerve fibers with a predilection for the loss of the large-diameter fibers and Schwann cell proliferation around thinly or demyelinated fibers, forming so-called onion bulbs.

CMT1A is the most common subtype of CMT1, representing 70% of cases, and is caused by a 1.5-megabase (Mb) duplication within chromosome 17p11.2-12 wherein the gene for peripheral myelin protein-22 (PMP-22) lies. T is results in patients having three copies of the PMP-22 gene rather than two. T is protein accounts for 2–5% of myelin protein and is expressed in compact portions of the peripheral myelin sheath. Approximately 20% of patients with CMT1 have CMT1B, which is caused by mutations in the myelin protein zero (MPZ). CMT1B is for the most part clinically, electrophysiologically, and histologically indistinguishable from CMT1A. MPZ is an integral myelin protein and accounts for more than half of the myelin protein in peripheral nerves. Other forms of CMT1 are much less common and again indistinguishable from one another clinically and electrophysiologically.

CMT2

CMT2 tends to present later in life compared to CMT1. Affected individuals usually become symptomatic in the second decade of life; some cases present earlier in childhood, whereas others remain asymptomatic into late adult life. Clinically, CMT2 is for the most part indistinguishable from CMT1. NCS are helpful in this regard; in contrast to CMT1, the velocities are normal or only slightly slowed. T e most common cause of CMT2 is a mutation in the gene for mitofusin 2 (MFN2), which accounts for one-third of CMT2 cases overall. MFN2 localizes to the outer mitochondrial membrane, where it regulates the mitochondrial network architecture by fusion of mitochondria. T e other genes associated with CMT2 are much less common.

CMTDI

In dominant-intermediate CMTs (CMTDIs), the NCVs are faster than usually seen in CMT1 (e.g., >38 m/s) but slower than in CMT2.

CMT3

CMT3 was originally described by Dejerine and Sottas as a hereditary demyelinating sensorimotor polyneuropathy presenting in infancy or early childhood. Affected children are severely weak. Motor NCVs are markedly slowed, typically 5–10 m/s or less. Most cases of CMT3 are caused by point mutations in the genes for PMP-22, MPZ, or ERG-2, which are also the genes responsible for CMT1.

CMT4

CMT4 is extremely rare and is characterized by a severe, childhood-onset sensorimotor polyneuropathy that is usually inherited in an autosomal recessive fashion. Electrophysiologic and histologic evaluations can show demyelinating or axonal features. CMT4 is genetically heterogenic (Table 53-4).

CMT1X

CMT1X is an X-linked dominant disorder with clinical features similar to CMT1 and CMT2, except that the neuropathy is much more severe in men than in women. CMT1X accounts for approximately 10–15% of CMT overall. Men usually present in the first two decades of life with atrophy and weakness of the distal arms and legs, areflexia, pes cavus, and hammertoes. Obligate women carriers are frequently asymptomatic, but can develop signs and symptoms. Onset in women is usually af er the second decade of life, and the neuropathy is milder in severity.

NCS reveal features of both demyelination and axonal degeneration that are more severe in men compared to women. In men, motor NCVs in the arms and legs are moderately slowed (in the low to mid 30-m/s range). About 50% of men with CMT1X have motor NCVs between 15 and 35 m/s with about 80% of these falling between 25 and 35 m/s (intermediate slowing). In

www.ketabpezeshki.com (021) 66485457 - 66485438

contrast, about 80% of women with CMT1X have NCVs in the normal range and 20% have NCVs in the intermediate range. CMT1X is caused by mutations in the connexin 32 gene. Connexins are gap junction structural proteins that are important in cell-to-cell communication.

Hereditary neuropathy with liability to pressure palsies (HNPP)

HNPP is an autosomal dominant disorder related to CMT1A. Although CMT1A is usually associated with a 1.5-Mb duplication in chromosome 17p11.2 that results in an extra copy of PMP-22 gene, HNPP is caused by inheritance of the chromosome with the corresponding 1.5-Mb deletion of this segment, and thus affected individuals have only one copy of the PMP-22 gene. Patients usually manifest in the second or third decade of life with painless numbness and weakness in the distribution of single peripheral nerves, although multiple mononeuropathies can occur. Symptomatic mononeuropathy or multiple mononeuropathies are often precipitated by trivial compression of nerve(s) as can occur with wearing a backpack, leaning on the elbows, or crossing one's legs for even a short period of time. These pressure-related mononeuropathies may take weeks or months to resolve. In addition, some affected individuals manifest with a progressive or relapsing, generalized and symmetric, sensorimotor peripheral neuropathy that resembles CMT.

Hereditary neuralgic amyotrophy (HNA)

HNA is an autosomal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood. These attacks are similar to those seen with idiopathic brachial plexitis (see below). Attacks may occur in the postpartum period, following surgery, or at other times of stress. Most patients recover over several weeks or months. Slightly dysmorphic features, including hypotelorism, epicanthal folds, cleft palate, syndactyly, micrognathia, and facial asymmetry, are evident in some individuals. EDx demonstrate an axonal process. HNA is caused by mutations in septin 9 (SEPT9). Septins may be important in formation of the neuronal cytoskeleton and have a role in cell division, but the mechanism of causing HNA is unclear.

Hereditary sensory and autonomic neuropathy (HSAN)

The HSANs are a very rare group of hereditary neuropathies in which sensory and autonomic dysfunction predominates over muscle weakness, unlike CMT, in which motor findings are most prominent (Table 53-4). Nevertheless, affected individuals can develop motor weakness and there can be overlap with CMT. There are no medical therapies available to treat these neuropathies, other than prevention and treatment of mutilating skin and bone lesions.

Of the HSANs, only HSAN1 typically presents in adults. HSAN1 is the most common of the HSANs and is inherited in an autosomal dominant fashion. Affected individuals with HSAN1 usually manifest in the second through fourth decades of life. HSAN1 is associated with the degeneration of small myelinated and unmyelinated nerve fibers leading to severe loss of pain and temperature sensation, deep dermal ulcerations, recurrent osteomyelitis, Charcot joints, bone loss, gross foot and hand deformities, and amputated digits. Although most people with HSAN1 do not complain of numbness, they often describe burning, aching, or lancinating pains. Autonomic neuropathy is not a prominent feature, but bladder dysfunction and reduced sweating in the feet may occur. HSAN1A, which is most common, is caused by mutations in the serine palmitoyltransferase long-chain base 1 (SPTLC1) gene.

OTHER HEREDITARY NEUROPATHIES

FABRY'S DISEASE

Fabry's disease (angiokeratoma corporis diffusum) is an X-linked dominant disorder **(Table 53-5)**. Although men are more commonly and severely affected, women can also show severe signs of the disease. Angiokeratomas are reddish-purple maculopapular lesions that are usually found around the umbilicus, scrotum, inguinal region, and perineum. Burning or lancinating pain in the hands and feet often develops in males in late childhood or early adult life. However, the neuropathy is usually overshadowed by complications arising from the associated premature atherosclerosis (e.g., hypertension, renal failure, cardiac disease, and stroke) that often lead to death by the fifth decade of life. Some patients also manifest primarily with a dilated cardiomyopathy.

Fabry's disease is caused by mutations in the a-galactosidase gene that leads to the accumulation of ceramide trihexoside in nerves and blood vessels. A decrease in a-galactosidase activity is evident in leukocytes and cultured fibroblasts. Glycolipid granules may be appreciated in ganglion cells of the peripheral and sympathetic nervous systems and in perineurial cells. Enzyme replacement therapy with a-galactosidase B can improve the neuropathy if patients are treated early, before irreversible nerve fiber loss.

ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are allelic X-linked dominant disorders caused by mutations in the peroxisomal

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-5

RARE HEREDITARY NEUROPATHIES
Hereditary Disorders of Lipid Metabolism
Metachromatic leukodystrophy
Krabbe's disease (globoid cell leukodystrophy)
Fabry's disease
Adrenoleukodystrophy/adrenomyeloneuropathy
Refsum's disease
Tangier disease
Cerebrotendinous xanthomatosis
Hereditary Ataxias with Neuropathy
Friedreich's ataxia
Vitamin E deficiency
Spinocerebellar ataxia
Abetalipoproteinemia (Bassen-Kornzweig disease)
Disorders of Defective DNA Repair
Ataxia-telangiectasia
Cockayne's syndrome
Giant Axonal Neuropathy
Porphyria
Acute intermittent porphyria (AIP)
Hereditary coproporphyria (HCP)
Variegate porphyria (VP)
Familial Amyloid Polyneuropathy (FAP)
Transthyretin-related
Gelsolin-related
Apolipoprotein A1-related

transmembrane adenosine triphosphate-binding cassette (ABC) transporter gene. Patients with ALD manifest with central nervous system (CNS) abnormalities. However, 30% with mutations in this gene present with the AMN phenotype that typically manifests in the third to fifth decade of life with mild to moderate peripheral neuropathy combined with progressive spastic paraplegia **(Chap. 43)**. Rare patients present with an adult-onset spinocerebellar ataxia or only with adrenal insufficiency.

EDx is suggestive of a primary axonopathy with secondary demyelination. Nerve biopsies demonstrate a loss of myelinated and unmyelinated nerve fibers with lamellar inclusions in the cytoplasm of Schwann cells. Very long chain fatty acid (VLCFA) levels (C24, C25, and C26) are increased in the urine. Laboratory evidence of adrenal insufficiency is evident in approximately two-thirds of patients. The diagnosis can be confirmed by genetic testing.

Adrenal insufficiency is managed by replacement therapy; however, there is no proven effective therapy for the neurologic manifestations of ALD/AMN. Diets low in VLCFAs and supplemented with Lorenzo's oil (erucic and oleic acids) reduce the levels of VLCFAs and increase the levels of C22 in serum, fibroblasts, and liver; however, several large, open-label trials of Lorenzo's oil failed to demonstrate efficacy.

REFSUM'S DISEASE

Refsum's disease can manifest in infancy to early adulthood with the classic tetrad of (1) peripheral neuropathy, (2) retinitis pigmentosa, (3) cerebellar ataxia, and (4) elevated CSF protein concentration. Most affected individuals develop progressive distal sensory loss and weakness in the legs leading to footdrop by their 20s. Subsequently, the proximal leg and arm muscles may become weak. Patients may also develop sensorineural hearing loss, cardiac conduction abnormalities, ichthyosis, and anosmia.

Serum phytanic acid levels are elevated. Sensory and motor NCS reveal reduced amplitudes, prolonged latencies, and slowed conduction velocities. Nerve biopsy demonstrates a loss of myelinated nerve fibers, with remaining axons of en thinly myelinated and associated with onion bulb formation.

Refsum disease is genetically heterogeneous but autosomal recessive in nature. Classical Refsum disease with childhood or early adult onset is caused by mutations in the gene that encodes for phytanoyl-CoA α-hydroxylase (PAHX). Less commonly, mutations in the gene encoding peroxin 7 receptor protein (PRX7) are responsible. These mutations lead to the accumulation of phytanic acid in the central and peripheral nervous systems. Refsum's disease is treated by removing phytanic precursors (phytols: fish oils, dairy products, and ruminant fats) from the diet.

TANGIER DISEASE

Tangier disease is a rare autosomal recessive disorder that can present as (1) asymmetric multiple mononeuropathies, (2) a slowly progressive symmetric polyneuropathy predominantly in the legs, or (3) a pseudo-syringomyelia pattern with dissociated sensory loss (i.e., abnormal pain/temperature perception but preserved position/vibration in the arms **[Chap. 43]**). The tonsils may appear swollen and yellowish-orange in color, and there may also be splenomegaly and lymphadenopathy.

Tangier disease is caused by mutations in the ATP-binding cassette transporter 1 (ABC1) gene, which leads to markedly reduced levels of high-density lipoprotein (HDL) cholesterol levels, whereas triacylglycerol levels are increased. Nerve biopsies reveal axonal degeneration with demyelination and remyelination.

www.ketabpezeshki.com (021) 66485457 - 66485438

Electron microscopy demonstrates abnormal accumulation of lipid in Schwann cells, particularly those encompassing umyelinated and small myelinated nerves. T ere is no specific treatment.

PORPHYRIA

Porphyria is a group of inherited disorders caused by defects in heme biosynthesis. T ree forms of porphyria are associated with peripheral neuropathy: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). T e acute neurologic manifestations are similar in each, with the exception that a photosensitive rash is seen with HCP and VP but not in AIP. Attacks of porphyria can be precipitated by certain drugs (usually those metabolized by the P450 system), hormonal changes (e.g., pregnancy, menstrual cycle), and dietary restrictions.

An acute attack of porphyria may begin with sharp abdominal pain. Subsequently, patients may develop agitation, hallucinations, or seizures. Several days later, back and extremity pain followed by weakness ensues, mimicking GBS. Weakness can involve the arms or the legs and can be asymmetric, proximal, or distal in distribution, as well as affecting the face and bulbar musculature. Dysautonomia and signs of sympathetic overactivity are common (e.g., pupillary dilation, tachycardia, and hypertension). Constipation, urinary retention, and incontinence can also be seen.

T e CSF protein is typically normal or mildly elevated. Liver function tests and hematologic parameters are usually normal. Some patients are hyponatremic due to inappropriate secretion of antidiuretic hormone. T e urine may appear brownish in color secondary to the high concentration of porphyrin metabolites. Accumulation of intermediary precursors of heme (i.e., d-aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen) is found in urine. Specific enzyme activities can also be measured in erythrocytes and leukocytes. T e primary abnormalities on EDx are marked reductions in compound motor action potential (CMAP) amplitudes and signs of active axonal degeneration on needle EMG.

T e porphyrias are inherited in an autosomal dominant fashion. AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporphyrin oxidase, and VP is associated with protoporphyrinogen oxidase deficiency. T e pathogenesis of the neuropathy is not completely understood. Treatment with glucose and hematin may reduce the accumulation of heme precursors. Intravenous glucose is started at a rate of 10–20 g/h. If there is no improvement within 24 h, intravenous hematin 2–5 mg/kg per day for 3–14 days should be given.

FAMILIAL AMYLOID POLYNEUROPATHY

Familial amyloid polyneuropathy (FAP) is phenotypically and genetically heterogeneous and is caused by mutations in the genes for transthyretin (TTR), apolipoprotein A1, or gelsolin. T e majority of patients with FAP have mutations in the TTR gene. Amyloid deposition may be evident in abdominal fat pad, rectal, or nerve biopsies. T e clinical features, histopathology, and EDx reveal abnormalities consistent with a generalized or multifocal, predominantly axonal but occasionally demyelinating, sensorimotor polyneuropathy.

Patients with TTR-related FAP usually develop insidious onset of numbness and painful paresthesias in the distal lower limbs in the third to fourth decade of life, although some patients develop the disorder later in life. Carpal tunnel syndrome (CTS) is common. Autonomic involvement can be severe, leading to postural hypotension, constipation or persistent diarrhea, erectile dysfunction, and impaired sweating. Amyloid deposition also occurs in the heart, kidneys, liver, and corneas. Patients usually die 10–15 years af er the onset of symptoms from cardiac failure or complications from malnutrition. Because the liver produces much of the body's TTR, liver transplantation has been used to treat FAP related to TTR mutations. Serum TTR levels decrease af er transplantation, and improvement in clinical and EDx features has been reported.

Patients with apolipoprotein A1-related FAP (Van Allen type) usually present in the fourth decade with numbness and painful dysesthesias in the distal limbs. Gradually, the symptoms progress, leading to proximal and distal weakness and atrophy. Although autonomic neuropathy is not severe, some patients develop diarrhea, constipation, or gastroparesis. Most patients die from systemic complications of amyloidosis (e.g., renal failure) 12–15 years af er the onset of the neuropathy.

Gelsolin-related amyloidosis (Finnish type) is characterized by the combination of lattice corneal dystrophy and multiple cranial neuropathies that usually begin in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops. Autonomic dysfunction does not occur.

ACQUIRED NEUROPATHIES

PRIMARY OR AL AMYLOIDOSIS

Besides FAP, amyloidosis can also be acquired. In primary or AL amyloidosis, the abnormal protein deposition is composed of immunoglobulin light chains. AL amyloidosis occurs in the setting of multiple myeloma, Waldenström's macroglobulinemia, lymphoma, other plasmacytomas, or lymphoproliferative disorders, or without any other identifiable disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

Approximately 30% of patients with AL primary amyloidosis present with a polyneuropathy, most typically painful dysesthesias and burning sensations in the feet. However, the trunk can be involved, and some patients manifest with a mononeuropathy multiplex pattern. CTS occurs in 25% of patients and may be the initial manifestation. The neuropathy is slowly progressive, and eventually weakness develops along with large-fiber sensory loss. Most patients develop autonomic involvement with postural hypertension, syncope, bowel and bladder incontinence, constipation, impotence, and impaired sweating. Patients generally die from their systemic illness (renal failure, cardiac disease).

The monoclonal protein may be composed of IgG, IgA, IgM, or only free light chain. Lambda (λ) is more common than κ light chain (>2:1) in AL amyloidosis. The CSF protein is often increased (with normal cell count), and thus the neuropathy may be mistaken for CIDP **(Chap. 54)**. Nerve biopsies reveal axonal degeneration and amyloid deposition in either a globular or diffuse pattern infiltrating the perineurial, epineurial, and endoneurial connected tissue and in blood vessel walls.

The median survival of patients with primary amyloidosis is less than 2 years, with death usually from progressive congestive heart failure or renal failure. Chemotherapy with melphalan, prednisone, and colchicine, to reduce the concentration of monoclonal proteins, and autologous stem cell transplantation may prolong survival, but whether the neuropathy improves is controversial.

DIABETIC NEUROPATHY

Diabetes mellitus (DM) is the most common cause of peripheral neuropathy in developed countries. DM is associated with several types of polyneuropathy: distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradiculoneuropathies, cranial neuropathies, and other mononeuropathies. Risk factors for the development of neuropathy include long-standing, poorly controlled DM and the presence of retinopathy and nephropathy.

Diabetic distal symmetric sensory and sensorimotor polyneuropathy (DSPN)

DSPN is the most common form of diabetic neuropathy and manifests as sensory loss beginning in the toes that gradually progresses over time up the legs and into the fingers and arms. When severe, a patient may develop sensory loss in the trunk (chest and abdomen), initially in the midline anteriorly and later extending laterally. Tingling, burning, deep aching pains may also be apparent. NCS usually show reduced amplitudes and mild to moderate slowing of conduction velocities (CVs). Nerve biopsy reveals axonal degeneration, endothelial hyperplasia, and, occasionally, perivascular inflammation. Tight control of glucose can reduce the risk of developing neuropathy or improve the underlying neuropathy. A variety of medications have been used with variable success to treat painful symptoms associated with DSPN, including antiepileptic medications, antidepressants, sodium channel blockers, and other analgesics **(Table 53-6)**.

Diabetic autonomic neuropathy

Autonomic neuropathy is typically seen in combination with DSPN. The autonomic neuropathy can manifest as abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, pupillary abnormalities, cardiac arrhythmias, postural hypotension, GI abnormalities (e.g., gastroparesis, postprandial bloating, chronic diarrhea or constipation), and genitourinary dysfunction (e.g., impotence, retrograde ejaculation, incontinence). Tests of autonomic function are generally abnormal, including sympathetic skin responses and quantitative sudomotor axon reflex testing. Sensory and motor NCS generally demonstrate features described above with DSPN.

Diabetic radiculoplexus neuropathy (diabetic amyotrophy or Bruns-Garland syndrome)

Diabetic radiculoplexus neuropathy is the presenting manifestation of DM in approximately one-third of patients. Typically, patients present with severe pain in the low back, hip, and thigh in one leg. Rarely, the diabetic polyradiculoneuropathy begins in both legs at the same time. Atrophy and weakness of proximal and distal muscles in the affected leg become apparent within a few days or weeks. The neuropathy is often accompanied or heralded by severe weight loss. Weakness usually progresses over several weeks or months, but can continue to progress for 18 months or more. Subsequently, there is slow recovery but many are left with residual weakness, sensory loss, and pain. In contrast to the more typical lumbosacral radiculoplexus neuropathy, some patients develop thoracic radiculopathy or, even less commonly, a cervical polyradiculoneuropathy. CSF protein is usually elevated, while the cell count is normal. ESR is often increased. EDx reveals evidence of active denervation in affected proximal and distal muscles in the affected limbs and in paraspinal muscles. Nerve biopsies may demonstrate axonal degeneration along with perivascular inflammation. Patients with severe pain are sometimes treated in the acute period with glucocorticoids, although a randomized controlled trial has yet to be performed, and the natural history of this neuropathy is gradual improvement.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-6

TREATMENT OF PAINFUL SENSORY NEUROPATHIES

THERAPY	ROUTE	DOSE	SIDE EFFECTS
First-Line			
Lidoderm 5% patch	Apply to painful area	Up to 3 patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	PO	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	PO	300–1200 mg tid	Cognitive changes, sedation, peripheral edema
Pregabalin	PO	50–100 mg tid	Cognitive changes, sedation, peripheral edema
Duloxetine	PO	30–60 mg qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
Second-Line			
Carbamazepine	PO	200–400 mg q 6–8 h	Cognitive changes, dizziness, leukopenia, liver dysfunction
Phenytoin	PO	200–400 mg qhs	Cognitive changes, dizziness, liver dysfunction
Venlafaxine	PO	37.5–150 mg/d	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence
Tramadol	PO	50 mg qid	Cognitive changes, gastrointestinal upset
Third-Line			
Mexiletine	PO	200–300 mg tid	Arrhythmias
Other Agents			
EMLA cream	Apply cutaneously	qid	Local erythema
2.5% lidocaine			
2.5% prilocaine			
Capsaicin 0.025–0.075% cream	Apply cutaneously	qid	Painful burning skin

Source: Modified from AA Amato, J Russell: Neuromuscular Disease. New York, McGraw-Hill, 2008.

Diabetic mononeuropathies or multiple mononeuropathies

The most common mononeuropathies are median neuropathy at the wrist and ulnar neuropathy at the elbow, but peroneal neuropathy at the fibular head, and sciatic, lateral femoral, cutaneous, or cranial neuropathies also occur. In regard to cranial mononeuropathies, seventh nerve palsies are relatively common but may have other, nondiabetic etiologies. In diabetics, a third nerve palsy is most common, followed by sixth nerve, and, less frequently, fourth nerve palsies. Diabetic third nerve palsies are characteristically pupil-sparing **(Chap. 25)**.

HYPOTHYROIDISM

Hypothyroidism is more commonly associated with a proximal myopathy, but some patients develop a neuropathy, most typically CTS. Rarely, a generalized sensory polyneuropathy characterized by painful paresthesias and numbness in both the legs and hands can occur. Treatment is correction of the hypothyroidism.

SJÖGREN'S SYNDROME

Sjögren's syndrome, characterized by the sicca complex of xerophthalmia, xerostomia, and dryness of other mucous membranes, can be complicated by neuropathy. Most common is a length-dependent axonal sensorimotor neuropathy characterized mainly by sensory loss in the distal extremities. A pure small-fiber neuropathy or a cranial neuropathy, particularly involving the trigeminal nerve, can also be seen. Sjögren's syndrome is also associated with sensory neuronopathy/ganglionopathy. Patients with sensory ganglionopathies develop progressive numbness and tingling of the limbs, trunk, and face in a non-length-dependent manner such that symptoms can involve the face or arms more than the legs. The onset can be acute or insidious. Sensory examination demonstrates severe vibratory and proprioceptive loss leading to sensory ataxia.

Patients with neuropathy due to Sjögren's syndrome may have ANAs, SS-A/Ro, and SS-B/La antibodies in the serum, but most do not. NCS demonstrate reduced amplitudes of sensory studies in the affected limbs.

www.ketabpezeshki.com (021) 66485457 - 66485438

Nerve biopsy demonstrates axonal degeneration. Nonspecific perivascular inflammation may be present, but only rarely is there necrotizing vasculitis. T ere is no specific treatment for neuropathies related to Sjögren's syndrome. When vasculitis is suspected, immunosuppressive agents may be beneficial. Occasionally, the sensory neuronopathy/ganglionopathy stabilizes or improves with immunotherapy, such as IVIg.

RHEUMATOID ARTHRITIS

Peripheral neuropathy occurs in at least 50% of patients with rheumatoid arthritis (RA) and may be vasculitic in nature. Vasculitic neuropathy can present with a mononeuropathy multiplex, a generalized symmetric pattern of involvement, or a combination of these patterns. Neuropathies may also be due to drugs used to treat the RA (e.g., tumor necrosis blockers, leflunomide). Nerve biopsy of en reveals thickening of the epineurial and endoneurial blood vessels as well as perivascular inflammation or vasculitis, with transmural inflammatory cell infiltration and fibrinoid necrosis of vessel walls. T e neuropathy of en is responsive to immunomodulating therapies.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Between 2 and 27% of individuals with SLE develop a peripheral neuropathy. Affected patients typically present with a slowly progressive sensory loss beginning in the feet. Some patients develop burning pain and paresthesias with normal reflexes, and NCS suggest a pure small-fiber neuropathy. Less common are multiple mononeuropathies presumably secondary to necrotizing vasculitis. Rarely, a generalized sensorimotor polyneuropathy meeting clinical, laboratory, electrophysiologic, and histologic criteria for either GBS or CIDP may occur. Immunosuppressive therapy is beneficial in SLE patients with neuropathy due to vasculitis. Immunosuppressive agents are less likely to be effective in patients with a generalized sensory or sensorimotor polyneuropathy without evidence of vasculitis. Patients with a GBS or CIDP-like neuropathy should be treated accordingly.

SYSTEMIC SCLEROSIS (SCLERODERMA)

A distal symmetric, mainly sensory, polyneuropathy complicates 5–67% of scleroderma cases. Cranial mononeuropathies can also develop, most commonly of the trigeminal nerve, producing numbness and dysesthesias in the face. Multiple mononeuropathies also occur. T e EDx and histologic features of nerve biopsy are those of an axonal sensory greater than motor polyneuropathy.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

A mild distal axonal sensorimotor polyneuropathy occurs in approximately 10% of patients with MCTD.

SARCOIDOSIS

T e peripheral or central nervous system is involved in about 5% of patients with sarcoidosis. T e most common cranial nerve involved is the seventh nerve, which can be affected bilaterally. Some patients develop radiculopathy or polyradiculopathy. With a generalized root involvement, the clinical presentation can mimic GBS or CIDP. Patients can also present with multiple mononeuropathies or a generalized, slowly progressive, sensory greater than motor polyneuropathy. Some have features of a pure small-fiber neuropathy. EDx reveals an axonal neuropathy. Nerve biopsy can reveal noncaseating granulomas infiltrating the endoneurium, perineurium, and epineurium along with lymphocytic necrotizing angiitis. Neurosarcoidosis may respond to treatment with glucocorticoids or other immunosuppressive agents.

HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome is characterized by eosinophilia associated with various skin, cardiac, hematologic, and neurologic abnormalities. A generalized peripheral neuropathy or a mononeuropathy multiplex occurs in 6–14% of patients.

CELIAC DISEASE (GLUTEN-INDUCED ENTEROPATHY OR NONTROPICAL SPRUE)

Neurologic complications, particularly ataxia and peripheral neuropathy, are estimated to occur in 10% of patients with celiac disease. A generalized sensorimotor polyneuropathy, pure motor neuropathy, multiple mononeuropathies, autonomic neuropathy, small-fiber neuropathy, and neuromyotonia have all been reported in association with celiac disease or antigliadin/antiendomysial antibodies. Nerve biopsy may reveal a loss of large myelinated fibers. T e neuropathy may be secondary to malabsorption of vitamins B_{12} and E. However, some patients have no appreciable vitamin deficiencies. T e pathogenic basis for the neuropathy in these patients is unclear but may be autoimmune in etiology. T e neuropathy does not appear to respond to a gluten-free diet. In patients with vitamin B_{12} or vitamin E deficiency, replacement therapy may improve or stabilize the neuropathy.

www.ketabpezeshki.com (021) 66485457 - 66485438

INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease may be complicated by GBS, CIDP, generalized axonal sensory or sensorimotor polyneuropathy, small-fiber neuropathy, or mononeuropathy. T ese neuropathies may be autoimmune, nutritional (e.g., vitamin B_{12} deficiency), treatment related (e.g., metronidazole), or idiopathic in nature. An acute neuropathy with demyelination resembling GBS, CIDP, or multifocal motor neuropathy may occur in patients treated with tumor necrosis factor α blockers.

UREMIC NEUROPATHY

Approximately 60% of patients with renal failure develop a polyneuropathy characterized by length-dependent numbness, tingling, allodynia, and mild distal weakness. Rarely, a rapidly progressive weakness and sensory loss very similar to GBS can occur that improves with an increase in the intensity of renal dialysis or with transplantation. Mononeuropathies can also occur, the most common of which is CTS. Ischemic monomelic neuropathy (see below) can complicate arteriovenous shunts created in the arm for dialysis. EDx in uremic patients reveals features of a length-dependent, primarily axonal, sensorimotor polyneuropathy. Sural nerve biopsies demonstrate a loss of nerve fibers (particularly large myelinated nerve fibers), active axonal degeneration, and segmental and paranodal demyelination. T e sensorimotor polyneuropathy can be stabilized by hemodialysis and improved with successful renal transplantation.

CHRONIC LIVER DISEASE

A generalized sensorimotor neuropathy characterized by numbness, tingling, and minor weakness in the distal aspects of primarily the lower limbs commonly occurs in patients with chronic liver failure. EDx studies are consistent with a sensory greater than motor axonopathy. Sural nerve biopsy reveals both segmental demyelination and axonal loss. It is not known if hepatic failure in isolation can cause peripheral neuropathy, as the majority of patients have liver disease secondary to other disorders, such as alcoholism or viral hepatitis, which can also cause neuropathy.

CRITICAL ILLNESS POLYNEUROPATHY

T e most common causes of acute generalized weakness leading to admission to a medical intensive care unit (ICU) are GBS and myasthenia gravis **(Chap. 55)**. However, weakness developing in critically ill patients while in the ICU is usually caused by critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) or, much less commonly, by prolonged neuromuscular blockade. From a clinical and EDx standpoint, it can be quite difficult to distinguish these disorders. Most specialists suggest that CIM is more common. Both CIM and CIP develop as a complication of sepsis and multiple organ failure. T ey usually present as an inability to wean a patient from a ventilator. A coexisting encephalopathy may limit the neurologic exam, in particular the sensory examination. Muscle stretch reflexes are absent or reduced.

Serum creatine kinase (CK) is usually normal; an elevated serum CK would point to CIM as opposed to CIP. NCS reveal absent or markedly reduced amplitudes of motor and sensory studies in CIP, whereas sensory studies are relatively preserved in CIM. Needle EMG usually reveals profuse positive sharp waves and fibrillation potentials, and it is not unusual in patients with severe weakness to be unable to recruit motor unit action potentials. T e pathogenic basis of CIP is not known. Perhaps circulating toxins and metabolic abnormalities associated with sepsis and multiorgan failure impair axonal transport or mitochondrial function, leading to axonal degeneration.

LEPROSY (HANSEN'S DISEASE)

Leprosy, caused by the acid-fast bacteria Mycobacterium leprae, is the most common cause of peripheral neuropathy in Southeast Asia, Africa, and South America. Clinical manifestations range from tuberculoid leprosy at one end to lepromatous leprosy at the other end of the spectrum, with borderline leprosy in between. Neuropathies are most common in patients with borderline leprosy. Superficial cutaneous nerves of the ears and distal limbs are commonly affected. Mononeuropathies, multiple mononeuropathies, or a slowly progressive symmetric sensorimotor polyneuropathy may develop. Sensory NCS are usually absent in the lower limb and are reduced in amplitude in the arms. Motor NCS may demonstrate reduced amplitudes in affected nerves but occasionally can reveal demyelinating features. Leprosy is usually diagnosed by skin lesion biopsy. Nerve biopsy can also be diagnostic, particularly when there are no apparent skin lesions. T e tuberculoid form is characterized by granulomas, and bacilli are not seen. In contrast, with lepromatous leprosy, large numbers of infiltrating bacilli, T_H2 lymphocytes, and organism-laden, foamy macrophages with minimal granulomatous infiltration are evident. T e bacilli are best appreciated using the Fite stain, where they can be seen as red-staining rods of en in clusters free in the

www.ketabpezeshki.com (021) 66485457 - 66485438

endoneurium, within macrophages, or within Schwann cells.

Patients are generally treated with multiple drugs: dapsone, rifampin, and clofazimine. Other medications that are used include thalidomide, pefloxacin, ofloxacin, sparfloxacin, minocycline, and clarithromycin. Patients are generally treated for 2 years. Treatment is sometimes complicated by the so-called reversal reaction, particularly in borderline leprosy. T e reversal reaction can occur at any time during treatment and develops because of a shif to the tuberculoid end of the spectrum, with an increase in cellular immunity during treatment. T e cellular response is upregulated as evidenced by an increased release of tumor necrosis factor α, interferon γ, and interleukin 2, with new granuloma formation. T is can result in an exacerbation of the rash and the neuropathy as well as in appearance of new lesions. High-dose glucocorticoids blunt this adverse reaction and may be used prophylactically at treatment onset in high-risk patients. Erythema nodosum leprosum (ENL) is also treated with glucocorticoids or thalidomide.

LYME DISEASE

Lyme disease is caused by infection with Borrelia burgdorferi, a spirochete usually transmitted by the deer tick Ixodes dammini. Neurologic complications may develop during the second and third stages of infection. Facial neuropathy is most common and is bilateral in about half of cases, which is rare for idiopathic Bell's palsy. Involvement of nerves is frequently asymmetric. Some patients present with a polyradiculoneuropathy or multiple mononeuropathies. EDx is suggestive of a primary axonopathy. Nerve biopsies can reveal axonal degeneration with perivascular inflammation. Treatment is with antibiotics.

DIPHTHERITIC NEUROPATHY

Diphtheria is caused by the bacteria Corynebacterium diphtheriae. Infected individuals present with flulike symptoms of generalized myalgias, headache, fatigue, low-grade fever, and irritability within a week to 10 days of the exposure. About 20–70% of patients develop a peripheral neuropathy caused by a toxin released by the bacteria. T ree to 4 weeks af er infection, patients may note decreased sensation in their throat and begin to develop dysphagia, dysarthria, hoarseness, and blurred vision due to impaired accommodation. A generalized polyneuropathy may manifest 2 or 3 months following the initial infection, characterized by numbness, paresthesias, and weakness of the arms and legs and occasionally ventilatory failure. CSF protein can be elevated with or without lymphocytic pleocytosis. EDx suggests a diffuse axonal sensorimotor polyneuropathy. Antitoxin and antibiotics should be given within 48 h of symptom onset. Although early treatment reduces the incidence and severity of some complications (i.e., cardiomyopathy), it does not appear to alter the natural history of the associated peripheral neuropathy. T e neuropathy usually resolves af er several months.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV infection can result in a variety of neurologic complications, including peripheral neuropathies **(Chap. 48)**. Approximately 20% of HIV-infected individuals develop a neuropathy either as a direct result of the virus itself, other associated viral infections (e.g., CMV), or neurotoxicity secondary to antiviral medications (see below). T e major presentations of peripheral neuropathy associated with HIV infection include (1) distal symmetric polyneuropathy, (2) inflammatory demyelinating polyneuropathy (including both GBS and CIDP), (3) multiple mononeuropathies (e.g., vasculitis, CMV-related), (4) polyradiculopathy (usually CMV-related), (5) autonomic neuropathy, and (6) sensory ganglionitis.

HIV-related distal symmetric polyneuropathy (DSP)

DSP is the most common form of peripheral neuropathy associated with HIV infection and usually is seen in patients with AIDS. It is characterized by numbness and painful paresthesias involving the distal extremities. T e pathogenic basis for DSP is unknown but is not due to actual infection of the peripheral nerves. T e neuropathy may be immune mediated, perhaps caused by the release of cytokines from surrounding inflammatory cells. Vitamin B_{12} deficiency may contribute in some instances but is not a major cause of most cases of DSP. Some antiretroviral agents (e.g., dideoxycytidine, dideoxyinosine, stavudine) are also neurotoxic and can cause a painful sensory neuropathy.

HIV-related inf ammatory demyelinating polyradiculoneuropathy

Both AIDP and CIDP can occur as a complication of HIV infection. AIDP usually develops at the time of seroconversion, whereas CIDP can occur any time in the course of the infection. Clinical and EDx features are indistinguishable from idiopathic AIDP or CIDP (discussed in **Chap. 54**). In addition to elevated protein levels, lymphocytic pleocytosis is evident in the CSF, a finding that helps distinguish this HIV-associated polyradiculoneuropathy from idiopathic AIDP/CIDP.

www.ketabpezeshki.com (021) 66485457 - 66485438

HIV-related progressive polyradiculopathy

An acute, progressive lumbosacral polyradiculoneuropathy usually secondary to CMV infection can develop in patients with AIDS. Patients present with severe radicular pain, numbness, and weakness in the legs, which is usually asymmetric. CSF is abnormal, demonstrating an increased protein along with reduced glucose concentration and notably a neutrophilic pleocytosis. EDx studies reveal features of active axonal degeneration. T e polyradiculoneuropathy may improve with antiviral therapy.

HIV-related multiple mononeuropathies

Multiple mononeuropathies can also develop in patients with HIV infection, usually in the context of AIDS. Weakness, numbness, paresthesias, and pain occur in the distribution of affected nerves. Nerve biopsies can reveal axonal degeneration with necrotizing vasculitis or perivascular inflammation. Glucocorticoid treatment is indicated for vasculitis directly due to HIV infection.

HIV-related sensory neuronopathy/ganglionopathy

Dorsal root ganglionitis is a very rare complication of HIV infection, and neuronopathy can be the presenting manifestation. Patients develop sensory ataxia similar to idiopathic sensory neuronopathy/ganglionopathy. NCS reveal reduced amplitudes or absence of sensory nerve action potentials (SNAPs).

HERPES VARICELLA-ZOSTER VIRUS

Peripheral neuropathy from herpes varicella-zoster (HVZ) infection results from reactivation of latent virus or from a primary infection. Two-thirds of infections in adults are characterized by dermal zoster in which severe pain and paresthesias develop in a dermatomal region followed within a week or two by a vesicular rash in the same distribution. Weakness in muscles innervated by roots corresponding to the dermatomal distribution of skin lesions occurs in 5–30% of patients. Approximately 25% of affected patients have continued pain (postherpetic neuralgia [PHN]). A large clinical trial demonstrated that vaccination against zoster reduces the incidence of HVZ among vaccine recipients by 51% and reduces the incidence of PHN by 67%. Treatment of PHN is symptomatic (Table 53-6).

CYTOMEGALOVIRUS

CMV can cause an acute lumbosacral polyradiculopathy and multiple mononeuropathies in patients with HIV infection and in other immune deficiency conditions.

EPSTEIN-BARR VIRUS

EBV infection has been associated with GBS, cranial neuropathies, mononeuropathy multiplex, brachial plexopathy, lumbosacral radiculoplexopathy, and sensory neuronopathies.

HEPATITIS VIRUSES

Hepatitis B and C can cause multiple mononeuropathies related to vasculitis, AIDP, or CIDP.

NEUROPATHIES ASSOCIATED WITH MALIGNANCY

Patients with malignancy can develop neuropathies due to (1) a direct effect of the cancer by invasion or compression of the nerves, (2) remote or paraneoplastic effect, (3) a toxic effect of treatment, or (4) as a consequence of immune compromise caused by immunosuppressive medications. T e most common associated malignancy is lung cancer, but neuropathies also complicate carcinoma of the breast, ovaries, stomach, colon, rectum, and other organs, including the lymphoproliferative system.

PARANEOPLASTIC SENSORY NEURONOPATHY/GANGLIONOPATHY

Paraneoplastic encephalomyelitis/sensory neuronopathy (PEM/SN) usually complicates small-cell lung carcinoma **(Chap. 50)**. Patients usually present with numbness and paresthesias in the distal extremities that are of en asymmetric. T e onset can be acute or insidiously progressive. Prominent loss of proprioception leads to sensory ataxia. Weakness can be present, usually secondary to an associated myelitis, motor neuronopathy, or concurrent Lambert-Eaton myasthenic syndrome (LEMS). Many patients also develop confusion, memory loss, depression, hallucinations or seizures, or cerebellar ataxia. Polyclonal antineuronal antibodies (IgG) directed against a 35- to 40-kDa protein or complex of proteins, the so-called Hu antigen, are found in the sera or CSF in the majority of patients with paraneoplastic PEM/SN. CSF may be normal or may demonstrate mild lymphocytic pleocytosis and elevated protein. PEM/SN is probably the result of

www.ketabpezeshki.com (021) 66485457 - 66485438

antigenic similarity between proteins expressed in the tumor cells and neuronal cells, leading to an immune response directed against both cell types. Treatment of the underlying cancer generally does not affect the course of PEM/SN. However, occasional patients may improve following treatment of the tumor. Unfortunately, plasmapheresis, intravenous immunoglobulin, and immunosuppressive agents have not shown benefit.

NEUROPATHY SECONDARY TO TUMOR INFILTRATION

Malignant cells, in particular leukemia and lymphoma, can infiltrate cranial and peripheral nerves, leading to mononeuropathy, mononeuropathy multiplex, polyradiculopathy, plexopathy, or even a generalized symmetric distal or proximal and distal polyneuropathy. Neuropathy related to tumor infiltration is often painful; it can be the presenting manifestation of the cancer or the heralding symptom of a relapse. The neuropathy may improve with treatment of the underlying leukemia or lymphoma or with glucocorticoids.

NEUROPATHY AS A COMPLICATION OF BONE MARROW TRANSPLANTATION

Neuropathies may develop in patients who undergo bone marrow transplantation (BMT) because of the toxic effects of chemotherapy, radiation, infection, or an autoimmune response directed against the peripheral nerves. Peripheral neuropathy in BMT is often associated with graft-versus-host disease (GVHD). Chronic GVHD shares many features with a variety of autoimmune disorders, and it is possible that an immune-mediated response directed against peripheral nerves is responsible. Patients with chronic GVHD may develop cranial neuropathies, sensorimotor polyneuropathies, multiple mononeuropathies, and severe generalized peripheral neuropathies resembling AIDP or CIDP. The neuropathy may improve by increasing the intensity of immunosuppressive or immunomodulating therapy and resolution of the GVHD.

LYMPHOMA

Lymphomas may cause neuropathy by infiltration or direct compression of nerves or by a paraneoplastic process. The neuropathy can be purely sensory or motor, but most commonly is sensorimotor. The pattern of involvement may be symmetric, asymmetric, or multifocal, and the course may be acute, gradually progressive, or relapsing and remitting. EDx can be compatible with either an axonal or demyelinating process. CSF may reveal lymphocytic pleocytosis and an elevated protein. Nerve biopsy may demonstrate endoneurial inflammatory cells in both the infiltrative and the paraneoplastic etiologies. A monoclonal population of cells favors lymphomatous invasion. The neuropathy may respond to treatment of the underlying lymphoma or immunomodulating therapies.

MULTIPLE MYELOMA

Multiple myeloma (MM) usually presents in the fifth to seventh decade of life with fatigue, bone pain, anemia, and hypercalcemia. Clinical and EDx features of neuropathy occur in as many as 40% of patients. The most common pattern is that of a distal, axonal, sensory, or sensorimotor polyneuropathy. Less frequently, a chronic demyelinating polyradiculoneuropathy may develop (see POEMS, **Chap. 54**). MM can be complicated by amyloid polyneuropathy and should be considered in patients with painful paresthesias, loss of pinprick and temperature discrimination, and autonomic dysfunction (suggestive of a small-fiber neuropathy) and CTS. Expanding plasmacytomas can compress cranial nerves and spinal roots as well. A monoclonal protein, usually composed of γ or μ heavy chains or κ light chains, may be identified in the serum or urine. EDx usually shows reduced amplitudes with normal or only mildly abnormal distal latencies and conduction velocities. A superimposed median neuropathy at the wrist is common. Abdominal fat pad, rectal, or sural nerve biopsy can be performed to look for amyloid deposition. Unfortunately, the treatment of the underlying MM does not usually affect the course of the neuropathy.

NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE

Toxic neuropathies secondary to chemotherapy

Many of the commonly used chemotherapy agents can cause a toxic neuropathy **(Table 53-7)** **(See Chap. 54)**. The mechanisms by which these agents cause toxic neuropathies vary, as does the specific type of neuropathy produced. The risk of developing a toxic neuropathy or more severe neuropathy appears to be greater in patients with a preexisting neuropathy (e.g., Charcot-Marie-Tooth disease, diabetic neuropathy) and those who also take other potentially neurotoxic drugs (e.g., nitrofurantoin, isoniazid, disulfiram, pyridoxine). Chemotherapeutic agents usually cause a sensory greater than motor length-dependent axonal neuropathy or neuronopathy/ganglionopathy.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-7

TOXIC NEUROPATHIES SECONDARY TO CHEMOTHERAPY

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)	Interfere with axonal microtubule assembly; impairs axonal transport	Symmetric, S-M, large-/small-fiber PN; autonomic symptoms common; infrequent cranial neuropathies	Axonal degeneration of myelinated and unmyelinated fibers; regenerating clusters, minimal segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Cisplatin	Preferential damage to dorsal root ganglia: ? binds to and cross-links DNA ? inhibits protein synthesis ? impairs axonal transport	Predominant large-fiber sensory neuronopathy; sensory ataxia	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Low-amplitude or unobtainable SNAPs with normal CMAPs and EMG; abnormal QST, particularly vibratory perception
Taxanes (paclitaxel, docetaxel)	Promotes axonal microtubule assembly; interferes with axonal transport	Symmetric, predominantly sensory PN; large-fiber modalities affected more than small-fiber	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Suramin				
Axonal PN	Unknown; ? inhibition of neurotrophic growth factor binding; ? neuronal lysosomal storage	Symmetric, length-dependent, sensory-predominant PN	None described	Abnormalities consistent with an axonal S-M PN
Demyelinating PN	Unknown; ? immunomodulating effects	Subacute, S-M PN with diffuse proximal and distal weakness; areflexia; increased CSF protein	Loss of large and small myelinated fibers with primary demyelination and secondary axonal degeneration; occasional epi- and endoneurial inflammatory cell infiltrates	Features suggestive of an acquired demyelinating sensorimotor PN (e.g., slow CVs, prolonged distal latencies and F-wave latencies, conduction block, temporal dispersion)
Cytarabine (ARA-C)	Unknown; ? selective Schwann cell toxicity; ? immunomodulating effects	GBS-like syndrome; pure sensory neuropathy; brachial plexopathy	Loss of myelinated nerve fibers; axonal degeneration; segmental demyelination; no inflammation	Axonal, demyelinating, or mixed S-M PN; denervation on EMG
Etoposide (VP-16)	Unknown; ? selective dorsal root ganglia toxicity	Length-dependent, sensory-predominant PN; autonomic neuropathy	None described	Abnormalities consistent with an axonal S-M PN
Bortezomib (Velcade)	Unknown	Length-dependent, sensory, predominantly small-fiber PN	Not reported	Abnormalities consistent with an axonal sensory neuropathy with early small-fiber involvement (abnormal autonomic studies)

Abbreviations: CMAP, compound motor action potential; CSF, cerebrospinal fluid; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; NCS, nerve conduction studies; PN, polyneuropathy; QST, quantitative sensory testing; S-M, sensorimotor; SNAP, sensory nerve action potential.
Source: From AA Amato, J Russell: Neuromuscular Disease. New York, McGraw-Hill, 2008.

www.ketabpezeshki.com (021) 66485457 - 66485438

OTHER TOXIC NEUROPATHIES

Neuropathies can develop as complications of toxic effects of various drugs and other environmental exposures **(Table 53-8)**. T e more common neuropathies associated with these agents are discussed here.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine and hydroxychloroquine can cause a toxic myopathy characterized by slowly progressive, painless, proximal weakness and atrophy, which is worse in the legs than the arms. In addition, neuropathy can also develop with or without the myopathy leading to sensory loss and distal weakness. T e "neuromyopathy" usually appears in patients taking 500 mg daily for a year or more but has been reported with doses as low as 200 mg/d. Serum CK levels are usually elevated due to the superimposed myopathy. NCS reveal mild slowing of motor and sensory NCVs with a mild to moderate reduction in the amplitudes, although NCS may be normal in patients with only the myopathy. EMG demonstrates myopathic muscle action potentials (MUAPs), increased insertional activity in the form of positive sharp waves, fibrillation potentials, and occasionally myotonic potentials, particularly in the proximal muscles. Neurogenic MUAPs and reduced recruitment are found in more distal muscles. Nerve biopsy demonstrates autophagic vacuoles within Schwann cells. Vacuoles may also be evident in muscle biopsies. T e pathogenic basis of the neuropathy is not known but may be related to the

TABLE 53-8

TOXIC NEUROPATHIES

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Misonidazole	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration of large myelinated fibers; axonal swellings; segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or only slightly reduced CMAPs amplitudes
Metronidazole	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal CMAPs
Chloroquine and hydroxychloroquine	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration with autophagic vacuoles in nerves as well as muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
Amiodarone	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Paresthesias and pain with loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration and segmental demyelination with myeloid inclusions in nerves and muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; can also have prominent slowing of CVs; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-8

TOXIC NEUROPATHIES (CONTINUED)

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Colchicine	Inhibits polymerization of tubulin in microtubules and impairs axoplasmic flow	Numbness and paresthesias with loss of large-fiber modalities in a length-dependent fashion; superimposed myopathy may lead to proximal in addition to distal weakness	Nerve biopsy demonstrates axonal degeneration; muscle biopsy reveals fibers with vacuoles	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
Podophyllin	Binds to microtubules and impairs axoplasmic flow	Sensory loss, tingling, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern; autonomic neuropathy	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Thalidomide	Unknown	Numbness, tingling, and burning pain and weakness in a length-dependent pattern	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Disulfiram	Accumulation of neurofilaments and impaired axoplasmic flow	Numbness, tingling, and burning pain in a length-dependent pattern	Axonal degeneration with accumulation of neurofilaments in the axons	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Dapsone	Unknown	Distal weakness that may progress to proximal muscles; sensory loss	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable CMAPs with normal or reduced SNAP amplitudes
Leflunomide	Unknown	Paresthesias and numbness in a length-dependent pattern	Unknown	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Nitrofurantoin	Unknown	Numbness, painful paresthesias, and severe weakness that may resemble GBS	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia and anterior horn cells	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Pyridoxine (vitamin B_6)	Unknown	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia	Reduced amplitudes or absent SNAPs
Isoniazid	Inhibits pyridoxal phosphokinase leading to pyridoxine deficiency	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia and degeneration of the dorsal columns	Reduced amplitudes or absent SNAPs and, to a lesser extent, CMAPs
Ethambutol	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
Antinucleosides	Unknown	Dysesthesia and sensory ataxia; impaired large-fiber sensory modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-8

TOXIC NEUROPATHIES (CONTINUED)

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Phenytoin	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Lithium	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Acrylamide	Unknown; may be caused by impaired axonal transport	Numbness with loss of large-fiber modalities on examination; sensory ataxia; mild distal weakness	Degeneration of sensory axons in peripheral nerves and posterior columns, spinocerebellar tracts, mammillary bodies, optic tracts, and corticospinal tracts in the CNS	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Carbon disulfide	Unknown	Length-dependent numbness and tingling with mild distal weakness	Axonal swellings with accumulation of neurofilaments	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Ethylene oxide	Unknown; may act as alkylating agent and bind DNA	Length-dependent numbness and tingling; may have mild distal weakness	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Organophosphates	Bind and inhibit neuropathy target esterase	Early features are those of neuromuscular blockade with generalized weakness; later axonal sensorimotor PN ensues	Axonal degeneration along with degeneration of gracile fasciculus and corticospinal tracts	Early: repetitive firing of CMAPs and decrement with repetitive nerve stimulation; late: axonal sensorimotor PN
Hexacarbons	Unknown; may lead to covalent cross-linking between neurofilaments	Acute, severe sensorimotor PN that may resemble GBS	Axonal degeneration and giant axons swollen with neurofilaments	Features of a mixed axonal and/or demyelinating sensorimotor axonal PN—reduced amplitudes, prolonged distal latencies, conduction block, and slowing of CVs
Lead	Unknown; may interfere with mitochondria	Encephalopathy; motor neuropathy (often resembles radial neuropathy with wrist and finger drop); autonomic neuropathy; bluish-black discoloration of gums	Axonal degeneration of motor axons	Reduction of CMAP amplitudes with active denervation on EMG
Mercury	Unknown; may combine with sulfhydryl groups	Abdominal pain and nephrotic syndrome; encephalopathy; ataxia; paresthesias	Axonal degeneration; degeneration of dorsal root ganglia, calcarine, and cerebellar cortex	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-8

TOXIC NEUROPATHIES (CONTINUED)

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Thallium	Unknown	Encephalopathy; painful sensory symptoms; mild loss of vibration; distal or generalized weakness may also develop; autonomic neuropathy; alopecia	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Arsenic	Unknown; may combine with sulfhydryl groups	Abdominal discomfort, burning pain, and paresthesias; generalized weakness; autonomic insufficiency; can resemble GBS	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; may have demyelinating features: prolonged distal latencies and slowing of CVs
Gold	Unknown	Distal paresthesias and reduction of all sensory modalities	Axonal degeneration	Low-amplitude or unobtainable SNAPs

Abbreviations: CMAP, compound motor action potential; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; MUAP, muscle action potential; NCS, nerve conduction studies; PN, polyneuropathy; S-M, sensorimotor; SNAP, sensory nerve action potential
Source: From AA Amato, J Russell: Neuromuscular Disease. New York, McGraw-Hill, 2008.

amphiphilic properties of the drug. These agents contain both hydrophobic and hydrophilic regions that allow them to interact with the anionic phospholipids of cell membranes and organelles. The drug-lipid complexes may be resistant to digestion by lysosomal enzymes, leading to the formation of autophagic vacuoles filled with myeloid debris that may in turn cause degeneration of nerves and muscle fibers. The signs and symptoms of the neuropathy and myopathy are usually reversible following discontinuation of medication.

AMIODARONE

Amiodarone can cause a neuromyopathy similar to chloroquine and hydroxychloroquine. The neuromyopathy typically appears after patients have taken the medication for 2–3 years. Nerve biopsy demonstrates a combination of segmental demyelination and axonal loss. Electron microscopy reveals lamellar or dense inclusions in Schwann cells, pericytes, and endothelial cells. The inclusions in muscle and nerve biopsies have persisted as long as 2 years following discontinuation of the medication.

COLCHICINE

Colchicine can also cause a neuromyopathy. Patients usually present with proximal weakness and numbness and tingling in the distal extremities. EDx reveals features of an axonal polyneuropathy. Muscle biopsy reveals a vacuolar myopathy, whereas sensory nerves demonstrate axonal degeneration. Colchicine inhibits the polymerization of tubulin into microtubules. The disruption of the microtubules probably leads to defective intracellular movement of important proteins, nutrients, and waste products in muscle and nerves.

THALIDOMIDE

Thalidomide is an immunomodulating agent used to treat multiple myeloma, GVHD, leprosy, and other autoimmune disorders. Thalidomide is associated with severe teratogenic effects as well as peripheral neuropathy that can be dose-limiting. Patients develop numbness, painful tingling, and burning discomfort in the feet and hands and less commonly muscle weakness and atrophy. Even after stopping the drug for 4–6 years, as many as 50% patients continue to have significant symptoms. NCS demonstrate reduced amplitudes or complete absence of SNAPs, with preserved conduction velocities when obtainable. Motor NCS are usually normal. Nerve biopsy reveals a loss of large-diameter myelinated fibers and axonal degeneration. Degeneration of dorsal root ganglion cells has been reported at autopsy.

PYRIDOXINE (VITAMIN B_6) TOXICITY

Pyridoxine is an essential vitamin that serves as a coenzyme for transamination and decarboxylation. However, at high doses (116 mg/d), patients can develop a severe sensory neuropathy with dysesthesias and

www.ketabpezeshki.com (021) 66485457 - 66485438

sensory ataxia. NCS reveal absent or markedly reduced SNAP amplitudes with relatively preserved CMAPs. Nerve biopsy reveals axonal loss of fiber at all diameters. Loss of dorsal root ganglion cells with subsequent degeneration of both the peripheral and central sensory tracts have been reported in animal models.

ISONIAZID

One of the most common side effects of isoniazid (INH) is peripheral neuropathy. Standard doses of INH (3–5 mg/kg per day) are associated with a 2% incidence of neuropathy, whereas neuropathy develops in at least 17% of patients taking in excess of 6 mg/kg per day. T e elderly, malnourished, and "slow acetylators" are at increased risk for developing the neuropathy. INH inhibits pyridoxal phosphokinase, resulting in pyridoxine deficiency and the neuropathy. Prophylactic administration of pyridoxine 100 mg/d can prevent the neuropathy from developing.

ANTIRETROVIRAL AGENTS

T e nucleoside analogues zalcitabine (dideoxycytidine or ddC), didanosine (dideoxyinosine or ddI), stavudine (d4T), lamivudine (3TC), and antiretroviral nucleoside reverse transcriptase inhibitor (NRTI) are used to treat HIV infection. One of the major dose-limiting side effects of these medications is a predominantly sensory, length-dependent, symmetrically painful neuropathy. Zalcitabine (ddC) is the most extensively studied of the nucleoside analogues, and at doses greater than 0.18 mg/kg per day, it is associated with a subacute onset of severe burning and lancinating pains in the feet and hands. NCS reveal decreased amplitudes of the SNAPs with normal motor studies. T e nucleoside analogues inhibit mitochondrial DNA polymerase, which is the suspected pathogenic basis for the neuropathy. Because of a "coasting effect," patients can continue to worsen even 2–3 weeks af er stopping the medication. Following dose reduction, improvement in the neuropathy is seen in most patients af er several months (mean time about 10 weeks).

HEXACARBONS (n-HEXANE, METHYL n-BUTYL KETONE)/GLUE SNIFFER'S NEUROPATHY

n-Hexane and methyl n-butyl ketone are water-insoluble industrial organic solvents that are also present in some glues. Exposure through inhalation, accidentally or intentionally (glue sniffing), or through skin absorption can lead to a profound subacute sensory and motor polyneuropathy. NCS demonstrate decreased amplitudes of the SNAPs and CMAPs with slightly slow CVs. Nerve biopsy reveals a loss of myelinated fibers and giant axons that are filled with 10-nm neurofilaments. Hexacarbon exposure leads to covalent cross-linking between axonal neurofilaments that result in their aggregation, impaired axonal transport, swelling of the axons, and eventual axonal degeneration.

LEAD

Lead neuropathy is uncommon, but it can be seen in children who accidentally ingest lead-based paints in older buildings and in industrial workers exposed to lead-containing products. T e most common presentation of lead poisoning is an encephalopathy; however, symptoms and signs of a primarily motor neuropathy can also occur. T e neuropathy is characterized by an insidious and progressive onset of weakness usually beginning in the arms, in particular involving the wrist and finger extensors, resembling a radial neuropathy. Sensation is generally preserved; however, the autonomic nervous system can be affected. Laboratory investigation can reveal a microcytic hypochromic anemia with basophilic stippling of erythrocytes, an elevated serum lead level, and an elevated serum coproporphyrin level. A 24-h urine collection demonstrates elevated levels of lead excretion. T e NCS may reveal reduced CMAP amplitudes, while the SNAPs are typically normal. T e pathogenic basis may be related to abnormal porphyrin metabolism. T e most important principle of management is to remove the source of the exposure. Chelation therapy with calcium disodium ethylene-diaminetetraacetic acid (EDTA), British anti-Lewisite (BAL), and penicillamine also demonstrates variable efficacy.

MERCURY

Mercury toxicity may occur as a result of exposure to either organic or inorganic mercurials. Mercury poisoning presents with paresthesias in hands and feet that progress proximally and may involve the face and tongue. Motor weakness can also develop. CNS symptoms of en overshadow the neuropathy. EDx shows features of a primarily axonal sensorimotor polyneuropathy. T e primary site of neuromuscular pathology appears to be the dorsal root ganglia. T e mainstay of treatment is removing the source of exposure.

THALLIUM

T allium can exist in a monovalent or trivalent form and is primarily used as a rodenticide. T e toxic neuropathy usually manifests as burning paresthesias of the feet, abdominal pain, and vomiting. Increased thirst, sleep disturbances, and psychotic behavior may be

www.ketabpezeshki.com (021) 66485457 - 66485438

noted. Within the first week, patients develop pigmentation of the hair, an acne-like rash in the malar area of the face, and hyperreflexia. By the second and third week, autonomic instability with labile heart rate and blood pressure may be seen. Hyporeflexia and alopecia also occur but may not be evident until the third or fourth week following exposure. With severe intoxication, proximal weakness and involvement of the cranial nerves can occur. Some patients require mechanical ventilation due to respiratory muscle involvement. T e lethal dose of thallium is variable, ranging from 8 to 15 mg/kg body weight. Death can result in less than 48 h following a particularly large dose. NCS demonstrate features of a primarily axonal sensorimotor polyneuropathy. With acute intoxication, potassium ferric ferrocyanide II may be effective in preventing absorption of thallium from the gut. However, there may be no benefit once thallium has been absorbed. Unfortunately, chelating agents are not very efficacious. Adequate diuresis is essential to help eliminate thallium from the body without increasing tissue availability from the serum.

ARSENIC

Arsenic is another heavy metal that can cause a toxic sensorimotor polyneuropathy. T e neuropathy manifests 5–10 days af er ingestion of arsenic and progresses for several weeks, sometimes mimicking GBS. T e presenting symptoms are typically an abrupt onset of abdominal discomfort, nausea, vomiting, pain, and diarrhea followed within several days by burning pain in the feet and hands. Examination of the skin can be helpful in the diagnosis as the loss of the superficial epidermal layer results in patchy regions of increased or decreased pigmentation on the skin several weeks af er an acute exposure or with chronic low levels of ingestion. Mee's lines, which are transverse lines at the base of the fingernails and toenails, do not become evident until 1 or 2 months af er the exposure. Multiple Mee's lines may be seen in patients with long fingernails who have had chronic exposure to arsenic. Mee's lines are not specific for arsenic toxicity as they can also be seen following thallium poisoning. Because arsenic is cleared from blood rapidly, the serum concentration of arsenic is not diagnostically helpful. However, arsenic levels are increased in the urine, hair, and fingernails of patients exposed to arsenic. Anemia with stippling of erythrocytes is common, and occasionally pancytopenia and aplastic anemia can develop. Increased CSF protein levels without pleocytosis can be seen; this can lead to misdiagnosis as GBS. NCS are usually suggestive of an axonal sensorimotor polyneuropathy; however, demyelinating features can be present. Chelation therapy with BAL has yielded inconsistent results; therefore, it is not generally recommended.

NUTRITIONAL NEUROPATHIES

COBALAMIN (VITAMIN B_{12})

Pernicious anemia is the most common cause of cobalamin deficiency. Other causes include dietary avoidance (vegetarians), gastrectomy, gastric bypass surgery, inflammatory bowel disease, pancreatic insufficiency, bacterial overgrowth, and possibly histamine-2 blockers and proton pump inhibitors. An underappreciated cause of cobalamin deficiency is food-cobalamin malabsorption. T is typically occurs in older individuals and results from an inability to adequately absorb cobalamin in food protein. No apparent cause of deficiency is identified in a significant number of patients with cobalamin deficiency. T e use of nitrous oxide as an anesthetic agent or as a recreational drug can produce acute cobalamin deficiency neuropathy and subacute combined degeneration.

Complaints of numb hands typically appear before lower extremity paresthesias are noted. A preferential large-fiber sensory loss affecting proprioception and vibration with sparing of small-fiber modalities is present; an unsteady gait reflects sensory ataxia. T ese features, coupled with diffuse hyperreflexia and absent Achilles reflexes, should always focus attention on the possibility of cobalamin deficiency. Optic atrophy and, in severe cases, behavioral changes ranging from mild irritability and forgetfulness to severe dementia and frank psychosis may appear. T e full clinical picture of subacute combined degeneration is uncommon. CNS manifestations, especially pyramidal tract signs, may be missing, and in fact some patients may only exhibit symptoms of peripheral neuropathy.

EDx shows an axonal sensorimotor neuropathy. CNS involvement produces abnormal somatosensory and visual evoked potential latencies. T e diagnosis is confirmed by finding reduced serum cobalamin levels. In up to 40% of patients, anemia and macrocytosis are lacking. Serum methylmalonic acid and homocysteine, the metabolites that accumulate when cobalamin-dependent reactions are blocked, are elevated. Antibodies to intrinsic factor are present in approximately 60%, and antiparietal cell antibodies in about 90%, of individuals with pernicious anemia.

Cobalamin deficiency can be treated with various regimens of cobalamin. One typical regimen consists of 1000 μg cyanocobalamin IM weekly for 1 month and monthly thereaf er. Patients with food cobalamin malabsorption can absorb free cobalamin and therefore can be treated with oral cobalamin supplementation. An oral cobalamin dose of 1000 μg per day should be sufficient. Treatment for cobalamin deficiency usually does not completely reverse the clinical manifestations, and at least 50% of patients exhibit some permanent neurologic deficit.

www.ketabpezeshki.com (021) 66485457 - 66485438

THIAMINE DEFICIENCY

T iamine (vitamin B_1) deficiency is an uncommon cause of peripheral neuropathy in developed countries. It is now most of en seen as a consequence of chronic alcohol abuse, recurrent vomiting, total parenteral nutrition, and bariatric surgery. T iamine deficiency polyneuropathy can occur in normal, healthy young adults who do not abuse alcohol but who engage in inappropriately restrictive diets. T iamine is water-soluble. It is present in most animal and plant tissues, but the greatest sources are unrefined cereal grains, wheat germ, yeast, soybean flour, and pork. Beriberi means "I can't, I can't" in Singhalese, the language of natives of what was once part of the Dutch East Indies (now Sri Lanka). Dry beriberi refers to neuropathic symptoms. T e term wet beriberi is used when cardiac manifestations predominate (in reference to edema). Beriberi was relatively uncommon until the late 1800s when it became widespread among people for whom rice was a dietary mainstay. T is epidemic was due to a new technique of processing rice that removed the germ from the rice shaf , rendering the so-called polished rice deficient in thiamine and other essential nutrients.

Symptoms of neuropathy follow prolonged deficiency. T ese begin with mild sensory loss and/or burning dysesthesias in the toes and feet and aching and cramping in the lower legs. Pain may be the predominant symptom. With progression, patients develop features of a nonspecific generalized polyneuropathy, with distal sensory loss in the feet and hands.

Blood and urine assays for thiamine are not reliable for diagnosis of deficiency. Erythrocyte transketolase activity and the percentage increase in activity (in vitro) following the addition of thiamine pyrophosphate (TPP) may be more accurate and reliable. EDx shows nonspecific findings of an axonal sensorimotor polyneuropathy. When a diagnosis of thiamine deficiency is made or suspected, thiamine replacement should be provided until proper nutrition is restored. T iamine is usually given intravenously or intramuscularly at a dose of 100 mg/d. Although cardiac manifestations show a striking response to thiamine replacement, neurologic improvement is usually more variable and less dramatic.

VITAMIN E DEFICIENCY

T e term vitamin E is usually used for a-tocopherol, the most active of the four main types of vitamin E. Because vitamin E is present in animal fat, vegetable oils, and various grains, deficiency is usually due to factors other than insufficient intake. Vitamin E deficiency usually occurs secondary to lipid malabsorption or in uncommon disorders of vitamin E transport. One hereditary disorder is abetalipoproteinemia, a rare autosomal dominant disorder characterized by steatorrhea, pigmentary retinopathy, acanthocytosis, and progressive ataxia. Patients with cystic fibrosis may also have vitamin E deficiency secondary to steatorrhea. T ere are genetic forms of isolated vitamin E deficiency not associated with lipid malabsorption. Vitamin E deficiency may also occur as a consequence of various cholestatic and hepatobiliary disorders as well as short-bowel syndromes resulting from the surgical treatment of intestinal disorders.

Clinical features may not appear until many years af er the onset of deficiency. T e onset of symptoms tends to be insidious, and progression is slow. T e main clinical features are spinocerebellar ataxia and polyneuropathy, thus resembling Friedreich's ataxia or other spinocerebellar ataxias. Patients manifest progressive ataxia and signs of posterior column dysfunction, such as impaired joint position and vibratory sensation. Because of the polyneuropathy, there is hyporeflexia, but plantar responses may be extensor as a result of the spinal cord involvement. Other neurologic manifestations may include ophthalmoplegia, pigmented retinopathy, night blindness, dysarthria, pseudoathetosis, dystonia, and tremor. Vitamin E deficiency may present as an isolated polyneuropathy, but this is very rare. T e yield of checking serum vitamin E levels in patients with isolated polyneuropathy is extremely low, and this test should not be part of routine practice.

Diagnosis is made by measuring a-tocopherol levels in the serum. EDx shows features of an axonal neuropathy. Treatment is replacement with oral vitamin E, but high doses are not needed. For patients with isolated vitamin E deficiency, treatment consists of 1500–6000 IU/d in divided doses.

VITAMIN B_6 DEFICIENCY

Vitamin B_6, or pyridoxine, can produce neuropathic manifestations from both deficiency and toxicity. Vitamin B_6 toxicity was discussed above. Vitamin B_6 deficiency is most commonly seen in patients treated with isoniazid or hydralazine. T e polyneuropathy of vitamin B_6 is nonspecific, manifesting as a generalized axonal sensorimotor polyneuropathy. Vitamin B_6 deficiency can be detected by direct assay. Vitamin B_6 supplementation with 50–100 mg/d is suggested for patients being treated with isoniazid or hydralazine. T is same dose is appropriate for replacement in cases of nutritional deficiency.

PELLAGRA (NIACIN DEFICIENCY)

Pellagra is produced by deficiency of niacin. Although pellagra may be seen in alcoholics, this disorder has essentially been eradicated in most Western countries by means of enriching bread with niacin. Nevertheless,

www.ketabpezeshki.com (021) 66485457 - 66485438

pellagra continues to be a problem in a number of underdeveloped regions, particularly in Asia and Africa, where corn is the main source of carbohydrate. Neurologic manifestations are variable; abnormalities can develop in the brain and spinal cord as well as peripheral nerves. When peripheral nerves are involved, the neuropathy is usually mild and resembles beriberi. Treatment is with niacin 40–250 mg/d.

COPPER DEFICIENCY

A syndrome that has only recently been described is myeloneuropathy secondary to copper deficiency. Most patients present with lower limb paresthesias, weakness, spasticity, and gait difficulties. Large-fiber sensory function is impaired, reflexes are brisk, and plantar responses are extensor. In some cases, light touch and pinprick sensation are affected, and NCS indicate sensorimotor axonal polyneuropathy in addition to myelopathy.

Hematologic abnormalities are a known complication of copper deficiency; these can include microcytic anemia, neutropenia, and occasionally pancytopenia. Because copper is absorbed in the stomach and proximal jejunum, many cases of copper deficiency are in the setting of prior gastric surgery. Excess zinc is an established cause of copper deficiency. Zinc upregulates enterocyte production of metallothionine, which results in decreased absorption of copper. Excessive dietary zinc supplements or denture cream containing zinc can produce this clinical picture. Other potential causes of copper deficiency include malnutrition, prematurity, total parenteral nutrition, and ingestion of copper-chelating agents.

Following oral or IV copper replacement, some patients show neurologic improvement, but this may take many months or not occur at all. Replacement consists of oral copper sulfate or gluconate 2 mg one to three times a day. If oral copper replacement is not effective, elemental copper in the copper sulfate or copper chloride forms can be given as 2 mg IV daily for 3–5 days, then weekly for 1–2 months until copper levels normalize. T ereaf er, oral daily copper therapy can be resumed. In contrast to the neurologic manifestations, most of the hematologic indices completely normalize in response to copper replacement therapy.

NEUROPATHY ASSOCIATED WITH GASTRIC SURGERY

Polyneuropathy may occur following gastric surgery for ulcer, cancer, or weight reduction. T is usually occurs in the context of rapid, significant weight loss and recurrent, protracted vomiting. T e clinical picture is one of acute or subacute sensory loss and weakness. Neuropathy following weight loss surgery usually occurs in the first several months af er surgery. Weight reduction surgical procedures include gastrojejunostomy, gastric stapling, vertical banded gastroplasty, and gastrectomy with Roux-en-Y anastomosis. T e initial manifestations are usually numbness and paresthesias in the feet. In many cases, no specific nutritional deficiency factor is identified.

Management consists of parenteral vitamin supplementation, especially including thiamine. Improvement has been observed following supplementation, parenteral nutritional support, and reversal of the surgical bypass. T e duration and severity of deficits before identification and treatment of neuropathy are important predictors of final outcome.

CRYPTOGENIC (IDIOPATHIC) SENSORY AND SENSORIMOTOR POLYNEUROPATHY

CSPN is a diagnosis of exclusion, established af er a careful medical, family, and social history; neurologic examination; and directed laboratory testing. Despite extensive evaluation, the cause of polyneuropathy in as many as 50% of all patients is idiopathic. CSPN should be considered a distinct diagnostic subset of peripheral neuropathy. T e onset of CSPN is predominantly in the sixth and seventh decades. Patients complain of distal numbness, tingling, and of en burning pain that invariably begins in the feet and may eventually involve the fingers and hands. Patients exhibit a distal sensory loss to pinprick, touch, and vibration in the toes and feet, and occasionally in the fingers. It is uncommon to see significant proprioception deficits, even though patients may complain of gait unsteadiness. However, tandem gait may be abnormal in a minority of cases. Neither subjective nor objective evidence of weakness is a prominent feature. Most patients have evidence of both large- and small-fiber loss on neurologic exam and EDx. Approximately 10% of patients have only evidence of small-fiber involvement. T e ankle muscle stretch reflex is frequently absent, but in cases with predominantly small-fiber loss, this may be preserved. T e EDx findings range from isolated sensory nerve action potential abnormalities (usually with loss of amplitude), to evidence for an axonal sensorimotor neuropathy, to a completely normal study (if primarily small fibers are involved). T erapy primarily involves the control of neuropathic pain (Table 53-6) if present. T ese drugs should not be used if the patient has only numbness and tingling but no pain.

Although no treatment is available that can reverse an idiopathic distal peripheral neuropathy, the prognosis is good. Progression of en does not occur or is

www.ketabpezeshki.com (021) 66485457 - 66485438

minimal, with sensory symptoms and signs progressing proximally up to the knees and elbows. T e disorder does not lead to significant motor disability over time. T e relatively benign course of this disorder should be explained to patients.

MONONEUROPATHIES/PLEXOPATHIES/RADICULOPATHIES

MEDIAN NEUROPATHY

CTS is a compression of the median nerve in the carpal tunnel at the wrist. T e median nerve enters the hand through the carpal tunnel by coursing under the transverse carpal ligament. T e symptoms of CTS consist of numbness and paresthesias variably in the thumb, index, middle, and half of the ring finger. At times, the paresthesias can include the entire hand and extend into the forearm or upper arm or can be isolated to one or two fingers. Pain is another common symptom and can be located in the hand and forearm and, at times, in the proximal arm. CTS is common and of en misdiagnosed as thoracic outlet syndrome. T e signs of CTS are decreased sensation in the median nerve distribution; reproduction of the sensation of tingling when a percussion hammer is tapped over the wrist (Tinel's sign) or the wrist is flexed for 30–60 s (Phalen's sign); and weakness of thumb opposition and abduction. EDx is extremely sensitive and shows slowing of sensory and, to a lesser extent, motor median potentials across the wrist. Treatment options consist of avoidance of precipitating activities; control of underlying systemic-associated conditions if present; nonsteroidal anti-inflammatory medications; neutral (volar) position wrist splints, especially for night use; glucocorticoid/anesthetic injection into the carpal tunnel; and surgical decompression by dividing the transverse carpal ligament. T e surgical option should be considered if there is a poor response to nonsurgical treatments; if there is thenar muscle atrophy and/or weakness; and if there are significant denervation potentials on EMG.

Other proximal median neuropathies are very uncommon and include the pronator teres syndrome and anterior interosseous neuropathy. T ese of en occur as a partial form of brachial plexitis.

ULNAR NEUROPATHY AT THE ELBOW—"CUBITAL TUNNEL SYNDROME"

T e ulnar nerve passes through the condylar groove between the medial epicondyle and the olecranon. Symptoms consist of paresthesias, tingling, and numbness in the medial hand and half of the fourth and the entire fif h fingers, pain at the elbow or forearm, and weakness. Signs consist of decreased sensation in an ulnar distribution, Tinel's sign at the elbow, and weakness and atrophy of ulnar-innervated hand muscles. T e Froment sign indicates thumb adductor weakness and consists of flexion of the thumb at the interphalangeal joint when attempting to oppose the thumb against the lateral border of the second digit. EDx may show slowing of ulnar motor NCV across the elbow with prolonged ulnar sensory latencies. Treatment consists of avoiding aggravating factors, using elbow pads, and surgery to decompress the nerve in the cubital tunnel. Ulnar neuropathies can also rarely occur at the wrist in the ulnar (Guyon) canal or in the hand, usually af er trauma.

RADIAL NEUROPATHY

T e radial nerve winds around the proximal humerus in the spiral groove and proceeds down the lateral arm and enters the forearm, dividing into the posterior interosseous nerve and superficial nerve. T e symptoms and signs consist of wristdrop; finger extension weakness; thumb abduction weakness; and sensory loss in the dorsal web between the thumb and index finger. Triceps and brachioradialis strength is of en normal, and triceps reflex is of en intact. Most cases of radial neuropathy are transient compressive (neuropraxic) injuries that recover spontaneously in 6–8 weeks. If there has been prolonged compression and severe axonal damage, it may take several months to recover. Treatment consists of cock-up wrist and finger splints, avoiding further compression, and physical therapy to avoid flexion contracture. If there is no improvement in 2–3 weeks, an EDx study is recommended to confirm the clinical diagnosis and determine the degree of severity.

LATERAL FEMORAL CUTANEOUS NEUROPATHY (MERALGIA PARESTHETICA)

T e lateral femoral cutaneous nerve arises from the upper lumbar plexus (spinal levels L2/3), crosses through the inguinal ligament near its attachment to the iliac bone, and supplies sensation to the anterior lateral thigh. T e neuropathy affecting this nerve is also known as meralgia paresthetica. Symptoms and signs consist of paresthesias, numbness, and occasionally pain in the lateral thigh. Symptoms are increased by standing or walking and are relieved by sitting. T ere is normal strength, and knee reflexes are intact. T e diagnosis is clinical, and further tests usually are not performed. EDx is only needed to rule out lumbar plexopathy, radiculopathy, or femoral neuropathy. If the symptoms and signs are classic, EMG is not necessary. Symptoms of en resolve spontaneously over weeks

www.ketabpezeshki.com (021) 66485457 - 66485438

or months, but the patient may be lef with permanent numbness. Treatment consists of weight loss and avoiding tight belts. Analgesics in the form of a lidocaine patch, nonsteroidal agents, and occasionally medications for neuropathic pain can be used (Table 53-6). Rarely, locally injecting the nerve with an anesthetic can be tried. T ere is no role for surgery.

FEMORAL NEUROPATHY

Femoral neuropathies can arise as complications of retroperitoneal hematoma, lithotomy positioning, hip arthroplasty or dislocation, iliac artery occlusion, femoral arterial procedures, infiltration by hematogenous malignancy, penetrating groin trauma, pelvic surgery including hysterectomy and renal transplantation, and diabetes (a partial form of lumbosacral diabetic plexopathy); some cases are idiopathic. Patients with femoral neuropathy have difficulty extending their knee and flexing the hip. Sensory symptoms occurring either on the anterior thigh and/or medial leg occur in only half of reported cases. A prominent painful component is the exception rather than the rule, may be delayed, and is of en self-limited in nature. T e quadriceps (patellar) reflex is diminished.

SCIATIC NEUROPATHY

Sciatic neuropathies commonly complicate hip arthroplasty, pelvic procedures in which patients are placed in a prolonged lithotomy position, trauma, hematomas, tumor infiltration, and vasculitis. In addition, many sciatic neuropathies are idiopathic. Weakness may involve all motions of the ankles and toes as well as flexion of the leg at the knee; abduction and extension of the thigh at the hip are spared. Sensory loss occurs in the entire foot and the distal lateral leg. T e ankle jerk and on occasion the internal hamstring reflex are diminished or more typically absent on the affected side. T e peroneal subdivision of the sciatic nerve is typically involved disproportionately to the tibial counterpart. T us, patients may have only ankle dorsiflexion and eversion weakness with sparing of knee flexion, ankle inversion, and plantar flexion; these features can lead to misdiagnosis of a common peroneal neuropathy.

PERONEAL NEUROPATHY

T e sciatic nerve divides at the distal femur into the tibial and peroneal nerve. T e common peroneal nerve passes posterior and laterally around the fibular head, under the fibular tunnel. It then divides into the superficial peroneal nerve, which supplies the ankle evertor muscles and sensation over the anterolateral distal leg and dorsum of the foot, and the deep peroneal nerve, which supplies ankle dorsiflexors and toe extensor muscles and a small area of sensation dorsally in the area of the first and second toes.

Symptoms and signs consist of footdrop (ankle dorsiflexion, toe extension, and ankle eversion weakness) and variable sensory loss, which may involve the superficial and deep peroneal pattern. T ere is usually no pain. Onset may be on awakening in the morning. Peroneal neuropathy needs to be distinguished from L5 radiculopathy. In L5 radiculopathy, ankle invertors and evertors are weak and needle EMG reveals denervation. EDx can help localize the lesion. Peroneal motor conduction velocity shows slowing and amplitude drop across the fibular head. Management consists of rapid weight loss and avoiding leg crossing. Footdrop is treated with an ankle brace. A knee pad can be worn over the lateral knee to avoid further compression. Most cases spontaneously resolve over weeks or months.

RADICULOPATHIES

Radiculopathies are most of en due to compression from degenerative joint disease and herniated disks, but there are a number of unusual etiologies **(Table 53-9).** Degenerative spine disease affects a number of different structures, which narrow the diameter of the neural foramen or canal of the spinal column and compromise nerve root integrity; these are discussed in detail in **Chap. 10**.

TABLE 53-9

CAUSES OF RADICULOPATHY
• Herniated nucleus pulposus
• Degenerative joint disease
• Rheumatoid arthritis
• Trauma
• Vertebral body compression fracture
• Pott's disease
• Compression by extradural mass (e.g., meningioma, metastatic tumor, hematoma, abscess)
• Primary nerve tumor (e.g., neurofibroma, schwannoma, neurinoma)
• Carcinomatous meningitis
• Perineurial spread of tumor (e.g., prostate cancer)
• Acute inflammatory demyelinating polyradiculopathy
• Chronic inflammatory demyelinating polyradiculopathy
• Sarcoidosis
• Amyloidoma
• Diabetic radiculopathy
• Infection (Lyme disease, herpes zoster, cytomegalovirus, syphilis, schistosomiasis, strongyloides)

www.ketabpezeshki.com (021) 66485457 - 66485438

PLEXOPATHIES

BRACHIAL PLEXUS

The brachial plexus is composed of three trunks (upper, middle, and lower), with two divisions (anterior and posterior) per trunk **(Fig. 53-2)**. Subsequently, the trunks divide into three cords (medial, lateral, and posterior), and from these arise the multiple terminal nerves innervating the arm. The anterior primary rami of C5 and C6 fuse to form the upper trunk; the anterior primary ramus of C7 continues as the middle trunk, while the anterior rami of C8 and T1 join to form the lower trunk. There are several disorders commonly associated with brachial plexopathy.

Immune-mediated brachial plexus neuropathy

Immune-mediated brachial plexus neuropathy (IBPN) goes by various terms, including acute brachial plexitis, neuralgic amyotrophy, and Parsonage-Turner syndrome. IBPN usually presents with an acute onset of severe pain in the shoulder region. The intense pain usually lasts several days to a few weeks, but a dull ache can persist. Individuals who are affected may not appreciate weakness of the arm early in the course because the pain limits movement. However, as the pain dissipates, weakness and often sensory loss are appreciated. Attacks can occasionally recur.

Clinical findings are dependent on the distribution of involvement (e.g., specific trunk, divisions, cords, or terminal nerves). The most common pattern of IBPN involves the upper trunk or a single or multiple mononeuropathies primarily involving the suprascapular, long thoracic, or axillary nerves. Additionally, the phrenic and anterior interosseous nerves may be concomitantly affected. Any of these nerves may also be affected in isolation. EDx is useful to confirm and localize the site(s) of involvement. Empirical treatment of severe pain with glucocorticoids is often used in the acute period.

Brachial plexopathies associated with neoplasms

Neoplasms involving the brachial plexus may be primary nerve tumors, local cancers expanding into the plexus (e.g., Pancoast lung tumor or lymphoma), and metastatic tumors. Primary brachial plexus tumors are less common than the secondary tumors and include schwannomas, neurinomas, and neurofibromas. Secondary tumors affecting the brachial plexus are more common and are always malignant. These may arise from local tumors, expanding into the plexus. For example, a Pancoast tumor of the upper lobe of the lung may invade or compress the lower trunk, whereas a primary lymphoma arising from the cervical or axillary lymph nodes may also infiltrate the plexus. Pancoast tumors typically present as an insidious onset of pain in the upper arm, sensory disturbance in the medial aspect of the forearm and hand, and weakness and atrophy of the intrinsic hand muscles along with an ipsilateral Horner's syndrome. Chest computed tomography (CT) scans or magnetic resonance imaging (MRI) can demonstrate extension of the tumor into the plexus. Metastatic involvement of the brachial plexus may occur with spread of breast cancer into the axillary lymph nodes with local spread into the nearby nerves.

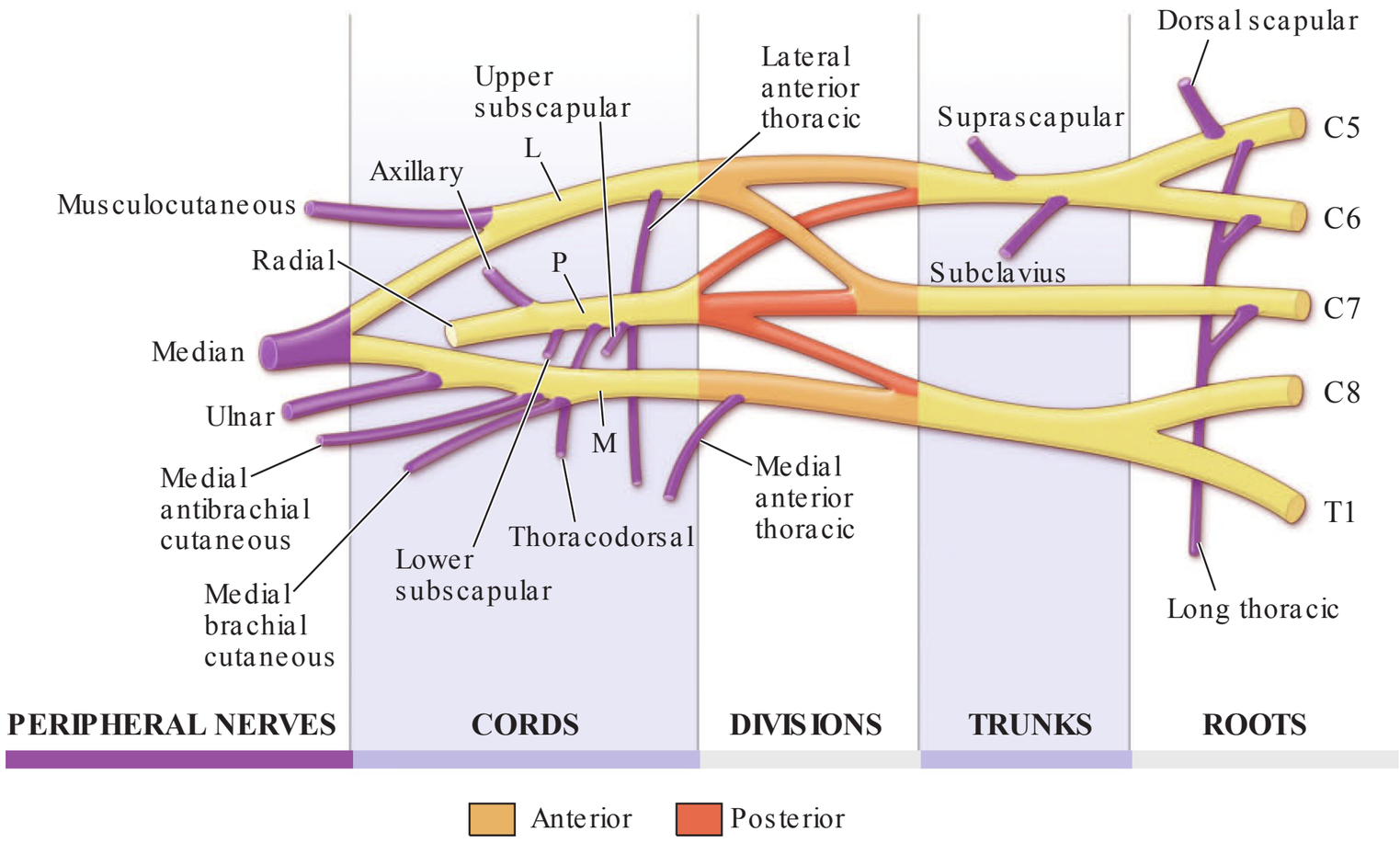


FIGURE 53-2

Brachial plexus anatomy. L, lateral; M, medial; P, posterior. (From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126, with permission.)

www.ketabpezeshki.com (021) 66485457 - 66485438

Perioperative plexopathies (median sternotomy)

The most common surgical procedures associated with brachial plexopathy as a complication are those that involve median sternotomies (e.g., open-heart surgeries and thoracotomies). Brachial plexopathies occur in as many as 5% of patients following a median sternotomy and typically affect the lower trunk. Thus, individuals manifest with sensory disturbance affecting the medial aspect of forearm and hand along with weakness of the intrinsic hand muscles. The mechanism is related to the stretch of the lower trunk, so most individuals who are affected recover within a few months.

Lumbosacral plexus

The lumbar plexus arises from the ventral primary rami of the first to the fourth lumbar spinal nerves **(Fig. 53-3)**. These nerves pass downward and laterally from the vertebral column within the psoas major muscle. The femoral nerve derives from the dorsal branches of the second to the fourth lumbar ventral rami. The obturator nerve arises from the ventral branches of the same lumbar rami. The lumbar plexus communicates with the sacral plexus by the lumbosacral trunk, which contains some fibers from the fourth and all of the fibers from the fifth lumbar ventral rami **(Fig. 53-4)**.

The sacral plexus is the part of the lumbosacral plexus that is formed by the union of the lumbosacral trunk with the ventral rami of the first to fourth sacral nerves. The plexus lies on the posterior and posterolateral wall of the pelvis with its components converging toward the sciatic notch. The lateral trunk of the sciatic nerve (which forms the common peroneal nerve) arises from the union of the dorsal branches of the lumbosacral trunk (L4, L5) and the dorsal branches of the S1 and S2 spinal nerve ventral rami. The medial trunk of the sciatic nerve (which forms the tibial nerve) derives from the ventral branches of the same ventral rami (L4-S2).

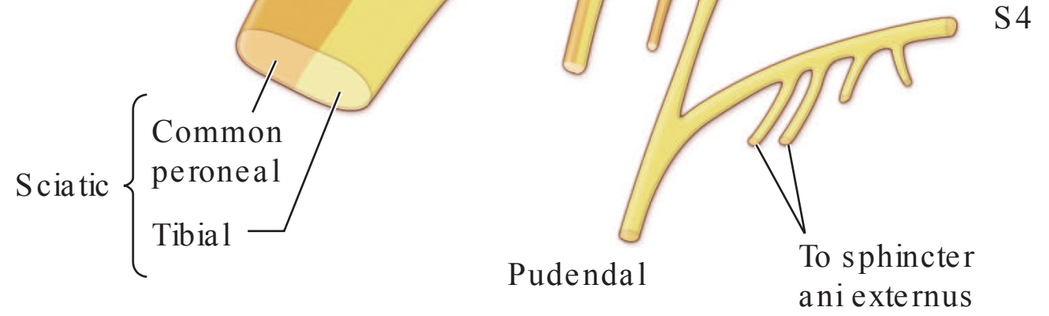


FIGURE 53-4
Lumbosacral plexus. Posterior divisions are in orange, and anterior divisions are in yellow. (From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126, with permission.)

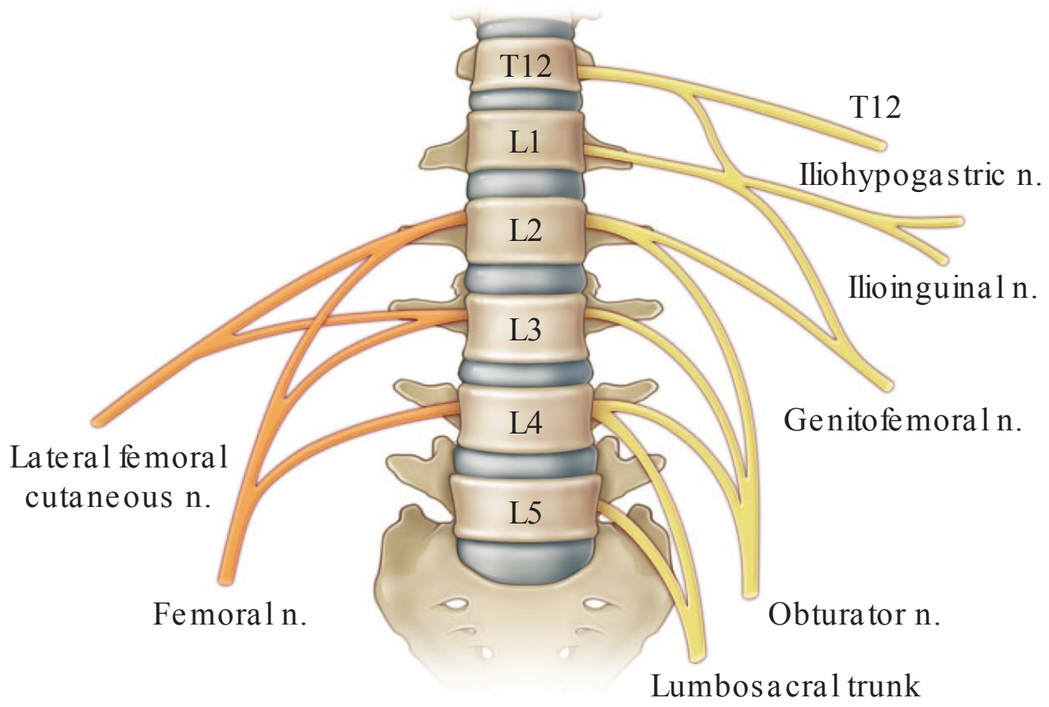


FIGURE 53-3
Lumbar plexus. Posterior divisions are in orange, and anterior divisions are in yellow. (From J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974, p. 126, with permission.)

LUMBOSACRAL PLEXOPATHIES

Plexopathies are typically recognized when motor, sensory, and if applicable, reflex deficits occur in multiple nerve and segmental distributions confined to one extremity. If localization within the lumbosacral plexus can be accomplished, designation as a lumbar plexopathy, a sacral plexopathy, a lumbosacral trunk lesion, or a pan-plexopathy is the best localization that can be expected. Although lumbar plexopathies may be bilateral, usually occurring in a stepwise and chronologically dissociated manner, sacral plexopathies are more likely to behave in this manner due to their closer anatomic proximity. The differential diagnosis of plexopathy includes disorders of the conus medullaris and cauda equina (polyradiculopathy). If there is a paucity of pain and sensory involvement, motor neuron disease should be considered as well.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 53-10

LUMBOSACRAL PLEXOPATHIES: ETIOLOGIES
• Retroperitoneal hematoma
• Psoas abscess
• Malignant neoplasm
• Benign neoplasm
• Radiation
• Amyloid
• Diabetic radiculoplexus neuropathy
• Idiopathic radiculoplexus neuropathy
• Sarcoidosis
• Aortic occlusion/surgery
• Lithotomy positioning
• Hip arthroplasty
• Pelvic fracture
• Obstetric injury

The causes of lumbosacral plexopathies are listed in **Table 53-10**. Diabetic radiculopathy (discussed above) is a fairly common cause of painful leg weakness. Lumbosacral plexopathies are a well-recognized complication of retroperitoneal hemorrhage. Various primary and metastatic malignancies can affect the lumbosacral plexus as well; these include carcinoma of the cervix, endometrium, and ovary; osteosarcoma; testicular cancer; multiple myeloma; lymphoma; acute myelogenous leukemia; colon cancer; squamous cell carcinoma of the rectum; adenocarcinoma of unknown origin; and intraneural spread of prostate cancer.

RECURRENT NEOPLASTIC DISEASE OR RADIATION-INDUCED PLEXOPATHY

The treatment for various malignancies is often radiation therapy, the field of which may include parts of the brachial plexus. It can be difficult in such situations to determine if a new brachial or lumbosacral plexopathy is related to tumor within the plexus or from radiation-induced nerve damage. Radiation can be associated with microvascular abnormalities and fibrosis of surrounding tissues, which can damage the axons and the Schwann cells. Radiation-induced plexopathy can develop months or years following therapy and is dose dependent.

Tumor invasion is usually painful and more commonly affects the lower trunk, whereas radiation injury is often painless and affects the upper trunk. Imaging studies such as MRI and CT scans are useful but can be misleading with small microscopic invasion of the plexus. EMG can be informative if myokymic discharges are appreciated, as this finding strongly suggests radiation-induced damage.

EVALUATION AND TREATMENT OF PLEXOPATHIES

Most patients with plexopathies will undergo both imaging with MRI and EDx evaluations. Severe pain from acute idiopathic lumbosacral plexopathy may respond to a short course of glucocorticoids.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 54

GUILLAIN-BARRÉ SYNDROME AND OTHER IMMUNE-MEDIATED NEUROPATHIES

Stephen L. Hauser ■ Anthony A. Amato

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is an acute, frequently severe, and fulminant polyradiculoneuropathy that is autoimmune in nature. It occurs year-round at a rate of between 1 and 4 cases per 100,000 annually; in the United States, ~5000–6000 cases occur per year. Males are at slightly higher risk for GBS than females, and in Western countries, adults are more frequently affected than children.

Clinical manifestations

GBS manifests as a rapidly evolving areflexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending paralysis that may be first noticed as rubbery legs. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The legs are usually more affected than the arms, and facial diparesis is present in 50% of affected individuals. The lower cranial nerves are also frequently involved, causing bulbar weakness with difficulty handling secretions and maintaining an airway; the diagnosis in these patients may initially be mistaken for brainstem ischemia. Pain in the neck, shoulder, back, or diffusely over the spine is also common in the early stages of GBS, occurring in ~50% of patients. Most patients require hospitalization, and in different series, up to 30% require ventilatory assistance at some time during the illness. The need for mechanical ventilation is associated with more severe weakness on admission, a rapid tempo of progression, and the presence of facial and/or bulbar weakness during the first week of symptoms. Fever and constitutional symptoms are absent at the onset and, if present, cast doubt on the diagnosis. Deep tendon reflexes attenuate or disappear within the first few days of onset. Cutaneous sensory deficits (e.g., loss of pain and temperature sensation) are usually relatively mild, but functions subserved by large sensory fibers, such as deep tendon reflexes and proprioception, are more severely affected. Bladder dysfunction may occur in severe cases but is usually transient. If bladder dysfunction is a prominent feature and comes early in the course, diagnostic possibilities other than GBS should be considered, particularly spinal cord disease. Once clinical worsening stops and the patient reaches a plateau (almost always within 4 weeks of onset), further progression is unlikely.

Autonomic involvement is common and may occur even in patients whose GBS is otherwise mild. The usual manifestations are loss of vasomotor control with wide fluctuation in blood pressure, postural hypotension, and cardiac dysrhythmias. These features require close monitoring and management and can be fatal. Pain is another common feature of GBS; in addition to the acute pain described above, a deep aching pain may be present in weakened muscles that patients liken to having overexercised the previous day. Other pains in GBS include dysesthetic pain in the extremities as a manifestation of sensory nerve fiber involvement. These pains are self-limited and often respond to standard analgesics **(Chap. 8)**.

Several subtypes of GBS are recognized, as determined primarily by electrodiagnostic (Edx) and pathologic distinctions **(Table 54-1)**. The most common variant is acute inflammatory demyelinating polyneuropathy (AIDP). Additionally, there are two axonal variants, which are often clinically severe—the acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN) subtypes. In addition, a range of limited or regional GBS syndromes are also encountered. Notable among these is the Miller Fisher syndrome (MFS), which presents as rapidly evolving ataxia and areflexia of limbs without

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 54-1

SUBTYPES OF GUILLAIN-BARRÉ SYNDROME (GBS)

SUBTYPE	FEATURES	ELECTRODIAGNOSIS	PATHOLOGY
Acute inflammatory demyelinating polyneuropathy (AIDP)	Adults affected more than children; 90% of cases in Western world; recovery rapid; anti-GM1 antibodies (<50%)	Demyelinating	First attack on Schwann cell surface; widespread myelin damage, macrophage activation, and lymphocytic infiltration; variable secondary axonal damage
Acute motor axonal neuropathy (AMAN)	Children and young adults; prevalent in China and Mexico; may be seasonal; recovery rapid; anti-GD1a antibodies	Axonal	First attack at motor nodes of Ranvier; macrophage activation, few lymphocytes, frequent periaxonal macrophages; extent of axonal damage highly variable
Acute motor sensory axonal neuropathy (AMSAN)	Mostly adults; uncommon; recovery slow, often incomplete; closely related to AMAN	Axonal	Same as AMAN, but also affects sensory nerves and roots; axonal damage usually severe
Miller Fisher syndrome (MFS)	Adults and children; ophthalmoplegia, ataxia, and areflexia; anti-GQ1b antibodies (90%)	Axonal or demyelinating	Few cases examined; resembles AIDP

weakness, and ophthalmoplegia, often with pupillary paralysis. The MFS variant accounts for ~5% of all cases and is strongly associated with antibodies to the ganglioside GQ1b (see "Immunopathogenesis," below). Other regional variants of GBS include (1) pure sensory forms; (2) ophthalmoplegia with anti-GQ1b antibodies as part of severe motor-sensory GBS; (3) GBS with severe bulbar and facial paralysis, sometimes associated with antecedent cytomegalovirus (CMV) infection and anti-GM2 antibodies; and (4) acute pandysautonomia **(Chap. 41)**.

Antecedent events

Approximately 70% of cases of GBS occur 1–3 weeks after an acute infectious process, usually respiratory or gastrointestinal. Culture and seroepidemiologic techniques show that 20–30% of all cases occurring in North America, Europe, and Australia are preceded by infection or reinfection with Campylobacter jejuni. A similar proportion is preceded by a human herpes virus infection, often CMV or Epstein-Barr virus. Other viruses (e.g., HIV, hepatitis E) and also Mycoplasma pneumoniae have been identified as agents involved in antecedent infections, as have recent immunizations. The swine influenza vaccine, administered widely in the United States in 1976, is the most notable example. Influenza vaccines in use from 1992 to 1994, however, resulted in only one additional case of GBS per million persons vaccinated, and the more recent seasonal influenza vaccines appear to confer a GBS risk of <1 per million. Epidemiologic studies looking at H1N1 vaccination demonstrated at most only a slight increased risk of GBS. Meningococcal vaccinations (Menactra) do not appear to carry an increased risk. Older-type rabies vaccine, prepared in nervous system tissue, is implicated as a trigger of GBS in developing countries where it is still used; the mechanism is presumably immunization against neural antigens. GBS also occurs more frequently than can be attributed to chance alone in patients with lymphoma (including Hodgkin's disease), in HIV-seropositive individuals, and in patients with systemic lupus erythematosus (SLE). C. jejuni has also been implicated in summer outbreaks of AMAN among children and young adults exposed to chickens in rural China.

Immunopathogenesis

Several lines of evidence support an autoimmune basis for acute inflammatory demyelinating polyneuropathy (AIDP), the most common and best-studied type of GBS; the concept extends to all of the subtypes of GBS (Table 54-1).

It is likely that both cellular and humoral immune mechanisms contribute to tissue damage in AIDP. T cell activation is suggested by the finding that elevated levels of cytokines and cytokine receptors are present in serum (interleukin [IL] 2, soluble IL-2 receptor) and in cerebrospinal fluid (CSF) (IL-6, tumor necrosis factor α, interferon γ). AIDP is also closely analogous to an experimental T cell–mediated immunopathy designated experimental allergic neuritis (EAN). EAN is induced in laboratory animals by immune sensitization against protein fragments derived from peripheral nerve proteins, and in particular against the P2 protein. Based on analogy to EAN, it was initially thought that AIDP was likely to be primarily a T cell–mediated

www.ketabpezeshki.com (021) 66485457 - 66485438

disorder; however, abundant data now suggest that autoantibodies directed against nonprotein determinants may be central to many cases.

Circumstantial evidence suggests that all GBS results from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance-of-epitope (molecular mimicry) mechanism **(Fig. 54-1)**. T e neural targets are likely to be glycoconjugates, specifically gangliosides **(Table 54-2; Fig. 54-2)**. Gangliosides are complex glycosphingolipids that contain one or more sialic acid residues; various gangliosides participate in cell-cell interactions (including those between axons and glia), modulation of receptors, and regulation of growth. T ey are typically exposed on the plasma membrane of cells, rendering them susceptible to an antibody-mediated attack. Gangliosides and other glycoconjugates are present in large quantity in human nervous tissues and in key sites, such as nodes of Ranvier. Antiganglioside antibodies, most frequently to GM1, are common in GBS (20–50% of cases), particularly in AMAN and AMSAN and in those cases preceded by C. jejuni infection. Furthermore, isolates of C. jejuni from stool cultures of patients with GBS have surface glycolipid structures that antigenically cross react with gangliosides, including GM1, concentrated in human nerves. Sialic acid residues from pathogenic C. jejuni strains can also trigger activation of dendritic cells via signaling through a toll-like receptor (TLR4), promoting B cell differentiation and further amplifying humoral autoimmunity. Another line of evidence is derived from experience in Europe with parenteral use of purified bovine brain gangliosides for treatment of various neuropathic disorders. Between 5 and 15 days af er injection, some recipients developed acute motor axonal GBS with high titers of anti-GM1 antibodies that recognized epitopes at nodes of Ranvier and motor endplates. Experimentally, anti-GM1 antibodies can trigger complement-mediated injury at paranodal axon-glial junctions, disrupting the clustering of sodium channels and likely contributing to conduction block (see "Pathophysiology," below).

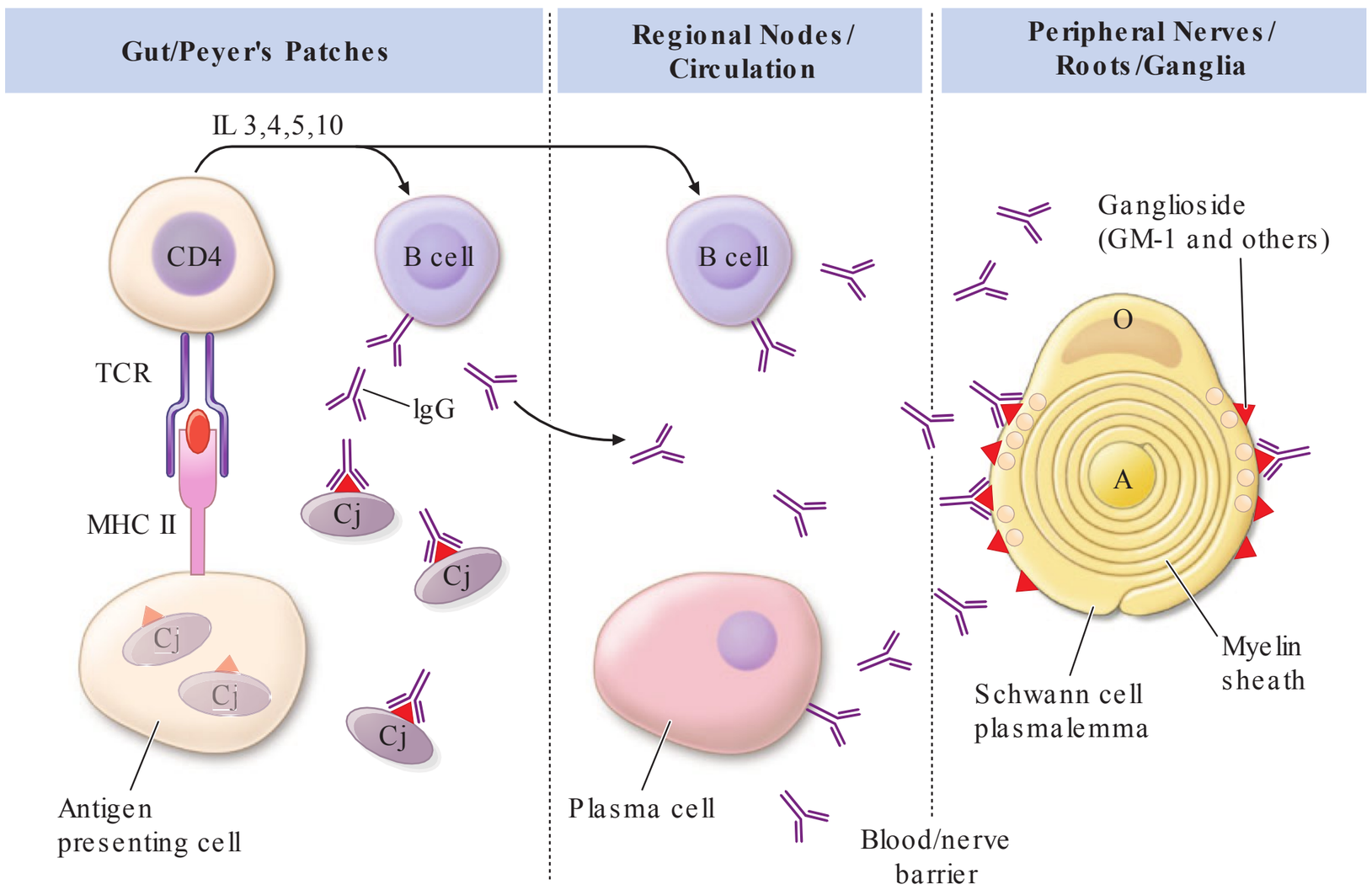


FIGURE 54-1

Postulated immunopathogenesis of Guillain-Barré syndrome (GBS) associated with Campylobacter jejuni infection. B cells recognize glycoconjugates on C. jejuni (Cj) (triangles) that cross-react with ganglioside present on Schwann cell surface and subjacent peripheral nerve myelin. Some B cells, activated via a T cell–independent mechanism, secrete primarily IgM (not shown). Other B cells (upper le*f*t side) are activated via a partially T cell–dependent route and secrete primarily IgG; T cell help is provided by CD4 cells activated locally by fragments of Cj proteins that are presented on the surface of antigen-presenting cells (APCs). A critical event in the development of GBS is the escape of activated B cells from Peyer's patches into regional lymph nodes. Activated T cells probably also function to assist in opening of the blood-nerve barrier, facilitating penetration of pathogenic autoantibodies. The earliest changes in myelin (right) consist of edema between myelin lamellae and vesicular disruption (shown as circular blebs) of the outermost myelin layers. These effects are associated with activation of the C5b-C9 membrane attack complex and probably mediated by calcium entry; it is possible that the macrophage cytokine tumor necrosis factor (TNF) also participates in myelin damage. A, axon; B, B cell; MHC II, class II major histocompatibility complex molecule; O, oligodendrocyte; TCR, T cell receptor.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 54-2

PRINCIPAL ANTIGLYCOLIPID ANTIBODIES IMPLICATED IN IMMUNE NEUROPATHIES

CLINICAL PRESENTATION	ANTIBODY TARGET	USUAL ISOTYPE
Acute Immune Neuropathies (Guillain-Barré Syndrome)		
Acute inflammatory demyelinating polyneuropathy (AIDP)	No clear patterns	IgG (polyclonal)
	GM1 most common	
Acute motor axonal neuropathy (AMAN)	GD1a, GM1, GM1b, GalNAc–GD1a (<50% for any)	IgG (polyclonal)
Miller Fisher syndrome (MFS)	GQ1b (>90%)	IgG (polyclonal)
Acute pharyngeal cervicobrachial neuropathy (APCBN)	GT1a (? most)	IgG (polyclonal)
Chronic Immune Neuropathies		
Chronic inflammatory demyelinating polyneuropathy (CIDP) (75%)	P0, myelin P2 protein, PMP22, neurofascin	No clear pattern
CIDP-M (MGUS associated) (25%)	Neural binding sites	IgG, IgA (monoclonal)
Chronic sensory > motor neuropathy	SPGP, SGLPG (on MAG) (50%)	IgM (monoclonal)
	Uncertain (50%)	IgM (monoclonal)
Multifocal motor neuropathy (MMN)	GM1, GalNAc–GD1a, others (25–50%)	IgM (polyclonal, monoclonal)
Chronic sensory ataxic neuropathy	GD1b, GQ1b, and other b-series gangliosides	IgM (monoclonal)

Abbreviations: CIDP-M, CIDP with a monoclonal gammopathy; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance.
Source: Modified from HJ Willison, N Yuki: Brain 125:2591, 2002.

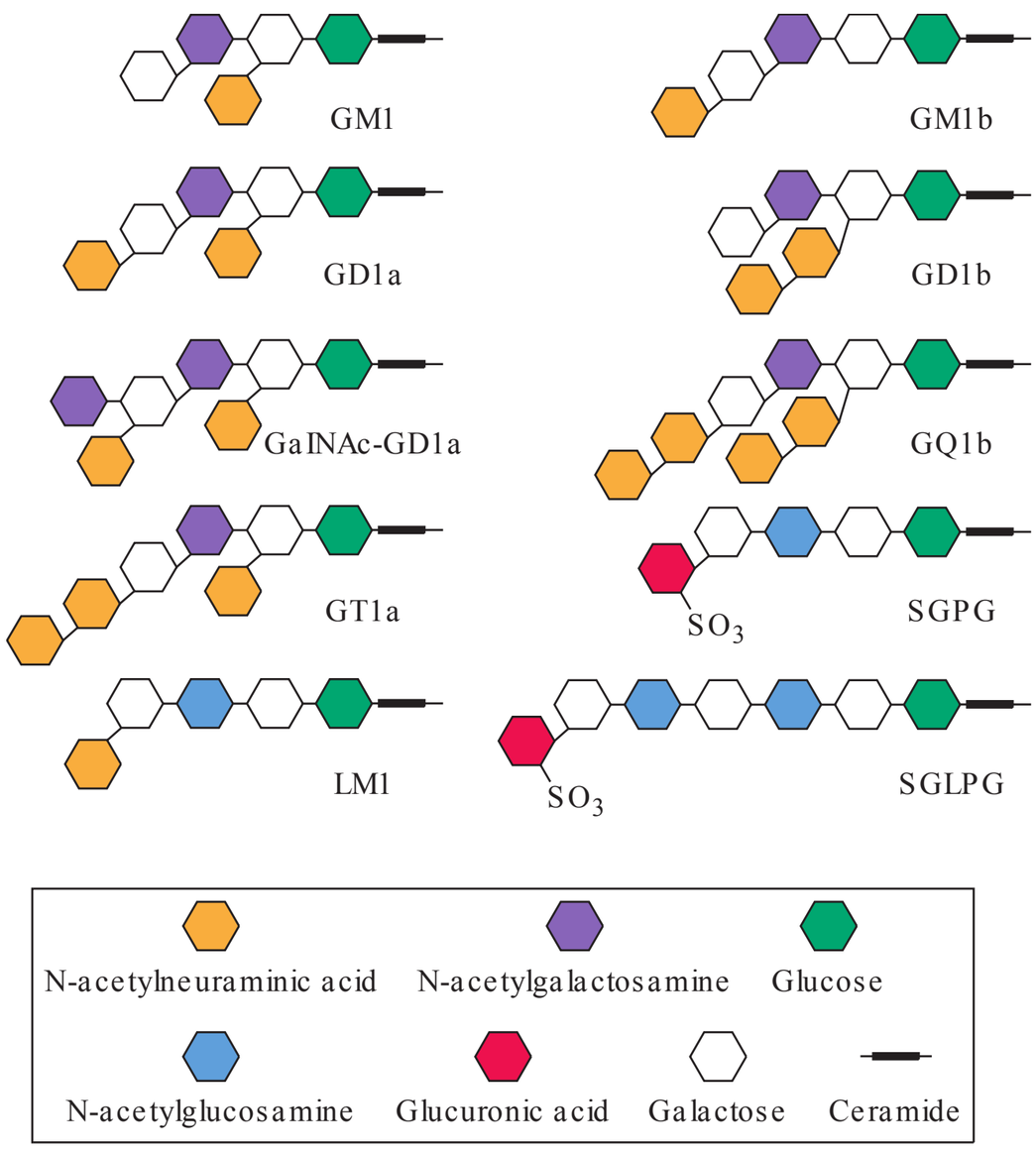


FIGURE 54-2
Glycolipids implicated as antigens in immune-mediated neuropathies. (Modified from HJ Willison, N Yuki: Brain 125: 2591, 2002.)

Anti-GQ1b IgG antibodies are found in >90% of patients with MFS (Table 54-2; Fig. 54-2), and titers of IgG are highest early in the course. Anti-GQ1b antibodies are not found in other forms of GBS unless there is extraocular motor nerve involvement. A possible explanation for this association is that extraocular motor nerves are enriched in GQ1b gangliosides in comparison to limb nerves. In addition, a monoclonal anti-GQ1b antibody raised against C. jejuni isolated from a patient with MFS blocked neuromuscular transmission experimentally.

Taken together, these observations provide strong but still inconclusive evidence that autoantibodies play an important pathogenic role in GBS. Although anti-ganglioside antibodies have been studied most intensively, other antigenic targets may also be important. One report identified IgG antibodies against Schwann cells and neurons (nerve growth cone region) in some GBS cases. Proof that these antibodies are pathogenic requires that they be capable of mediating disease following direct passive transfer to naïve hosts; this has not yet been demonstrated, although one case of possible maternal-fetal transplacental transfer of GBS has been described.

In AIDP, an early step in the induction of tissue damage appears to be complement deposition along the outer surface of the Schwann cell. Activation of complement initiates a characteristic vesicular disintegration

www.ketabpezeshki.com (021) 66485457 - 66485438

of the myelin sheath and also leads to recruitment of activated macrophages, which participate in damage to myelin and axons. In AMAN, the pattern is different in that complement is deposited along with IgG at the nodes of Ranvier along large motor axons. Interestingly, in cases of AMAN, antibodies against GD1a appear to have a fine specificity that favors binding to motor rather than sensory nerve roots, even though this ganglioside is expressed on both fiber types.

Pathophysiology

In the demyelinating forms of GBS, the basis for flaccid paralysis and sensory disturbance is conduction block. This finding, demonstrable electrophysiologically, implies that the axonal connections remain intact. Hence, recovery can take place rapidly as remyelination occurs. In severe cases of demyelinating GBS, secondary axonal degeneration usually occurs; its extent can be estimated electrophysiologically. More secondary axonal degeneration correlates with a slower rate of recovery and a greater degree of residual disability. When a severe primary axonal pattern is encountered electrophysiologically, the implication is that axons have degenerated and become disconnected from their targets, specifically the neuromuscular junctions, and must therefore regenerate for recovery to take place. In motor axonal cases in which recovery is rapid, the lesion is thought to be localized to preterminal motor branches, allowing regeneration and reinnervation to take place quickly. Alternatively, in mild cases, collateral sprouting and reinnervation from surviving motor axons near the neuromuscular junction may begin to reestablish physiologic continuity with muscle cells over a period of several months.

Laboratory features

CSF findings are distinctive, consisting of an elevated CSF protein level (1–10 g/L [100–1000 mg/dL]) without accompanying pleocytosis. The CSF is often normal when symptoms have been present for ≤48 h; by the end of the first week, the level of protein is usually elevated. A transient increase in the CSF white cell count (10–100/μL) occurs on occasion in otherwise typical GBS; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as unrecognized HIV infection, leukemia or lymphoma with infiltration of nerves, or neurosarcoidosis. Edx features are mild or absent in the early stages of GBS and lag behind the clinical evolution. In AIDP, the earliest features are prolonged F-wave latencies, prolonged distal latencies, and reduced amplitudes of compound muscle action potentials (CMAPs), probably owing to the predilection for involvement of nerve roots and distal motor nerve terminals early in the course. Later, slowing of conduction velocity, conduction block, and temporal dispersion may be appreciated (Table 54-1). Occasionally, sensory nerve action potentials (SNAPs) may be normal in the feet (e.g., sural nerve) when abnormal in the arms. This is also a sign that the patient does not have one of the more typical "length-dependent" polyneuropathies. In cases with primary axonal pathology, the principal Edx finding is reduced amplitude of CMAPs (and also SNAPS with AMSAN) without conduction slowing or prolongation of distal latencies.

Diagnosis

GBS is a descriptive entity. The diagnosis of AIDP is made by recognizing the pattern of rapidly evolving paralysis with areflexia, absence of fever or other systemic symptoms, and characteristic antecedent events. In 2011, the Brighton Collaboration developed a new set of case definitions for GBS in response to needs of epidemiologic studies of vaccination and assessing risks of GBS **(Table 54-3)**. These criteria have subsequently been validated. Other disorders that may enter into the differential diagnosis include acute myelopathies (especially with prolonged back pain and sphincter disturbances); diphtheria (early oropharyngeal disturbances); Lyme polyradiculitis and other tick-borne paralyses; porphyria (abdominal pain, seizures, psychosis); vasculitic neuropathy (check erythrocyte sedimentation rate, described below); poliomyelitis (fever and meningismus common); West Nile virus; CMV polyradiculitis (in immunocompromised patients); critical illness neuropathy or myopathy; neuromuscular junction disorders such as myasthenia gravis and botulism (pupillary reactivity lost early); poisonings with organophosphates, thallium, or arsenic; paralytic shellfish poisoning; or severe hypophosphatemia (rare). Laboratory tests are helpful primarily to exclude mimics of GBS. Edx features may be minimal, and the CSF protein level may not rise until the end of the first week. If the diagnosis is strongly suspected, treatment should be initiated without waiting for evolution of the characteristic Edx and CSF findings to occur. GBS patients with risk factors for HIV or with CSF pleocytosis should have a serologic test for HIV.

TREATMENT Guillain-Barré Syndrome

In the vast majority of patients with GBS, treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, it is not known whether immunotherapy is still effective. If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 54-3

BRIGHTON CRITERIA FOR DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME (GBS) AND MILLER FISHER SYNDROME

Clinical case definitions for diagnosis of GBS

Level 1 of diagnostic certainty
- Bilateral AND flaccid weakness of the limbs
  - AND
- Decreased or absent deep tendon reflexes in weak limbs
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- Electrophysiologic findings consistent with GBS
  - AND
- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μL)
  - AND
- Absence of an identified alternative diagnosis for weakness

Level 2 of diagnostic certainty
- Bilateral AND flaccid weakness of the limbs
  - AND
- Decreased or absent deep tendon reflexes in weak limbs
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- CSF total white cell count <50 cells/μL (with or without CSF protein elevation above laboratory normal value)
  - OR
- If CSF not collected or results not available, electrophysiologic studies consistent with GBS
  - AND
- Absence of identified alternative diagnosis for weakness

Level 3 of diagnostic certainty
- Bilateral and flaccid weakness of the limbs
  - AND
- Decreased or absent deep tendon reflexes in weak limbs
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- Absence of identified alternative diagnosis for weakness

Clinical case definitions for diagnosis of Miller Fisher syndrome

Level 1 of diagnostic certainty
- Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes, and ataxia
  - AND
- Absence of limb weakness
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal and total CSF white cell count <50 cells/μL)
  - AND
- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
  - AND
- No alterations in consciousness or corticospinal tract signs
  - AND
- Absence of identified alternative diagnosis

Level 2 of diagnostic certainty
- Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
  - AND
- Absence of limb weakness
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- CSF with a total white cell count <50 cells/μL) (with or without CSF protein elevation above laboratory normal value)
  - OR
- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only
  - AND
- No alterations in consciousness or corticospinal tract signs
  - AND
- Absence of identified alternative diagnosis

Level 3 of diagnostic certainty
- Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
  - AND
- Absence of limb weakness
  - AND
- Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
  - AND
- No alterations in consciousness or corticospinal tract signs
  - AND
- Absence of identified alternative diagnosis

Abbreviation: CSF, cerebrospinal fluid.

Source: From JJ Sejvar et al: Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 29:599, 2011. Validation study published by C Fokke et al: Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain 137:33, 2014.

that an immunologic attack is still ongoing. Either high-dose intravenous immune globulin (IVIg) or plasmapheresis can be initiated, as they are equally effective for typical GBS. A combination of the two therapies is not significantly better than either alone. IVIg is often the initial therapy chosen because of its ease of administration and good safety record. Anecdotal data have also suggested that IVIg may be preferable to plasma exchange (PE) for the AMAN and MFS variants of GBS. IVIg is administered as five daily infusions for a total dose of 2 g/kg body weight. There is some evidence that GBS autoantibodies are neutralized by anti-idiotypic antibodies present in IVIg preparations, perhaps accounting for the therapeutic effect. A course of plasmapheresis usually consists of ~40–50 mL/kg PE four to five times over

www.ketabpezeshki.com (021) 66485457 - 66485438

a week. Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27% to 14% with PE) and increases the likelihood of full recovery at 1 year (from 55% to 68%). Functionally significant improvement may occur toward the end of the first week of treatment or may be delayed for several weeks. The lack of noticeable improvement following a course of IVIg or PE is not an indication to treat with the alternate treatment. However, there are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month. Brief retreatment with the original therapy is usually effective in such cases. Glucocorticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PE.

In the worsening phase of GBS, most patients require monitoring in a critical care setting, with particular attention to vital capacity, heart rhythm, blood pressure, nutrition, deep vein thrombosis prophylaxis, cardiovascular status, early consideration (after 2 weeks of intubation) of tracheotomy, and chest physiotherapy. As noted, ~30% of patients with GBS require ventilatory assistance, sometimes for prolonged periods of time (several weeks or longer). Frequent turning and assiduous skin care are important, as are daily range-of-motion exercises to avoid joint contractures and daily reassurance as to the generally good outlook for recovery.

Prognosis and recovery

Approximately 85% of patients with GBS achieve a full functional recovery within several months to a year, although minor findings on examination (such as areflexia) may persist and patients often complain of continued symptoms, including fatigue. The mortality rate is <5% in optimal settings; death usually results from secondary pulmonary complications. The outlook is worst in patients with severe proximal motor and sensory axonal damage. Such axonal damage may be either primary or secondary in nature (see "Pathophysiology," above), but in either case successful regeneration cannot occur. Other factors that worsen the outlook for recovery are advanced age, a fulminant or severe attack, and a delay in the onset of treatment. Between 5 and 10% of patients with typical GBS have one or more late relapses; such cases are then classified as chronic inflammatory demyelinating polyneuropathy (CIDP).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CIDP is distinguished from GBS by its chronic course. In other respects, this neuropathy shares many features with the common demyelinating form of GBS, including elevated CSF protein levels and the Edx findings of acquired demyelination. Most cases occur in adults, and males are affected slightly more often than females. The incidence of CIDP is lower than that of GBS, but due to the protracted course, the prevalence is greater.

Clinical manifestations

Onset is usually gradual over a few months or longer, but in a few cases, the initial attack is indistinguishable from that of GBS. An acute-onset form of CIDP should be considered when GBS deteriorates >9 weeks after onset or relapses at least three times. Symptoms are both motor and sensory in most cases. Weakness of the limbs is usually symmetric but can be strikingly asymmetric in multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy variant (Lewis-Sumner syndrome) in which discrete peripheral nerves are involved. There is considerable variability from case to case. Some patients experience a chronic progressive course, whereas others, usually younger patients, have a relapsing and remitting course. Some have only motor findings, and a small proportion present with a relatively pure syndrome of sensory ataxia. Tremor occurs in ~10% and may become more prominent during periods of subacute worsening or improvement. A small proportion have cranial nerve findings, including external ophthalmoplegia. CIDP tends to ameliorate over time with treatment; the result is that many years after onset, nearly 75% of patients have reasonable functional status. Death from CIDP is uncommon.

Diagnosis

The diagnosis rests on characteristic clinical, CSF, and electrophysiologic findings. The CSF is usually acellular with an elevated protein level, sometimes several times normal. As with GBS, a CSF pleocytosis should lead to the consideration of HIV infection, leukemia or lymphoma, and neurosarcoidosis. Edx findings reveal variable degrees of conduction slowing, prolonged distal latencies, distal and temporal dispersion of CMAPs, and conduction block as the principal features. In particular, the presence of conduction block is a certain sign of an acquired demyelinating process. Evidence of axonal loss, presumably secondary to demyelination, is present in >50% of patients. Serum protein electrophoresis with immunofixation is indicated to search for monoclonal gammopathy and associated conditions (see "Monoclonal Gammopathy of Undetermined Significance," below). In all patients with presumptive CIDP, it is also reasonable to exclude vasculitis, collagen vascular disease (especially SLE), chronic hepatitis, HIV infection, amyloidosis, and diabetes mellitus. Other associated conditions include inflammatory bowel disease and lymphoma.

www.ketabpezeshki.com (021) 66485457 - 66485438

Pathogenesis

Although there is evidence of immune activation in CIDP, the precise mechanisms of pathogenesis are unknown. Biopsy typically reveals little inflammation and onion-bulb changes (imbricated layers of attenuated Schwann cell processes surrounding an axon) that result from recurrent demyelination and remyelination (Fig. 54-1). T e response to therapy suggests that CIDP is immune-mediated; CIDP responds to glucocorticoids, whereas GBS does not. Passive transfer of demyelination into experimental animals has been accomplished using IgG purified from the serum of some patients with CIDP, lending support for a humoral autoimmune pathogenesis. A minority of patients have serum antibodies against P0, myelin P2 protein, PMP22, or neurofascin. It is also of interest that a CIDP-like illness developed spontaneously in the nonobese diabetic (NOD) mouse when the immune co-stimulatory molecule B7-2 (CD86) was genetically deleted; this suggests that CIDP can result from altered triggering of T cells by antigen-presenting cells.

Approximately 25% of patients with clinical features of CIDP also have a monoclonal gammopathy of undetermined significance (MGUS). Cases associated with monoclonal IgA or IgG kappa usually respond to treatment as favorably as cases without a monoclonal gammopathy. Patients with IgM monoclonal gammopathy and antibodies directed against myelin-associated glycoprotein (MAG) have a distinct polyneuropathy, tend to have more sensory findings and a more protracted course, and usually have a less satisfactory response to treatment.

TREATMENT Chronic Inf ammatory Demyelinating Polyneuropathy

Most authorities initiate treatment for CIDP when progression is rapid or walking is compromised. If the disorder is mild, management can be expectant, awaiting spontaneous remission. Controlled studies have shown that high-dose IVIg, PE, and glucocorticoids are all more effective than placebo. Initial therapy is usually with IVIg, administered as 2.0 g/kg body weight given in divided doses over 2–5 days; three monthly courses are generally recommended before concluding a patient is a treatment failure. If the patient responds, the infusion intervals can be gradually increased or the dosage decreased (e.g., 1 g/kg per month). PE, which appears to be as effective as IVIg, is initiated at two to three treatments per week for 6 weeks; periodic re-treatment may also be required. Treatment with glucocorticoids is another option (60–80 mg prednisone PO daily for 1–2 months, followed by a gradual dose reduction of 10 mg per month as tolerated), but long-term adverse effects including bone demineralization, gastrointestinal bleeding, and cushingoid changes are problematic. As many as one-third of patients with CIDP fail to respond adequately to the initial therapy chosen; a different treatment should then be tried. Patients who fail therapy with IVIg, PE, and glucocorticoids may benefit from treatment with immunosuppressive agents such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide, either alone or as adjunctive therapy. Early experience with anti-CD20 (rituximab) has also shown promise. Use of these therapies requires periodic reassessment of their risks and benefits. In patients with a CIDP-like neuropathy who fail to respond to treatment, it is important to evaluate for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; see below).

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) is a distinctive but uncommon neuropathy that presents as slowly progressive motor weakness and atrophy evolving over years in the distribution of selected nerve trunks, associated with sites of persistent focal motor conduction block in the same nerve trunks. Sensory fibers are relatively spared. T e arms are affected more frequently than the legs, and >75% of all patients are male. Some cases have been confused with lower motor neuron forms of amyotrophic lateral sclerosis **(Chap. 39)**. Less than 50% of patients present with high titers of polyclonal IgM antibody to the ganglioside GM1. It is uncertain how this finding relates to the discrete foci of persistent motor conduction block, but high concentrations of GM1 gangliosides are normal constituents of nodes of Ranvier in peripheral nerve fibers. Pathology reveals demyelination and mild inflammatory changes at the sites of conduction block.

Most patients with MMN respond to high-dose IVIg (dosages as for CIDP, above); periodic re-treatment is required (usually at least monthly) to maintain the benefit. Some refractory patients have responded to rituximab or cyclophosphamide. Glucocorticoids and PE are not effective.

NEUROPATHIES WITH MONOCLONAL GAMMOPATHY

MULTIPLE MYELOMA

Clinically overt polyneuropathy occurs in ~5% of patients with the commonly encountered type of multiple myeloma, which exhibits either lytic or diffuse osteoporotic bone lesions. T ese neuropathies are sensorimotor, are usually mild and slowly progressive but may be severe, and generally do not reverse with successful suppression of the myeloma. In most cases, Edx

www.ketabpezeshki.com (021) 66485457 - 66485438

and pathologic features are consistent with a process of axonal degeneration.

In contrast, myeloma with osteosclerotic features, although representing only 3% of all myelomas, is associated with polyneuropathy in one-half of cases. T ese neuropathies, which may also occur with solitary plasmacytoma, are distinct because they (1) are usually demyelinating in nature and resemble CIDP; (2) of en respond to radiation therapy or removal of the primary lesion; (3) are associated with different monoclonal proteins and light chains (almost always lambda as opposed to primarily kappa in the lytic type of multiple myeloma); (4) are typically refractory to standard treatments of CIDP; and (5) may occur in association with other systemic findings including thickening of the skin, hyperpigmentation, hypertrichosis, organomegaly, endocrinopathy, anasarca, and clubbing of fingers. T ese are features of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Levels of vascular endothelial growth factor (VEGF) are increased in the serum, and this factor is felt to somehow play a pathogenic role in this syndrome. Treatment of the neuropathy is best directed at the osteosclerotic myeloma using surgery, radiotherapy, chemotherapy, or autologous peripheral blood stem cell transplantation.

Neuropathies are also encountered in other systemic conditions with gammopathy, including Waldenström's macroglobulinemia, primary systemic amyloidosis, and cryoglobulinemic states (mixed essential cryoglobulinemia, some cases of hepatitis C).

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Chronic polyneuropathies occurring in association with MGUS are usually associated with the immunoglobulin isotypes IgG, IgA, and IgM. Most patients present with isolated sensory symptoms in their distal extremities and have Edx features of an axonal sensory or sensorimotor polyneuropathy. T ese patients otherwise resemble idiopathic sensory polyneuropathy, and the MGUS might just be coincidental. T ey usually do not respond to immunotherapies designed to reduce the concentration of the monoclonal protein. Some patients, however, present with generalized weakness and sensory loss and Edx studies indistinguishable from CIDP without monoclonal gammopathy (see "Chronic Inflammatory Demyelinating Polyneuropathy," above), and their response to immunosuppressive agents is also similar. An exception is the syndrome of IgM kappa monoclonal gammopathy associated with an indolent, longstanding, sometimes static sensory neuropathy, frequently with tremor and sensory ataxia. Most patients are male and older than age 50 years. In the majority, the monoclonal IgM immunoglobulin binds to a normal peripheral nerve constituent, MAG, found in the paranodal regions of Schwann cells. Binding appears to be specific for a polysaccharide epitope that is also found in other normal peripheral nerve myelin glycoproteins, P0 and PMP22, and also in other normal nerve-related glycosphingolipids (Fig. 54-1). In the MAG-positive cases, IgM paraprotein is incorporated into the myelin sheaths of affected patients and widens the spacing of the myelin lamellae, thus producing a distinctive ultrastructural pattern. Demyelination and remyelination are the hallmarks of the lesions, but axonal loss develops over time. T ese anti-MAG polyneuropathies are typical refractory to immunotherapy. In a small proportion of patients (30% at 10 years), MGUS will in time evolve into frankly malignant conditions such as multiple myeloma or lymphoma.

VASCULITIC NEUROPATHY

Peripheral nerve involvement is common in polyarteritis nodosa (PAN), appearing in half of all cases clinically and in 100% of cases at postmortem studies. T e most common pattern is multifocal (asymmetric) motor-sensory neuropathy (mononeuropathy multiplex) due to ischemic lesions of nerve trunks and roots; however, some cases of vasculitic neuropathy present as a distal, symmetric sensorimotor polyneuropathy. Symptoms of neuropathy are a common presenting complaint in patients with PAN. T e Edx findings are those of an axonal process. Small- to medium-sized arteries of the vasa nervorum, particularly the epineural vessels, are affected in PAN, resulting in a widespread ischemic neuropathy. A high frequency of neuropathy occurs in allergic angiitis and granulomatosis (Churg-Strauss syndrome [CSS]).

Systemic vasculitis should always be considered when a subacute or chronically evolving mononeuropathy multiplex occurs in conjunction with constitutional symptoms (fever, anorexia, weight loss, loss of energy, malaise, and nonspecific pains). Diagnosis of suspected vasculitic neuropathy is made by a combined nerve and muscle biopsy, with serial section or skip-serial techniques.

Approximately one-third of biopsy-proven cases of vasculitic neuropathy are "nonsystemic" in that the vasculitis appears to affect only peripheral nerves. Constitutional symptoms are absent, and the course is more indolent than that of PAN. T e erythrocyte sedimentation rate may be elevated, but other tests for systemic disease are negative. Nevertheless, clinically silent involvement of other organs is likely, and vasculitis is frequently found in muscle biopsied at the same time as nerve.

www.ketabpezeshki.com (021) 66485457 - 66485438

Vasculitic neuropathy may also be seen as part of the vasculitis syndrome occurring in the course of other connective tissue disorders. The most frequent is rheumatoid arthritis, but ischemic neuropathy due to involvement of vasa nervorum may also occur in mixed cryoglobulinemia, Sjögren's syndrome, granulomatosis with polyangiitis (Wegener's), hypersensitivity angiitis, systemic lupus erythematosus, and progressive systemic sclerosis.

Some vasculitides are associated with antineutrophil cytoplasmic antibodies (ANCAs), which in turn, are subclassified as cytoplasmic (cANCA) or perinuclear (pANCA). cANCAs are directed against proteinase 3 (PR3), whereas pANCAs target myeloperoxidase (MPO). PR3/cANCAs are associated with granulomatosis with polyangiitis (Wegener's), whereas MPO/pANCAs are typically associated with microscopic polyangiitis, CSS, and less commonly PAN. Of note, MPO/pANCA has also been seen in minocycline-induced vasculitis.

Management of these neuropathies, including the "nonsystemic" vasculitic neuropathy, consists of treatment of the underlying condition as well as the aggressive use of glucocorticoids and cyclophosphamide. Use of these immunosuppressive agents has resulted in dramatic improvements in outcome, with 5-year survival rates now greater than 80%. Recent clinical trials found that the combination of rituximab and glucocorticoids is not inferior to cyclophosphamide and glucocorticoids. Thus, combination therapy with glucocorticoids and rituximab is increasingly recommended as the standard initial treatment, particularly for ANCA-associated vasculitis.

ANTI-Hu PARANEOPLASTIC NEUROPATHY

This uncommon immune-mediated disorder manifests as a sensory neuronopathy (i.e., selective damage to sensory nerve bodies in dorsal root ganglia) **(Chap. 50)**. The onset is often asymmetric with dysesthesias and sensory loss in the limbs that soon progress to affect all limbs, the torso, and the face. Marked sensory ataxia, pseudoathetosis, and inability to walk, stand, or even sit unsupported are frequent features and are secondary to the extensive deafferentation. Subacute sensory neuronopathy may be idiopathic, but more than half of cases are paraneoplastic, primarily related to lung cancer, and most of those are small-cell lung cancer (SCLC). Diagnosis of the underlying SCLC requires awareness of the association, testing for the paraneoplastic antibody, and often positron emission tomography (PET) scanning for the tumor. The target antigens are a family of RNA-binding proteins (HuD, HuC, and Hel-N1) that in normal tissues are only expressed by neurons. The same proteins are usually expressed by SCLC, triggering in some patients an immune response characterized by antibodies and cytotoxic T cells that cross-react with the Hu proteins of the dorsal root ganglion neurons, resulting in immune-mediated neuronal destruction. An encephalomyelitis may accompany the sensory neuronopathy and presumably has the same pathogenesis. Neurologic symptoms usually precede, by ≤6 months, the identification of SCLC. The sensory neuronopathy runs its course in a few weeks or months and stabilizes, leaving the patient disabled. Most cases are unresponsive to treatment with glucocorticoids, IVIg, PE, or immunosuppressant drugs.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 55

MYASTHENIA GRAVIS AND OTHER DISEASES OF THE NEUROMUSCULAR JUNCTION

Daniel B. Drachman ■ Anthony A. Amato

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack. Treatment now available for MG is highly effective, although a specific cure has remained elusive.

PATHOPHYSIOLOGY

At the neuromuscular junction **(Fig. 55-1, Video 55-1)**, acetylcholine (ACh) is synthesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the nerve terminal, ACh from 150 to 200 vesicles is released and combines with AChRs that are densely packed at the peaks of postsynaptic folds. The AChR consists of five subunits (2α, 1β, 1δ, and 1γ or ε) arranged around a central pore. When ACh combines with the binding sites on the α subunits of the AChR, the channel in the AChR opens, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle

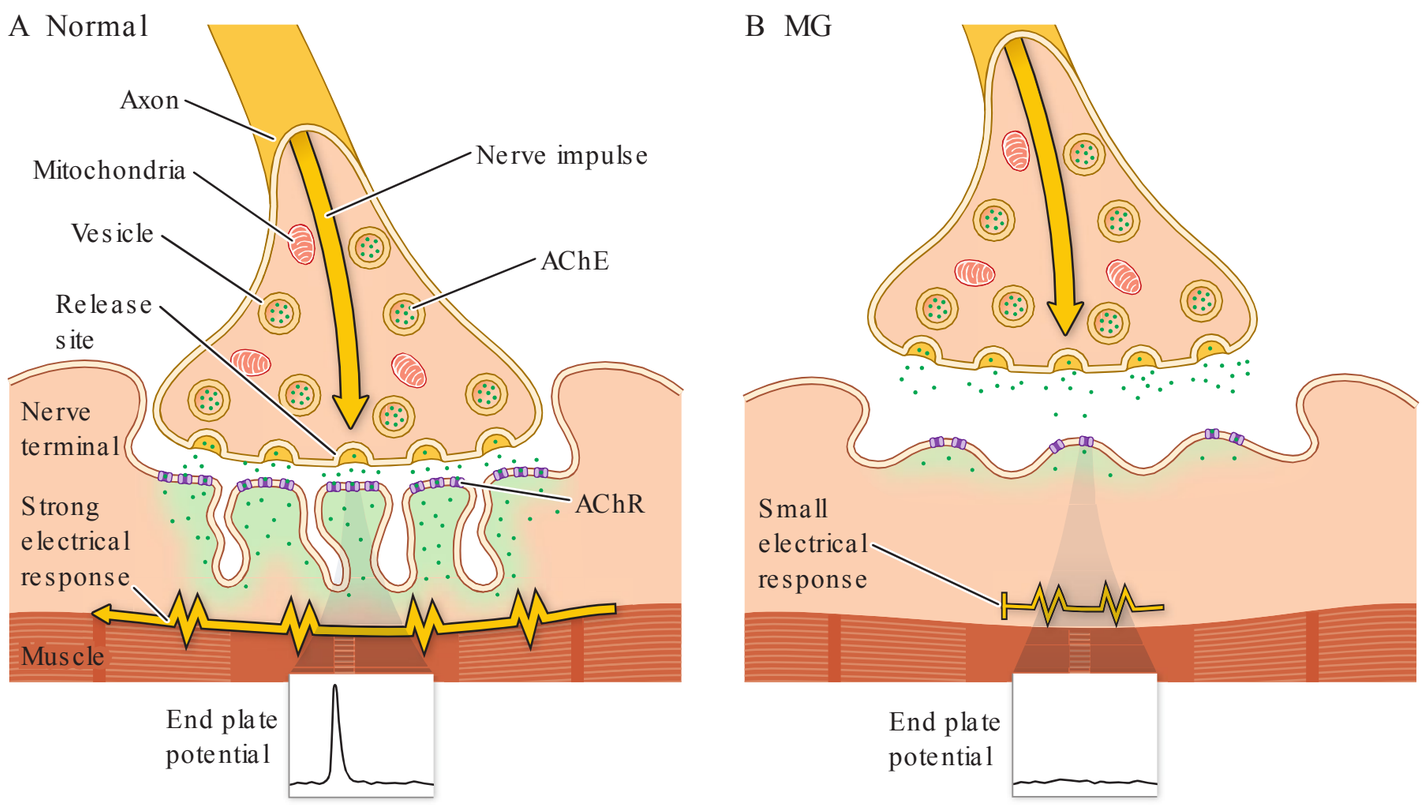


FIGURE 55-1

Diagrams of **(A)** normal and **(B)** myasthenic neuromuscular junctions. AChE, acetylcholinesterase. See text for description of normal neuromuscular transmission. The myasthenia gravis (MG) junction demonstrates a normal nerve terminal; a reduced number of acetylcholine receptors (AChRs) (stippling); flattened, simplified postsynaptic folds; and a widened synaptic space. See Video 55-1 also at the following link: https://www.mhprofessional.com/mediacenter/. (Modified from DB Drachman: N Engl J Med 330:1797, 1994; with permission.)

www.ketabpezeshki.com (021) 66485457 - 66485438

fiber, triggering muscle contraction. T is process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase (AChE), which is present within the synaptic folds, and by diffusion of ACh away from the receptor.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 55–1 Myasthenia Gravis and Other Diseases Of The Neuromuscular Junction

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or "simplified." T ese changes result in decreased efficiency of neuromuscular transmission. T erefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission at many neuromuscular junctions results in weakness of muscle contraction.

T e amount of ACh released per impulse normally declines on repeated activity (termed presynaptic rundown). In the myasthenic patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or myasthenic fatigue. T is mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

T e neuromuscular abnormalities in MG are caused by an autoimmune response mediated by specific anti-AChR antibodies. T e anti-AChR antibodies reduce the number of available AChRs at neuromuscular junctions by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) damage to the postsynaptic muscle membrane by the antibody in collaboration with complement; and (3) blockade of the active site of the AChR, i.e., the site that normally binds ACh. An immune response to muscle-specific kinase (MuSK), a protein involved in AChR clustering at neuromuscular junctions, can also result in MG, with reduction of AChRs demonstrated experimentally. Anti-MuSK antibody occurs in about 40% of patients without AChR antibody. A small proportion of patients whose sera are negative for both AChR and MuSK antibodies have antibodies to another protein at the neuromuscular junction—low-density lipoprotein receptor-related protein 4 (lrp4)—that is important for clustering of AChRs. T e pathogenic antibodies are IgG and are T cell dependent. T us, immunotherapeutic strategies directed against either the antibody-producing B cells or helper T cells are effective in this antibody-mediated disease.

How the autoimmune response is initiated and maintained in MG is not completely understood, but the thymus appears to play a role in this process. T e thymus is abnormal in ~75% of patients with AChR antibody–positive MG; in ~65% the thymus is "hyperplastic," with the presence of active germinal centers detected histologically, although the hyperplastic thymus is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which express AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

CLINICAL FEATURES

MG is not rare, having a prevalence as high as 2–7 in 10,000. It affects individuals in all age groups, but peaks of incidence occur in women in their twenties and thirties and in men in their fif ies and sixties. Overall, women are affected more frequently than men, in a ratio of ~3:2. T e cardinal features are weakness and fatigability of muscles. T e weakness increases during repeated use (fatigue) or late in the day and may improve following rest or sleep. T e course of MG is of en variable. Exacerbations and remissions may occur, particularly during the first few years af er the onset of the disease. Remissions are rarely complete or permanent. Unrelated infections or systemic disorders can lead to increased myasthenic weakness and may precipitate "crisis" (see below).

T e distribution of muscle weakness of en has a characteristic pattern. T e cranial muscles, particularly the lids and extraocular muscles, are typically involved early in the course of MG; diplopia and ptosis are common initial complaints. Facial weakness produces a "snarling" expression when the patient attempts to smile. Weakness in chewing is most noticeable af er prolonged effort, as in chewing meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric "mushy" quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food. Bulbar weakness is especially prominent in MuSK antibody–positive MG. In ~85% of patients, the weakness becomes generalized, affecting the limb muscles as well. If weakness remains restricted to the extraocular muscles for 3 years, it is likely that it will not become generalized, and these patients are said to have ocular MG. T e limb weakness in MG is of en proximal and may be asymmetric. Despite the muscle weakness, deep tendon reflexes are preserved. If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be in crisis.

www.ketabpezeshki.com (021) 66485457 - 66485438

DIAGNOSIS AND EVALUATION

(Table 55-1) The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function. The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG and (2) the treatment of MG may involve surgery and the prolonged use of drugs with potentially adverse side effects.

Antibodies to AChR, MuSK, or lpr4

As noted above, anti-AChR antibodies are detectable in the serum of ~85% of all myasthenic patients but in only about 50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. However, in an individual patient, a treatment-induced fall in the antibody level often correlates with clinical improvement, whereas a rise in the level may occur with exacerbations. Antibodies to MuSK have been found to be present in ~40% of AChR antibody–negative patients with generalized MG, and their presence is a useful diagnostic test in these patients. MuSK antibodies are rarely present in AChR antibody–positive patients or in patients with MG limited to ocular muscles. These antibodies may interfere with clustering of AChRs at neuromuscular junctions, as MuSK is known to do during early development. A small proportion of MG patients without antibodies to AChR or MuSK may have antibodies to lrp4, although a test for lrp4 antibodies is not yet commercially available. Finally, antibodies against agrin have recently been found in some patients with MG. Agrin is a protein derived from motor nerves that normally binds to lrp4 and thus may also interfere with clustering of AChRs at neuromuscular junctions. There may well be other—as yet undefined—antibodies that impair neuromuscular transmission.

TABLE 55-1

DIAGNOSIS OF MYASTHENIA GRAVIS (MG)

History
- Diplopia, ptosis, dysarthria, dysphagia, dyspnea
- Weakness in characteristic distribution: proximal limbs, neck extensors, generalized
- Fluctuation and fatigue: worse with repeated activity, improved by rest
- Effects of previous treatments

Physical examination
- Ptosis, diplopia
- Motor power survey: quantitative testing of muscle strength
- Forward arm abduction time (5 min)
- Vital capacity measurement
- Absence of other neurologic signs

Laboratory testing
- Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; ~40% of AChR antibody–negative patients with generalized MG have anti-MuSK antibodies
- Repetitive nerve stimulation: decrement of >15% at 3 Hz: highly probable
- Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
- Edrophonium chloride (Enlon®) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive
- For ocular or cranial MG: exclude intracranial lesions by CT or MRI

Abbreviations: AChR, acetylcholine receptor; CT, computed tomography; MRI, magnetic resonance imaging; MuSK, muscle-specific tyrosine kinase.

Electrodiagnostic testing

Repetitive nerve stimulation may provide helpful diagnostic evidence of MG. Anti-AChE medication is stopped 6–24 h before testing. It is best to test weak muscles or proximal muscle groups. Electric shocks are delivered at a rate of two or three per second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change at these rates of stimulation. However, in myasthenic patients, there is a rapid reduction of >10–15% in the amplitude of the evoked responses.

Anticholinesterase test

Drugs that inhibit the enzyme AChE allow ACh to interact repeatedly with the limited number of AChRs in MG, producing improvement in muscle strength. Edrophonium is used most commonly for diagnostic testing because of the rapid onset (30 s) and short duration (~5 min) of its effect. An objective end point must be selected to evaluate the effect of edrophonium, such as weakness of extraocular muscles, impairment of speech, or the length of time that the patient can maintain the arms in forward abduction. An initial IV dose of 2 mg of edrophonium is given. If definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8 mg IV. The dose is administered in two parts because some patients react to edrophonium with side effects such as nausea, diarrhea, salivation, fasciculations, and rarely with severe symptoms of syncope or bradycardia. Atropine (0.6 mg) should be drawn up in a syringe and ready for IV administration if these symptoms become troublesome. The edrophonium test is

www.ketabpezeshki.com (021) 66485457 - 66485438

now reserved for patients with clinical findings that are suggestive of MG but who have negative antibody and electrodiagnostic test results. False-positive tests occur in occasional patients with other neurologic disorders, such as amyotrophic lateral sclerosis, and in placebo-reactors. False-negative or equivocal tests may also occur. In some cases, it is helpful to use a longer-acting drug such as neostigmine (15 mg PO), because this permits more time for detailed evaluation of strength.

Inherited myasthenic syndromes

The congenital myasthenic syndromes (CMS) comprise a heterogeneous group of disorders of the neuromuscular junction that are not autoimmune but rather are due to genetic mutations in which virtually any component of the neuromuscular junction may be affected. Alterations in function of the presynaptic nerve terminal, in the various subunits of the AChR, AChE, or the other molecules involved in end-plate development or maintenance, have been identified in the different forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of skeletal muscles, in some cases involving extraocular muscles (EOMs), lids, and proximal muscles, similar to the distribution in autoimmune MG. CMS should be suspected when symptoms of myasthenia have begun in infancy or childhood and AChR antibody tests are consistently negative. By far the most common genetic defects occur in the AChR or other postsynaptic molecules (67% in the Mayo Clinic series of 350 CMS patients), with about equal frequencies of abnormalities in AChE (13%) and the various maintenance molecules (DOK7, GFPT, etc.; ~14%). In the forms that involve the AChR, a wide variety of mutations have been identified in each of the subunits, but the ε subunit is affected in ~75% of these cases. In most of the recessively inherited forms of CMS, the mutations are heteroallelic; that is, different mutations affecting each of the two alleles are present. Features of the four most common forms of CMS are summarized in **Table 55-2**. Although clinical features and electrodiagnostic and pharmacologic tests may suggest the correct diagnosis, molecular analysis is required for precise elucidation of the defect; this may lead to helpful treatment as well as genetic counseling.

Differential diagnosis

Other conditions that cause weakness of the cranial and/or somatic musculature include the nonautoimmune CMS discussed above, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), neurasthenia, hyperthyroidism (Graves' disease), botulism, intracranial mass lesions, oculopharyngeal dystrophy, and mitochondrial myopathy (Kearns-Sayre syndrome,

TABLE 55-2

THE CONGENITAL MYASTHENIC SYNDROMES

TYPE	CLINICAL FEATURES	ELECTROPHYSIOLOGY	GENETICS	END-PLATE EFFECTS	TREATMENT
Slow channel	Most common; weak forearm extensors; onset second to third decade; variable severity	Repetitive muscle response on nerve stimulation; prolonged channel opening and MEPP duration	Autosomal dominant; α, β, ε; AChR mutations	Excitotoxic end-plate myopathy; decreased AChRs; postsynaptic damage	Quinidine, fluoxetine: decrease end-plate damage; made worse by anti-AChE
Low-affinity fast channel	Onset early; moderately severe; ptosis, EOM involvement; weakness and fatigue	Brief and infrequent channel openings; opposite of slow channel syndrome	Autosomal recessive; may be heteroallelic	Normal end-plate structure	3,4-DAP; anti-AChE
Severe AChR deficiencies	Early onset; variable severity; fatigue; typical MG features	Decremental response to repetitive nerve stimulation; decreased MEPP amplitudes	Autosomal recessive; ε mutations most common; many different mutations	Increased length of end plates; variable synaptic folds	Anti-AChE; 3,4-DAP
AChE deficiency	Early onset; variable severity; scoliosis; may have normal EOM, absent pupillary responses	Decremental response to repetitive nerve stimulation	Mutant gene for AChE's collagen anchor (COLQ)	Small nerve terminals; degenerated junctional folds	Worse with anti-AChE drugs; use albuterol, ephedrine, 3,4-DAP

Abbreviations: AChE, acetylcholinesterase; AChR, acetylcholine receptor; EOM, extraocular muscles; MEPP, miniature end-plate potentials; MG, myasthenia gravis; 3,4-DAP, 3,4-diaminopyridine.

www.ketabpezeshki.com (021) 66485457 - 66485438

progressive external ophthalmoplegia). Treatment with penicillamine (used for scleroderma or rheumatoid arthritis) may result in true autoimmune MG, but the weakness is usually mild, and recovery occurs within weeks or months af er discontinuing its use. Aminoglycoside antibiotics or procainamide can cause exacerbation of weakness in myasthenic patients; very large doses can cause neuromuscular weakness in normal individuals.

LEMS is a presynaptic disorder of the neuromuscular junction that can cause weakness similar to that of MG. T e proximal muscles of the lower limbs are most commonly affected, but other muscles may be involved as well. Cranial nerve findings, including ptosis of the eyelids and diplopia, occur in up to 70% of patients and resemble features of MG. However, the two conditions are usually readily distinguished, because patients with LEMS have depressed or absent reflexes and experience autonomic changes such as dry mouth and impotence. Nerve stimulation produces an initial low-amplitude response and, at low rates of repetitive stimulation (2–3 Hz), decremental responses like those of MG; however, at high rates (50 Hz), or following exercise, incremental responses occur. LEMS is caused by autoantibodies directed against P/Q-type calcium channels at the motor nerve terminals, which can be detected in ~85% of LEMS patients by radioimmunoassay. T ese autoantibodies result in impaired release of ACh from nerve terminals. Many patients with LEMS have an associated malignancy, most commonly small-cell carcinoma of the lung, which may express calcium channels that stimulate the autoimmune response. T e diagnosis of LEMS may signal the presence of a tumor long before it would otherwise be detected, permitting early removal. Treatment of LEMS involves plasmapheresis and immunosuppression, as for MG. 3,4-Diaminopyridine (3,4-DAP) and pyridostigmine may also be symptomatically helpful. 3,4-DAP acts by blocking potassium channels, which results in prolonged depolarization of the motor nerve terminals and thus enhances ACh release. Pyridostigmine prolongs the action of ACh, allowing repeated interactions with AChRs.

Botulism is due to potent bacterial toxins produced by any of eight different strains of Clostridium botulinum. T e toxins enzymatically cleave specific proteins essential for the release of ACh from the motor nerve terminal, thereby interfering with neuromuscular transmission. Most commonly, botulism is caused by ingestion of improperly prepared food containing toxin. Rarely, the nearly ubiquitous spores of C. botulinum may germinate in wounds. In infants, the spores may germinate in the gastrointestinal (GI) tract and release toxin, causing muscle weakness. Patients present with myasthenia-like bulbar weakness (e.g., diplopia, dysarthria, dysphagia) and lack sensory symptoms and signs. Weakness may generalize to the limbs and may result in respiratory failure. Reflexes are present early, but they may be diminished as the disease progresses. Mentation is normal. Autonomic findings include paralytic ileus, constipation, urinary retention, dilated or poorly reactive pupils, and dry mouth. T e demonstration of toxin in serum by bioassay is definitive, but the results usually take a relatively long time to be completed and may be negative. Nerve stimulation studies reveal findings of presynaptic neuromuscular blockade with reduced compound muscle action potentials (CMAPs) that increase in amplitude following high-frequency repetitive stimulation. Treatment includes ventilatory support and aggressive inpatient supportive care (e.g., nutrition, deep vein thrombosis prophylaxis) as needed. Antitoxin should be given as early as possible to be effective and can be obtained through the Centers for Disease Control and Prevention. A preventive vaccine is available for laboratory workers or other highly exposed individuals.

Neurasthenia is the historic term for a myasthenia-like fatigue syndrome without an organic basis. T ese patients may present with subjective symptoms of weakness and fatigue, but muscle testing usually reveals the "give-away weakness" characteristic of nonorganic disorders; the complaint of fatigue in these patients means tiredness or apathy rather than decreasing muscle power on repeated effort. Hyperthyroidism is readily diagnosed or excluded by tests of thyroid function, which should be carried out routinely in patients with suspected MG. Abnormalities of thyroid function (hyper- or hypothyroidism) may increase myasthenic weakness. Diplopia resembling that in MG may occasionally be due to an intracranial mass lesion that compresses nerves to the EOMs (e.g., sphenoid ridge meningioma), but magnetic resonance imaging (MRI) of the head and orbits usually reveals the lesion.

Progressive external ophthalmoplegia is a rare condition resulting in weakness of the EOMs, which may be accompanied by weakness of the proximal muscles of the limbs and other systemic features. Most patients with this condition have mitochondrial disorders that can be detected on muscle biopsy **(Chap. 56)**.

Search for associated conditions

(Table 55-3) Myasthenic patients have an increased incidence of several associated disorders. T ymic abnormalities occur in ~75% of AChR antibody–positive patients, as noted above. Neoplastic change (thymoma) may produce enlargement of the thymus, which is detected by computed tomography (CT) scanning of the anterior mediastinum. A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient age

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 55-3

DISORDERS ASSOCIATED WITH MYASTHENIA GRAVIS AND RECOMMENDED LABORATORY TESTS

Associated disorders
Disorders of the thymus: thymoma, hyperplasia
Other autoimmune disorders: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, lupus erythematosus, skin disorders, family history of autoimmune disorder
Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 55-4)
Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity
Recommended laboratory tests or procedures
CT or MRI of chest
Tests for lupus erythematosus, antinuclear antibody, rheumatoid factor, antithyroid antibodies
Thyroid function tests
PPD skin test
Fasting blood glucose, hemoglobin A1c
Pulmonary function tests
Bone densitometry

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PPD, purified protein derivative.

>40 years is highly suspicious of thymoma. Hyperthyroidism occurs in 3–8% of patients and may aggravate the myasthenic weakness. T yroid function tests should be obtained in all patients with suspected MG. Because of the association of MG with other autoimmune disorders, blood tests for rheumatoid factor and antinuclear antibodies should also be carried out. Chronic infection of any kind can exacerbate MG and should be sought carefully. Finally, measurements of ventilatory function are valuable because of the frequency and seriousness of respiratory impairment in myasthenic patients.

Because of the side effects of glucocorticoids and other immunosuppressive agents used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tuberculosis or hepatitis), hypertension, diabetes, renal disease, and glaucoma.

TREATMENT Myasthenia Gravis

T e prognosis has improved strikingly as a result of advances in treatment. Nearly all myasthenic patients can be returned to full productive lives with proper therapy. T e most useful treatments for MG include anticholinesterase medications, immunosuppressive agents, thymectomy, and plasmapheresis or intravenous immunoglobulin (IVIg) **(Fig. 55-2)**.

ANTICHOLINESTERASE MEDICATIONS Anticholinesterase medication produces at least partial improvement in most myasthenic patients, although improvement is complete in only a few. Patients with anti-MuSK MG generally obtain less benefit from anticholinesterase agents than those with AChR antibodies. Pyridostigmine is the most widely used anticholinesterase drug. T e beneficial action of oral pyridostigmine begins within 15–30 min and lasts for 3–4 h, but individual responses vary. Treatment is begun with a moderate dose, e.g., 30–60 mg three to four times daily. T e frequency and amount of the dose should be tailored to the patient's individual requirements throughout the day. For example, patients with weakness in chewing and swallowing may benefit by taking the medication before meals so that peak strength coincides with mealtimes. Long-acting pyridostigmine may

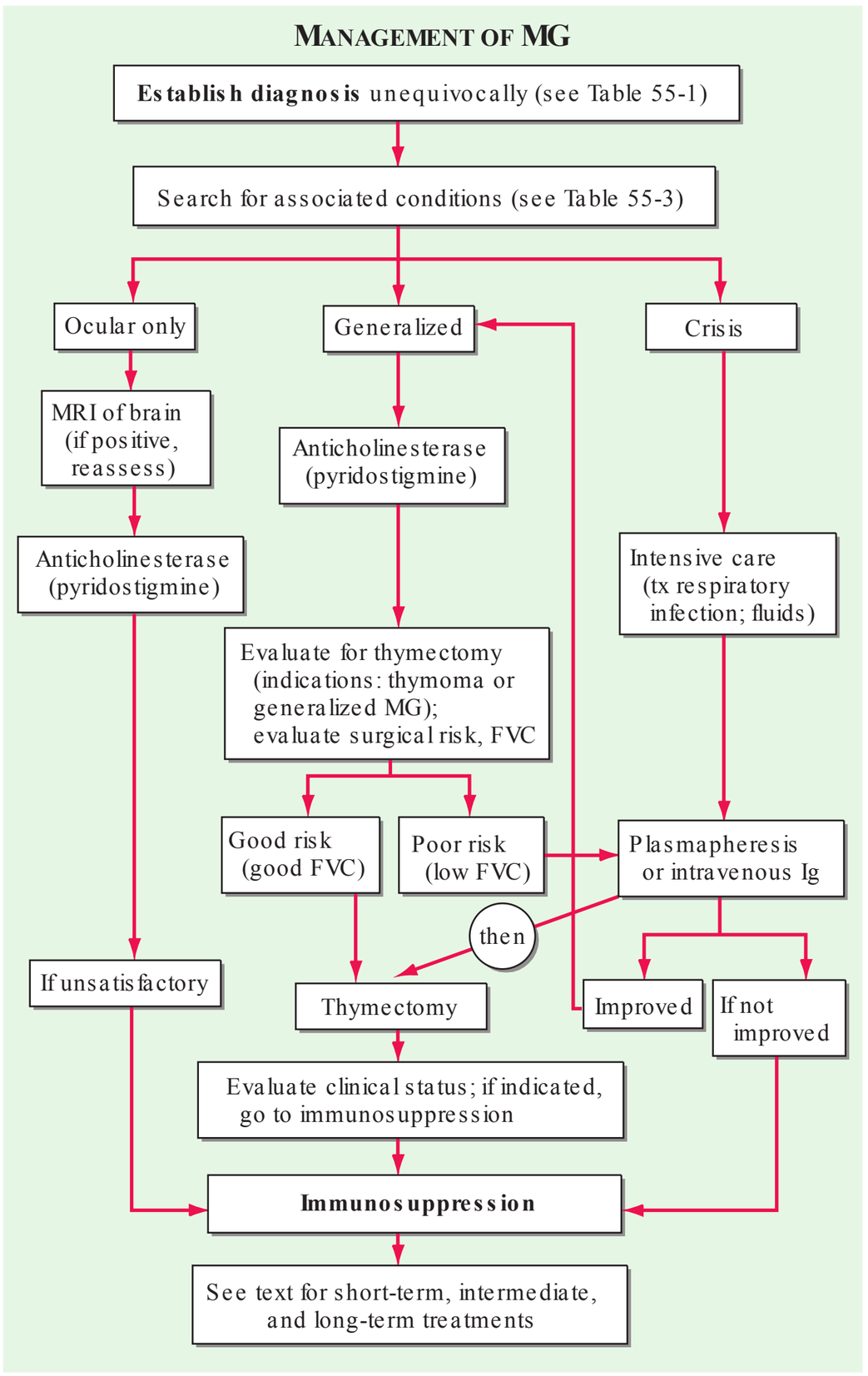


FIGURE 55-2
Algorithm for the management of myasthenia gravis. FVC, forced vital capacity; MRI, magnetic resonance imaging.

www.ketabpezeshki.com (021) 66485457 - 66485438

occasionally be useful to get the patient through the night but should not be used for daytime medication because of variable absorption. The maximum useful dose of pyridostigmine rarely exceeds 120 mg every 4–6 h during daytime. Overdosage with anticholinesterase medication may cause increased weakness and other side effects. In some patients, muscarinic side effects of the anticholinesterase medication (diarrhea, abdominal cramps, salivation, nausea) may limit the dose tolerated. Atropine/diphenoxylate or loperamide is useful for the treatment of GI symptoms.

THYMECTOMY Two separate issues should be distinguished: (1) surgical removal of thymoma, and (2) thymectomy as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are histologically benign. In the absence of a tumor, the available evidence suggests that up to 85% of patients experience improvement after thymectomy; of these, ~35% achieve drug-free remission. However, the improvement is typically delayed for months to years. The advantage of thymectomy is that it offers the possibility of long-term benefit, in some cases diminishing or eliminating the need for continuing medical treatment. Review of the published studies showed that following thymectomy, MG patients were 1.7 times as likely to improve and twice as likely to attain remission as those who did not have surgical thymectomy. In view of these potential benefits and of the negligible risk in skilled hands, thymectomy has gained widespread acceptance in the treatment of MG. It is the consensus that thymectomy should be carried out in all patients with generalized MG who are between the ages of puberty and at least 55 years. Whether thymectomy should be recommended in children, in adults >55 years of age, and in patients with weakness limited to the ocular muscles is still a matter of debate. There is also evidence that patients with MuSK antibody–positive MG respond less well to thymectomy than those with AChR antibody. Thymectomy must be carried out in a hospital where it is performed regularly and where the staff is experienced in the pre- and postoperative management, anesthesia, and surgical techniques of total thymectomy. Thymectomy should never be carried out as an emergency procedure, but only when the patient is adequately prepared. If necessary, treatment with IVIg or plasmapheresis may be used before surgery, but it is helpful to try to avoid immunosuppressive agents because of the risk of infection.

IMMUNOSUPPRESSION Immunosuppression using one or more of the available agents is effective in nearly all patients with MG. The choice of drugs or other immunomodulatory treatments should be guided by the relative benefits and risks for the individual patient and the urgency of treatment. It is helpful to develop a treatment plan based on short-term, intermediate-term, and long-term objectives. For example, if immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, IVIg should be administered or plasmapheresis should be undertaken. For the intermediate term, glucocorticoids and cyclosporine or tacrolimus generally produce clinical improvement within a period of 1–3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (as long as a year), but these drugs have advantages for the long-term treatment of patients with MG. There is a growing body of evidence that rituximab is effective in many MG patients, especially those with MuSK antibody.

Glucocorticoid therapy Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great majority of patients. To minimize adverse side effects, prednisone should be given in a single dose rather than in divided doses throughout the day. The initial dose should be relatively low (15–25 mg/d) to avoid the early weakening that occurs in up to one-third of patients treated initially with a high-dose regimen. The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached. This dose is maintained for 1–3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1–3 months; the goal is to reduce the dose on the "off day" to zero or to a minimal level. Generally, patients begin to improve within a few weeks after reaching the maximum dose, and improvement continues to progress for months or years. The prednisone dosage may gradually be reduced, but usually months or years may be needed to determine the minimum effective dose, and close monitoring is required. Few patients are able to do without immunosuppressive agents entirely. Patients on long-term glucocorticoid therapy must be followed carefully to prevent or treat adverse side effects. The most common errors in glucocorticoid treatment of myasthenic patients include (1) insufficient persistence—improvement may be delayed and gradual; (2) tapering the dosage too early, too rapidly, or excessively; and (3) lack of attention to prevention and treatment of side effects.

Other immunosuppressive drugs Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab, and occasionally cyclophosphamide are effective in many patients, either alone or in various combinations.

Mycophenolate mofetil has become one of the most widely used drugs in the treatment of MG because of its effectiveness and relative lack of side effects. A dose of 1–1.5 g bid is recommended. Its mechanism of action involves inhibition of purine synthesis by the de novo pathway. Since lymphocytes have only the de novo pathway, but lack the alternative salvage pathway that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes but not proliferation of other cells. It does not kill or eliminate preexisting autoreactive lymphocytes, and therefore clinical improvement may be delayed for many months to a year, until the preexisting autoreactive lymphocytes die spontaneously. The advantage of

www.ketabpezeshki.com (021) 66485457 - 66485438

mycophenolate lies in its relative lack of adverse side effects, with only occasional production of GI symptoms, rare development of leukopenia, and very small risks of malignancy or progressive multifocal leukoencephalopathy inherent in nearly all immunosuppressive treatments. Although two published studies did not show positive outcomes, most experts attribute the negative results to flaws in the trial designs, and mycophenolate is widely used for long-term treatment of myasthenic patients.

Until recently, azathioprine has been the most commonly used immunosuppressive agent for MG because of its relative safety in most patients and long track record. Its therapeutic effect may add to that of glucocorticoids and/or allow the glucocorticoid dose to be reduced. However, up to 10% of patients are unable to tolerate azathioprine because of idiosyncratic reactions consisting of flu-like symptoms of fever and malaise, bone marrow suppression, or abnormalities of liver function. An initial dose of 50 mg/d should be used for several days to test for these side effects. If this dose is tolerated, it is increased gradually to about 2–3 mg/kg of total body weight, or until the white blood count falls to 3000–4000/μL. The beneficial effect of azathioprine takes 3–6 months to begin and even longer to peak. In patients taking azathioprine, allopurinol should never be used to treat hyperuricemia. Because the two drugs share a common degradation pathway; the result may be severe bone marrow suppression due to increased effects of the azathioprine.

The calcineurin inhibitors cyclosporine and tacrolimus (FK506) are approximately as effective as azathioprine and are being used increasingly in the management of MG. Their beneficial effect appears more rapidly than that of azathioprine. Either drug may be used alone, but they are usually used as an adjunct to glucocorticoids to permit reduction of the glucocorticoid dose. The usual dose of cyclosporine is 4–5 mg/kg per day, and the average dose of tacrolimus is 0.07–0.1 mg/kg per day, given in two equally divided doses (to minimize side effects). Side effects of these drugs include hypertension and nephrotoxicity, which must be closely monitored. "Trough" blood levels are measured 12 h after the evening dose. The therapeutic range for the trough level of cyclosporine is 150–200 ng/L, and for tacrolimus, it is 5–15 ng/L.

Rituximab (Rituxan) is a monoclonal antibody that binds to the CD20 molecule on B lymphocytes. It has been widely used for the treatment of B cell lymphomas and has also proven successful in the treatment of several autoimmune diseases including rheumatoid arthritis, pemphigus, and some IgM-related neuropathies. There is now an extensive literature on the benefit of rituximab in MG. It is particularly effective in MuSK antibody–positive MG, although some patients with AChR antibody MG respond to it as well. The usual dose is 375 mg/m^2, given IV in 4 weekly infusions, or 1 g, given IV on two occasions 2 weeks apart.

For the occasional patient with MG that is genuinely refractory to optimal treatment with conventional immunosuppressive agents, a course of high-dose cyclophosphamide may induce long-lasting benefit by "rebooting" the immune system. At high doses, cyclophosphamide eliminates mature lymphocytes but spares hematopoietic precursors (stem cells), because they express the enzyme aldehyde dehydrogenase, which hydrolyzes cyclophosphamide. At present, this procedure is reserved for refractory patients and should be administered only in a facility fully familiar with this approach. Maintenance immunotherapy after rebooting is usually required to sustain the beneficial effect.

PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN Plasmapheresis has been used therapeutically in MG. Plasma, which contains the pathogenic antibodies, is mechanically separated from the blood cells, which are returned to the patient. A course of five exchanges (3–4 L per exchange) is generally administered over a 10- to 14-day period. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients. It is useful as a temporary expedient in seriously affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy).

The indications for the use of IVIg are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness or prior to surgery. This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 5 days (400 mg/kg per day). If tolerated, the total dose of IVIg can be given over a 3- to 4-day period. Improvement occurs in ~70% of patients, beginning during treatment, or within a week, and continuing for weeks to months. The mechanism of action of IVIg is not known; the treatment has no consistent effect on the measurable amount of circulating AChR antibody. Adverse reactions are generally not serious but may include headache, fluid overload, and rarely aseptic meningitis or renal failure. IVIg should rarely be used as a long-term treatment in place of rationally managed immunosuppressive therapy. Unfortunately, there is a tendency for physicians unfamiliar with immunosuppressive treatments to rely on repeated IVIg infusions, which usually produce only intermittent benefit, do not reduce the underlying autoimmune response, and are very costly. The intermediate and long-term treatment of myasthenic patients requires other methods of therapy outlined earlier in this chapter.

MANAGEMENT OF MYASTHENIC CRISIS Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually consists of respiratory failure caused by diaphragmatic and intercostal muscle weakness. Crisis rarely occurs in properly managed patients. Treatment should be carried out in intensive care units staffed with teams experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy. The possibility that deterioration could be due to excessive anticholinesterase medication ("cholinergic crisis") is best excluded by temporarily stopping anticholinesterase drugs. The most common

www.ketabpezeshki.com (021) 66485457 - 66485438

cause of crisis is intercurrent infection. T is should be treated immediately, because the mechanical and immunologic defenses of the patient can be assumed to be compromised. T e myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, respiratory assistance (preferably noninvasive, using bilevel positive airway pressure), and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or IVIg is frequently helpful in hastening recovery.

DRUGS TO AVOID IN MYASTHENIC PATIENTS Many drugs have been reported to exacerbate weakness in patients with MG **(Table 55-4)**, but not all patients react adversely to all of these. Conversely, not all "safe" drugs can be used with impunity in patients with MG. As a rule, the listed drugs should be avoided whenever possible, and myasthenic patients should be followed closely when any new drug is introduced.

TABLE 55-4

DRUGS WITH INTERACTIONS IN MYASTHENIA GRAVIS (MG)

Drugs That May Exacerbate MG
Antibiotics
Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin
Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin
Macrolides: e.g., erythromycin, azithromycin
Nondepolarizing muscle relaxants for surgery
d-Tubocurarine (curare), pancuronium, vecuronium, atracurium
Beta-blocking agents
Propranolol, atenolol, metoprolol
Local anesthetics and related agents
Procaine, Xylocaine in large amounts
Procainamide (for arrhythmias)
Botulinum toxin
Botox exacerbates weakness
Quinine derivatives
Quinine, quinidine, chloroquine, mefloquine (Lariam)
Magnesium
Decreases acetylcholine release
Penicillamine
May cause MG
Drugs with Important Interactions in MG
Cyclosporine
Broad range of drug interactions, which may raise or lower cyclosporine levels
Azathioprine
Avoid allopurinol—combination may result in myelosuppression

PATIENT ASSESSMENT

To evaluate the effectiveness of treatment as well as drug-induced side effects, it is important to assess the patient's clinical status systematically at baseline and on repeated interval examinations. Because of the variability of symptoms of MG, the interval history and physical findings on examination must be taken into account. T e most useful clinical tests include forward arm abduction time (up to a full 5 min), spirometry with determination of forced vital capacity, range of eye movements, and time to development of ptosis on upward gaze. Manual muscle testing or, preferably, quantitative dynamometry of limb muscles, especially proximal muscles, is also important. An interval form can provide a succinct summary of the patient's status and a guide to treatment results; an abbreviated form is shown in **Fig. 55-3**. A progressive reduction in the patient's AChR antibody level also provides clinically valuable confirmation of the effectiveness of treatment; conversely, a rise in AChR antibody levels during tapering of immunosuppressive medication may predict clinical exacerbation. For reliable quantitative measurement of AChR antibody levels, it is best to compare antibody levels from prior frozen serum aliquots with current serum samples in simultaneously run assays.

Myasthenia Gravis Worksheet

History				
General	Normal	Good	Fair	Poor
Diplopia	None	Rare	Occasional	Constant
Ptosis	None	Rare	Occasional	Constant
Arms	Normal	Slightly limited	Some ADL impairment	Definitely limited
Legs	Normal	Walks/runs fatigues	Can walk limited distances	Minimal walking
Speech	Normal	Dysarthric	Severely dysarthric	Unintelligible
Voice	Normal	Fades	Impaired	Severely impaired
Chew	Normal	Fatigue on normal foods	Fatigue on soft foods	Feeding tube
Swallow	Normal	Normal foods	Soft foods only	Feeding tube
Respiration	Normal	Dyspnea on unusual effort	Dyspnea on any effort	Dyspnea at rest

Examination

BP _____ Pulse _____ Wt _____
Edema _____
Vital capacity _____
Cataracts? R _____ L _____
EOMS _____
Ptosis time _____
Face _____

Arm abduction time R _____ L _____
Deltoids R _____ L _____
Biceps R _____ L _____
Triceps R _____ L _____
Grip R _____ L _____
Iliopsoas R _____ L _____
Quadriceps R _____ L _____
Hamstrings R _____ L _____
Other R _____ L _____

FIGURE 55-3
Abbreviated interval assessment form for use in evaluating treatment for myasthenia gravis.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 56

MUSCULAR DYSTROPHIES AND OTHER MUSCLE DISEASES

Anthony A. Amato ■ Robert H. Brown, Jr.

Skeletal muscle diseases, or myopathies, are disorders with structural changes or functional impairment of muscle. T ese conditions can be differentiated from other diseases of the motor unit (e.g., lower motor neuron or neuromuscular junction pathologies) by characteristic clinical and laboratory findings.

Myasthenia gravis and related disorders are discussed in Chap. 55; dermatomyositis, polymyositis, and inclusion body myositis are discussed in Chap. 57.

CLINICAL FEATURES

Most myopathies present with proximal, symmetric limb weakness (arms or legs) with preserved reflexes and sensation. However, asymmetric and predominantly distal weakness can be seen in some myopathies. An associated sensory loss suggests injury to a peripheral nerve or the central nervous system (CNS) rather than myopathy. On occasion, disorders affecting the motor nerve cell bodies in the spinal cord (anterior horn cell disease), the neuromuscular junction, or peripheral nerves can mimic findings of myopathy.

Muscle weakness

Symptoms of muscle weakness can be either intermittent or persistent. Disorders causing intermittent weakness **(Fig. 56-1)** include myasthenia gravis, periodic paralyses (hypokalemic, hyperkalemic, and paramyotonia congenita), and metabolic energy deficiencies of glycolysis (especially myophosphorylase deficiency), fatty acid utilization (carnitine palmitoyltransferase deficiency), and some mitochondrial myopathies. T e states of energy deficiency cause activity-related muscle breakdown accompanied by myoglobinuria, appearing as light-brown- to dark-brown-colored urine.

Most muscle disorders cause persistent weakness **(Fig. 56-2)**. In the majority of these, including most types of muscular dystrophy, polymyositis, and dermatomyositis, the proximal muscles are weaker than the distal and are symmetrically affected, and the facial muscles are spared, a pattern referred to as limb-girdle. T e differential diagnosis is more restricted for other patterns of weakness. Facial weakness (difficulty with eye closure and impaired smile) and scapular winging **(Fig. 56-3)** are characteristic of facioscapulohumeral dystrophy (FSHD). Facial and distal limb weakness associated with hand grip myotonia is virtually diagnostic of myotonic dystrophy type 1. When other cranial nerve muscles are weak, causing ptosis or extraocular muscle weakness, the most important disorders to consider include neuromuscular junction disorders, oculopharyngeal muscular dystrophy, mitochondrial myopathies, or some of the congenital myopathies **(Table 56-1)**. A pathognomonic pattern characteristic of inclusion body myositis is atrophy and weakness of the flexor forearm (e.g., wrist and finger flexors) and quadriceps muscles that is of en asymmetric. Less frequently, but important diagnostically, is the presence of a dropped head syndrome indicative of selective neck extensor muscle weakness. T e most important neuromuscular diseases associated with this pattern of weakness include myasthenia gravis, amyotrophic lateral sclerosis, late-onset nemaline myopathy, hyperparathyroidism, focal myositis, and some forms of inclusion body myopathy. A final pattern, recognized because of preferential distal extremity weakness, is typical of a unique category of muscular dystrophy, the distal myopathies.

It is important to examine functional capabilities to help disclose certain patterns of weakness **(Table 56-2)**. T e Gowers' sign **(Fig. 56-4)** is particularly useful.

www.ketabpezeshki.com (021) 66485457 - 66485438

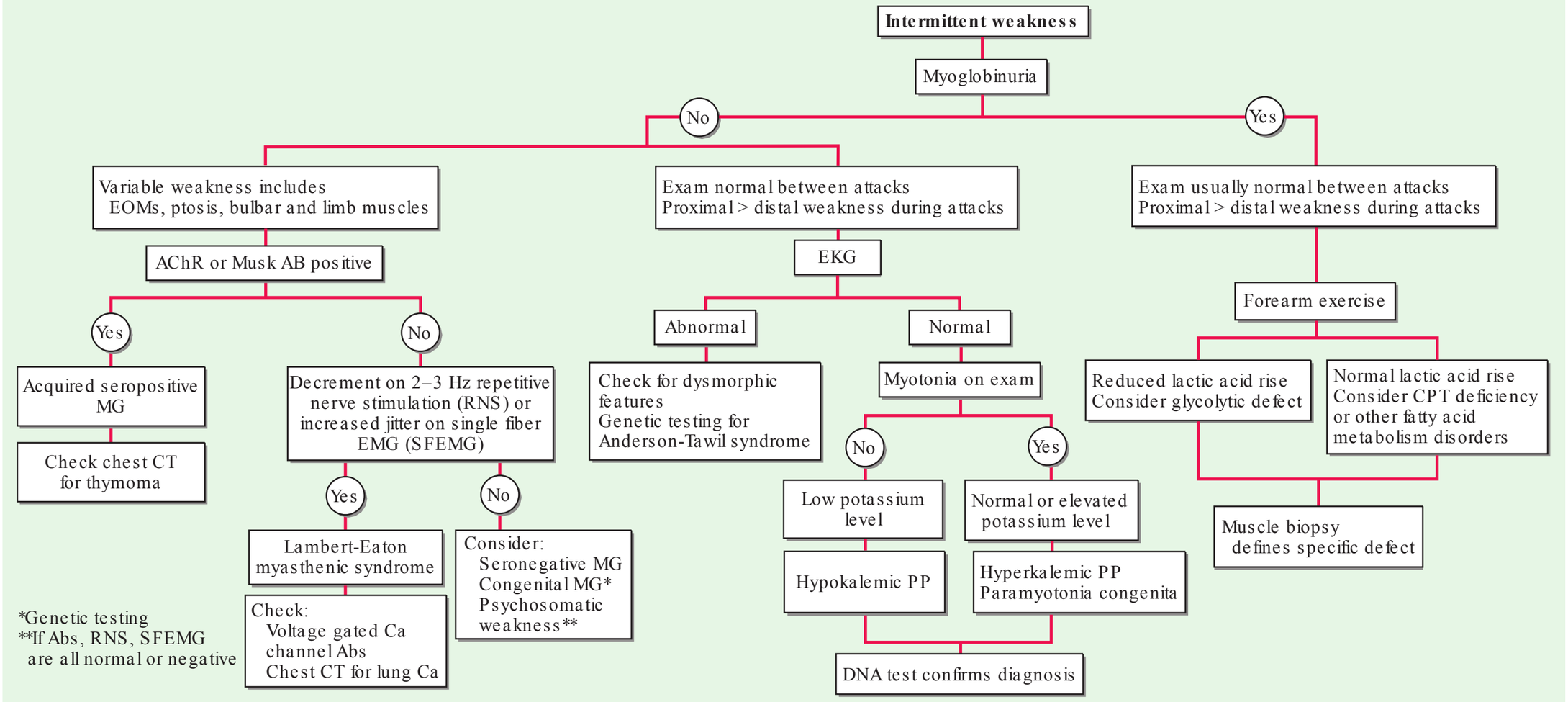


FIGURE 56-1

Diagnostic evaluation of intermittent weakness. AChR AB, acetylcholine receptor antibody; CPT, carnitine palmitoyltransferase; EOMs, extraocular muscles; MG, myasthenia gravis; PP, periodic paralysis.

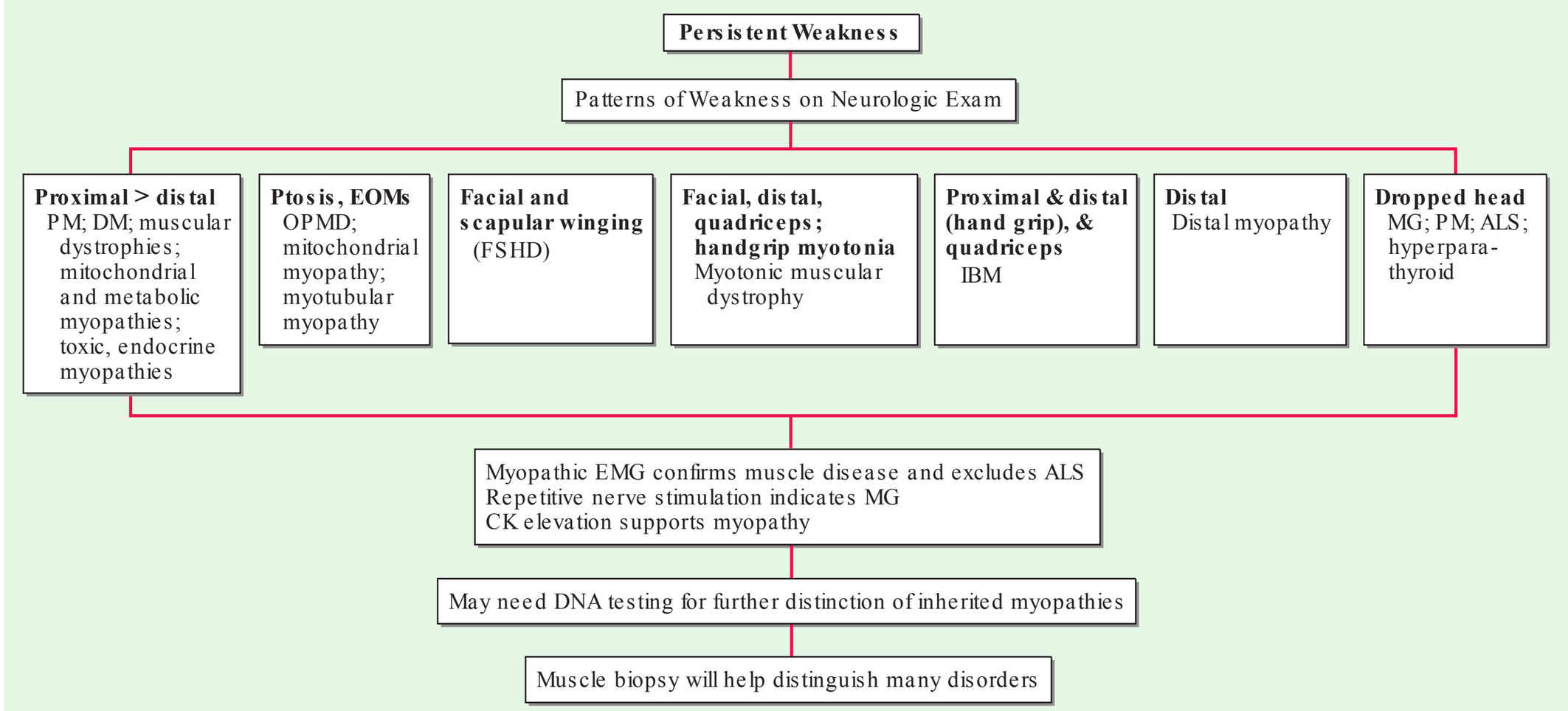


FIGURE 56-2

Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern of weakness in combination with the laboratory evaluation leads to a diagnosis. ALS, amyotrophic lateral sclerosis; CK, creatine kinase; DM, dermatomyositis; EMG, electromyography; EOMs, extraocular muscles; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PM, polymyositis.

www.ketabpezeshki.com (021) 66485457 - 66485438

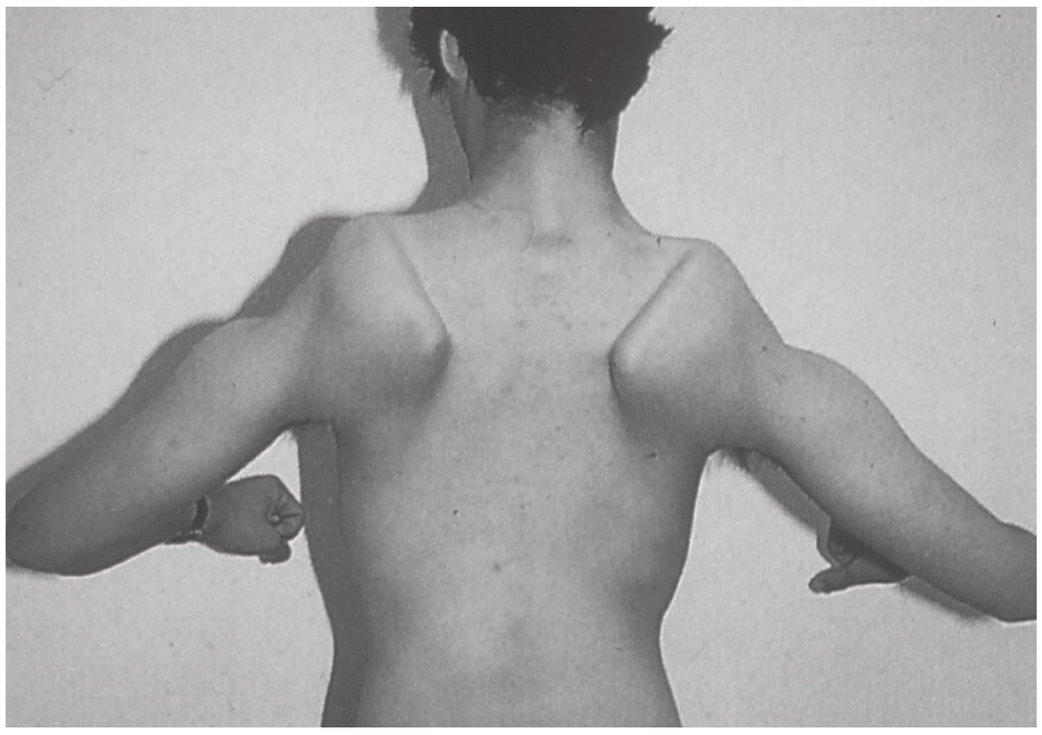


FIGURE 56-3
Facioscapulohumeral dystrophy with prominent scapular winging.

TABLE 56-1

NEUROMUSCULAR CAUSES OF PTOSIS OR OPHTHALMOPLEGIA
Peripheral Neuropathy
Guillain-Barré syndrome
Miller Fisher syndrome
Neuromuscular Junction
Botulism
Lambert-Eaton syndrome
Myasthenia gravis
Congenital myasthenia
Myopathy
Mitochondrial myopathies
Kearns-Sayre syndrome
Progressive external ophthalmoplegia
Oculopharyngeal and oculopharyngodistal muscular dystrophy
Myotonic dystrophy (ptosis only)
Congenital myopathy
Myotubular
Nemaline (ptosis only)
Hyperthyroidism/Graves' disease (ophthalmoplegia without ptosis)
Hereditary inclusion body myopathy type 3

Observing the gait of an individual may disclose a lordotic posture caused by combined trunk and hip weakness, frequently exaggerated by toe walking **(Fig. 56-5)**. A waddling gait is caused by the inability of weak hip muscles to prevent hip drop or hip dip. Hyperextension of the knee (genu recurvatum or back-kneeing) is characteristic of quadriceps muscle weakness; and a steppage gait, due to footdrop, accompanies distal weakness.

TABLE 56-2

OBSERVATIONS ON EXAMINATION THAT DISCLOSE MUSCLE WEAKNESS	
FUNCTIONAL IMPAIRMENT	MUSCLE WEAKNESS
Inability to forcibly close eyes	Upper facial muscles
Impaired pucker	Lower facial muscles
Inability to raise head from prone position	Neck extensor muscles
Inability to raise head from supine position	Neck flexor muscles
Inability to raise arms above head	Proximal arm muscles (may be only scapular stabilizing muscles)
Inability to walk without hyperextending knee (back-kneeing or genu recurvatum)	Knee extensor muscles
Inability to walk with heels touching the floor (toe walking)	Shortening of the Achilles tendon
Inability to lift foot while walking (steppage gait or footdrop)	Anterior compartment of leg
Inability to walk without a waddling gait	Hip muscles
Inability to get up from the floor without climbing up the extremities (Gowers' sign)	Hip, thigh, and trunk muscles
Inability to get up from a chair without using arms	Hip muscles

Any disorder causing muscle weakness may be accompanied by *f*atigue, referring to an inability to maintain or sustain a force (pathologic fatigability). T is condition must be differentiated from asthenia, a type of fatigue caused by excess tiredness or lack of energy. Associated symptoms may help differentiate asthenia and pathologic fatigability. Asthenia is of en accompanied by a tendency to avoid physical activities, complaints of daytime sleepiness, necessity for frequent naps, and difficulty concentrating on activities such as reading. T ere may be feelings of overwhelming stress and depression. T us, asthenia is not a myopathy. In contrast, pathologic fatigability occurs in disorders of neuromuscular transmission and in disorders altering energy production, including defects in glycolysis, lipid metabolism, or mitochondrial energy production. Pathologic fatigability also occurs in chronic myopathies because of difficulty accomplishing a task with less muscle. Pathologic fatigability is accompanied by abnormal clinical or laboratory findings. Fatigue without those supportive features almost never indicates a primary muscle disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

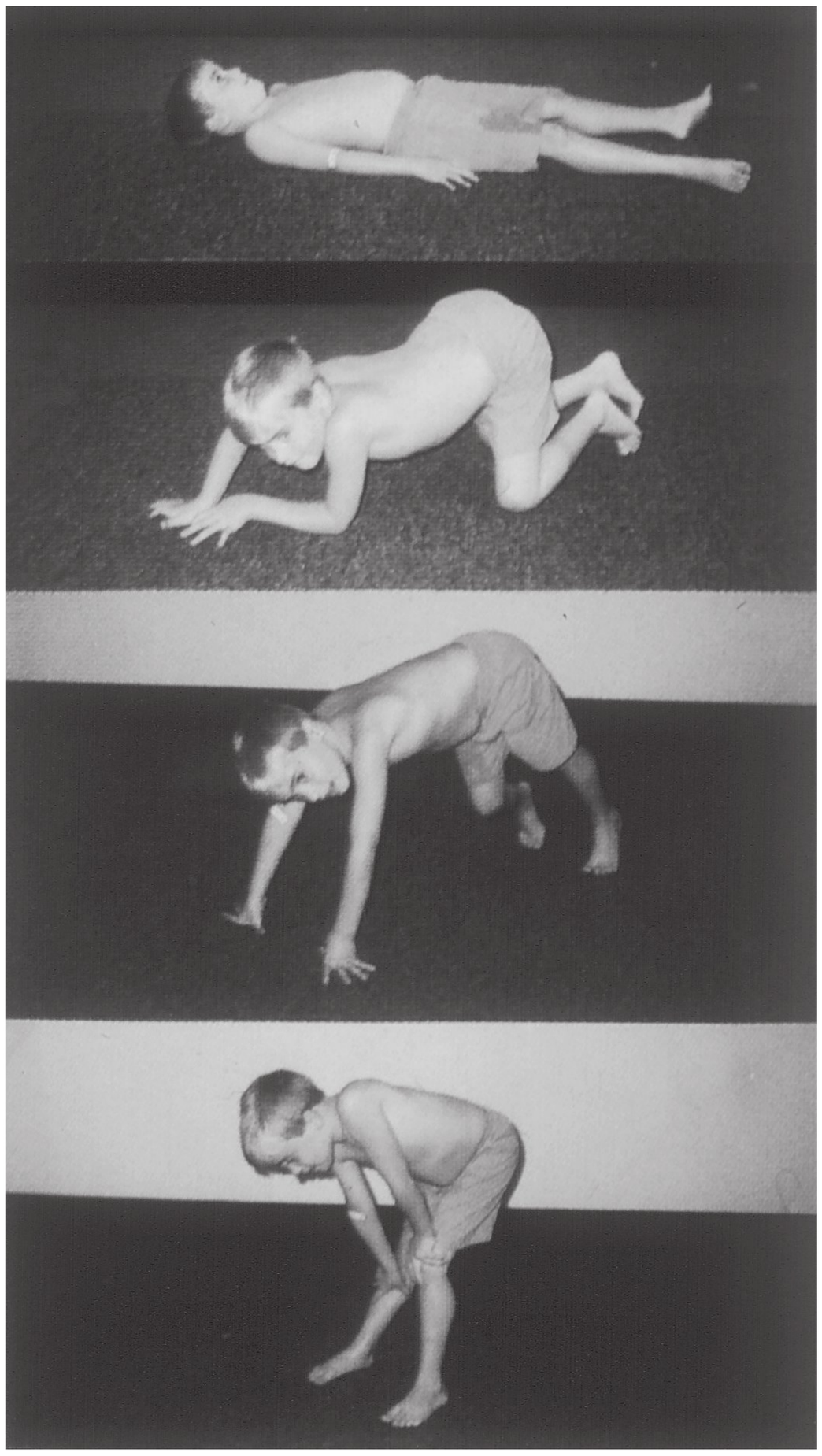


FIGURE 56-4
Gowers' sign showing a patient using his arms to climb up the legs in attempting to get up from the floor.

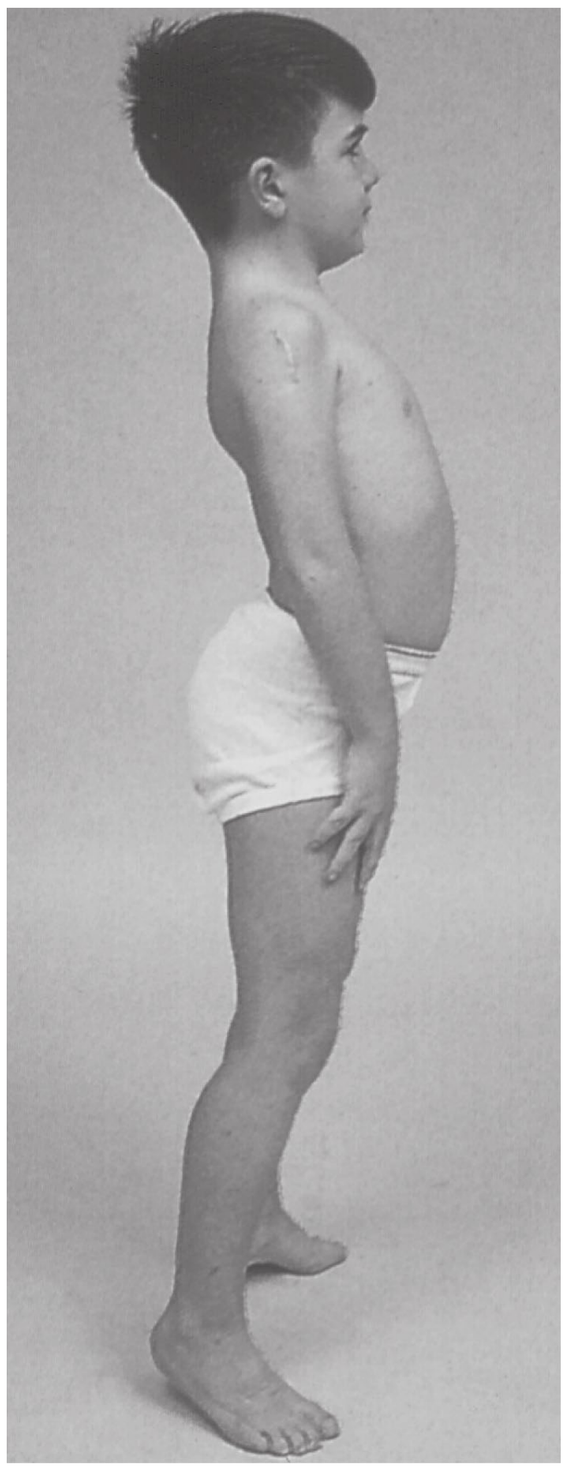


FIGURE 56-5
Lordotic posture, exaggerated by standing on toes, associated with trunk and hip weakness.

TABLE 56-3

DRUGS THAT CAUSE TRUE MYALGIA
Cimetidine
Cocaine
Cyclosporine
Danazol
Emetine
Gold
Heroin
Labetalol
Methadone
d-Penicillamine
Statins and other cholesterol-lowering agents
l-Tryptophan
Zidovudine

Muscle pain (myalgias), cramps, and stiffness

Muscle pain can be associated with cramps, spasms, contractures, and stiff or rigid muscles. In distinction, true myalgia (muscle aching), which can be localized or generalized, may be accompanied by weakness, tenderness to palpation, or swelling. Certain drugs cause true myalgia **(Table 56-3)**.

There are two painful muscle conditions of particular importance, neither of which is associated with muscle weakness. Fibromyalgia is a common, yet poorly understood, type of myofascial pain syndrome. Patients complain of severe muscle pain and tenderness and have specific painful trigger points, sleep disturbances, and easy fatigability. Serum creatine kinase (CK), erythrocyte sedimentation rate (ESR), electromyography (EMG), and muscle biopsy are normal. Polymyalgia rheumatica occurs mainly in patients >50 years and is characterized by stiffness and pain in the shoulders, lower back, hips, and thighs. The ESR is

www.ketabpezeshki.com (021) 66485457 - 66485438

elevated, while serum CK, EMG, and muscle biopsy are normal. Temporal arteritis, an inflammatory disorder of medium- and large-sized arteries, usually involving one or more branches of the carotid artery, may accompany polymyalgia rheumatica. Vision is threatened by ischemic optic neuritis. Glucocorticoids can relieve the myalgias and protect against visual loss.

Localized muscle pain is most often traumatic. A common cause of sudden abrupt-onset pain is a ruptured tendon, which leaves the muscle belly appearing rounded and shorter in appearance compared to the normal side. The biceps brachii and Achilles tendons are particularly vulnerable to rupture. Infection or neoplastic infiltration of the muscle is a rare cause of localized muscle pain.

A muscle cramp or spasm is a painful, involuntary, localized muscle contraction with a visible or palpable hardening of the muscle. Cramps are abrupt in onset, short in duration, and may cause abnormal posturing of the joint. The EMG shows firing of motor units, reflecting an origin from spontaneous neural discharge. Muscle cramps often occur in neurogenic disorders, especially motor neuron disease **(Chap. 39)**, radiculopathies, and polyneuropathies **(Chap. 53)**, but are not a feature of most primary muscle diseases. Duchenne muscular dystrophy is an exception because calf muscle complaints are a common complaint. Muscle cramps are also common during pregnancy.

A muscle contracture is different from a muscle cramp. In both conditions, the muscle becomes hard, but a contracture is associated with energy failure in glycolytic disorders. The muscle is unable to relax after an active muscle contraction. The EMG shows electrical silence. Confusion is created because contracture also refers to a muscle that cannot be passively stretched to its proper length (fixed contracture) because of fibrosis. In some muscle disorders, especially in Emery-Dreifuss muscular dystrophy and Bethlem myopathy, fixed contractures occur early and represent distinctive features of the disease.

Muscle stiffness can refer to different phenomena. Some patients with inflammation of joints and periarticular surfaces feel stiff. This condition is different from the disorders of hyperexcitable motor nerves causing stiff or rigid muscles. In stiff-person syndrome, spontaneous discharges of the motor neurons of the spinal cord cause involuntary muscle contractions mainly involving the axial (trunk) and proximal lower extremity muscles. The gait becomes stiff and labored, with hyperlordosis of the lumbar spine. Superimposed episodic muscle spasms are precipitated by sudden movements, unexpected noises, and emotional upset. The muscles relax during sleep. Serum antibodies against glutamic acid decarboxylase are present in approximately two-thirds of cases. In neuromyotonia (Isaacs' syndrome), there is hyperexcitability of the peripheral nerves manifesting as continuous muscle fiber activity. Myokymia (groups of fasciculations associated with continuous undulations of muscle) and impaired muscle relaxation are the result. Muscles of the leg are stiff, and the constant contractions of the muscle cause increased sweating of the extremities. This is peripheral nerve hyperexcitability is mediated by antibodies that target voltage-gated potassium channels. The site of origin of the spontaneous nerve discharges is principally in the distal portion of the motor nerves.

Myotonia is a condition of prolonged muscle contraction followed by slow muscle relaxation. It always follows muscle activation (action myotonia), usually voluntary, but may be elicited by mechanical stimulation (percussion myotonia) of the muscle. Myotonia typically causes difficulty in releasing objects after a firm grasp. In myotonic muscular dystrophy type 1 (DM1), distal weakness usually accompanies myotonia, whereas in DM2, proximal muscles are more affected; thus the related term proximal myotonic myopathy (PROMM) is used to describe this condition. Myotonia also occurs with myotonia congenita (a chloride channel disorder), but in this condition muscle weakness is not prominent. Myotonia may also be seen in individuals with sodium channel mutations (hyperkalemic periodic paralysis or potassium-sensitive myotonia). Another sodium channelopathy, paramyotonia congenita, also is associated with muscle stiffness. In contrast to other disorders associated with myotonia in which the myotonia is eased by repetitive activity, paramyotonia congenita is named for a paradoxical phenomenon whereby the myotonia worsens with repetitive activity.

Muscle enlargement and atrophy

In most myopathies muscle tissue is replaced by fat and connective tissue, but the size of the muscle is usually not affected. However, in many limb-girdle muscular dystrophies (and particularly the dystrophinopathies), enlarged calf muscles are typical. The enlargement represents true muscle hypertrophy; thus the term pseudohypertrophy should be avoided when referring to these patients. The calf muscles remain very strong even late in the course of these disorders. Muscle enlargement can also result from infiltration by sarcoid granulomas, amyloid deposits, bacterial and parasitic infections, and focal myositis. In contrast, muscle atrophy is characteristic of other myopathies. In dysferlinopathies (LGMD2B) and anoctaminopathies (LGMD2L), there is a predilection for early atrophy of the gastrocnemius muscles, particularly the medial aspect. Atrophy of the humeral muscles is characteristic of FSHD.

www.ketabpezeshki.com (021) 66485457 - 66485438

LABORATORY EVALUATION

A limited battery of tests can be used to evaluate a suspected myopathy. Nearly all patients require serum enzyme level measurements and electrodiagnostic studies as screening tools to differentiate muscle disorders from other motor unit diseases. T e other tests described—DNA studies, the forearm exercise test, and muscle biopsy—are used to diagnose specific types of myopathies.

Serum enzymes

CK is the preferred muscle enzyme to measure in the evaluation of myopathies. Damage to muscle causes the CK to leak from the muscle fiber to the serum. T e MM isoenzyme predominates in skeletal muscle, whereas creatine kinase-myocardial bound (CK-MB) is the marker for cardiac muscle. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis or af er strenuous activity, minor trauma (including the EMG needle), a prolonged muscle cramp, or a generalized seizure. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), aldolase, and lactic dehydrogenase (LDH) are enzymes sharing an origin in both muscle and liver. Problems arise when the levels of these enzymes are found to be elevated in a routine screening battery, leading to the erroneous assumption that liver disease is present when in fact muscle could be the cause. An elevated γ-glutamyl transferase (GGT) helps to establish a liver origin because this enzyme is not found in muscle.

Electrodiagnostic studies

EMG, repetitive nerve stimulation, and nerve conduction studies **(Chap. 6)** are essential methods for evaluation of the patient with suspected muscle disease. In combination, they provide the information necessary to differentiate myopathies from neuropathies and neuromuscular junction diseases. Routine nerve conduction studies are typically normal in myopathies but reduced amplitudes of compound muscle action potentials may be seen in atrophied muscles. T e needle EMG may reveal irritability on needle placement suggestive of a necrotizing myopathy (inflammatory myopathies, dystrophies, toxic myopathies, myotonic myopathies), whereas a lack of irritability is characteristic of long-standing myopathic disorders (muscular dystrophies, endocrine myopathies, disuse atrophy, and many of the metabolic myopathies). In addition, the EMG may demonstrate myotonic discharges that will narrow the differential diagnosis **(Table 56-4)**. Another important EMG finding is the presence of short-duration, small-amplitude, polyphasic motor unit action potentials (MUAPs). Such MUAPs can be seen in both myopathic and neuropathic disorders; however, the recruitment or firing pattern is different. In myopathies, the MUAPs fire early but at a normal rate to compensate for the loss of individual muscle fibers, whereas in neurogenic disorders the MUAPs fire faster. T e EMG is usually normal in steroid or disuse myopathy, both of which are associated with type 2 fiber atrophy; this is because the EMG preferentially assesses the physiologic function of type 1 fibers. T e EMG can also be invaluable in helping to choose an appropriately affected muscle to sample for biopsy.

TABLE 56-4

MYOTONIC DISORDERS
Myotonic dystrophy type 1
Myotonic dystrophy type 2/proximal myotonic myopathy
Myotonia congenita
Paramyotonia congenita
Hyperkalemic periodic paralysis
Chondrodystrophic myotonia (Schwartz-Jampel syndrome)
Centronuclear/myotubular myopathy[a]
Drug-induced
Cholesterol-lowering agents (statin medications, fibrates)
Cyclosporine
Chloroquine
Glycogen storage disorders[a] (Pompe's disease, branching enzyme deficiency, debranching enzyme deficiency)
Myofibrillar myopathies (MFM)[a]

[a]Associated with myotonic discharges on electromyography but no clinical myotonia.

DNA analysis

T is serves as an important tool for the definitive diagnosis of many muscle disorders. Nevertheless, there are a number of limitations in currently available molecular diagnostics. For example, in Duchenne and Becker dystrophies, two-thirds of patients have deletion or duplication mutations in the dystrophin gene that are easy to detect, while the remainder have point mutations that are much more difficult to find. For patients without identifiable gene defects, the muscle biopsy remains the main diagnostic tool.

Forearm exercise test

In myopathies with intermittent symptoms, and especially those associated with myoglobinuria, there may be a defect in glycolysis. Many variations of the forearm exercise test exist. For safety, the test should not be performed under ischemic conditions to avoid an unnecessary insult to the muscle, causing rhabdomyolysis. T e test is performed by placing a small indwelling catheter into an antecubital vein. A baseline blood

www.ketabpezeshki.com (021) 66485457 - 66485438

sample is obtained for lactic acid and ammonia. The forearm muscles are exercised by asking the patient to vigorously open and close the hand for 1 min. Blood is then obtained at intervals of 1, 2, 4, 6, and 10 min for comparison with the baseline sample. A three- to fourfold rise of lactic acid is typical. The simultaneous measurement of ammonia serves as a control, because it should also rise with exercise. In patients with myophosphorylase deficiency or other glycolytic defects, the lactic acid rise will be absent or below normal, while the rise in ammonia will reach control values. If there is lack of effort, neither lactic acid nor ammonia will rise. Patients with selective failure to increase ammonia may have myoadenylate deaminase deficiency. This is condition has been reported to be a cause of myoglobinuria, but deficiency of this enzyme in asymptomatic individuals makes interpretation controversial.

Muscle biopsy

Muscle biopsy is an important step in establishing the diagnosis of a suspected myopathy. The biopsy is usually obtained from a quadriceps or biceps brachii muscle, less commonly from a deltoid muscle. Evaluation includes a combination of techniques—light microscopy, histochemistry, immunocytochemistry with a battery of antibodies, and electron microscopy. Not all techniques are needed for every case. A specific diagnosis can be established in many disorders. Endomysial inflammatory cells surrounding and invading muscle fibers are seen in polymyositis; similar endomysial infiltrates associated with muscle fibers containing rimmed vacuoles and amyloid deposits consisting of SMI-31-, p62-, and TDP-43-positive inclusions within fibers are characteristic of inclusion body myositis; and perivascular, perimysial inflammation associated with perifascicular atrophy is a feature of dermatomyositis. In addition, the congenital myopathies have distinctive light and electron microscopy features essential for diagnosis. Mitochondrial and metabolic (e.g., glycogen and lipid storage diseases) myopathies also demonstrate distinctive histochemical and electron-microscopic profiles. Biopsied muscle tissue can be sent for metabolic enzyme or mitochondrial DNA analyses. A battery of antibodies is available for the identification of abnormal proteins to help diagnose specific types of muscular dystrophies. Western blot analysis on muscle specimens can be performed to determine whether specific muscle proteins are reduced in quantity or are of abnormal size.

HEREDITARY MYOPATHIES

Muscular dystrophy refers to a group of hereditary progressive diseases each with unique phenotypic and genetic features **(Tables 56-5, 56-6, and 56-7)**.

DUCHENNE MUSCULAR DYSTROPHY

This is X-linked recessive disorder, sometimes also called pseudohypertrophic muscular dystrophy, has an incidence of ~1 per 5200 live-born males.

Clinical features

Duchenne dystrophy is present at birth, but the disorder usually becomes apparent between ages 3 and 5 years. The boys fall frequently and have difficulty keeping up with friends when playing. Running, jumping, and hopping are invariably abnormal. By age 5 years, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself (Gowers' maneuver [Fig. 56-4]). Contractures of the heel cords and iliotibial bands become apparent by age 6 years, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between ages 8 and 10 years, walking may require the use of braces; joint contractures and limitations of hip flexion, knee, elbow, and wrist extension are made worse by prolonged sitting. Prior to the use of glucocorticoids, most boys became wheelchair dependent by 12 years of age. Contractures become fixed, and a progressive scoliosis often develops that may be associated with pain. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By age 16–18 years, patients are predisposed to serious, sometimes fatal pulmonary infections. Other causes of death include aspiration of food and acute gastric dilation.

A cardiac cause of death is uncommon despite the presence of a cardiomyopathy in almost all patients. Congestive heart failure seldom occurs except with severe stress such as pneumonia. Cardiac arrhythmias are rare. The typical electrocardiogram (ECG) shows an increased net RS in lead V_1; deep, narrow Q waves in the precordial leads; and tall right precordial R waves in V_1. Intellectual impairment in Duchenne dystrophy is common; the average intelligence quotient (IQ) is ~1 standard deviation (SD) below the mean. Impairment of intellectual function appears to be nonprogressive and affects verbal ability more than performance.

Laboratory features

Serum CK levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and loss of muscle mass. EMG demonstrates features typical of myopathy. The muscle biopsy shows muscle fibers of varying size as well as small groups of necrotic and regenerating fibers. Connective tissue and fat replace lost muscle fibers. A definitive diagnosis of Duchenne

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-5

PROGRESSIVE MUSCULAR DYSTROPHIES

TYPE	INHERITANCE	DEFECTIVE GENE/ PROTEIN	ONSET AGE	CLINICAL FEATURES	OTHER ORGAN SYSTEMS INVOLVED
Duchenne	XR	Dystrophin	Before 5 years	Progressive weakness of girdle muscles Unable to walk after age 12 Progressive kyphoscoliosis Respiratory failure in second or third decade	Cardiomyopathy Mental impairment
Becker	XR	Dystrophin	Early childhood to adult	Progressive weakness of girdle muscles Able to walk after age 15 Respiratory failure may develop by fourth decade	Cardiomyopathy
Limb-girdle	AD/AR	Several (Tables 56-6, 56-7)	Early childhood to early adult	Slow progressive weakness of shoulder and hip girdle muscles	± Cardiomyopathy
Emery-Dreifuss	XR/AD	Emerin, lamin A/C Nesprin-1, nesprin-2,TMEM43	Childhood to adult	Elbow/knee/ankle contractures, humeral and peroneal weakness	Cardiomyopathy
Congenital	AR	Several	At birth or within first few months	Hypotonia, contractures, delayed milestones Progression to respiratory failure in some; static course in others	CNS abnormalities (hypomyelination, malformation) Eye abnormalities
Myotonic[a] (DM1, DM2)	AD	DM1: Expansion CTG repeat DM2: Expansion CCTG repeat	Childhood to adult; possibly infancy if mother affected (DM1 only)	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion Preferential proximal weakness in DM2	Cardiac conduction defects Mental impairment Cataracts Frontal baldness Gonadal atrophy
FSHD1	AD	DUX4 4q	Childhood to adult	Slowly progressive weakness of face, shoulder girdle, and foot dorsiflexion	Deafness
FSHD2	AD	SMCHD1			Coats'(eye) disease
Oculopharyngeal	AD	Expansion, poly-A RNA binding protein	Fifth to sixth decade	Slowly progressive weakness of extraocular, pharyngeal, and limb muscles	—

[a]Two forms of myotonic dystrophy, DM1 and DM2, have been identified. Many features overlap (see text).
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; XR, X-linked recessive.

dystrophy can be established on the basis of dystrophin deficiency in a biopsy of muscle tissue or mutation analysis on peripheral blood leukocytes, as discussed below.

Duchenne dystrophy is caused by a mutation of the gene that encodes dystrophin, a 427-kDa protein localized to the inner surface of the sarcolemma of the muscle fiber. T e dystrophin gene is >2000 kb in size and thus is one of the largest identified human genes. It is localized to the short arm of the X chromosome at Xp21. T e most common gene mutation is a deletion. T e size varies but does not correlate with disease severity. Deletions are not uniformly distributed over the gene but rather are most common near the beginning (5′ end) and middle of the gene. Less of en, Duchenne dystrophy is caused by a gene duplication or point mutation. Identification of a specific mutation allows for an unequivocal diagnosis, makes possible accurate testing of potential carriers, and is useful for prenatal diagnosis.

A diagnosis of Duchenne dystrophy can also be made by Western blot analysis of muscle biopsy specimens, revealing abnormalities on the quantity and

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-6

AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDS)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD1A	Onset second to eighth decade Muscle weakness affects proximal and distal limb muscles, vocal cords, and pharyngeal muscles	Serum CK 2× normal EMG myopathic and may have pseudomotonic discharges Muscle biopsy: features of MFM	Myotilin
LGMD1B	Onset first or second decade Proximal lower limb weakness and cardiomyopathy with conduction defects Some cases indistinguishable from Emery-Dreifuss muscular dystrophy with joint contractures	Serum CK 3–5× normal EMG myopathic	Lamin A/C
LGMD1C	Onset in early childhood Proximal weakness Gowers' sign, calf hypertrophy, rippling muscles Exercise-related muscle cramps	Serum CK 4–25× normal EMG myopathic	Caveolin-3
LGMD1D	Onset second to sixth decade Proximal and distal muscle weakness	Serum CK 2–3× normal EMG myopathic Muscle biopsy: features of MFM	DNAJB6
LGMD1E	Onset first to sixth decade Proximal or distal muscle weakness Cardiomyopathy and arrhythmias	Serum CK 2–4× normal EMG myopathic and may have pseudomotonic discharges Muscle biopsy: features of MFM	Desmin
LGMD1F	Onset infancy to sixth decade Proximal or distal weakness May have early contractures resembling Emery-Dreifuss syndrome	Serum CK normal to 20× normal EMG myopathic Muscle biopsy may show enlarged nuclei with central pallor, rimmed vacuoles, and filamentous inclusions	TNPO3

Abbreviations: CK, creatine kinase; EMG, electromyography; MFM, myofibrillar myopathy; NCS, nerve conduction studies.

molecular weight of dystrophin protein. In addition, immunocytochemical staining of muscle with dystrophin antibodies can be used to demonstrate absence or deficiency of dystrophin localizing to the sarcolemmal membrane. Carriers of the disease may demonstrate a mosaic pattern, but dystrophin analysis of muscle biopsy specimens for carrier detection is not reliable.

Pathogenesis

Dystrophin is part of a large complex of sarcolemmal proteins and glycoproteins **(Fig. 56-6)**. Dystrophin binds to F-actin at its amino terminus and to β-dystroglycan at the carboxyl terminus. β-Dystroglycan complexes to α-dystroglycan, which binds to laminin in the extracellular matrix (ECM). Laminin has a heterotrimeric molecular structure arranged in the shape of a cross with one heavy chain and two light chains, β_1 and γ_1. The laminin heavy chain of skeletal muscle is designated laminin α_2. Collagen proteins IV and VI are also found in the ECM. Like β-dystroglycan, the transmembrane sarcoglycan proteins also bind to dystrophin; these five proteins (designated α- through ε-sarcoglycan) complex tightly with each other. More recently, other membrane proteins implicated in muscular dystrophy have been found to be loosely affiliated with constituents of the dystrophin complex. These include caveolin-3, α_7 integrin, and collagen VI.

Dystrophin localizes to the cytoplasmic face of the muscle cell membrane. It complexes with two transmembrane protein complexes, the dystroglycans and the sarcoglycans. The dystroglycans bind to the extracellular matrix protein merosin, which is also complexed with β_1 and α_7 integrins (Tables 56-5, 56-6, and 56-7). Dysferlin complexes with caveolin-3 (which binds to neuronal nitric oxide synthase, or nNOS) but not with the dystrophin-associated proteins or the integrins. In some of the congenital dystrophies and limb-girdle muscular dystrophies (LGMDs), there is loss of function of different enzymes that glycosylate α-dystroglycan, which thereby inhibits proper binding to merosin: POMT1, POMT2, POMGnT1, Fukutin, Fukutin-related protein, and LARGE.

The dystrophin-glycoprotein complex appears to confer stability to the sarcolemma, although the function of each individual component of the complex is incompletely understood. Deficiency of one member of the complex may cause abnormalities in other components.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-7

AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDS)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD2A	Onset first or second decade Scapular winging; no calf hypertrophy; no cardiac or respiratory muscle weakness Proximal and distal weakness; may have contractures at elbows, wrists, and fingers	Serum CK 3–15× normal EMG myopathic Muscle biopsy may show lobulated muscle fibers	Calpain-3
LGMD2B	Onset second or third decade Proximal muscle weakness at onset, later distal (calf) muscles affected Miyoshi's myopathy is variant of LGMD2B with calf muscles affected at onset	Serum CK 3–100× normal EMG myopathic Inflammation on muscle biopsy may simulate polymyositis	Dysferlin
LGMD2C–F	Onset in childhood to teenage years Clinical condition similar to Duchenne and Becker muscular dystrophies Cognitive function normal	Serum CK 5–100× normal EMG myopathic	γ, α, β, δ sarcoglycans
LGMD2G	Onset age 10 to 15 Proximal and distal muscle weakness	Serum CK 3–17× normal EMG myopathic Muscle biopsy may show rimmed vacuoles	Telethonin
LGMD2H	Onset first to third decade Proximal muscle weakness	Serum CK 2–25× normal EMG myopathic	TRIM32 gene
LGMD2I	Onset first to third decade Clinical condition similar to Duchenne or Becker dystrophies Cardiomyopathy and respiratory failure may occur early before significant weakness Cognitive function normal	Serum CK 10–30× normal EMG myopathic	Fukutin-related protein
LGMD2J[a]	Onset first to third decade Proximal lower limb weakness Mild distal weakness Progressive weakness causes loss of ambulation	Serum CK 1.5–2× normal EMG myopathic Muscle biopsy reveals rimmed vacuoles	Titin
LGMD2K	Usually presents in infancy as Walker-Warburg syndrome but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 10–20× normal EMG myopathic	POMT1
LGMD2L	Presents in childhood or adult life May manifest with quadriceps atrophy and myalgia Some present with early involvement of the calves in the second decade of life, resembling Miyoshi's myopathy (dysferlinopathy)	CK 8–20× normal EMG myopathic	Anoctamin 5
LGMD2M	Usually presents in infancy as Fukuyama's congenital muscular dystrophy but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 10–50× normal EMG myopathic	Fukutin
LGMD2N	Usually presents in infancy as muscle-eye-brain disease but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 5–20× normal EMG myopathic	POMGnT1
LGMD2O	Usually presents in infancy as Walker-Warburg syndrome but can present in early adult life with proximal weakness and only minor CNS abnormalities	CK 5–20× normal EMG myopathic	POMT2
LGMD2P	One case reported presenting in early childhood	CK >10× normal	α-Dystroglycan

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-7

AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDS) (CONTINUED)

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
LGMD2Q	Onset in infancy to fourth decade; proximal weakness; may have ptosis and extraocular weakness; epidermolysis bullosa (also considered a congenital myasthenic syndrome)	CK variable, but usually only mildly elevated EMG myopathic Repetitive nerve stimulation may show decrement	Plectin 1
LGMD2R	See LGMD1E (Table 56-6)	See LGMD1E	Desmin
LGMD2S	Onset in infancy to sixth decade Proximal weakness Eye abnormalities common; truncal ataxia and chorea Mild to moderate intellectual disability Hutterite descent	CK 1.5–20× normal	TRAPC11

[a]Udd's type distal myopathy is a form of titin deficiency with only distal muscle weakness (see Table 56-9).
Abbreviations: CK, creatine kinase; EMG, electromyography; NCS, nerve conduction studies; POMT1, protein-O-mannosyltransferase 1; POMT2, protein-O-mannosyltransferase 2; POMGNT1, O-linked mannose beta 1,2-N-acetylglucosaminyltransferase; TNPO3, transportin 3; TRAPC11, transport (traf cking) protein particle complex, subunit 11.

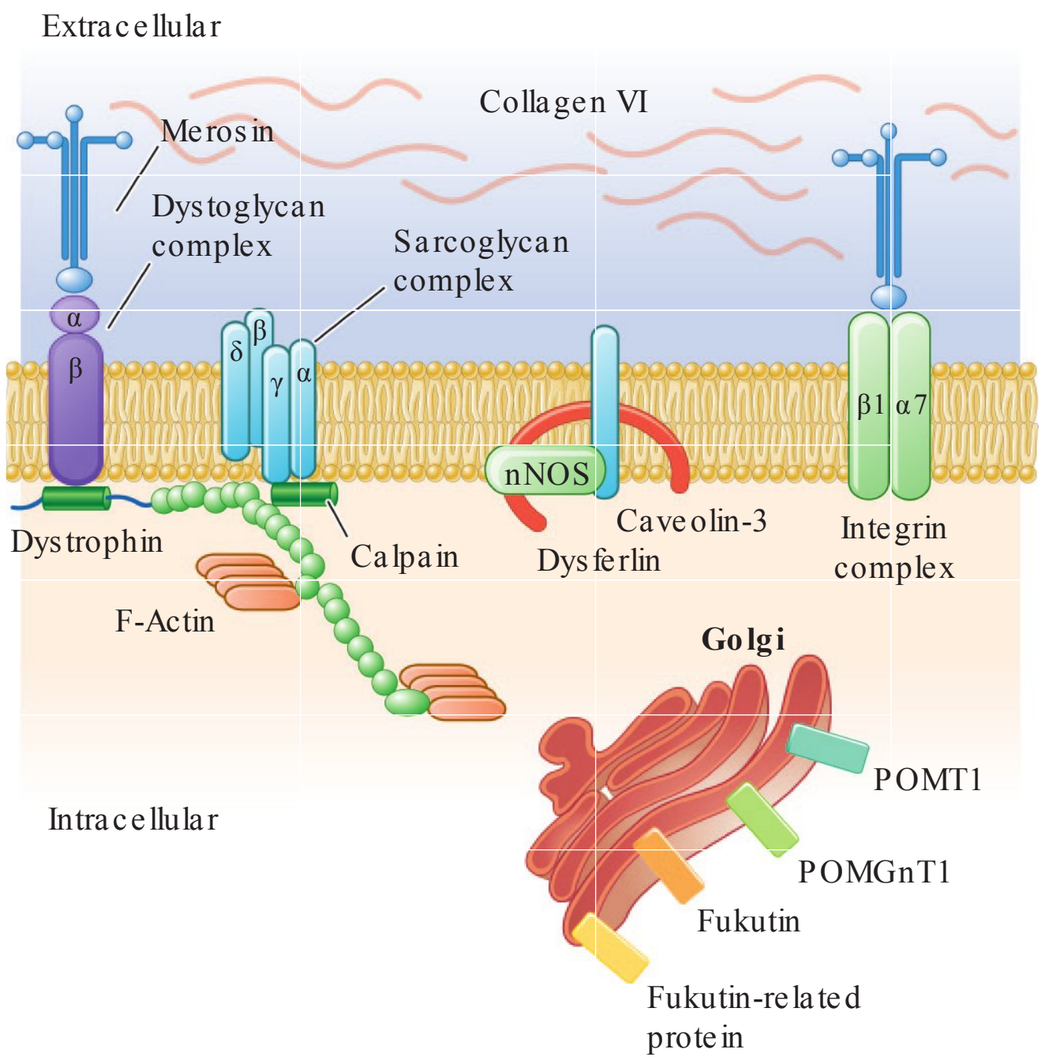


FIGURE 56-6
Selected muscular dystrophy–associated proteins in the cell membrane and Golgi complex.

For example, a primary deficiency of dystrophin (Duchenne dystrophy) may lead to secondary loss of the sarcoglycans and dystroglycan. T e primary loss of a single sarcoglycan (see "Limb-Girdle Muscular Dystrophy," below) results in a secondary loss of other sarcoglycans in the membrane without uniformly affecting dystrophin. In either instance, disruption of the dystrophin-glycoprotein complexes weakens the sarcolemma, causing membrane tears and a cascade of events leading to muscle fiber necrosis. T is sequence of events occurs repeatedly during the life of a patient with muscular dystrophy.

TREATMENT Duchenne Muscular Dystrophy

Glucocorticoids, administered as prednisone in a dose of 0.75 mg/kg per day, significantly slow progression of Duchenne dystrophy for up to 3 years. Some patients cannot tolerate glucocorticoid therapy; weight gain and increased risk of fractures in particular represent a significant deterrent for some boys. As in other recessively inherited dystrophies presumed to arise from loss of function of a critical muscle gene, there is optimism that Duchenne disease may benefit from novel therapies that either replace the defective gene or missing protein or implement downstream corrections (e.g., skipping mutated exons or reading through mutations that introduce stop codons).

BECKER MUSCULAR DYSTROPHY

T is less severe form of X-linked recessive muscular dystrophy results from allelic defects of the same gene responsible for Duchenne dystrophy. Becker muscular dystrophy is ~10 times less frequent than Duchenne.

Clinical features

T e pattern of muscle wasting in Becker muscular dystrophy closely resembles that seen in Duchenne. Proximal muscles, especially of the lower extremities, are prominently involved. As the disease progresses, weakness becomes more generalized. Significant facial muscle weakness is not a feature. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding.

Most patients with Becker dystrophy first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur. By definition, patients with Becker dystrophy walk beyond

www.ketabpezeshki.com (021) 66485457 - 66485438

age 15, whereas patients with Duchenne dystrophy are typically in a wheelchair by the age of 12. Patients with Becker dystrophy have a reduced life expectancy, but most survive into the fourth or fifth decade.

Mental retardation may occur in Becker dystrophy, but it is not as common as in Duchenne. Cardiac involvement occurs in Becker dystrophy and may result in heart failure; some patients manifest with only heart failure. Other less common presentations are asymptomatic hyper-CK-emia, myalgias without weakness, and myoglobinuria.

Laboratory features

Serum CK levels, results of EMG, and muscle biopsy findings closely resemble those in Duchenne dystrophy. The diagnosis of Becker muscular dystrophy requires Western blot analysis of muscle biopsy samples, demonstrating a reduced amount or abnormal size of dystrophin or mutation analysis of DNA from peripheral blood leukocytes. Genetic testing reveals deletions or duplications of the dystrophin gene in 65% of patients with Becker dystrophy, approximately the same percentage as in Duchenne dystrophy. In both Becker and Duchenne dystrophies, the size of the DNA deletion does not predict clinical severity; however, in ~95% of patients with Becker dystrophy, the DNA deletion does not alter the translational reading frame of messenger RNA. These "in-frame" mutations allow for production of some dystrophin, which accounts for the presence of altered rather than absent dystrophin on Western blot analysis.

TREATMENT Becker Muscular Dystrophy

The use of glucocorticoids has not been adequately studied in Becker dystrophy.

LIMB-GIRDLE MUSCULAR DYSTROPHY

The syndrome of LGMD represents more than one disorder. Both males and females are affected, with onset ranging from late in the first decade to the fourth decade. The LGMDs typically manifest with progressive weakness of pelvic and shoulder girdle musculature. Respiratory insufficiency from weakness of the diaphragm may occur, as may cardiomyopathy.

A systematic classification of LGMD is based on autosomal dominant (LGMD1) and autosomal recessive (LGMD2) inheritance. Superimposed on the backbone of LGMD1 and LGMD2, the classification uses a sequential alphabetical lettering system (LGMD1A, LGMD2A, etc.). Disorders receive letters in the order in which they are found to have chromosomal linkage. This results in an ever-expanding list of conditions summarized in Tables 56-6 and 56-7. None of the conditions is as common as the dystrophinopathies; however, prevalence data for the LGMDs have not been systematically gathered for any large heterogeneous population. In referral-based clinical populations, Fukutin-related protein (FKRP) deficiency (LGMD2I), calpainopathy (LGMD2A), anoctaminopathy (LGMD2L), and to a lesser extent dysferlinopathy (LGMD2B) have emerged as the most common disorders.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

There are at least five genetically distinct forms of Emery-Dreifuss muscular dystrophy (EDMD). Emerin mutations are the most common cause of X-linked EDMD, although mutations in FHL1 may also be associated with a similar phenotype, which is X-linked as well. Mutations involving the gene for lamin A/C are the most common cause of autosomal dominant EDMD (also known as LGMD1B) and are also a common cause of hereditary cardiomyopathy. Less commonly, autosomal dominant EDMD has been reported with mutations in nesprin-1, nesprin-2, and *T*MEM43.

Clinical features

Prominent contractures can be recognized in early childhood and teenage years, often preceding muscle weakness. The contractures persist throughout the course of the disease and are present at the elbows, ankles, and neck. Muscle weakness affects humeral and peroneal muscles at first and later spreads to a limb-girdle distribution. The cardiomyopathy is potentially life threatening and may result in sudden death. A spectrum of atrial rhythm and conduction defects includes atrial fibrillation and paralysis and atrioventricular heart block. Some patients have a dilated cardiomyopathy. Female carriers of the X-linked variant may have cardiac manifestations that become clinically significant.

Laboratory features

Serum CK may be elevated two- to tenfold. EMG is myopathic. Muscle biopsy usually shows nonspecific dystrophic features, although cases associated with FHL1 mutations have features of myofibrillar myopathy. Immunohistochemistry reveals absent emerin staining of myonuclei in X-linked EDMD due to emerin mutations. ECGs demonstrate atrial and atrioventricular rhythm disturbances.

X-linked EDMD usually arises from defects in the emerin gene encoding a nuclear envelope protein. FHL1 mutations are also a cause of X-linked scapuloperoneal dystrophy, but can also present with an X-linked form of EDMD. The autosomal dominant disease can be caused by mutations in the LMNA gene encoding

www.ketabpezeshki.com (021) 66485457 - 66485438

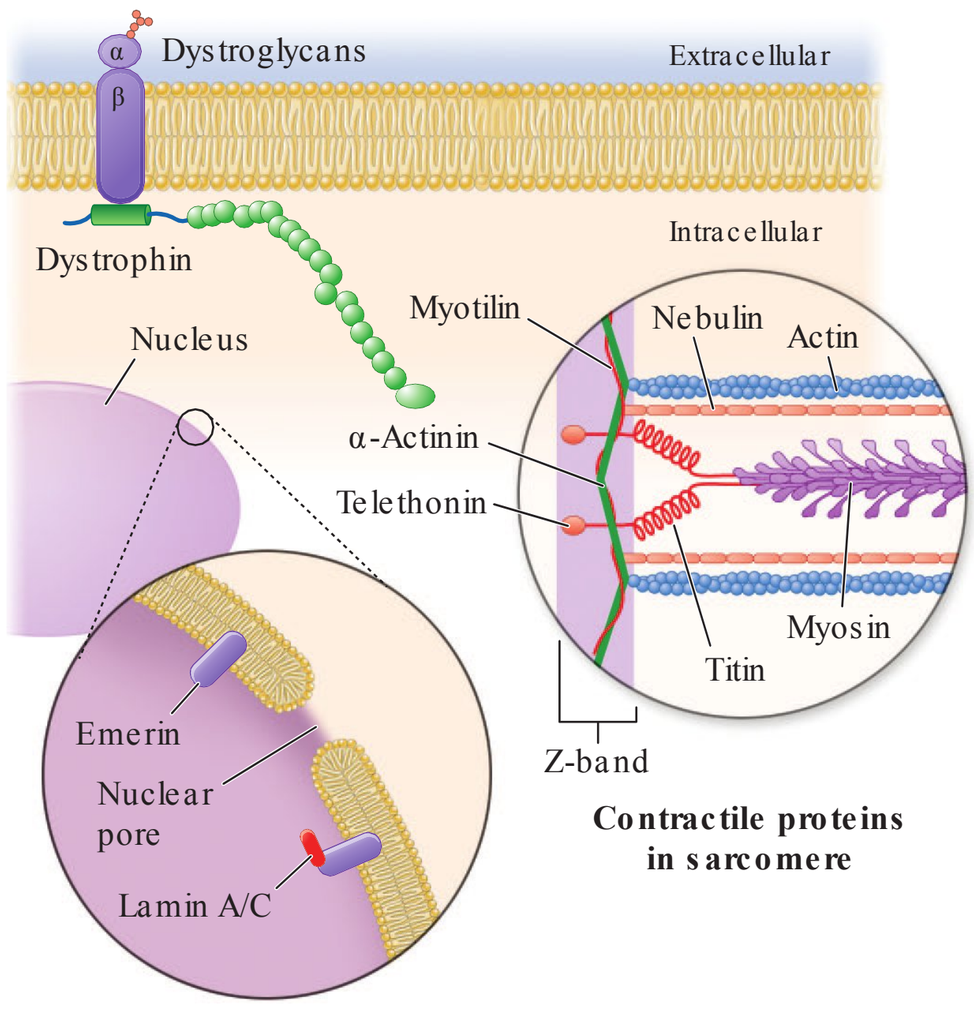


FIGURE 56-7
Selected muscular dystrophy–associated proteins in the nuclear membrane and sarcomere. As shown in the exploded view, emerin and lamin A/C are constituents of the inner nuclear membrane. Several dystrophy-associated proteins are represented in the sarcomere including titin, nebulin, calpain, telethonin, actinin, and myotilin. The position of the dystrophin-dystroglycan complex is also illustrated.

lamin A and C; in the synaptic nuclear envelope protein 1 (SYNE1) or 2 (SYNE2) encoding nesprin-1 and nesprin-2, respectively; and most recently in *T*MEM43 encoding LUMA. T ese proteins are essential components of the filamentous network underlying the inner nuclear membrane. Loss of structural integrity of the nuclear envelope from defects in emerin, lamin A/C, nesprin-1, nesprin-2, and LUMA accounts for overlapping phenotypes **(Fig. 56-7)**.

TREATMENT Emery-Dreifuss Muscular Dystrophy

Supportive care should be offered for neuromuscular disability, including ambulatory aids, if necessary. Stretching of contractures is difficult. Management of cardiomyopathy and arrhythmias (e.g., early use of a defibrillator or cardiac pacemaker) may be life saving.

CONGENITAL MUSCULAR DYSTROPHY (CMD)

T is is not one entity but rather a group of disorders with varying degrees of muscle weakness, CNS impairment, and eye abnormalities.

Clinical features

As a group, CMDs present at birth or in the first few months of life with hypotonia and proximal or generalized muscle weakness. Calf muscle hypertrophy is seen in some patients. Facial muscles may be weak, but other cranial nerve–innervated muscles are spared (e.g., extraocular muscles are normal). Most patients have joint contractures of varying degrees at elbows, hips, knees, and ankles. Contractures present at birth are referred to as arthrogryposis. Respiratory failure may be seen in some cases.

T e CNS is affected in some forms of CMD. In merosin and FKRP deficiency, cerebral hypomyelination may be seen by magnetic resonance imaging (MRI), although only a small number of patients have mental retardation and seizures. T ree forms of congenital muscular dystrophy have severe brain impairment. T ese include Fukuyama's congenital muscular dystrophy (FCMD), muscle-eye-brain (MEB) disease, and Walker-Warburg syndrome (WWS). Patients are severely disabled in all three of these conditions. In MEB disease and WWS, but not in FCMD, ocular abnormalities impair vision. WWS is the most severe congenital muscular dystrophy, causing death by 1 year of age.

Laboratory features

Serum CK is markedly elevated in all of these conditions. T e EMG is myopathic and muscle biopsies show nonspecific dystrophic features. Merosin, or laminin α_2 chain (a basal lamina protein), is deficient in surrounding muscle fibers in merosin deficiency. Skin biopsies can also demonstrate defects in laminin α_2 chain. In the other disorders (FKRP deficiency, FCMD, MEB disease, WWS), there is abnormal α-dystroglycan staining in muscle. In merosin deficiency, cerebral hypomyelination is common, and a host of brain malformations are seen in FCMD, MEB disease, and WWS.

All forms of CMD are inherited as autosomal recessive disorders. Chromosomal linkage and specific gene defects are presented in **Table 56-8**. With the exception of merosin, the other gene defects affect posttranslational glycosylation of α-dystroglycan. T is abnormality is thought to impair binding with merosin and leads to weakening of the dystrophin-glycoprotein complex, instability of the muscle membrane, and/or abnormalities in muscle contraction. CMDs with brain and eye phenotypes probably involve defective glycosylation of additional proteins, accounting for the more extensive phenotypes.

TREATMENT Congenital Muscular Dystrophy

T ere is no specific treatment for CMD. Proper wheelchair seating is important. Management of epilepsy and cardiac manifestations is necessary for some patients.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-8

CONGENITAL MUSCULAR DYSTROPHIES[a]

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
Merosin deficiency	Onset at birth with hypotonia, joint contractures, delayed milestones, generalized muscle weakness Cerebral hypomyelination, less often cortical dysplasia Normal intelligence usually, some with MR (~6%) and seizures (~8%) Partial deficiency leads to milder phenotype (LGMD picture)	Serum CK 5–35× normal EMG myopathic NCS abnormal in some cases	Laminin α_2 chain
Fukutin-related protein deficiency[b]	Onset at birth or shortly after Hypotonia and feeding problems Weakness of proximal muscles, especially shoulder girdles Hypertrophy of leg muscles Joint contractures Cognition normal	Serum CK 10–50× normal EMG myopathic NCS normal	Fukutin-related protein
Fukuyama's congenital muscular dystrophy[b]	Onset at birth Hypotonia, joint contractures Generalized muscle weakness Hypertrophy of calf muscles Seizures, MR Cardiomyopathy	Serum CK 10–50× normal EMG myopathic NCS normal MRI shows hydrocephalus and periventricular and frontal hypomyelination	Fukutin
Muscle-eye-brain disease	Onset at birth, hypotonia Eye abnormalities include: progressive myopia, cataracts, and optic nerve, glaucoma, retinal pigmentary changes Progressive muscle weakness Joint contractures Seizures, MR	Serum CK 5–20× normal MRI shows hydrocephalus, cobblestone lissencephaly, corpus callosum and cerebellar hypoplasia, cerebral hypomyelination	N-Acetyl-glucosaminyl transferase (POMGnT1)
Walker-Warburg syndrome[b]	Onset at birth, hypotonia Generalized muscle weakness Joint contractures Microphthalmos, retinal dysplasia, buphthalmos, glaucoma, cataracts Seizures, MR	Serum CK 5–20× normal MRI shows cobblestone lissencephaly, hydrocephalus, encephalocele, absent corpus callosum	O-Mannoxyl-transferase-1 (POMT1)

[a] All are inherited as recessive traits.
[b] There is phenotypic overlap between disorders related to defective glycosylation. In muscle, this is a consequence of altered glycosylation of dystroglycans; in brain/eye, other glycosylated proteins are involved. Clinically, Walker-Warburg syndrome is more severe, with death by 1 year.
Abbreviations: CK, creatine kinase; EMG, electromyography; LGMD, limb-girdle muscular dystrophy; MR, mental retardation; MRI, magnetic resonance imaging; NCS, nerve conduction studies.

MYOTONIC DYSTROPHY

Myotonic dystrophy is also known as dystrophia myotonica (DM). The condition is composed of at least two clinical disorders with overlapping phenotypes and distinct molecular genetic defects: myotonic dystrophy type 1 (DM1), the classic disease originally described by Steinert, and myotonic dystrophy type 2 (DM2), also called proximal myotonic myopathy (PROMM).

Clinical features

The clinical expression of DM1 varies widely and involves many systems other than muscle. Affected patients have a typical "hatchet-faced" appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Frontal baldness is also characteristic of the disease. Neck muscles, including flexors and sternocleidomastoids, and distal limb muscles are involved early. Weakness of wrist extensors, finger extensors, and intrinsic hand muscles impairs function. Ankle dorsiflexor weakness may cause footdrop. Proximal muscles remain stronger throughout the course, although preferential atrophy and weakness of quadriceps muscles occur in many patients. Palatal, pharyngeal, and tongue involvement produce a dysarthric speech, nasal voice, and swallowing problems. Some patients have diaphragm and intercostal muscle weakness, resulting in respiratory insufficiency.

www.ketabpezeshki.com (021) 66485457 - 66485438

Myotonia, which usually appears by age 5 years, is demonstrable by percussion of the thenar eminence, the tongue, and wrist extensor muscles. Myotonia causes a slow relaxation of hand grip af er a forced voluntary closure. Advanced muscle wasting makes myotonia more difficult to detect.

Cardiac disturbances occur commonly in patients with DM1. ECG abnormalities include first-degree heart block and more extensive conduction system involvement. Complete heart block and sudden death can occur. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Mitral valve prolapse also occurs commonly. Other associated features include intellectual impairment, hypersomnia, posterior subcapsular cataracts, gonadal atrophy, insulin resistance, and decreased esophageal and colonic motility.

Congenital myotonic dystrophy is a more severe form of DM1 and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness, transient neonatal respiratory insufficiency, and mental retardation.

DM2, or PROMM, has a distinct pattern of muscle weakness affecting mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur but are less common, and the hatchet face and frontal baldness are less consistent features. A very striking difference is the failure to clearly identify a congenital form of DM2.

Laboratory features

T e diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present in most cases of DM1 but may be more patchy in DM2. Muscle biopsy shows muscle atrophy, which selectively involves type 1 fibers in 50% of cases, and ringed fibers in DM1 but not in DM2. Typically, numerous internalized nuclei can be seen in individual muscle fibers as well as atrophic fibers with pyknotic nuclear clumps in both DM1 and DM2. Necrosis of muscle fibers and increased connective tissue, common in other muscular dystrophies, are less apparent in myotonic dystrophy.

DM1 and DM2 are both autosomal dominant disorders. New mutations do not appear to contribute to the pool of affected individuals. DM1 is transmitted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat in a serine-threonine protein kinase gene (named DMPK) on chromosome 19q13.3. An increase in the severity of the disease phenotype in successive generations (genetic anticipation) is accompanied by an increase in the number of trinucleotide repeats. A similar type of mutation has been identified in fragile X syndrome **(Chap. 38)**. T e unstable triplet repeat in myotonic dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers; it is possible that sperm with greatly expanded triplet repeats do not function well.

DM2 is caused by a DNA expansion mutation consisting of a CCTG repeat in intron 1 of the ZNF9 gene located at chromosome 3q13.3-q24. T e gene is believed to encode an RNA-binding protein expressed in many different tissues, including skeletal and cardiac muscle.

T e DNA expansions in DM1 and DM2 almost certainly impair muscle function by a toxic gain of function of the mutant mRNA. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA. T ese RNA inclusions sequester RNA-binding proteins essential for proper splicing of a variety of other mRNAs. T is leads to abnormal transcription of multiple proteins in a variety of tissues/organ systems, in turn causing the systemic manifestations of DM1 and DM2.

TREATMENT Myotonic Dystrophy

T e myotonia in DM1 rarely warrants treatment, although some patients with DM2 are significantly bothered by the discomfort related to the associated muscle stiffness. Phenytoin and mexiletine are the preferred agents for the occasional patient who requires an antimyotonia drug; other agents, particularly quinine and procainamide, may worsen cardiac conduction. A cardiac pacemaker should be considered for patients with unexplained syncope, advanced conduction system abnormalities with evidence of second-degree heart block, or trifascicular conduction disturbances with marked prolongation of the PR interval. Molded ankle-foot orthoses help stabilize gait in patients with foot drop. Excessive daytime somnolence with or without sleep apnea is not uncommon. Sleep studies, noninvasive respiratory support (biphasic positive airway pressure [BiPAP]), and treatment with modafinil may be beneficial.

FACIOSCAPULOHUMERAL (FSH) MUSCULAR DYSTROPHY

T is form of muscular dystrophy has a prevalence of ~1 in 20,000. T ere are two forms of FSHD that have similar pathogenesis, as will be discussed. Most patients have FSHD type 1 (95%), whereas approximately 5% have FSHD2. FSHD1 and FSHD2 are clinically and histopathologically identical. FSHD is not to be confused with the genetically distinct scapuloperoneal dystrophies.

Clinical features

T e condition typically has an onset in childhood or young adulthood. In most cases, facial weakness is the initial manifestation, appearing as an inability to smile, whistle, or fully close the eyes. Weakness of the shoulder girdles, rather than the facial muscles, usually brings the patient

www.ketabpezeshki.com (021) 66485457 - 66485438

to medical attention. Loss of scapular stabilizer muscles makes arm elevation difficult. Scapular winging (Fig. 56-3) becomes apparent with attempts at abduction and forward movement of the arms. Biceps and triceps muscles may be severely affected, with relative sparing of the deltoid muscles. Weakness is invariably worse for wrist extension than for wrist flexion, and weakness of the anterior compartment muscles of the legs may lead to footdrop.

In most patients, the weakness remains restricted to facial, upper extremity, and distal lower extremity muscles. In 20% of patients, weakness progresses to involve the pelvic girdle muscles, and severe functional impairment and possible wheelchair dependency result.

Characteristically, patients with FSHD do not have involvement of other organ systems, although labile hypertension is common, and there is an increased incidence of nerve deafness. Coats' disease, a disorder consisting of telangiectasia, exudation, and retinal detachment, also occurs.

Laboratory features

The serum CK level may be normal or mildly elevated. EMG usually indicates a myopathic pattern. The muscle biopsy shows nonspecific features of a myopathy. A prominent inflammatory infiltrate, which is often multifocal in distribution, is present in some biopsy samples. The cause or significance of this finding is unknown.

An autosomal dominant inheritance pattern with almost complete penetrance has been established, but each family member should be examined for the presence of the disease, since ~30% of those affected are unaware of involvement. FSHD1 is associated with deletions of tandem 3.3-kb repeats at 4q35. The deletion reduces the number of repeats to a fragment of <35 kb in most patients. Within these repeats lies the DUX4 gene, which usually is not expressed. In patients with FSHD1 these deletions in the setting of a specific polymorphism leads to hypomethylation of the region and toxic expression of the DUX4 gene. In patients with FSHD2, there is no deletion, but a mutation in SMCHD1. Interestingly, in the setting of the same polymorphism, there again is seen hypomethylation of the region and the permissive expression of the DUX4 gene. In both FSHD1 and FSHD2, there is overexpression of the DUX4 transcript.

TREATMENT Facioscapulohumeral Muscular Dystrophy

No specific treatment is available; ankle-foot orthoses are helpful for footdrop. Scapular stabilization procedures improve scapular winging but may not improve function.

OCULOPHARYNGEAL DYSTROPHY

This form of muscular dystrophy represents one of several disorders characterized by progressive external ophthalmoplegia, which consists of slowly progressive ptosis and limitation of eye movements with sparing of pupillary reactions for light and accommodation. Patients usually do not complain of diplopia, in contrast to patients having conditions with a more acute onset of ocular muscle weakness (e.g., myasthenia gravis).

Clinical features

Oculopharyngeal muscular dystrophy has a late onset; it usually presents in the fourth to sixth decade with ptosis and/or dysphagia. The extraocular muscle impairment is less prominent in the early phase but may be severe later. The swallowing problem may become debilitating and result in pooling of secretions and repeated episodes of aspiration. Mild weakness of the neck and extremities also occurs.

Laboratory features

The serum CK level may be two to three times normal. Myopathic EMG findings are typical. On biopsy, muscle fibers are found to contain rimmed vacuoles, which by electron microscopy are shown to contain membranous whorls, accumulation of glycogen, and other nonspecific debris related to lysosomes. A distinct feature of oculopharyngeal dystrophy is the presence of tubular filaments, 8.5 nm in diameter, in muscle cell nuclei.

Oculopharyngeal dystrophy has an autosomal dominant inheritance pattern with complete penetrance. The incidence is high in French-Canadians and in Spanish-American families of the southwestern United States. Large kindreds of Italian and of eastern European Jewish descent have been reported. The molecular defect in oculopharyngeal muscular dystrophy is a subtle expansion of a modest polyalanine repeat tract in a poly-RNA-binding protein (PABP2) in muscle.

TREATMENT Oculopharyngeal Dystrophy

Dysphagia can lead to significant undernourishment and inanition, making oculopharyngeal muscular dystrophy a potentially life-threatening disease. Cricopharyngeal myotomy may improve swallowing, although it does not prevent aspiration. Eyelid crutches can improve vision when ptosis obstructs vision; candidates for ptosis surgery must be carefully selected—those with severe facial weakness are not suitable.

DISTAL MYOPATHIES

A group of muscle diseases, the distal myopathies, are notable for their preferential distal distribution of muscle weakness in contrast to most muscle conditions associated with proximal weakness. The major distal myopathies are summarized in **Table 56-9**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-9

DISTAL MYOPATHIES

DISEASE	CLINICAL FEATURES	LABORATORY FEATURES	ABNORMAL PROTEIN
Welander's distal myopathy	Onset in fifth decade Weakness begins in hands Slow progression with spread to distal lower extremities Lifespan normal	Serum CK 2–3× normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features and rimmed vacuoles	AD Chromosome 2p13 TIA1
Tibial muscular dystrophy (Udd's)	Onset fourth to eighth decade Distal lower extremity weakness (tibial distribution) Upper extremities usually normal Lifespan normal	Serum CK 2–4× normal EMG myopathic NCS normal Muscle biopsy shows dystrophic features and rimmed vacuoles Titin absent in M-line of muscle	AD Titin AR (associated with more proximal weakness—LGMD2J)
Markesbery-Griggs distal myopathy	Onset fourth to eighth decade Distal lower extremity weakness (tibial distribution) with progression to distal arms and proximal muscles	Serum CK is usually mildly elevated EMG reveals irritative myopathy Muscle biopsies demonstrate rimmed vacuoles and features of MFM	AD Z-band alternatively spliced PDX motif-containing protein (ZASP)
Laing's distal myopathy	Onset childhood to third decade Distal lower extremity weakness (anterior tibial distribution) and neck flexors affected early May have cardiomyopathy	Serum CK is normal or slightly elevated Muscle biopsies do not typically show rimmed vacuoles, but may show hyaline bodies with accumulation of myosin Large deposits of myosin heavy chain are seen in type 1 muscle fibers	AD Myosin heavy chain 7
Nonaka's distal myopathy (autosomal recessive hereditary inclusion body myopathy)	Onset: second to third decade Distal lower extremity weakness (anterior tibial distribution) Mild distal upper limb weakness may be present early Progression to other muscles sparing quadriceps Ambulation may be lost in 10–15 y	Serum CK 3–10× normal EMG myopathic NCS normal Dystrophic features on muscle biopsy plus rimmed vacuoles and 15- to 19-nm filaments within vacuoles	AR GNE gene: UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase Allelic to hereditary inclusion body myopathy
Miyoshi's myopathy[a]	Onset: second to third decade Lower extremity weakness in posterior compartment muscles Progression leads to weakness in other muscle groups Ambulation lost after 10–15 y in about one-third of cases	Serum CK 20–100× normal EMG myopathic NCS normal Muscle biopsy shows nonspecific dystrophic features often with prominent inflammatory cell infiltration; no rimmed vacuoles	AR Allelic to LGMD2B (see Tables 56-7) Dysferlin
Williams' myopathy	Distal lower extremity weakness (anterior tibial distribution)	Muscle biopsy may show rimmed vacuoles and features of MFM	X-linked Filamin-C
Myofibrillar myopathies	Onset from early childhood to late adult life Weakness may be distal, proximal, or generalized Cardiomyopathy and respiratory involvement is not uncommon	Serum CKs can be normal or moderately elevated EMG is myopathic and often associated with myotonic discharges Muscle biopsy demonstrates abnormal accumulation of desmin and other proteins, rimmed vacuoles, and myofibrillar degeneration	Genetically heterogeneous AD Myotilin (also known as LGMD 1A) ZASP (see Markesbery-Griggs distal myopathy) Filamin-C Desmin Alpha B crystallin Bag3 Titin DNAJB6 TNPO3 AR Desmin X-linked FHL1

[a]Miyoshi's myopathy phenotype may also be seen with mutations in ANO-5 that encodes for anoctamin 5 (allelic to LGMD2L).
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CK, creatine kinase; EMG, electromyography; MFM, myofibrillar myopathy; NCS, nerve conduction studies.

www.ketabpezeshki.com (021) 66485457 - 66485438

Clinical features

Welander's, Udd's, and Markesbery-Griggs type distal myopathies are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years. Welander's distal myopathy preferentially involves the wrist and finger extensors, whereas the others are associated with anterior tibial weakness leading to progressive footdrop. Laing's distal myopathy is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life. Nonaka's distal myopathy and Miyoshi's myopathy are distinguished by autosomal recessive inheritance and onset in the late teens or twenties. Nonaka's and Williams' myopathy entails anterior tibial weakness, whereas Miyoshi's myopathy is unique in that gastrocnemius muscles are preferentially affected at onset. Finally, the myofibrillar myopathies (MFMs) are a clinically and genetically heterogeneous group of disorders that can be associated with prominent distal weakness; they can be inherited in an autosomal dominant or recessive pattern. Of note, Markesbery-Griggs myopathy (caused by mutations in ZASP) and LGMD1B (caused by mutations in myotilin) are in fact subtypes of myofibrillar myopathy.

Laboratory features

Serum CK level is particularly helpful in diagnosing Miyoshi's myopathy because it is very elevated. In the other conditions, serum CK is only slightly increased. EMGs are myopathic. In the MFMs, myotonic or pseudomyotonic discharges are common. Muscle biopsy shows nonspecific dystrophic features and, with the exception of Laing's and Miyoshi's myopathies, often shows rimmed vacuoles. MFM is associated with the accumulation of dense inclusions, as well as amorphous material best seen on Gomori trichrome and myofibrillar disruption on electron microscopy. Immunostaining sometimes demonstrates accumulation of desmin and other proteins in MFM, large deposits of myosin heavy chain in the subsarcolemmal region of type 1 muscle fibers in Laing's myopathy, and reduced or absent dysferlin in Miyoshi's myopathy.

The affected genes and their gene products are listed in Table 56-9.

TREATMENT Distal Myopathies

Occupational therapy is offered for loss of hand function; ankle-foot orthoses can support distal lower limb muscles. The MFMs can be associated with cardiomyopathy (congestive heart failure or arrhythmias) and respiratory failure that may require medical management. Laing's-type distal myopathy can also be associated with a cardiomyopathy.

CONGENITAL MYOPATHIES

These rare disorders are distinguished from muscular dystrophies by the presence of specific histochemical and structural abnormalities in muscle. Although primarily disorders of infancy or childhood, three forms that may present in adulthood are described here: central core disease, nemaline (rod) myopathy, and centronuclear (myotubular) myopathy. Sarcotubular myopathy is caused by mutations in *T*RIM-32 and is identical to LGMD2H. Other types, such as minicore myopathy (multi-minicore disease), fingerprint body myopathy, and cap myopathy, are not discussed.

CENTRAL CORE DISEASE

Patients with central core disease may have decreased fetal movements and breech presentation. Hypotonia and delay in motor milestones, particularly in walking, are common. Later in childhood, patients develop problems with stair climbing, running, and getting up from the floor. On examination, there is mild facial, neck-flexor, and proximal-extremity muscle weakness. Legs are more affected than arms. Skeletal abnormalities include congenital hip dislocation, scoliosis, and pes cavus; clubbed feet also occur. Most cases are nonprogressive, but exceptions are well documented. Susceptibility to malignant hyperthermia must be considered as a potential risk factor for patients with central core disease. Recent series have demonstrated that many cases of late-onset axial myopathy in which patients manifest with bent spine (camptocormia) or neck extensor weakness (neck extensor myopathy) are caused by mutations in the ryanodine receptor gene (RYR1). This illustrates the interesting spectrum of RYR1 mutations.

The serum CK level is usually normal. Needle EMG demonstrates a myopathic pattern. Muscle biopsy shows fibers with single or multiple central or eccentric discrete zones (cores) devoid of oxidative enzymes. Cores occur preferentially in type 1 fibers and represent poorly aligned sarcomeres associated with Z disk streaming.

Autosomal dominant inheritance is characteristic; sporadic cases also occur. As alluded above, this myopathy is caused by point mutations of RYR1, encoding the calcium-release channel of the sarcoplasmic reticulum of skeletal muscle; mutations of this gene also account for some cases of inherited malignant hyperthermia **(Chap. 23)**. Malignant hyperthermia is an allelic condition; C-terminal mutations of the RYR1 gene predispose to this complication.

Specific treatment is not required, but establishing a diagnosis of central core disease is extremely important because these patients have a known predisposition to malignant hyperthermia during anesthesia.

www.ketabpezeshki.com (021) 66485457 - 66485438

NEMALINE MYOPATHY

T e term nemaline refers to the distinctive presence in muscle fibers of rods or threadlike structures (Greek nema, "thread"). Nemaline myopathy is clinically heterogeneous. A severe neonatal form presents with hypotonia and feeding and respiratory difficulties, leading to early death. Nemaline myopathy usually presents in infancy or childhood with delayed motor milestones. T e course is nonprogressive or slowly progressive. T e physical appearance is striking because of the long, narrow facies, high-arched palate, and open-mouthed appearance due to a prognathous jaw. Other skeletal abnormalities include pectus excavatum, kyphoscoliosis, pes cavus, and clubfoot deformities. Facial and generalized muscle weakness, including respiratory muscle weakness, is common. An adult-onset disorder with progressive proximal or distal weakness may be seen. Myocardial involvement is occasionally present in both the childhood and adult-onset forms. T e serum CK level is usually normal or slightly elevated. T e EMG demonstrates a myopathic pattern. Muscle biopsy shows clusters of small rods (nemaline bodies), which occur preferentially, but not exclusively, in the sarcoplasm of type 1 muscle fibers. Occasionally, the rods are also apparent in myonuclei. T e muscle of en shows type 1 muscle fiber predominance. Rods originate from the Z disk material of the muscle fiber.

Six genes have been associated with nemaline myopathy. Five of these code for thin filament–associated proteins, suggesting disturbed assembly or interplay of these structures as a pivotal mechanism. Mutations of the nebulin (NEB) gene account for most cases, including both severe neonatal and early childhood forms, inherited as autosomal recessive disorders. Neonatal and childhood cases, inherited as predominantly autosomal dominant disorders, are caused by mutations of the skeletal muscle a-actinin (AC*T*A1) gene. In milder forms of the disease with autosomal dominant inheritance, mutations have been identified in both the slow a-tropomyosin (*T*PM3) and β;-tropomyosin (*T*PM2) genes accounting for <3% of cases. Muscle troponin T (*T*NN*T*1) gene mutations appear to be limited to the Amish population in North America. Mutations may also be seen in NEM6 that encodes a putative BTB/Kelch protein. No specific treatment is available.

CENTRONUCLEAR (MYOTUBULAR) MYOPATHY

T ree distinct variants of centronuclear myopathy occur. A neonatal form, also known as myotubular myopathy, presents with severe hypotonia and weakness at birth. T e late infancy–early childhood form presents with delayed motor milestones. Later, difficulty with running and stair climbing becomes apparent. A marfanoid, slender body habitus, long narrow face, and high-arched palate are typical. Scoliosis and clubbed feet may be present. Most patients exhibit progressive weakness, some requiring wheelchairs. Progressive external ophthalmoplegia with ptosis and varying degrees of extraocular muscle impairment are characteristic of both the neonatal and the late-infantile forms. A third variant, the late childhood–adult form, has an onset in the second or third decade. Patients have full extraocular muscle movements and rarely exhibit ptosis. T ere is mild, slowly progressive limb weakness that may be distally predominant (some of these patients have been classified as having Charcot-Marie-Tooth disease type 2 [CMT2; **Chap. 53**]).

Normal or slightly elevated CK levels occur in each of the forms. Nerve conduction studies may reveal reduced amplitudes of distal compound muscle action potentials, in particular in adult-onset cases that resemble CMT2. EMG studies of en give distinctive results, showing positive sharp waves and fibrillation potentials, complex and repetitive discharges, and rarely myotonic discharges. Muscle biopsy specimens in longitudinal section demonstrate rows of central nuclei, of en surrounded by a halo. In transverse sections, central nuclei are found in 25–80% of muscle fibers.

A gene for the neonatal form of centronuclear myopathy has been localized to Xq28; this gene encodes myotubularin, a protein tyrosine phosphatase. Missense, frameshif , and splice-site mutations predict loss of myotubularin function in affected individuals. Carrier identification and prenatal diagnosis are possible. Autosomal recessive forms are caused by mutations in BIB1 that encodes for amphyphysin-2, whereas some autosomal dominant cases, which are allelic to a form of CMT2, are associated with mutations in the gene that encodes dynamin-2. No specific medical treatments are available at this time.

DISORDERS OF MUSCLE ENERGY METABOLISM

T ere are two principal sources of energy for skeletal muscle—fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglobinuria to a chronic, progressive muscle weakness simulating muscular dystrophy.

GLYCOGEN STORAGE AND GLYCOLYTIC DEFECTS

Disorders of glycogen storage causing progressive weakness

α-Glucosidase, or acid maltase, def ciency (Pompe's disease)

T ree clinical forms of α-glucosidase, or acid maltase, deficiency (type II glycogenosis) can be distinguished.

www.ketabpezeshki.com (021) 66485457 - 66485438

The infantile form is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, cardiomegaly, hepatomegaly, and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem contributes to muscle weakness. Death usually occurs by 1 year of age. In the childhood form, the picture resembles muscular dystrophy. Delayed motor milestones result from proximal limb muscle weakness and involvement of respiratory muscles. The heart may be involved, but the liver and brain are unaffected. The adult form usually begins in the third or fourth decade but can present as late as the seventh decade. Respiratory failure and diaphragmatic weakness are often initial manifestations, heralding progressive proximal muscle weakness. The heart and liver are not involved.

The serum CK level is 2–10 times normal in infantile or childhood-onset Pompe's disease but can be normal in adult-onset cases. EMG examination demonstrates a myopathic pattern, but other features are especially distinctive, including myotonic discharges, trains of fibrillation and positive waves, and complex repetitive discharges. EMG discharges are very prominent in the paraspinal muscles. The muscle biopsy in infants typically reveals vacuoles containing glycogen and the lysosomal enzyme acid phosphatase. Electron microscopy reveals membrane-bound and free tissue glycogen. However, muscle biopsies in late-onset Pompe's disease may demonstrate only nonspecific abnormalities. Enzyme analysis of dried blood spots is a sensitive technique to screen for Pompe's disease. A definitive diagnosis is established by enzyme assay in muscle or cultured fibroblasts or by genetic testing.

Pompe's disease is inherited as an autosomal recessive disorder caused by mutations of the α-glucosidase gene. Enzyme replacement therapy (ERT) with IV recombinant human α-glucosidase has been shown to be beneficial in infantile-onset Pompe's disease. Clinical benefits in the infantile disease include reduced heart size, improved muscle function, reduced need for ventilatory support, and longer life. In late-onset cases, ERT has not been associated with the dramatic response that can be seen in classic infantile Pompe's disease, yet it appears to stabilize the disease process.

Other glycogen storage diseases with progressive weakness

In de-branching enzyme deficiency (type III glycogenosis), a slowly progressive form of muscle weakness can develop after puberty. Rarely, myoglobinuria may be seen. Patients are usually diagnosed in infancy, however, because of hypotonia and delayed motor milestones, hepatomegaly, growth retardation, and hypoglycemia. Branching enzyme deficiency (type IV glycogenosis) is a rare and fatal glycogen storage disease characterized by failure to thrive and hepatomegaly. Hypotonia and muscle wasting may be present, but the skeletal muscle manifestations are minor compared to liver failure.

Disorders of glycolysis causing exercise intolerance

Several glycolytic defects are associated with recurrent myoglobinuria: myophosphorylase deficiency (type V glycogenosis), phosphofructokinase deficiency (type VII glycogenosis), phosphoglycerate kinase deficiency, phosphorylase kinase deficiency (type IX glycogenosis), phosphoglycerate mutase deficiency (type X glycogenosis), lactate dehydrogenase deficiency (glycogenosis type XI), and β-enolase deficiency. Myophosphorylase deficiency, also known as McArdle's disease, is by far the most common of the glycolytic defects associated with exercise intolerance. These glycolytic defects result in a common failure to support energy production at the initiation of exercise, although the exact site of energy failure remains controversial.

Clinical muscle manifestations in these conditions usually begin in adolescence. Symptoms are precipitated by brief bursts of high-intensity exercise such as running or lifting heavy objects. A history of myalgia and muscle stiffness usually precedes the intensely painful muscle contractures, which may be followed by myoglobinuria. Acute renal failure accompanies significant pigmenturia.

Certain features help distinguish some enzyme defects. In McArdle's disease, exercise tolerance can be enhanced by a slow induction phase (warm-up) or brief periods of rest, allowing for the start of the "second-wind" phenomenon (switching to utilization of fatty acids). Varying degrees of hemolytic anemia accompany deficiencies of both phosphofructokinase (mild) and phosphoglycerate kinase (severe). In phosphoglycerate kinase deficiency, the usual clinical presentation is a seizure disorder associated with mental retardation; exercise intolerance is an infrequent manifestation.

In all of these conditions, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected, accompanying myoglobinuria. All patients with suspected glycolytic defects leading to exercise intolerance should undergo a forearm exercise test. An impaired rise in venous lactate is highly indicative of a glycolytic defect. In lactate dehydrogenase deficiency, venous levels of lactate do not increase, but pyruvate rises to normal. A definitive diagnosis of glycolytic disease is made by muscle biopsy and subsequent enzyme analysis or by genetic testing.

Myophosphorylase deficiency, phosphofructokinase deficiency, and phosphoglycerate mutase deficiency are inherited as autosomal recessive disorders. Phosphoglycerate kinase deficiency is X-linked recessive.

www.ketabpezeshki.com (021) 66485457 - 66485438

Mutations can be found in the respective genes encoding the abnormal proteins in each of these disorders.

Training may enhance exercise tolerance, perhaps by increasing perfusion to muscle. Dietary intake of free glucose or fructose prior to activity may improve function but care must be taken to avoid obesity from ingesting too many calories.

LIPID AS AN ENERGY SOURCE AND ASSOCIATED DEFECTS

Lipid is an important muscle energy source during rest and during prolonged, submaximal exercise. Fatty acids are derived from circulating very-low-density lipoprotein (VLDL) in the blood or from triglycerides stored in muscle fibers. Oxidation of fatty acids occurs in the mitochondria. To enter the mitochondria, a fatty acid must first be converted to an "activated fatty acid," acyl-CoA. T e acyl-CoA must be linked with carnitine by the enzyme carnitine palmitoyltransferase (CPT) I for transport into the mitochondria. CPT I is present on the inner side of the outer mitochondrial membrane. Carnitine is removed by CPT II, an enzyme attached to the inside of the inner mitochondrial membrane, allowing transport of acyl-CoA into the mitochondrial matrix for β-oxidation.

Carnitine palmitoyltransferase deficiency

CPT II deficiency is the most common recognizable cause of recurrent myoglobinuria, more common than the glycolytic defects. Onset is usually in the teenage years or early twenties. Muscle pain and myoglobinuria typically occur after prolonged exercise but can also be precipitated by fasting or infections; up to 20% of patients do not exhibit myoglobinuria, however. Strength is normal between attacks. In contrast to disorders caused by defects in glycolysis, in which muscle cramps follow short, intense bursts of exercise, the muscle pain in CPT II deficiency does not occur until the limits of utilization have been exceeded and muscle breakdown has already begun. Episodes of rhabdomyolysis may produce severe weakness. In young children and newborns, CPT II deficiency can present with a very severe clinical picture including hypoketotic hypoglycemia, cardiomyopathy, liver failure, and sudden death.

Serum CK levels and EMG findings are both usually normal between episodes. A normal rise of venous lactate during forearm exercise distinguishes this condition from glycolytic defects, especially myophosphorylase deficiency. Muscle biopsy does not show lipid accumulation and is usually normal between attacks. T e diagnosis requires direct measurement of muscle CPT or genetic testing.

CPT II deficiency is much more common in men than women (5:1); nevertheless, all evidence indicates autosomal recessive inheritance. A mutation in the gene for CPT II (chromosome 1p36) causes the disease in some individuals. Attempts to improve exercise tolerance with frequent meals and a low-fat, high-carbohydrate diet, or by substituting medium-chain triglycerides in the diet, have not proven to be beneficial.

Myoadenylate deaminase deficiency

T e muscle enzyme myoadenylate deaminase converts adenosine-5′-monophosphate (5′-AMP) to inosine monophosphate (IMP) with liberation of ammonia. Myoadenylate deaminase may play a role in regulating adenosine triphosphate (ATP) levels in muscles. Most individuals with myoadenylate deaminase deficiency have no symptoms. T ere have been a few reports of patients with this disorder who have exercise-exacerbated myalgia and myoglobinuria. Many questions have been raised about the clinical effects of myoadenylate deaminase deficiency, and, specifically, its relationship to exertional myalgia and fatigability, but there is no consensus.

MITOCHONDRIAL MYOPATHIES

In 1972, Olson and colleagues recognized that muscle fibers with significant numbers of abnormal mitochondria could be highlighted with the modified trichrome stain; the term ragged red fibers was coined. By electron microscopy, the mitochondria in ragged red fibers are enlarged and often bizarrely shaped and have crystalline inclusions. Since that seminal observation, the understanding of these disorders of muscle and other tissues has expanded.

Mitochondria play a key role in energy production. Oxidation of the major nutrients derived from carbohydrate, fat, and protein leads to the generation of reducing equivalents. T e latter are transported through the respiratory chain in the process known as oxidative phosphorylation. T e energy generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical gradient coupled to ATP synthesis.

A novel feature of mitochondria is their genetic composition. Each mitochondrion possesses a DNA genome that is distinct from that of the nuclear DNA. Human mitochondrial DNA (mtDNA) consists of a double-strand, circular molecule comprising 16,569 base pairs. It codes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 polypeptides of the respiratory chain enzymes. T e genetics of mitochondrial diseases differ from the genetics of chromosomal disorders. T e

www.ketabpezeshki.com (021) 66485457 - 66485438

DNA of mitochondria is directly inherited from the cytoplasm of the gametes, mainly from the oocyte. The sperm contributes very little of its mitochondria to the offspring at the time of fertilization. Thus, mitochondrial genes are derived almost exclusively from the mother, accounting for maternal inheritance of some mitochondrial disorders.

Patients with mitochondrial myopathies have clinical manifestations that usually fall into three groups: chronic progressive external ophthalmoplegia (CPEO), skeletal muscle–CNS syndromes, and pure myopathy simulating muscular dystrophy or metabolic myopathy.

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA SYNDROMES WITH RAGGED RED FIBERS

The single most common sign of a mitochondrial myopathy is CPEO, occurring in >50% of all mitochondrial myopathies. Varying degrees of ptosis and weakness of extraocular muscles are seen, usually in the absence of diplopia, a point of distinction from disorders with fluctuating eye weakness (e.g., myasthenia gravis).

KEARNS-SAYRE SYNDROME (KSS)

KSS is a widespread multiorgan system disorder with a defined triad of clinical findings: onset before age 20, CPEO, and pigmentary retinopathy, plus one or more of the following features: complete heart block, cerebrospinal fluid (CSF) protein >1 g/L (100 mg/dL), or cerebellar ataxia. Some patients with CPEO and ragged red fibers may not fulfill all of the criteria for KSS. The cardiac disease includes syncopal attacks and cardiac arrest related to the abnormalities in the cardiac conduction system: prolonged intraventricular conduction time, bundle branch block, and complete atrioventricular block. Death attributed to heart block occurs in ~20% of the patients. Varying degrees of progressive limb muscle weakness and easy fatigability affect activities of daily living. Endocrine abnormalities are common, including gonadal dysfunction in both sexes with delayed puberty, short stature, and infertility. Diabetes mellitus is a cardinal sign of mitochondrial disorders and is estimated to occur in 13% of KSS patients. Other less common endocrine disorders include thyroid disease, hyperaldosteronism, Addison's disease, and hypoparathyroidism. Both mental retardation and dementia are common accompaniments to this disorder. Serum CK levels are normal or slightly elevated. Serum lactate and pyruvate levels may be elevated. EMG is myopathic. Nerve conduction studies may be abnormal related to an associated neuropathy. Muscle biopsies reveal ragged red fibers, highlighted in oxidative enzyme stains, many showing defects in cytochrome oxidase. By electron microscopy, there are increased numbers of mitochondria that often appear enlarged and contain paracrystalline inclusions.

KSS is a sporadic disorder. The disease is caused by single mtDNA deletions presumed to arise spontaneously in the ovum or zygote. The most common deletion, occurring in about one-third of patients, removes 4977 bp of contiguous mtDNA. Monitoring for cardiac conduction defects is critical. Prophylactic pacemaker implantation is indicated when ECGs demonstrate a bifascicular block. In KSS, no benefit has been shown for supplementary therapies, including multivitamins or coenzyme Q10. Of all the proposed options, exercise might be the most applicable but must be approached cautiously because of defects in the cardiac conduction system.

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (PEO)

This condition is caused by nuclear DNA mutations affecting mtDNA copy number and integrity and is thus inherited in a Mendelian fashion. Onset is usually after puberty. Fatigue, exercise intolerance, and complaints of muscle weakness are typical. Some patients notice swallowing problems. The neurologic examination confirms the ptosis and ophthalmoplegia, usually asymmetric in distribution. A sensorineural hearing loss may be encountered. Mild facial, neck flexor, and proximal weakness are typical. Rarely, respiratory muscles may be progressively affected and may be the direct cause of death. Serum CK is normal or mildly elevated. The resting lactate level is normal or slightly elevated but may rise excessively after exercise. CSF protein is normal. The EMG is myopathic, and nerve conduction studies are usually normal. Ragged red fibers are prominently displayed in the muscle biopsy. Southern blots of muscle reveal a normal mtDNA band at 16.6 kb and several additional mtDNA deletion bands with genomes varying from 0.5 to 10 kb.

This is autosomal dominant form of CPEO has been linked to loci on three chromosomes: 4q35, 10q24, and 15q22–26. In the chromosome 4q-related form of disease, mutations of the gene encoding the heart and skeletal muscle–specific isoform of the adenine nucleotide translocator 1 (AN*T*1) gene are found. This is highly abundant mitochondrial protein forms a homodimeric inner mitochondrial channel through which adenosine diphosphate (ADP) enters and ATP leaves the mitochondrial matrix. In the chromosome 10q–related disorder, mutations of the gene C10or*f*2 are found. Its gene product, twinkle, co-localizes with the mtDNA and is named for its punctate, starlike staining properties. The function of twinkle is presumed to be critical for

www.ketabpezeshki.com (021) 66485457 - 66485438

lifetime maintenance of mitochondrial integrity. In the cases mapped to chromosome 15q, a mutation affects the gene encoding mtDNA polymerase (POLG), an enzyme important in mtDNA replication. Autosomal recessive PEO has also been described with mutations in the POLG gene. Point mutations have been identified within various mitochondrial tRNA (Leu, Ile, Asn, Trp) genes in families with maternal inheritance of PEO.

Exercise may improve function but will depend on the patient's ability to participate.

MITOCHONDRIAL DNA SKELETAL MUSCLE–CENTRAL NERVOUS SYSTEM SYNDROMES

Myoclonic epilepsy with ragged red fibers (MERRF)

The onset of MERRF is variable, ranging from late childhood to middle adult life. Characteristic features include myoclonic epilepsy, cerebellar ataxia, and progressive muscle weakness. The seizure disorder is an integral part of the disease and may be the initial symptom. Cerebellar ataxia precedes or accompanies epilepsy. It is slowly progressive and generalized. The third major feature of the disease is muscle weakness in a limb-girdle distribution. Other more variable features include dementia, peripheral neuropathy, optic atrophy, hearing loss, and diabetes mellitus.

Serum CK levels are normal or slightly increased. The serum lactate may be elevated. EMG is myopathic, and in some patients nerve conduction studies show a neuropathy. The electroencephalogram is abnormal, corroborating clinical findings of epilepsy. Typical ragged red fibers are seen on muscle biopsy. MERRF is caused by maternally inherited point mutations of mitochondrial tRNA genes. The most common mutation found in 80% of MERRF patients is an A to G substitution at nucleotide 8344 of tRNA lysine (A8344G $tRNA^{lys}$). Other $tRNA^{lys}$ mutations include base-pair substitutions T8356C and G8363A. Only supportive treatment is possible, with special attention to epilepsy.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS)

MELAS is the most common mitochondrial encephalomyopathy. The term strokelike is appropriate because the cerebral lesions do not conform to a strictly vascular distribution. The onset in the majority of patients is before age 20. Seizures, usually partial motor or generalized, are common and may represent the first clearly recognizable sign of disease. The cerebral insults that resemble strokes cause hemiparesis, hemianopia, and cortical blindness. A presumptive stroke occurring before age 40 should place this mitochondrial encephalomyopathy high in the differential diagnosis. Associated conditions include hearing loss, diabetes mellitus, hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, and absence of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and a fatal outcome. Serum lactic acid is typically elevated. The CSF protein is also increased but is usually ≤1 g/L (100 mg/dL). Muscle biopsies show ragged red fibers. Neuroimaging demonstrates basal ganglia calcification in a high percentage of cases. Focal lesions that mimic infarction are present predominantly in the occipital and parietal lobes. Strict vascular territories are not respected, and cerebral angiography fails to demonstrate lesions of the major cerebral blood vessels.

MELAS is caused by maternally inherited point mutations of mitochondrial tRNA genes. Most of the tRNA mutations are lethal, accounting for the paucity of multigeneration families with this syndrome. The A3243G point mutation in $tRNA^{Leu(UUR)}$ is the most common, occurring in ~80% of MELAS cases. About 10% of MELAS patients have other mutations of the $tRNA^{Leu(UUR)}$ gene, including 3252G, 3256T, 3271C, and 3291C. Other tRNA gene mutations have also been reported in MELAS, including G583A $tRNA^{Phe}$, G1642A $tRNA^{Val}$, G4332A $tRNA^{Glu}$, and T8316C $tRNA^{Lys}$. Mutations have also been reported in mtDNA polypeptide-coding genes. Two mutations were found in the ND5 subunit of complex I of the respiratory chain. A missense mutation has been reported at mtDNA position 9957 in the gene for subunit III of cytochrome C oxidase. No specific treatment is available. Supportive treatment is essential for the strokelike episodes, seizures, and endocrinopathies.

PURE MYOPATHY SYNDROMES

Muscle weakness and fatigue can be the predominant manifestations of mtDNA mutations. When the condition affects exclusively muscle (pure myopathy), the disorder becomes difficult to recognize. Occasionally, mitochondrial myopathies can present with recurrent myoglobinuria without fixed weakness and thus resemble a glycogen storage disorder or CPT deficiency.

Mitochondrial DNA depletion syndromes

Mitochondrial DNA depletion syndrome (MDS) is a heterogeneous group of disorders that are inherited in an autosomal recessive fashion and can present in infancy or adults. MDS can be caused by mutations in genes (*T*K2, DGUOK, RRM2B, *T*YMP, SUCLA1, and SUCLA2) that lead to depletion of pools of mitochondrial deoxyribonucleotide (dNTP) pools necessary for mtDNA replication The other major cause of MDS is a set of mutations in genes essential for mtDNA

www.ketabpezeshki.com (021) 66485457 - 66485438

replication (e.g., POLG1 and C10or*f*2). T e clinical phenotypes associated with MDS vary. Patients may develop a severe encephalopathy (e.g., Leigh's syndrome), PEO, an isolated myopathy, myo-neuro-gastrointestinal-encephalopathy (MNGIE), and a sensory neuropathy with ataxia.

DISORDERS OF MUSCLE MEMBRANE EXCITABILITY

Muscle membrane excitability is affected in a group of disorders referred to as channelopathies. T e heart may also be involved, resulting in life-threatening complications **(Table 56-10)**.

CALCIUM CHANNEL DISORDERS OF MUSCLE

Hypokalemic periodic paralysis (HypoKPP)

Onset occurs at adolescence. Men are more of en affected because of decreased penetrance in women. Episodic weakness with onset af er age 25 is almost never due to periodic paralyses, with the exception of thyrotoxic periodic paralysis (see below). Attacks are of en provoked by meals high in carbohydrates or sodium and may accompany rest following prolonged exercise. Weakness usually affects proximal limb muscles more than distal. Ocular and bulbar muscles are less likely to be affected. Respiratory muscles are usually spared, but when they are involved, the condition may prove fatal. Weakness may take as long as 24 h to resolve. Life-threatening cardiac arrhythmias related to hypokalemia may occur during attacks. As a late complication, patients commonly develop severe, disabling proximal lower extremity weakness.

Attacks of thyrotoxic periodic paralysis resemble those of primary HypoKPP. Despite a higher incidence of thyrotoxicosis in women, men, particularly those of Asian descent, are more likely to manifest this complication. Attacks abate with treatment of the underlying thyroid condition.

A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis. Interattack muscle biopsies show the presence of single or multiple centrally placed vacuoles or tubular aggregates. Provocative tests with glucose and insulin to establish a diagnosis are usually not necessary and are potentially hazardous.

In the midst of an attack of weakness, motor conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In between attacks, the EMG and routine nerve conduction studies are normal. However, a long exercise test may demonstrate a decrementing

TABLE 56-10

CLINICAL FEATURES OF PERIODIC PARALYSIS AND NONDYSTROPHIC MYOTONIAS

	CALCIUM CHANNEL	SODIUM CHANNEL		POTASSIUM CHANNEL
FEATURE	HYPOKALEMIC PP	HYPERKALEMIC PP	PARAMYOTONIA CONGENITA	ANDERSEN-TAWIL SYNDROME[a]
Mode of inheritance	AD	AD	AD	AD
Age of onset	Adolescence	Early childhood	Early childhood	Early childhood
Myotonia[b]	No	Yes	Yes	No
Episodic weakness	Yes	Yes	Yes	Yes
Frequency of attacks of weakness	Daily to yearly	May be 2–3/d	With cold, usually rare	Daily to yearly
Duration of attacks of weakness	2–12 h	From 1–2 h to >1 d	2–24 h	2–24 h
Serum K^+ level during attacks of weakness	Decreased	Increased or normal	Usually normal	Variable
Effect of K^+ loading	No change	Increased myotonia, then weakness	Increased myotonia	No change
Effect of muscle cooling	No change	Increased myotonia	Increased myotonia, then weakness	No change
Fixed weakness	Yes	Yes	Yes	Yes

[a]Dysmorphic features and cardiac arrhythmias are distinguishing features (see text).
[b]May be paradoxical in paramyotonia congenita.
Abbreviations: AD, autosomal dominant; PP, periodic paralysis.

www.ketabpezeshki.com (021) 66485457 - 66485438

amplitude, and myopathic MUAPs may be seen on EMG in patients with fixed weakness.

HypoKPP is caused by mutations in either of two genes. HypoKPP type 1, the most common form, is inherited as an autosomal dominant disorder with incomplete penetrance. T ese patients have mutations in the voltage-sensitive, skeletal muscle calcium channel gene, CALCL1A3 **(Fig. 56-8)**. Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (SCN4A). In either instance, the mutations lead to an abnormal gating pore current that predisposes the muscle cell to depolarize when potassium levels are low. It is also now recognized that some cases of thyrotoxic HypoKPP are caused by genetic variants in a potassium channel (Kir 2.6), whose expression is regulated by thyroid hormone.

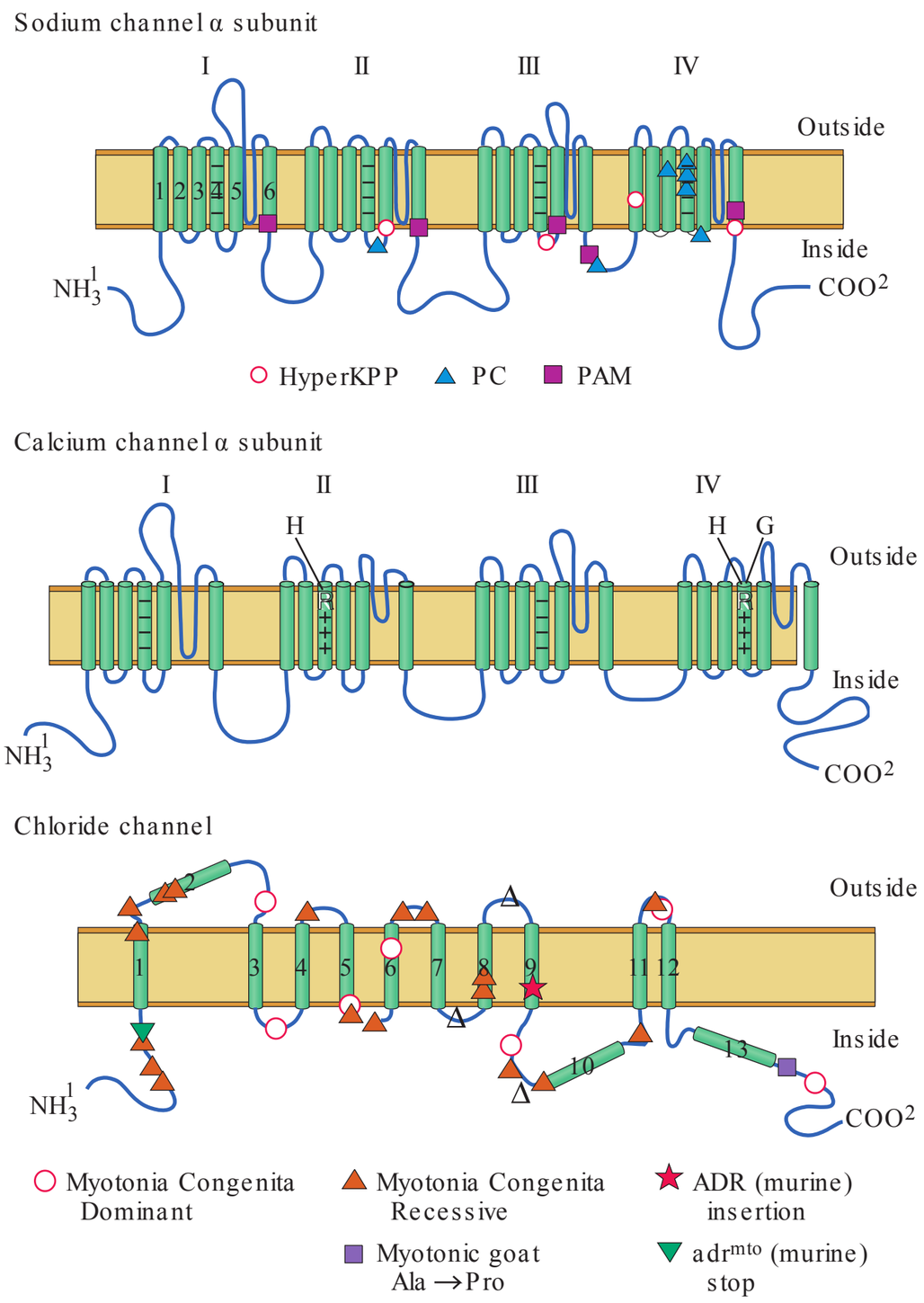


FIGURE 56-8

The sodium and calcium channels are depicted here as containing four homologous domains, each with six membrane-spanning segments. The fourth segment of each domain bears positive charges and acts as the "voltage sensor" for the channel. The association of the four domains is thought to form a pore through which ions pass. Sodium channel mutations are shown along with the phenotype that they confer. HyperKPP, hyperkalemic periodic paralysis; PC, paramyotonia congenita; PAM, potassium-aggravated myotonia. See text for details.

T e chloride channel is envisioned to have 10 membrane-spanning domains. T e positions of mutations causing dominantly and recessively inherited myotonia congenita are indicated, along with mutations that cause this disease in mice and goats.

TREATMENT Hypokalemic Periodic Paralysis

T e acute paralysis improves af er the administration of potassium. Muscle strength and ECG should be monitored. Oral KCl (0.2–0.4 mmol/kg) should be given every 30 min. Only rarely is IV therapy necessary (e.g., when swallowing problems or vomiting is present). Administration of potassium in a glucose solution should be avoided because it may further reduce serum potassium levels. Mannitol is the preferred vehicle for administration of IV potassium. T e long-term goal of therapy is to avoid attacks. T is may reduce late-onset, fixed weakness. Patients should be made aware of the importance of a low-carbohydrate, low-sodium diet and consequences of intense exercise. Prophylactic administration of acetazolamide (125–1000 mg/d in divided doses) reduces or may abolish attacks in HypoKPP type 1. Paradoxically the potassium is lowered, but this is offset by the beneficial effect of metabolic acidosis. If attacks persist on acetazolamide, oral KCl should be added. Some patients require treatment with triamterene (25–100 mg/d) or spironolactone (25–100 mg/d). However, in patients with HypoKPP type 2, attacks of weakness can be exacerbated with acetazolamide.

SODIUM CHANNEL DISORDERS OF MUSCLE

Hyperkalemic periodic paralysis (HyperKPP)

T e term hyperkalemic is misleading because patients are of en normokalemic during attacks. T e fact that attacks are precipitated by potassium administration best defines the disease. T e onset is in the first decade; males and females are affected equally. Attacks are brief and mild, usually lasting 30 min to 4 ho. Weakness affects proximal muscles, sparing bulbar muscles. Attacks are precipitated by rest following exercise and fasting. In a variant of this disorder, the predominant symptom is myotonia without weakness (potassium-aggravated myotonia). T e symptoms are aggravated by cold, and myotonia makes the muscles stiff and painful. T is disorder can be confused with paramyotonia congenita, myotonia congenita, and proximal myotonic myopathy (DM2).

Potassium may be slightly elevated but may also be normal during an attack. As in HypoKPP, nerve conduction studies in HyperKPP muscle may demonstrate reduced motor amplitudes and the EMG may be silent in very weak muscles. In between attacks of weakness, the conduction studies are normal. T e EMG will of en

www.ketabpezeshki.com (021) 66485457 - 66485438

demonstrate myotonic discharges during and between attacks.

T e muscle biopsy shows vacuoles that are smaller, less numerous, and more peripheral compared to the hypokalemic form or tubular aggregates. Provocative tests by administration of potassium can induce weakness but are usually not necessary to establish the diagnosis. HyperKPP and potassium-aggravated myotonia are inherited as autosomal dominant disorders. Mutations of the voltage-gated sodium channel SCN4A gene (Fig. 56-8) cause these conditions. For patients with frequent attacks, acetazolamide (125–1000 mg/d) is helpful. We have found mexiletine to be helpful in patients with significant myotonia.

Paramyotonia congenita

In paramyotonia congenita (PC), the attacks of weakness are cold-induced or occur spontaneously and are mild. Myotonia is a prominent feature but worsens with muscle activity (paradoxical myotonia). T is is in contrast to classic myotonia in which exercise alleviates the condition. Attacks of weakness are seldom severe enough to require emergency room treatment. Over time patients develop interattack weakness as they do in other forms of periodic paralysis. PC is usually associated with normokalemia or hyperkalemia.

Serum CK is usually mildly elevated. Routine sensory and motor nerve conduction studies are normal. Short exercise test may be abnormal however, and cooling of the muscle of en dramatically reduces the amplitude of the compound muscle action potentials. EMG reveals diffuse myotonic potentials in PC. Upon local cooling of the muscle, the myotonic discharges disappear as the patient becomes unable to activate MUAPs.

PC is inherited as an autosomal dominant condition; voltage-gated sodium channel mutations (Fig. 56-8) are responsible, and thus this disorder is allelic with HyperKPP and potassium-aggravated myotonia. Patients with PC seldom seek treatment during attacks. Oral administration of glucose or other carbohydrates hastens recovery. Because interattack weakness may develop af er repeated episodes, prophylactic treatment is usually indicated. T iazide diuretics (e.g., chlorothiazide, 250–1000 mg/d) and mexiletine (slowly increase dose from 450 mg/d) are reported to be helpful. Patients should be advised to increase carbohydrates in their diet.

POTASSIUM CHANNEL DISORDERS

Andersen-Ta wil syndrome

T is rare disease is characterized by episodic weakness, cardiac arrhythmias, and dysmorphic features (short stature, scoliosis, clinodactyly, hypertelorism, small or prominent low-set ears, micrognathia, and broad forehead). T e cardiac arrhythmias are potentially serious and life threatening. T ey include long QT, ventricular ectopy, bidirectional ventricular arrhythmias, and tachycardia. For many years, the classification of this disorder was uncertain because episodes of weakness are associated with elevated, normal, or reduced levels of potassium during an attack. In addition, the potassium levels differ among kindreds but are consistent within a family. Inheritance is autosomal dominant, with incomplete penetrance and variable expressivity. T e disease is caused by mutations of the inwardly rectifying potassium channel (Kir 2.1) gene that heighten muscle cell excitability. T e treatment is similar to that for other forms of periodic paralysis and must include cardiac monitoring. T e episodes of weakness may differ between patients because of potassium variability. Acetazolamide may decrease the attack frequency and severity.

CHLORIDE CHANNEL DISORDERS

Two forms of this disorder, autosomal dominant (T omsen's disease) and autosomal recessive (Becker disease), are related to the same gene abnormality. Symptoms are noted in infancy and early childhood. T e severity lessens in the third to fourth decade. Myotonia is worsened by cold and improved by activity. T e gait may appear slow and labored at first but improves with walking. In T omsen's disease, muscle strength is normal, but in Becker disease, which is usually more severe, there may be muscle weakness. Muscle hypertrophy is usually present. Myotonic discharges are prominently displayed by EMG recordings.

Serum CK is normal or mildly elevated. T e muscle biopsy shows hypertrophied fibers. T e disease is inherited as dominant or recessive and is caused by mutations of the chloride channel gene (Fig. 56-8) that increase muscle cell excitability. Many patients will not require treatment and learn that the symptoms improve with activity. Medications that can be used to decrease myotonia include quinine, phenytoin, and mexiletine.

ENDOCRINE AND METABOLIC MYOPATHIES

Many endocrine disorders cause weakness. Muscle fatigue is more common than true weakness. T e cause of weakness in these disorders is not well defined. It is not even clear that weakness results from disease of muscle as opposed to another part of the motor unit, since the serum CK level is of en normal (except in hypothyroidism) and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopathies respond to treatment.

www.ketabpezeshki.com (021) 66485457 - 66485438

THYROID DISORDERS

Abnormalities of thyroid function can cause a wide array of muscle disorders. T ese conditions relate to the important role of thyroid hormones in regulating the metabolism of carbohydrates and lipids as well as the rate of protein synthesis and enzyme production. T y-roid hormones also stimulate calorigenesis in muscle, increase muscle demand for vitamins, and enhance muscle sensitivity to circulating catecholamines.

Hypothyroidism

Patients with hypothyroidism have frequent muscle complaints, and proximal muscle weakness occurs in about one-third of them. Muscle cramps, pain, and stiffness are common. Some patients have enlarged muscles. Features of slow muscle contraction and relax-ation occur in 25% of patients; the relaxation phase of muscle stretch reflexes is characteristically prolonged and best observed at the ankle or biceps brachii reflexes. T e serum CK level is of en elevated (up to 10 times normal), even when there is minimal clinical evi-dence of muscle disease. EMG is typically normal. T e cause of muscle enlargement has not been determined, and muscle biopsy shows no distinctive morphologic abnormalities.

Hyperthyroidism

Patients who are thyrotoxic commonly have proxi-mal muscle weakness and atrophy on examination, but they rarely complain of myopathic symptoms. Activity of deep tendon reflexes may be enhanced. Bulbar, respiratory, and even esophageal muscles may occasionally be affected, causing dysphagia, dysphonia, and aspiration. When bulbar involve-ment occurs, it is usually accompanied by chronic proximal limb weakness, but occasionally it presents in the absence of generalized thyrotoxic myopathy. Fasciculations may be apparent and, when coupled with increased muscle stretch reflexes, may lead to an erroneous diagnosis of amyotrophic lateral sclerosis. A form hypokalemic periodic paralysis can occur in patients who are thyrotoxic. Recently, mutations in the KCNJ18 gene that encodes for the inwardly rec-tifying potassium channel, Kir 2.6, have been discov-ered in up to a third of cases. Other neuromuscular disorders that occur in association with hyperthy-roidism include myasthenia gravis **(Chap. 55)** and a progressive ocular myopathy associated with propto-sis (Graves' ophthalmopathy). Serum CK levels are not elevated in thyrotoxic myopathy, the EMG is normal, and muscle histology usually shows only atrophy of muscle fibers.

PARATHYROID DISORDERS

Hyperparathyroidism

Muscle weakness is an integral part of primary and sec-ondary hyperparathyroidism. Proximal muscle weakness, muscle wasting, and brisk muscle stretch reflexes are the main features of this endocrinopathy. Some patients develop neck extensor weakness (part of the dropped head syndrome). Serum CK levels are usually normal or slightly elevated. Serum parathyroid hormone levels are elevated. Serum calcium and phosphorus levels show no correlation with the clinical neuromuscular manifesta-tions. Muscle biopsies show only varying degrees of atro-phy without muscle fiber degeneration.

Hypoparathyroidism

An overt myopathy due to hypocalcemia rarely occurs. Neuromuscular symptoms are usually related to localized or generalized tetany. Serum CK levels may be increased secondary to muscle damage from sustained tetany. Hyporeflexia or areflexia is usu-ally present and contrasts with the hyperreflexia in hyperparathyroidism.

ADRENAL DISORDERS

Conditions associated with glucocorticoid excess cause a myopathy; in fact, steroid myopathy is the most com-monly diagnosed endocrine muscle disease. Gluco-corticoid excess, either endogenous or exogenous (see "Drug-Induced Myopathies," below), produces vari-ous degrees of proximal limb weakness. Muscle wast-ing may be striking. A cushingoid appearance usually accompanies clinical signs of myopathy. Histologic sections demonstrate muscle fiber atrophy, preferen-tially affecting type 2b fibers, rather than degenera-tion or necrosis of muscle fibers. Adrenal insufficiency commonly causes muscle fatigue. T e degree of weak-ness may be difficult to assess but is typically mild. In primary hyperaldosteronism (Conn's syndrome), neu-romuscular complications are due to potassium deple-tion. T e clinical picture is one of persistent muscle weakness. Long-standing hyperaldosteronism may lead to proximal limb weakness and wasting. Serum CK lev-els may be elevated, and a muscle biopsy may demon-strate degenerating fibers, some with vacuoles. T ese changes relate to hypokalemia and are not a direct effect of aldosterone on skeletal muscle.

PITUITARY DISORDERS

(See also Chap. 51) Patients with acromegaly usually have mild proximal weakness without muscle atrophy. Muscles of en appear enlarged but exhibit decreased

www.ketabpezeshki.com (021) 66485457 - 66485438

force generation. T e duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy.

DIABETES MELLITUS

Neuromuscular complications of diabetes mellitus are most of en related to neuropathy, with cranial and peripheral nerve palsies or distal sensorimotor polyneuropathy. Diabetic amyotrophy is a clumsy term because the condition represents a neuropathy affecting the proximal major nerve trunks and lumbosacral plexus. More appropriate terms for this disorder include diabetic proximal neuropathy and lumbosacral radiculoplexus neuropathy.

T e only notable myopathy of diabetes mellitus is ischemic infarction of leg muscles, usually involving one of the thigh muscles but on occasion affecting the distal leg. T is condition occurs in patients with poorly controlled diabetes and presents with abrupt onset of pain, tenderness, and edema of one thigh. T e area of muscle infarction is hard and indurated. T e muscles most of en affected include the vastus lateralis, thigh adductors, and biceps femoris. Computed tomography (CT) or MRI can demonstrate focal abnormalities in the affected muscle. Diagnosis by imaging is preferable to muscle biopsy, if possible, as hemorrhage into the biopsy site can occur.

VITAMIN DEFICIENCY

Vitamin D deficiency due to decreased intake, decreased absorption, or impaired vitamin D metabolism (as occurs in renal disease) may lead to chronic muscle weakness. Pain reflects the underlying bone disease (osteomalacia). Vitamin E deficiency may result from malabsorption. Clinical manifestations include ataxic neuropathy due to loss of proprioception and myopathy with proximal weakness. Progressive external ophthalmoplegia is a distinctive finding. It has not been established that deficiency of other vitamins causes a myopathy.

MYOPATHIES OF SYSTEMIC ILLNESS

Systemic illnesses such as chronic respiratory, cardiac, or hepatic failure are frequently associated with severe muscle wasting and complaints of weakness. Fatigue is usually a more significant problem than weakness, which is typically mild.

Myopathy may be a manifestation of chronic renal failure (CRF), independent of the better known uremic polyneuropathy. Abnormalities of calcium and phosphorus homeostasis and bone metabolism in chronic renal failure result from a reduction in 1,25-dihydroxyvitamin D, leading to decreased intestinal absorption of calcium. Hypocalcemia, further accentuated by hyperphosphatemia due to decreased renal phosphate clearance, leads to secondary hyperparathyroidism. Renal osteodystrophy results from the compensatory hyperparathyroidism, which leads to osteomalacia from reduced calcium availability and to osteitis fibrosa from the parathyroid hormone excess. T e clinical picture of the myopathy of CRF is identical to that of primary hyperparathyroidism and osteomalacia. T ere is proximal limb weakness with bone pain.

Gangrenous calcification represents a separate, rare, and sometimes fatal complication of CRF. In this condition, widespread arterial calcification occurs and results in ischemia. Extensive skin necrosis may occur, along with painful myopathy and even myoglobinuria.

DRUG-INDUCED MYOPATHIES

Drug-induced myopathies are relatively uncommon in clinical practice with the exception of those caused by the cholesterol-lowering agents and glucocorticoids. Others impact practice to a lesser degree but are important to consider in specific situations. **Table 56-11** provides a comprehensive list of drug-induced myopathies with their distinguishing features.

MYOPATHY FROM LIPID-LOWERING AGENTS

All classes of lipid-lowering agents have been implicated in muscle toxicity, including fibrates (clofibrate, gemfibrozil), HMG-CoA reductase inhibitors (referred to as statins), niacin (nicotinic acid), and ezetimibe. Myalgia, malaise, and muscle tenderness are the most common manifestations. Muscle pain may be related to exercise. Patients may exhibit proximal weakness. Varying degrees of muscle necrosis are seen, and in severe reactions rhabdomyolysis and myoglobinuria occur. Concomitant use of statins with fibrates and cyclosporine is more likely to cause adverse reactions than use of one agent alone. Elevated serum CK is an important indication of toxicity. Muscle weakness is accompanied by a myopathic EMG, and muscle necrosis is observed by muscle biopsy. Severe myalgias, muscle weakness, significant elevations in serum CK (>three times baseline), and myoglobinuria are indications for stopping the drug. Patients usually improve with drug cessation, although this may take several weeks. Rare cases continue to progress af er the offending agent is discontinued. It is possible that in such cases the statin may have triggered an immune-mediated necrotizing myopathy, as these individuals require aggressive immunotherapy

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 56-11

DRUG-INDUCED MYOPATHIES

DRUGS	MAJOR TOXIC REACTION
Lipid-lowering agents Fibric acid derivatives HMG-CoA reductase inhibitors Niacin (nicotinic acid)	Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria.
Glucocorticoids	Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness.
Nondepolarizing neuromuscular blocking agents	Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids.
Zidovudine	Mitochondrial myopathy with ragged red fibers
Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine	All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures.
Autoimmune toxic myopathy d-Penicillamine	Use of this drug may cause polymyositis and myasthenia gravis.
Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine	All amphophilic drugs have the potential to produce painless, proximal weakness associated with autophagic vacuoles in the muscle biopsy.
Antimicrotubular drugs Colchicine	This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows autophagic vacuoles.

(e.g., prednisone and sometimes other agents) to improve and often relapse when these therapies are discontinued. Interestingly, antibodies directed against the 100-kDa HMG-CoA reductase receptor on muscle fibers have been identified in many of these cases.

GLUCOCORTICOID-RELATED MYOPATHIES

Glucocorticoid myopathy occurs with chronic treatment or as "acute quadriplegic" myopathy secondary to high-dose IV glucocorticoid use. Chronic administration produces proximal weakness accompanied by cushingoid manifestations, which can be quite debilitating; the chronic use of prednisone at a daily dose of ≥30 mg/d is most often associated with toxicity. Patients taking fluorinated glucocorticoids (triamcinolone, betamethasone, dexamethasone) appear to be at especially high risk for myopathy. In chronic steroid myopathy, the serum CK is usually normal. Serum potassium may be low. The muscle biopsy in chronic cases shows preferential type 2 muscle fiber atrophy; this is not reflected in the EMG, which is usually normal.

Patients receiving high-dose IV glucocorticoids for status asthmaticus, chronic obstructive pulmonary disease, organ transplantation, or other indications may develop severe generalized weakness (critical illness myopathy). This is myopathy, also known as acute quadriplegic myopathy, can also occur in the setting of sepsis. Involvement of the diaphragm and intercostal muscles causes respiratory failure and requires ventilatory support. In these settings, the use of glucocorticoids in combination with nondepolarizing neuromuscular blocking agents potentiates this complication. In critical illness myopathy, the muscle biopsy is abnormal, showing a distinctive loss of thick filaments (myosin) by electron microscopy. By light microscopy, there is focal loss of ATPase staining in central or paracentral areas of the muscle fiber. Calpain stains show diffusely reactive atrophic fibers. Withdrawal of glucocorticoids will improve the chronic myopathy. In acute quadriplegic myopathy, recovery is slow. Patients require supportive care and rehabilitation.

DRUG-INDUCED MITOCHONDRIAL MYOPATHY

Zidovudine, used in the treatment of HIV infection, is a thymidine analogue that inhibits viral replication by interrupting reverse transcriptase. Myopathy is a well-established complication of this agent. Patients present with myalgias, muscle weakness, and atrophy affecting the thigh and calf muscles. The complication occurs in about 17% of patients treated with doses of 1200 mg/d for 6 months. The introduction of protease inhibitors for treatment of HIV infection has led to lower doses of zidovudine therapy and a decreased incidence of myopathy. Serum CK is elevated and EMG is myopathic. Muscle biopsy shows ragged red fibers with minimal inflammation; the lack of inflammation serves to distinguish zidovudine toxicity from HIV-related myopathy. If the myopathy is thought to be drug related, the medication should be stopped or the dosage reduced.

DRUGS OF ABUSE AND RELATED MYOPATHIES

Myotoxicity is a potential consequence of addiction to alcohol and illicit drugs. Ethanol is one of the most commonly abused substances with potential to damage

www.ketabpezeshki.com (021) 66485457 - 66485438

muscle. Other potential toxins include cocaine, heroin, and amphetamines. T e most deleterious reactions occur from overdosing leading to coma and seizures, causing rhabdomyolysis, myoglobinuria, and renal failure. Direct toxicity can occur from cocaine, heroin, and amphetamines causing muscle breakdown and varying degrees of weakness. T e effects of alcohol are more controversial. Direct muscle damage is less certain, since toxicity usually occurs in the setting of poor nutrition and possible contributing factors such as hypokalemia and hypophosphatemia. Alcoholics are also prone to neuropathy **(Chap. 63)**.

Focal myopathies from self-administration of meperidine, heroin, and pentazocine can cause pain, swelling, muscle necrosis, and hemorrhage. T e cause is multifactorial; needle trauma, direct toxicity of the drug or vehicle, and infection may all play a role. When severe, there may be overlying skin induration and contractures with replacement of muscle by connective tissue. Elevated serum CK and myopathic EMG are characteristic of these reactions. T e muscle biopsy shows widespread or focal areas of necrosis. In conditions leading to rhabdomyolysis, patients need adequate hydration to reduce serum myoglobin and protect renal function. In all of these conditions, counseling is essential to limit drug abuse.

DRUG-INDUCED AUTOIMMUNE MYOPATHIES

As mentioned previously, an autoimmune necrotizing myopathy associated with autoantibodies directed against HMG-CoA rarely occurs in the setting of statin use. An inflammatory myopathy also may occur with d-penicillamine, sometimes used in the treatment of Wilson's disease scleroderma, rheumatoid arthritis, and primary biliary cirrhosis. T e incidence of this inflammatory muscle disease is about 1%. Myasthenia gravis is also induced by d-penicillamine, with a higher incidence estimated at 7%. T ese disorders resolve with drug withdrawal, although immunosuppressive therapy may be warranted in severe cases.

Scattered reports of other drugs causing an inflammatory myopathy are rare and include a heterogeneous group of agents: cimetidine, phenytoin, procainamide, and propylthiouracil. In most cases, a cause-and-effect relationship is uncertain. A complication of interest was related to l-tryptophan. In 1989 an epidemic of eosinophilia-myalgia syndrome (EMS) in the United States was caused by a contaminant in the product from one manufacturer. T e product was withdrawn, and incidence of EMS diminished abruptly following this action.

OTHER DRUG-INDUCED MYOPATHIES

Certain drugs produce painless, largely proximal, muscle weakness. T ese drugs include the amphophilic cationic drugs (amiodarone, chloroquine, hydroxychloroquine) and antimicrotubular drugs (colchicine) (Table 56-11). Muscle biopsy can be useful in the identification of toxicity because autophagic vacuoles are prominent pathologic features of these toxins.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 57

POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS

Marinos C. Dalakas

The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal muscle weakness. They are classified into three major groups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

CLINICAL FEATURES

The prevalence of the inflammatory myopathies is estimated at 1 in 100,000. PM as a stand-alone entity is a rare disease. DM affects both children and adults and women more often than men. IBM is three times more frequent in men than in women, more common in whites than blacks, and is most likely to affect persons age >50 years.

These disorders present as progressive and symmetric muscle weakness except for IBM, which can have an asymmetric pattern. Patients usually report increasing difficulty with everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, stepping onto a curb, lifting objects, or combing hair. Fine-motor movements that depend on the strength of distal muscles, such as buttoning a shirt, sewing, knitting, or writing, are affected only late in the course of PM and DM, but fairly early in IBM. Falling is common in IBM because of early involvement of the quadriceps muscle, with buckling of the knees. Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be questioned. Facial muscles are unaffected in PM and DM, but mild facial muscle weakness is common in patients with IBM. In all forms of inflammatory myopathy, pharyngeal and neck-flexor muscles are often involved, causing dysphagia or difficulty in holding up the head (head drop). In advanced and rarely in acute cases, respiratory muscles may also be affected. Severe weakness, if untreated, is almost always associated with muscle wasting. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles, especially in IBM, where atrophy of the quadriceps and the distal muscles is common. Myalgia and muscle tenderness may occur in a small number of patients, usually early in the disease, and particularly in DM associated with connective tissue disorders. Weakness in PM and DM progresses subacutely over a period of weeks or months and rarely acutely; by contrast, IBM progresses very slowly, over years, simulating a late-life muscular dystrophy **(Chap. 56)** or slowly progressive motor neuron disorder **(Chap. 39)**.

SPECIFIC FEATURES

(Table 57-1)

Polymyositis

The actual onset of PM is often not easily determined, and patients typically delay seeking medical advice for several weeks or even months. This is in contrast to DM, in which the rash facilitates early recognition (see below). PM mimics many other myopathies and is a diagnosis of exclusion. It is a subacute inflammatory myopathy affecting adults, and rarely children, who do not have any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy analysis (see below). As an isolated entity, PM is a rare (and overdiagnosed) disorder; more commonly, PM occurs in association with a systemic autoimmune or connective tissue

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 57-1

FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES

CHARACTERISTIC	POLYMYOSITIS	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Age at onset	>18 years	Adulthood and childhood	>50 years
Familial association	No	No	Yes, in some rare cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-1 (human T cell lymphotropic virus type 1).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), statins (necrotizing, toxic, or autoimmune myositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

disease or with a known viral or bacterial infection. Drugs, especially D-penicillamine, statins, or zidovudine (AZT), may also trigger an inflammatory myopathy similar to PM.

Dermatomyositis

DM is a distinctive entity identified by a characteristic rash accompanying, or more often preceding, muscle weakness. The rash may consist of a blue-purple discoloration on the upper eyelids with edema (heliotrope rash), a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron's sign). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a V sign), or back and shoulders (shawl sign), and may worsen after sun exposure. In some patients, the rash is pruritic, especially on the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are also characteristic. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling mechanic's hands. The weakness can be mild, moderate, or severe enough to lead to quadriparesis. At times, the muscle strength appears normal, hence the term dermatomyositis sine myositis. When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is often seen.

DM usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin, similar to that seen in chronic cases of DM, have occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated l-tryptophan.

Inclusion body myositis

In patients ≥50 years of age, IBM is the most common of the inflammatory myopathies. It is often misdiagnosed as PM and is suspected only later when a patient with presumed PM does not respond to therapy. Weakness and atrophy of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis. Some patients present with falls because their knees collapse due to early quadriceps weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold objects such as golf clubs or perform tasks such as turning keys or tying knots. On occasion, the weakness and accompanying atrophy can be asymmetric and selectively involve the quadriceps, iliopsoas, triceps, biceps, and finger flexors, resembling a lower motor neuron disease. Dysphagia is common, occurring in up to 60% of IBM

www.ketabpezeshki.com (021) 66485457 - 66485438

patients, and may lead to episodes of choking. Sensory examination is generally normal; some patients have mildly diminished vibratory sensation at the ankles that presumably is age-related. The pattern of distal weakness, which superficially resembles motor neuron or peripheral nerve disease, results from the myopathic process affecting distal muscles selectively. Disease progression is slow but steady, and most patients require an assistive device such as cane, walker, or wheelchair within several years of onset.

In at least 20% of cases, IBM is associated with systemic autoimmune or connective tissue diseases. Familial aggregation of typical IBM may occur; such cases have been designated as *f*amilial in*fl*ammatory IBM. This disorder is distinct from hereditary inclusion body myopathy (h-IBM), which describes a heterogeneous group of recessive, and less frequently dominant, inherited syndromes; the h-IBMs are noninflammatory myopathies. A subset of h-IBM that spares the quadriceps muscles has emerged as a distinct entity. This disorder, originally described in Iranian Jews and now seen in many ethnic groups, is linked to chromosome 9p1 and results from mutations in the UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) gene.

ASSOCIATED CLINICAL FINDINGS

Extramuscular manifestations

These may be present to a varying degree in patients with PM or DM, and include:

1. Systemic symptoms, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, especially when inflammatory myopathy is associated with a connective tissue disorder.
2. Joint contractures, mostly in DM and especially in children.
3. Dysphagia and gastrointestinal symptoms, due to involvement of oropharyngeal striated muscles and upper esophagus, especially in DM and IBM.
4. Cardiac disturbances, including atrioventricular conduction defects, tachyarrhythmias, dilated cardiomyopathy, a low ejection fraction, and congestive heart failure, which may rarely occur either from the disease itself or from hypertension associated with long-term use of glucocorticoids.
5. Pulmonary dys*f*unction, due to weakness of the thoracic muscles, interstitial lung disease, or drug-induced pneumonitis (e.g., from methotrexate), which may cause dyspnea, nonproductive cough, and aspiration pneumonia. Interstitial lung disease may precede myopathy or occur early in the disease and develops in up to 10% of patients with PM or DM, most of whom have antibodies to t-RNA synthetases, as described below.
6. Subcutaneous calcifications, in DM, sometimes extruding on the skin and causing ulcerations and infections.
7. Arthralgias, synovitis, or deforming arthropathy with subluxation in the interphalangeal joints, which can occur in some patients with DM and PM who have Jo-1 antibodies (see below).

Association with malignancies

Although all the inflammatory myopathies can have a chance association with malignant lesions, especially in older age groups, the incidence of malignant conditions appears to be specifically increased only in patients with DM and not in those with PM or IBM. The most common tumors associated with DM are ovarian cancer, breast cancer, melanoma, colon cancer, and non-Hodgkin's lymphoma. The extent of the search that should be conducted for an occult neoplasm in adults with DM depends on the clinical circumstances. Tumors in these patients are usually uncovered by abnormal findings in the medical history and physical examination and not through an extensive blind search. The weight of evidence argues against performing expensive, invasive, and nondirected tumor searches. A complete annual physical examination with pelvic, breast (mammogram, if indicated), and rectal examinations (with colonoscopy according to age and family history); urinalysis; complete blood count; blood chemistry tests; and a chest film should suffice in most cases. In Asians, nasopharyngeal cancer is common, and a careful examination of ears, nose, and throat is indicated. If malignancy is clinically suspected, screening with a whole-body positron emission tomography (PET) scan should be considered.

Overlap syndromes

These describe the association of inflammatory myopathies with connective tissue diseases. A well-characterized overlap syndrome occurs in patients with DM who also have manifestations of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits (Table 57-1). By contrast, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjögren's syndrome are very rare in patients with DM. Patients with the overlap syndrome of DM and systemic sclerosis may have a specific antinuclear antibody, the anti-PM/Scl, directed against a nucleolar-protein complex.

PATHOGENESIS

An autoimmune etiology of the inflammatory myopathies is indirectly supported by an association with other autoimmune or connective tissue diseases; the

www.ketabpezeshki.com (021) 66485457 - 66485438

presence of various autoantibodies; an association with specific major histocompatibility complex (MHC) genes; demonstration of T cell–mediated myocytotoxicity or complement-mediated microangiopathy; and a response to immunotherapy.

Autoantibodies and immunogenetics

Various autoantibodies against nuclear antigens (antinuclear antibodies) and cytoplasmic antigens are found in up to 30% of patients with inflammatory myopathies. T e antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti-signal-recognition particles). T e antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. Some patients with the anti-Jo-1 antibody also have Raynaud's phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. DR3 haplotypes (molecular designation DRB1*0301, DQB1*0201) occur in up to 75% of patients with PM and IBM, whereas in juvenile DM, there is an increased frequency of DQA1*0501. Antibodies against the cytosolic 5′-nucleotidase 1A, an enzyme abundantly expressed in muscle and thought to be involved in DNA degradation and repair, have been detected in one-third of IBM patients. Although the pathogenic significance of these antibodies is still unknown, they highlight the presence of an immune response, as discussed below.

Immunopathologic mechanisms

In DM, humoral immune mechanisms are implicated, resulting in a microangiopathy and muscle ischemia **(Fig. 57-1)**. Endomysial inflammatory infiltrates are

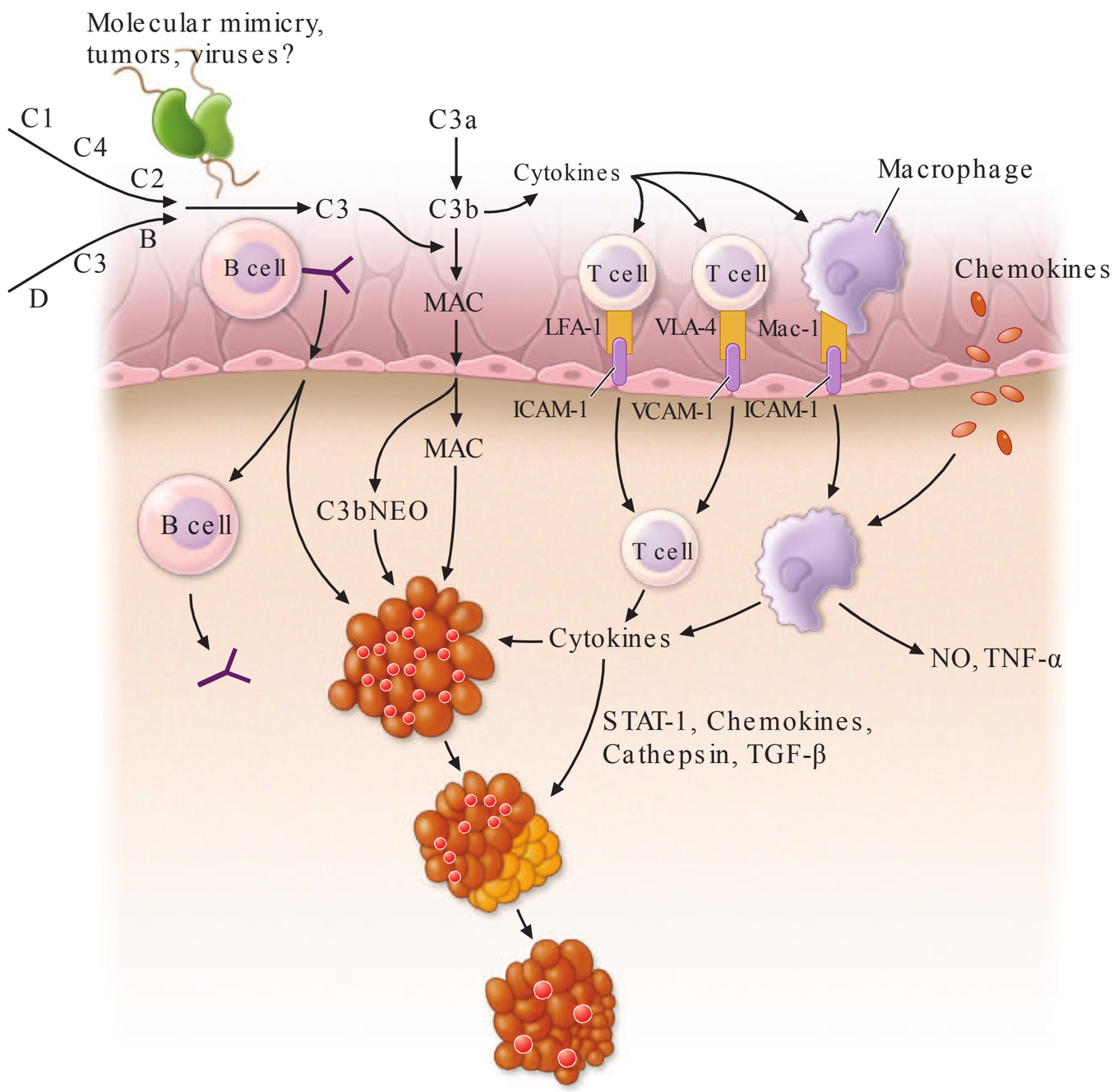


FIGURE 57-1

Immunopathogenesis of dermatomyositis. Activation of complement, possibly by autoantibodies (Y), against endothelial cells and formation of C3 via the classic or alternative pathway. Activated C3 leads to formation of C3b, C3bNEO, and membrane attack complexes (MAC), which are deposited in and around the endothelial cell wall of the endomysial capillaries. Deposition of MAC leads to destruction of capillaries, ischemia, or microinfarcts, most prominent in the periphery of the fascicles, and perifascicular atrophy. B cells, plasmacytoid dendritic cells, CD4 T cells, and macrophages traffic from the circulation to the muscle. Endothelial expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) is induced by cytokines released by the mononuclear cells. Integrins, specifically very late activation antigen (VLA)-4 and lymphocyte function–associated antigen (LFA)-1, bind VCAM and ICAM and promote T cell and macrophage infiltration of muscle through the endothelial cell wall.

www.ketabpezeshki.com (021) 66485457 - 66485438

composed of B cells located in proximity to CD4 T cells, plasmacytoid dendritic cells, and macrophages; there is a relative absence of lymphocytic invasion of nonnecrotic muscle fibers. Activation of the complement C5b-9 membranolytic attack complex is thought to be a critical early event that triggers release of proinflammatory cytokines and chemokines, induces expression of vascular cell adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1 on endothelial cells, and facilitates migration of activated lymphoid cells to the perimysial and endomysial spaces. Necrosis of the endothelial cells, reduced numbers of endomysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts occur. T e remaining capillaries often have dilated lumens in response to the ischemic process. Larger intramuscular blood vessels may also be affected in the same pattern. Residual perifascicular atrophy reflects the endofascicular hypoperfusion that is prominent in the periphery of muscle fascicles. Increased expression of type I interferon–inducible proteins is also noted in these regions.

By contrast, in PM and IBM, a mechanism of T cell–mediated cytotoxicity is likely. CD8 T cells, along with macrophages, initially surround and eventually invade and destroy healthy, nonnecrotic muscle fibers that aberrantly express class I MHC molecules. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells and macrophages. T e CD8/MHC-I complex is characteristic of PM and IBM; its detection can aid in confirming the histologic diagnosis of PM, as discussed below. T e cytotoxic CD8 T cells contain perforin and granzyme granules directed toward the surface of the muscle fibers and capable of inducing myonecrosis. Analysis of T cell receptor molecules expressed by the infiltrating CD8 cells has revealed clonal expansion and conserved sequences in the antigen-binding region, both suggesting an antigen-driven T cell response. Whether the putative antigens are endogenous (e.g., muscle) or exogenous (e.g., viral) sequences is unknown. Viruses have not been identified within the muscle fibers. Costimulatory molecules and their counterreceptors, which are fundamental for T cell activation and antigen recognition, are strongly upregulated in PM and IBM. As noted above, the possibility that B cells and the humoral immune system might also play a role in IBM is suggested by the identification of anti-cytosolic 5′-nucleotidase 1A antibodies in some patients. Key molecules involved in T cell–mediated cytotoxicity are depicted in **Fig. 57-2**.

The role of nonimmune factors in IBM

In IBM, the presence of Congo red–positive amyloid deposits within some vacuolated muscle fibers and abnormal mitochondria with cytochrome oxidase–negative fibers suggest that, in addition to the autoimmune component, there is also a degenerative process. Similar to Alzheimer's disease, the intracellular amyloid deposits in IBM are immunoreactive against amyloid precursor protein (APP), β-amyloid, chymotrypsin, apolipoprotein E, presenilin, ubiquitin, and phosphorylated tau, but it is unclear whether these deposits, which are also seen in other vacuolar myopathies, are directly pathogenic or represent secondary phenomena. T e same is true for the mitochondrial abnormalities, which may also be secondary to the effects of aging or a bystander effect of upregulated cytokines. Expression of cytokines and upregulation of MHC class I by the muscle fibers may cause an endoplasmic reticulum stress response resulting in intracellular accumulation of stressor molecules or misfolded glycoproteins and activation of nuclear factor κB (NF-κB), leading to further cytokine activation.

Association with viral infections and the role of retroviruses

Several viruses, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr virus, have been indirectly associated with myositis. For the coxsackieviruses, an autoimmune myositis triggered by molecular mimicry has been proposed because of structural homology between histidyl-transfer RNA synthetase that is the target of the Jo-1 antibody (see above) and genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Sensitive polymerase chain reaction (PCR) studies, however, have repeatedly failed to confirm the presence of such viruses in muscle biopsies.

T e best evidence of a viral connection in PM and IBM is with the retroviruses. Some individuals infected with HIV or with human T cell lymphotropic virus 1 (HTLV-1) develop PM or IBM; a similar disorder has been described in nonhuman primates infected with the simian immunodeficiency virus. T e inflammatory myopathy may occur as the initial manifestation of a retroviral infection, or myositis may develop later in the disease course. Retroviral antigens have been detected only in occasional endomysial macrophages and not within the muscle fibers themselves, suggesting that persistent infection and viral replication within the muscle does not occur. Histologic findings are identical to retroviral-negative PM or IBM. T e infiltrating T cells in the muscle have a clonal bias and a number of them are retroviral-specific. T is disorder should be distinguished from a toxic myopathy related to long-term therapy with AZT, characterized by fatigue, myalgia, mild muscle weakness, and mild elevation of creatine kinase (CK). AZT-induced myopathy, which generally improves when the drug is discontinued, is a

www.ketabpezeshki.com (021) 66485457 - 66485438

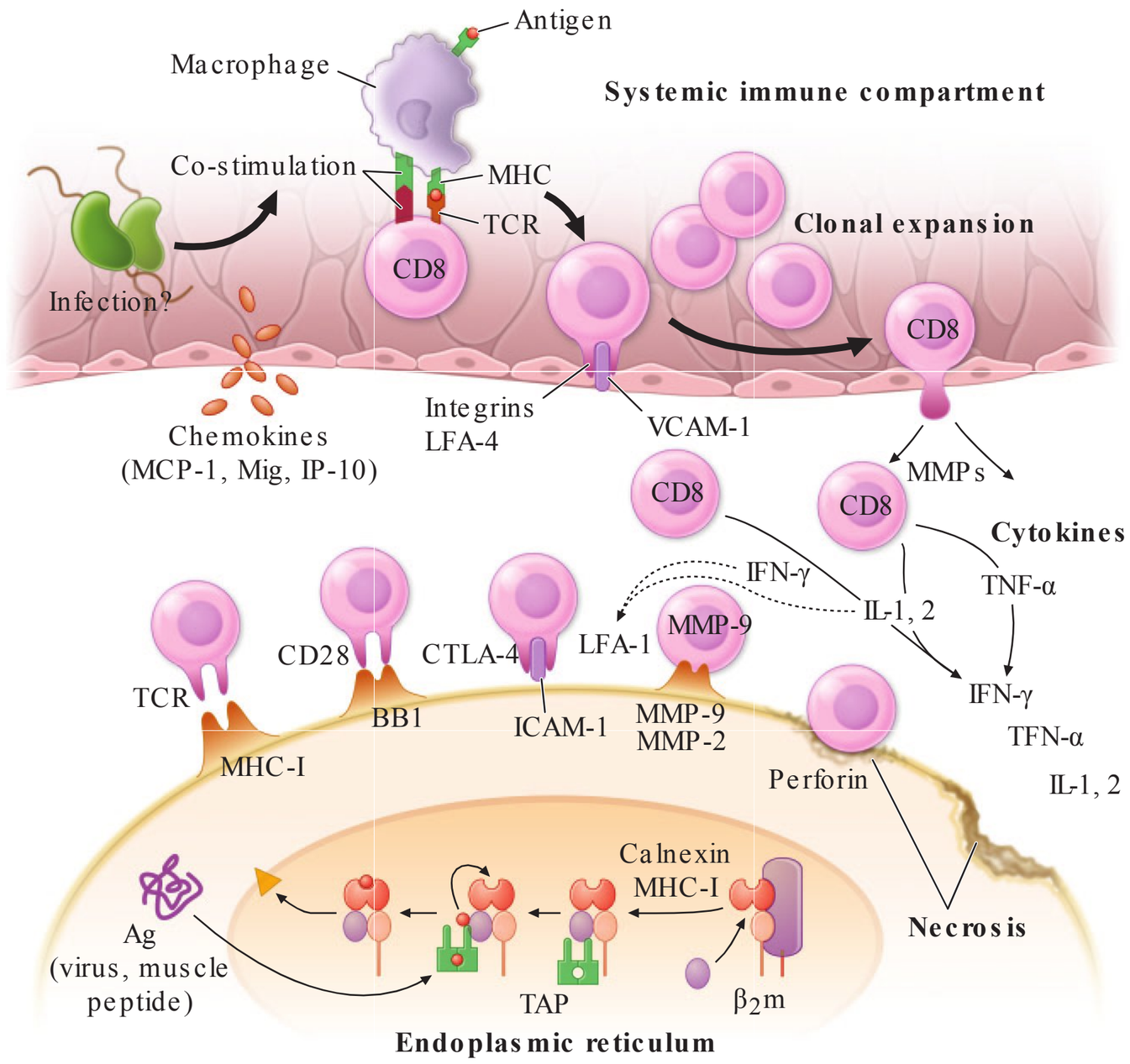


FIGURE 57-2

Cell-mediated mechanisms of muscle damage in polymyositis (PM) and inclusion body myositis (IBM). Antigen-specific CD8 cells are expanded in the periphery, cross the endothelial barrier, and bind directly to muscle fibers via T cell receptor (TCR) molecules that recognize aberrantly expressed major histocompatibility complex (MHC)-I. Engagement of costimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS), along with ICAM-1/LFA-1, stabilize the CD8–muscle fiber interaction. Metalloproteinases (MMPs) facilitate the migration of T cells and their attachment to the muscle surface. Muscle fiber necrosis occurs via perforin granules released by the autoaggressive T cells. A direct myocytotoxic effect exerted by the cytokines interferon (IFN) γ, interleukin (IL) 1, or tumor necrosis factor (TNF) α may also play a role. Death of the muscle fiber is mediated by necrosis. MHC class I molecules consist of a heavy chain and a light chain (β_2 microglobulin [β_2m]) complexed with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins.

mitochondrial disorder characterized histologically by "ragged-red" fibers. AZT inhibits γ-DNA polymerase, an enzyme found solely in the mitochondrial matrix.

GLOBAL ISSUES

Inadequate data exist with respect to possible differences in the prevalence of the inflammatory myopathies in various parts of the world. PM appears to be reported more often in Asia and southern Europe, whereas IBM seems to be more frequently recognized in North America, northern Europe, and Australia. Whether this represents differences in diagnostic methods and disease awareness or true disease prevalence remains unclear. Pyomyositis and parasitic myositis are clearly more common in the tropics, whereas HIV-associated PM and IBM are more commonly encountered in areas endemic for HIV. In patients from Asia, nasopharyngeal cancer appears to be a malignancy more commonly associated with DM, necessitating the need to specifically search for these tumors in this population.

DIFFERENTIAL DIAGNOSIS

The clinical picture of the typical skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM or IBM.

Subacute or chronic progressive muscle weakness

This may be due to denervating conditions such as the spinal muscular atrophies or amyotrophic lateral sclerosis **(Chap. 39)**. In addition to the muscle weakness, upper motor neuron signs in the latter and signs

www.ketabpezeshki.com (021) 66485457 - 66485438

of denervation detected by electromyography (EMG) aid in the diagnosis. The muscular dystrophies **(Chap. 56)** may be additional considerations; however, these disorders usually develop over years rather than weeks or months and rarely present after the age of 30 years. It may be difficult, even with a muscle biopsy, to distinguish chronic PM from a rapidly advancing muscular dystrophy. This is particularly true of facioscapulohumeral muscular dystrophy, dysferlin myopathy, and the dystrophinopathies where inflammatory cell infiltration is often found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy and undergo genetic testing to exclude muscular dystrophy. Identification of the MHC/CD8 lesion by muscle biopsy is helpful to identify cases of PM. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce weakness that is often associated with other characteristic clinical signs; diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. The endocrine myopathies such as those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis. Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely a paraneoplastic neuromyopathy **(Chap. 50)**.

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects ocular and other cranial muscles **(Chap. 55)**. Repetitive nerve stimulation and single-fiber EMG studies aid in diagnosis.

Acute muscle weakness

This may be caused by an acute neuropathy such as Guillain-Barré syndrome **(Chap. 54)**, transverse myelitis **(Chap. 43)**, a neurotoxin **(Chap. 56)**, or a neurotropic viral infection such as poliomyelitis or West Nile virus **(Chap. 46)**. When acute weakness is associated with very high levels of serum CK (often in the thousands), painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to a necrotizing autoimmune myositis, as discussed below, a viral infection or a metabolic disorder such as myophosphorylase deficiency, or carnitine palmitoyltransferase deficiency **(Chap. 56)**. Several animal parasites, including protozoa (Toxoplasma, Trypanosoma), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as parasitic polymyositis. Staphylococcus aureus, Yersinia, Streptococcus, or anaerobic bacteria may produce a suppurative myositis, known as tropical polymyositis, or pyomyositis. Pyomyositis, previously rare in the west, is now occasionally seen in AIDS patients. Other bacteria, such as Borrelia burgdorferi (Lyme disease) and Legionella pneumophila (Legionnaire's disease), may infrequently cause myositis.

Patients with periodic paralysis experience recurrent episodes of acute muscle weakness without pain, always beginning in childhood. Chronic alcoholics may develop painful myopathy with myoglobinuria after a bout of heavy drinking. Acute painless muscle weakness with myoglobinuria may occur with prolonged hypokalemia, or hypophosphatemia and hypomagnesemia, usually in chronic alcoholics or in patients on nasogastric suction receiving parenteral hyperalimentation.

Myofasciitis

This distinctive inflammatory disorder affecting muscle and fascia presents as diffuse myalgias, skin induration, fatigue, and mild muscle weakness; mild elevations of serum CK are usually present. The most common form is eosinophilic myofasciitis characterized by peripheral blood eosinophilia and eosinophilic infiltrates in the endomysial tissue. In some patients, the eosinophilic myositis/fasciitis occurs in the context of parasitic infections, vasculitis, mixed connective tissue disease, hypereosinophilic syndrome, or toxic exposures (e.g., toxic oil syndrome, contaminated l-tryptophan) or with mutations in the calpain gene. A distinct subset of myofasciitis is characterized by pronounced infiltration of the connective tissue around the muscle by sheets of periodic acid–Schiff-positive macrophages and occasional CD8 T cells (macrophagic myofasciitis or inflammatory myositis with abundant macrophages [IMAM]). A focal form of this disorder, limited to sites of previous vaccinations, administered months or years earlier, has been linked to an aluminum-containing substrate in vaccines. This disorder, which to date has not been observed outside of France, responds to glucocorticoid therapy, and the overall prognosis seems favorable.

Necrotizing autoimmune myositis

This is an increasingly recognized entity that has distinct features, even though it is often labeled as PM. It presents as an acute or subacute onset of symmetric muscle weakness; CK is typically extremely high. The weakness can be severe. Coexisting interstitial lung disease and cardiomyopathy may be present. The disorder may develop after a viral infection, in association with cancer, or in patients taking statins when the myopathy continues to worsen after statin withdrawal. Some patients have antibodies against signal recognition particle (SRP) or against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a 100-kDa protein considered the pharmacologic target of statins. The muscle biopsy demonstrates necrotic fibers infiltrated

www.ketabpezeshki.com (021) 66485457 - 66485438

by macrophages but only rare, if any, T cell infiltrates. Muscle MHC-I expression is only slightly and focally upregulated. T e capillaries may be swollen with hyalinization, thickening of the capillary wall, and deposition of complement. Most patients respond to immunotherapy, but some are resistant.

Hyperacute necrotizing fasciitis/myositis (flesh-eating disease)

T is a fulminant infectious disease, seen most often in the tropics or in conditions with poor hygiene, characterized by widespread necrosis of the superficial fascia and muscle of a limb; if the scrotum, perineum, and abdominal wall are affected, the condition is referred to as Fournier's gangrene. It may be caused by group A β-hemolytic Streptococcus, methicillin-sensitive S. aureus, Pseudomonas aeruginosa, Vibrio vulnif cus, clostridial species (gas gangrene), or polymicrobial infection with anaerobes and facultative bacteria; toxins from these bacteria may act as superantigens. T e port of bacterial entry is usually a trivial cut or skin abrasion, and the source is contact with carriers of the organism. Individuals with diabetes mellitus, immunodeficiency states, or systemic illnesses such as liver failure are most susceptible. Systemic varicella is a predisposing factor in children.

T e disease presents with swelling, pain, and redness in the involved area followed by a rapid tissue necrosis of fascia and muscle that progresses at an estimated rate of 3 cm/h. Emergency debridement, antibiotics, IV immunoglobulin (IVIg), and even hyperbaric oxygen have been recommended. In progressive or advanced cases, amputation of the affected limb may be necessary to avoid a fatal outcome.

Drug-induced myopathies

d-Penicillamine, procainamide, and statins may produce a true myositis resembling PM or necrotizing myositis. A DM-like illness has been associated with the contaminated preparations of l-tryptophan. As noted above, AZT causes a mitochondrial myopathy. Other drugs may elicit a toxic noninflammatory myopathy that is histologically different from DM, PM, or IBM. T ese include cholesterol-lowering agents such as clofibrate, lovastatin, simvastatin, or pravastatin, especially when combined with cyclosporine, amiodarone, or gemfibrozil. Mild statin-induced myopathic symptoms (such as myalgia, fatigue, or asymptomatic elevations of CK) are self-limited and usually improve after discontinuation of the drug. In rare patients, however, muscle weakness continues to progress even after the statin is withdrawn; in these cases, a diagnostic muscle biopsy is indicated and search for antibodies to HMGCR is suggested; if histologic evidence of PM or necrotizing myositis is present, immunotherapy should be initiated. Rhabdomyolysis and myoglobinuria have been rarely associated with amphotericin B, ε-aminocaproic acid, fenfluramine, heroin, and phencyclidine. T e use of amiodarone, chloroquine, colchicine, carbimazole, emetine, etretinate, and ipecac syrup; chronic laxative or licorice use resulting in hypokalemia; and glucocorticoid or growth hormone administration have also been associated with myopathic muscle weakness. Some neuromuscular blocking agents such as pancuronium, in combination with glucocorticoids, may cause an acute critical illness myopathy. A careful drug history is essential for diagnosis of these drug-induced myopathies, which do not require immunosuppressive therapy except when an autoimmune myopathy has been triggered, as noted above.

"Weakness" due to muscle pain and muscle tenderness

A number of conditions including polymyalgia rheumatica and arthritic disorders of adjacent joints may enter into the differential diagnosis of inflammatory myopathy, even though they do not cause myositis. T e muscle biopsy is either normal or discloses type II muscle fiber atrophy. Patients with f brositis and f bromyalgia complain of focal or diffuse muscle tenderness, fatigue, and aching, which is sometimes poorly differentiated from joint pain. Some patients, however, have muscle tenderness, painful muscles on movement, and signs suggestive of a collagen vascular disorder, such as an increased erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, or rheumatoid factor, along with modest elevation of the serum CK and aldolase. T ey demonstrate a "break-away" pattern of weakness with dif culty sustaining effort but not true muscle weakness. T e muscle biopsy is usually normal or nonspecific. Many such patients show some response to nonsteroidal anti-inflammatory agents or glucocorticoids, although most continue to have indolent complaints. An indolent fasciitis in the setting of an ill-defined connective tissue disorder may be at times present, and these patients should not be labeled as having a psychosomatic disorder. Chronic fatigue syndrome, which may follow a viral infection, can present with debilitating fatigue, sore throat, painful lymphadenopathy, myalgia, arthralgia, sleep disorder, and headache **(Chap. 59)**. T ese patients do not have muscle weakness, and the muscle biopsy is normal.

DIAGNOSIS

T e clinically suspected diagnosis of PM, DM, IBM, or necrotizing myositis is confirmed by analysis of serum muscle enzymes, EMG findings, and muscle biopsy **(Table 57-2)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 57-2

CRITERIA FOR DIAGNOSIS OF INFLAMMATORY MYOPATHIES

	POLYMYOSITIS			
CRITERION	DEFINITE	PROBABLE	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Myopathic muscle weakness[a]	Yes	Yes	Yes[b]	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy findings[c]	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Ubiquitous MHC-I expression but minimal inflammation and no vacuoles[d]	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with β-amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy[e]
Rash or calcinosis	Absent	Absent	Present[f]	Absent

[a]Myopathic muscle weakness, affecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, and no biochemical muscle disease (excluded on the basis of muscle biopsy findings).
[b]In some cases with the typical rash, the muscle strength is seemingly normal (dermatomyositis sine myositis); these patients often have new onset of easy fatigue and reduced endurance. Careful muscle testing may reveal mild muscle weakness.
[c]See text for details.
[d]An adequate trial of prednisone or other immunosuppressive drugs is warranted in probable cases. If, in retrospect, the disease is unresponsive to therapy, another muscle biopsy should be considered to exclude other diseases or possible evolution in inclusion body myositis.
[e]If the muscle biopsy does not contain vacuolated fibers but shows chronic myopathy with hypertrophic fibers, primary inflammation with the CD8/MHC-I complex, and cytochrome oxygenase–negative fibers, the diagnosis is probable inclusion body myositis.
[f]If rash is absent but muscle biopsy findings are characteristic of dermatomyositis, the diagnosis is probable dermatomyositis.

The most sensitive enzyme is CK, which in active disease can be elevated as much as 50-fold. Although the CK level usually parallels disease activity, it can be normal in some patients with active IBM or DM, especially when associated with a connective tissue disease. The CK is always elevated in patients with active PM. Along with the CK, the serum glutamic-oxaloacetic and glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

Needle EMG shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed potentials (polyphasic units of short and long duration) indicating a chronic process and muscle fiber regeneration are often present BM. These EMG findings are not diagnostic of an inflammatory myopathy but are useful to identify the presence of active or chronic myopathy and to exclude neurogenic disorders.

Magnetic resonance imaging (MRI) is not routinely used for the diagnosis of PM, DM, or IBM. However, it may provide information or guide the location of the muscle biopsy in certain clinical settings.

Muscle biopsy—despite occasional variability in demonstrating all of the typical pathologic findings—is the most sensitive and specific test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype **(Figs. 57-3, 57-4, and 57-5)**.

In PM the inflammation is primary, a term used to indicate that the inflammation is not reactive and the T cell infiltrates, located primarily within the muscle fascicles (endomysially), surround individual, healthy muscle fibers and result in phagocytosis and necrosis (Fig. 57-3). The MHC-I molecule is ubiquitously expressed on the sarcolemma, even in fibers not invaded by CD8+ cells. The CD8/MHC-I lesion is characteristic and useful to confirm or establish the diagnosis and to exclude disorders with secondary, nonspecific, inflammation, such as in some muscular dystrophies. When the disease is chronic, connective tissue is increased and may react positively with alkaline phosphatase. In necrotizing myositis, there are abundant necrotic fibers invaded or surrounded by macrophages, but no lymphocytic

www.ketabpezeshki.com (021) 66485457 - 66485438

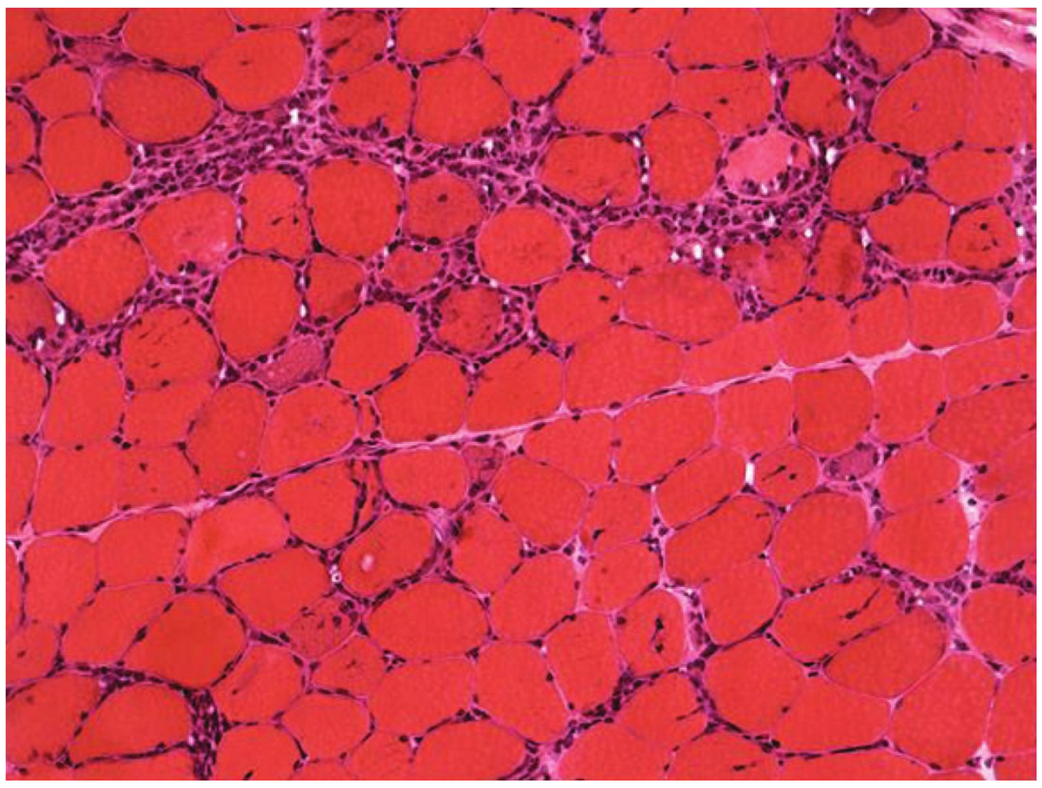


FIGURE 57-3
Cross-section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding muscle fibers. Note lack of chronic myopathic features (increased connective tissue, atrophic or hypertrophic fibers) as seen in inclusion body myositis.

infiltrates or MHC-I expression beyond the necrotic fibers.

In DM the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around—rather than within—the muscle fascicles (Fig. 57-4). T e intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, and obliteration of capillaries. T e muscle fibers undergo necrosis, degeneration, and phagocytosis, often in groups involving a portion of a muscle fasciculus in a wedge-like shape or at the periphery of the fascicle, due to microinfarcts within the muscle. T is results in perifascicular atrophy, characterized by 2–10 layers of atrophic fibers at the periphery of the fascicles. T e presence of perifascicular atrophy is diagnostic of DM, even in the absence of inflammation.

In IBM (Fig. 57-5), there is endomysial inflammation with T cells invading MHC-I-expressing nonvacuolated muscle fibers; basophilic granular deposits distributed around the edge of slit-like vacuoles (rimmed vacuoles); loss of fibers, replaced by fat and connective tissue, hypertrophic fibers, and angulated or round fibers; rare eosinophilic cytoplasmic inclusions; abnormal mitochondria characterized by the presence of ragged-red fibers or cytochrome oxidase–negative fibers; and amyloid deposits within or next to the vacuoles best visualized with crystal violet or Congo-red staining viewed with fluorescent optics. Electron microscopy demonstrates filamentous inclusions in the vicinity of the rimmed vacuoles. In at least 15% of patients with the typical clinical phenotype of IBM, there is brisk inflammation in the muscle biopsy but no vacuoles or amyloid deposits, leading to an erroneous diagnosis of PM. Such patients are often referred to as having "clinical IBM." Close clinicopathologic correlations are therefore essential; if uncertain, a repeat muscle biopsy from another site is often helpful.

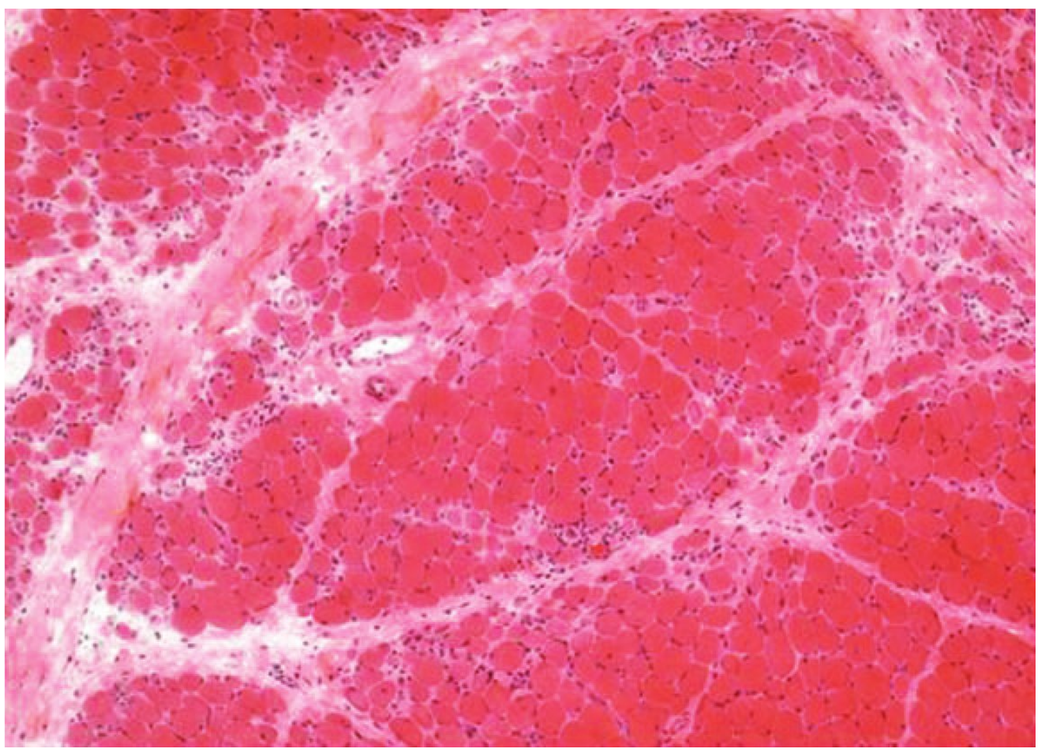


FIGURE 57-4
Cross-section of a muscle biopsy from a patient with dermatomyositis demonstrates atrophy of the fibers at the periphery of the fascicle (perifascicular atrophy).

TREATMENT Therapy of Inflammatory Myopathies

T e goal of therapy is to improve muscle strength, thereby improving function in activities of daily living, and ameliorate the extramuscular manifestations (rash, dysphagia, dyspnea, fever). When strength improves, the serum CK falls concurrently; however, the reverse is not always true. Unfortunately, there is a common tendency to "chase" or treat the CK level instead of the muscle weakness, a practice that has led to prolonged and unnecessary use of immunosuppressive drugs and erroneous assessment of their ef cacy. It is prudent to discontinue these drugs if, after an adequate trial, there is no objective improvement in muscle strength whether or not CK levels are reduced. Agents used in the treatment of PM and DM include the following:

1. Glucocorticoids. Oral prednisone is the initial treatment of choice; the effectiveness and side effects of this therapy determine the future need for stronger immunosuppressive drugs. High-dose prednisone, at least 1 mg/kg per day, is initiated as early in the disease as possible. After 3–4 weeks, prednisone is tapered slowly over a period of 10 weeks to 1 mg/kg every other day. If there is evidence of ef cacy and no serious side effects, the dosage is then further reduced by 5 or 10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. T e ef cacy of prednisone is determined by an objective increase in muscle strength and activities of daily living,

www.ketabpezeshki.com (021) 66485457 - 66485438

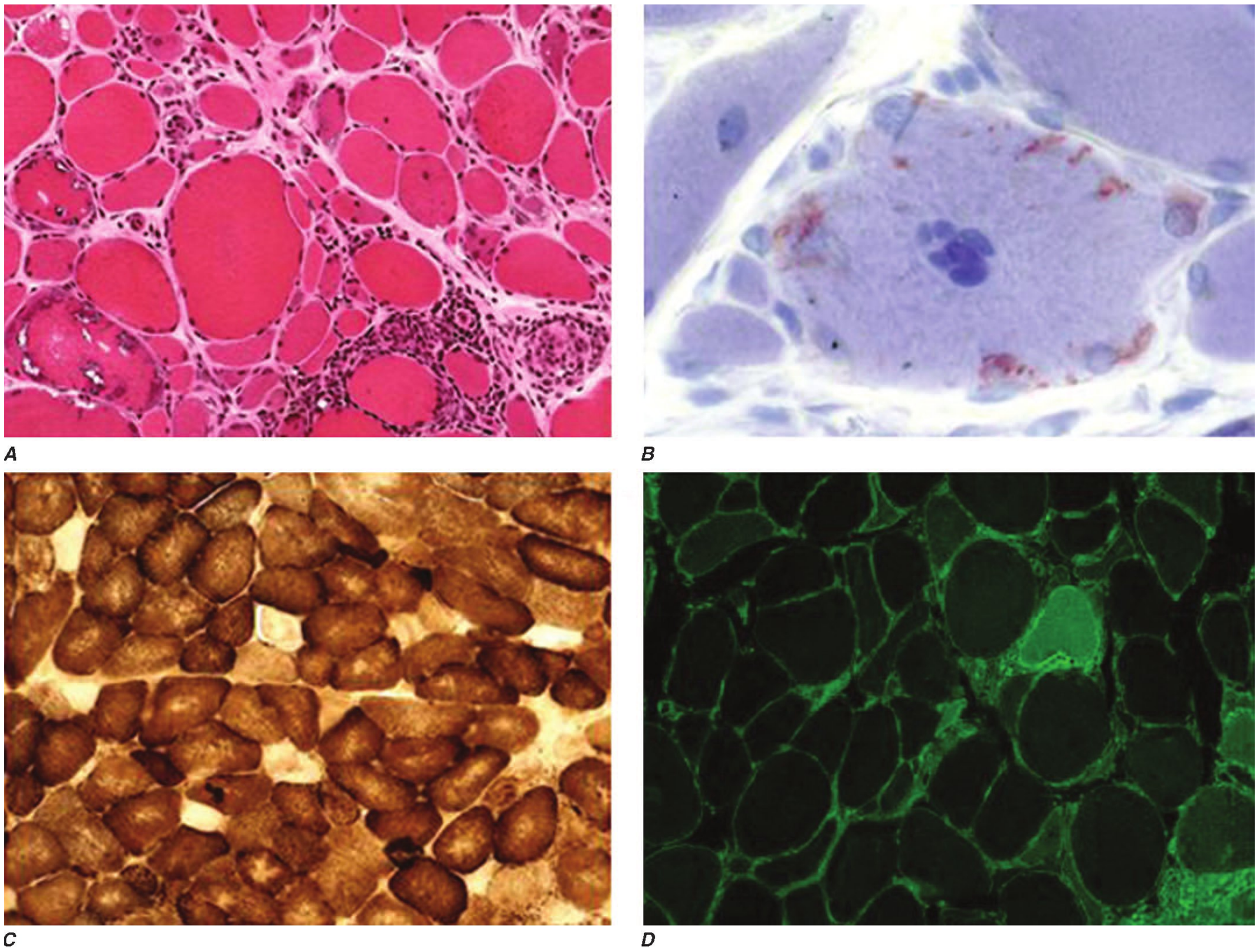


FIGURE 57-5
Cross-sections of a muscle biopsy from a patient with inclusion body myositis demonstrate the typical features of vacuoles with lymphocytic infiltrates surrounding nonvacuolated or necrotic fibers (A), tiny endomysial deposits of amyloid visualized with crystal violet (B), cytochrome oxidase–negative fibers, indicative of mitochondrial dysfunction (C), and ubiquitous major histocompatibility complex class I expression at the periphery of all fibers (D).

which almost always occurs by the third month of therapy. A feeling of increased energy or a reduction of the CK level without a concomitant increase in muscle strength is not a reliable sign of improvement. If prednisone provides no objective benefit after ~3 months of high-dose therapy, the disease is probably unresponsive to the drug and tapering should be accelerated while the next-in-line immunosuppressive drug is started. Although controlled trials have not been performed, almost all patients with true PM or DM respond to glucocorticoids to some degree and *for* some period *of* time; in general, DM responds better than PM.

T e long-term use of prednisone may cause increased weakness associated with a normal or unchanged CK level; this effect is referred to as steroid myopathy. In a patient who previously responded to high doses of prednisone, the development of new weakness may be related to steroid myopathy or to disease activity that either will respond to a higher dose of glucocorticoids or has become glucocorticoid-resistant. In uncertain cases, the prednisone dosage can be steadily increased or decreased as desired: the cause of the weakness is usually evident in 2–8 weeks.

2. Other immunosuppressive drugs. Approximately 75% of patients ultimately require additional treatment. T is occurs when a patient fails to respond adequately to glucocorticoids after a 3-month trial, the patient becomes glucocorticoid-resistant, glucocorticoid-related side effects appear, attempts to lower the prednisone dose repeatedly result in a new relapse, or rapidly progressive disease with evolving severe weakness and respiratory failure develops.

T e following drugs are commonly used but have never been tested in controlled studies: (1) Azathioprine is well tolerated, has few side effects, and appears to be as effective for long-term therapy as other drugs. T e dose is up to 3 mg/kg daily. (2) Methotrexate has a faster

www.ketabpezeshki.com (021) 66485457 - 66485438

onset of action than azathioprine. It is given orally starting at 7.5 mg weekly for the first 3 weeks (2.5 mg every 12 h for 3 doses), with gradual dose escalation by 2.5 mg per week to a total of 25 mg weekly. A rare side effect is methotrexate pneumonitis, which can be dif cult to distinguish from the interstitial lung disease of the primary myopathy associated with Jo-1 antibodies (described above). (3) Mycophenolate mofetil also has a faster onset of action than azathioprine. At doses up to 2.5 or 3 g/d in two divided doses, it is well tolerated for long-term use. (4) Monoclonal anti-CD20 antibody (rituximab) has been shown in a small uncontrolled series to benefit patients with DM and PM, but a controlled study did not show differences between patients randomized 8 weeks apart. (5) Cyclosporine has inconsistent and mild benefit. (6) Cyclophosphamide (0.5–1 g/m^2 IV monthly for 6 months) has limited success and significant toxicity. (7) Tacrolimus (formerly known as Fk506) has been effective in some dif cult cases of PM especially with interstitial lung disease.

3. Immunomodulation. In a controlled trial of patients with refractory DM, IVIg improved not only strength and rash but also the underlying immunopathology. T e benefit is often short-lived (≤8 weeks), and repeated infusions every 6–8 weeks are generally required to maintain improvement. A dose of 2 g/kg divided over 2–5 days per course is recommended. Uncontrolled observations suggest that IVIg may also be beneficial for patients with PM. Neither plasmapheresis nor leukapheresis appears to be effective in PM and DM.

T e following sequential empirical approach to the treatment of PM and DM is suggested: Step 1: high-dose prednisone; Step 2: azathioprine, mycophenolate, or methotrexate for steroid-sparing effect; Step 3: IVIg; Step 4: a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and general health: rituximab, cyclosporine, cyclophosphamide, or tacrolimus. Patients with interstitial lung disease may benefit from aggressive treatment with cyclophosphamide or tacrolimus.

A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or another disease, usually a metabolic myopathy, a muscular dystrophy, a drug-induced myopathy, or an endocrinopathy. In these cases, a repeat muscle biopsy and a renewed search for another cause of the myopathy is indicated.

Calcinosis, a manifestation of DM, is dif cult to treat; however, new calcium deposits may be prevented if the primary disease responds to the available therapies. Bisphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, calcium blockers, and surgical excision have all been tried without success.

IBM is generally resistant to immunosuppressive therapies. Prednisone together with azathioprine or methotrexate is often tried for a few months in newly diagnosed patients, although results are generally disappointing. Because occasional patients may feel subjectively weaker after these drugs are discontinued, some clinicians prefer to maintain these patients on low-dose, every-other-day prednisone along with mycophenolate in an effort to slow disease progression, even though there is no objective evidence or controlled study to support this practice. In two controlled studies of IVIg in IBM, minimal benefit in up to 30% of patients was found; the strength gains, however, were not of suf cient magnitude to justify its routine use. Another trial of IVIg combined with prednisone was ineffective. Nonetheless, some experts believe that a 2- to 3-month trial with IVIg may be reasonable for selected patients with IBM who experience rapid progression of muscle weakness or choking episodes due to worsening dysphagia.

PROGNOSIS

T e 5-year survival rate for treated patients with PM and DM is ~95%, and the 10-year survival rate is 84%; death is usually due to pulmonary, cardiac, or other systemic complications. T e prognosis is worse for patients who are severely affected at presentation, when initial treatment is delayed, and in cases with severe dysphagia or respiratory dif culties. Older patients and those with associated cancer also have a worse prognosis. DM responds more favorably to therapy than PM and thus has a better prognosis. Most patients improve with therapy, and many make a full functional recovery, which is often sustained with maintenance therapy. Up to 30% may be left with some residual muscle weakness. Relapses may occur at any time.

IBM has the least favorable prognosis of the inflammatory myopathies. Most patients will require the use of an assistive device such as a cane, walker, or wheelchair within 5–10 years of onset. In general, the older the age of onset in IBM, the more rapidly progressive is the course.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 58

SPECIAL ISSUES IN INPATIENT NEUROLOGIC CONSULTATION

S. Andrew Josephson ■ Martin A. Samuels

Inpatient neurologic consultations usually involve questions regarding specific disease processes or prognostication after various cerebral injuries. Common reasons for neurologic consultation include stroke **(Chap. 32)**, seizures **(Chap. 31)**, altered mental status **(Chap. 8)**, headache **(Chap. 9)**, and management of coma and other neurocritical care conditions **(Chaps. 19 and 33)**. T is chapter focuses on additional common reasons for consultation that are not addressed elsewhere in the text.

CONSULTATIONS REGARDING CENTRAL NERVOUS SYSTEM DYSFUNCTION

HYPERPERFUSION STATES LEADING TO POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

A group of neurologic disorders shares the common feature of hyperperfusion, probably related to endothelial dysfunction, playing a key role in pathogenesis. T ese seemingly diverse syndromes include hypertensive encephalopathy, eclampsia, postcarotid endarterectomy syndrome, and toxicity from calcineurin-inhibitor and other medications. Modern imaging techniques and experimental models suggest that vasogenic edema is typically the primary process leading to neurologic dysfunction; therefore, prompt recognition and management of this condition should allow for clinical recovery as long as superimposed hemorrhage or infarction has not occurred.

T e brain's autoregulatory capability successfully maintains a fairly stable cerebral blood flow in adults despite alterations in systemic mean arterial pressure (MAP) ranging from 50 to 150 mmHg **(Chap. 33)**. In patients with chronic hypertension, this cerebral autoregulation curve is shifted, resulting in autoregulation working over a much higher range of pressures (e.g., 70–175 mmHg). In these hypertensive patients, cerebral blood flow is kept steady at higher MAP, but a rapid lowering of pressure can lead to ischemia on the lower end of the autoregulatory curve, even at values typically thought of as normotensive. T is autoregulatory phenomenon is achieved through both myogenic and neurogenic influences causing small arterioles to contract and dilate. When the systemic blood pressure exceeds the limits of this mechanism, breakthrough of autoregulation occurs, resulting in hyperperfusion via increased cerebral blood flow, capillary leakage into the interstitium, and resulting edema. T e predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation or a vasculopathy that is more common in these blood vessels.

Although elevated or relatively elevated blood pressure is common in many of these disorders, some hyperperfusion states such as calcineurin-inhibitor toxicity occur with no apparent pressure rise. In these cases, vasogenic edema is likely due primarily to dysfunction of the capillary endothelium itself, leading to breakdown of the blood-brain barrier. It is useful to separate disorders of hyperperfusion into those caused primarily by increased pressure and those due mostly to endothelial dysfunction from a toxic or autoimmune etiology **(Table 58-1)**. In reality, both of these pathophysiologic processes likely play some role in each of these disorders.

T e clinical presentation of all of the hyperperfusion syndromes is similar with prominent headaches, seizures, or focal neurologic deficits. Headaches have no specific characteristics, range from mild to severe, and may be accompanied by alterations in consciousness ranging from confusion to coma. Seizures may be present, and these can be of multiple types depending on the severity and location of the edema. Nonconvulsive seizures have been described in hyperperfusion states;

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 58-1

SOME COMMON ETIOLOGIES OF HYPERPERFUSION SYNDROME
Disorders in which increased capillary pressure dominates the pathophysiology
Hypertensive encephalopathy, including secondary causes such as renovascular hypertension, pheochromocytoma, cocaine use, etc.
Postcarotid endarterectomy syndrome
Preeclampsia/eclampsia
High-altitude cerebral edema
Disorders in which endothelial dysfunction dominates the pathophysiology
Calcineurin-inhibitor toxicity
Chemotherapeutic agent toxicity (e.g., cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, tumor necrosis factor α antagonists)
Glucocorticoids
Erythropoietin
HELLP syndrome ([h]emolysis, [e]levated [l]iver enzyme levels, [l]ow [p]latelet count)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic-uremic syndrome (HUS)
Systemic lupus erythematosus (SLE)
Granulomatosis with polyangiitis (Wegener's)

therefore, a low threshold for obtaining an electroencephalogram (EEG) in these patients should be maintained. The typical focal deficit in hyperperfusion states is cortical visual loss, given the tendency of the process to involve the occipital lobes. However, any focal deficit can occur depending on the area affected, as evidenced by patients who, after carotid endarterectomy, exhibit neurologic dysfunction referable to the ipsilateral newly reperfused hemisphere. In conditions where increased cerebral blood flow plays a role, examination of the inpatient vital signs record will usually reveal a systemic blood pressure that is increased above the patient's baseline. It appears as if the rapidity of rise, rather than the absolute value of pressure, is the most important risk factor.

The diagnosis in all of these conditions is clinical. The symptoms of these disorders are common and nonspecific, so a long differential diagnosis should be entertained, including consideration of other causes of confusion, focal neurologic deficits, headache, and seizures. Magnetic resonance imaging (MRI) has improved the ability of clinicians to diagnose hyperperfusion syndromes, although cases have been reported with normal imaging. Patients classically exhibit the high T2 signal of edema primarily in the posterior occipital lobes, not respecting any single vascular territory **(Fig. 58-1)**. Diffusion-weighted images are typically normal, emphasizing the vasogenic rather than cytotoxic nature of this edema. Imaging with computed tomography (CT) is less sensitive but may show

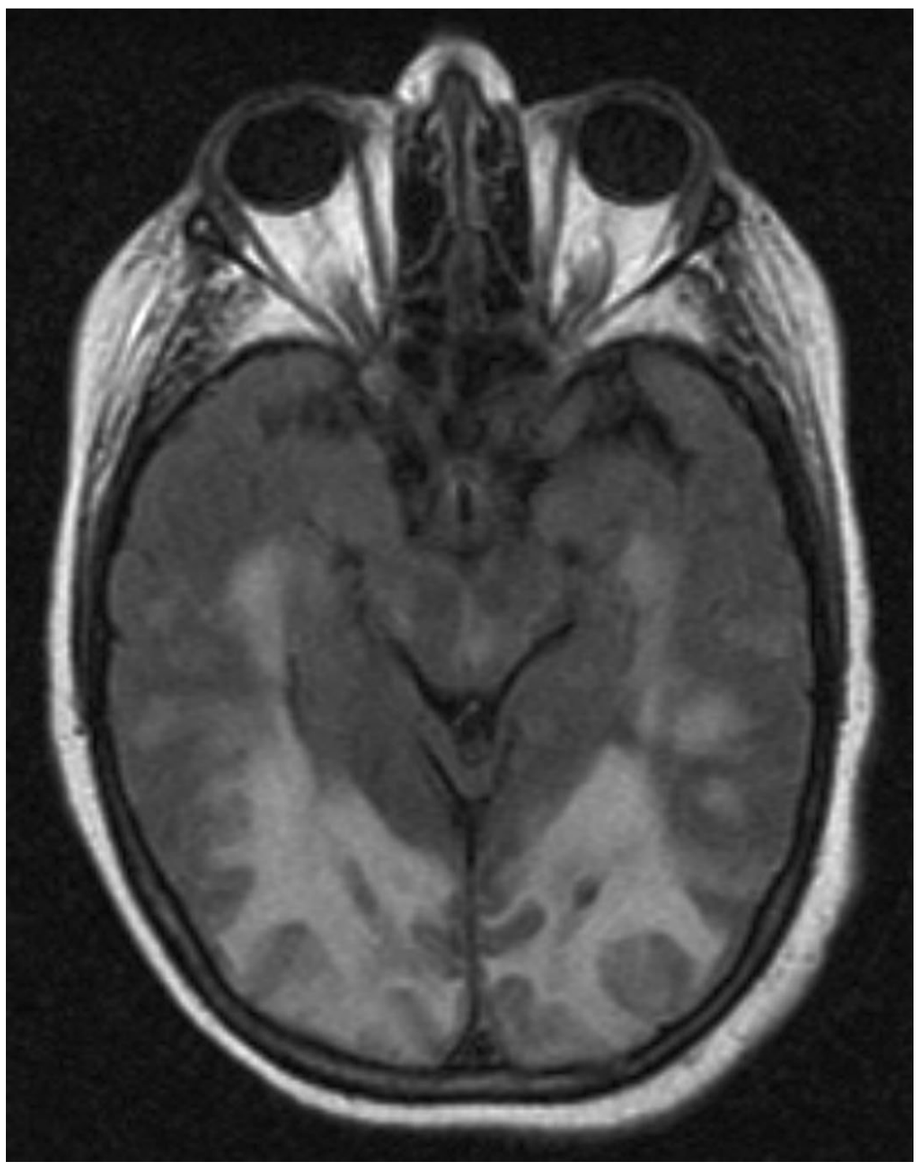


FIGURE 58-1
Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain in a patient taking cyclosporine after liver transplantation, who presented with seizures, headache, and cortical blindness. Increased signal is seen bilaterally in the occipital lobes predominantly involving the white matter, consistent with a hyperperfusion state secondary to calcineurin-inhibitor exposure.

a pattern of patchy hypodensity in the involved territory. Previously this classic radiographic appearance had been termed reversible posterior leukoencephalopathy (RPLE). However, this term has fallen out of favor because none of its elements are completely accurate. The radiographic and clinical changes are not always reversible; the territory involved is not uniquely posterior; and gray matter may be affected as well, rather than purely white matter as the term "leukoencephalopathy" intimates. The now more commonly used radiologic term posterior reversible encephalopathy syndrome (PRES) suffers from many of these same limitations. Vessel imaging may demonstrate narrowing of the cerebral vasculature, especially in the posterior circulation; whether this noninflammatory vasculopathy is a primary cause of the edema or occurs as a secondary phenomenon remains unclear. Other ancillary studies such as cerebrospinal fluid (CSF) analysis often yield nonspecific results. It should be noted that many of the substances that have been implicated, such as cyclosporine, can cause this syndrome even at low doses or after years of treatment. Therefore, normal serum levels of these medications do not exclude them as inciting agents.

www.ketabpezeshki.com (021) 66485457 - 66485438

In cases of hyperperfusion syndromes, treatment should commence urgently once the diagnosis is considered. Hypertension plays a key role commonly, and judicious lowering of the blood pressure with IV agents such as labetalol or nicardipine is advised along with continuous cardiac and blood pressure monitoring, often through an arterial line. It is reasonable to lower MAP by ~20% initially, as further lowering of the pressure may cause secondary ischemia and possibly infarction as pressure drops below the lower range of the patient's autoregulatory capability. In cases where there is an identified cause of the syndrome, these etiologies should be treated promptly, including discontinuation of offending substances such as calcineurin inhibitors in toxic processes, treatment of immune-mediated disorders such as thrombotic thrombocytopenic purpura (TTP), and prompt delivery of the fetus in eclampsia. Seizures must be identified and controlled, often necessitating continuous EEG monitoring. Anticonvulsants are effective when seizure activity is identified, but in the special case of eclampsia, there is evidence to support the use of magnesium sulfate for seizure control.

POST-CARDIAC BYPASS BRAIN INJURY

Central nervous system (CNS) injuries following open heart or coronary artery bypass grafting (CABG) surgery are common and include acute encephalopathy, stroke, and a chronic syndrome of cognitive impairment. Hypoperfusion and embolic disease are frequently involved in the pathogenesis of these syndromes, although multiple mechanisms may be involved in these critically ill patients who are at risk for various metabolic and polypharmaceutical complications.

The frequency of hypoxic injury secondary to inadequate blood flow intraoperatively has been markedly decreased by the use of modern surgical and anesthetic techniques. Despite these advances, some patients still experience neurologic complications from cerebral hypoperfusion or may suffer focal ischemia from carotid or focal intracranial stenoses in the setting of regional hypoperfusion. Postoperative infarcts in the border zones between vascular territories commonly are blamed on systemic hypotension, although these infarcts can also result from embolic disease **(Fig. 58-2)**.

Embolic disease is likely the predominant mechanism of cerebral injury during cardiac surgery as evidenced by diffusion-weighted MRI and intraoperative transcranial Doppler studies. It should be noted that some of the emboli that are found histologically in these patients are too small to be detected by standard imaging sequences; therefore, a negative MRI after surgery does not exclude the diagnosis of emboli-related complications. Thrombus in the heart itself as well as atheromas in the aortic arch can become dislodged during cardiac surgeries, releasing a shower of particulate matter into the cerebral circulation. Cross-clamping of the aorta, manipulation of the heart, extracorporeal circulation techniques ("bypass"), arrhythmias such as atrial fibrillation, and introduction of air through suctioning have all been implicated as potential sources of emboli. Histologic studies indicate that literally millions of tiny emboli may be released, even using modern surgical techniques.

This shower of microemboli results in a number of clinical syndromes. Occasionally, a single large embolus leads to an isolated large-vessel stroke that presents with obvious clinical focal deficits. More commonly, the emboli released are multiple and smaller. When there is a high burden of these small emboli, an acute encephalopathy can occur postoperatively, presenting as either a hyperactive or hypoactive confusional state, the latter of which is frequently and incorrectly ascribed to depression or a sedative-induced delirium. When the burden

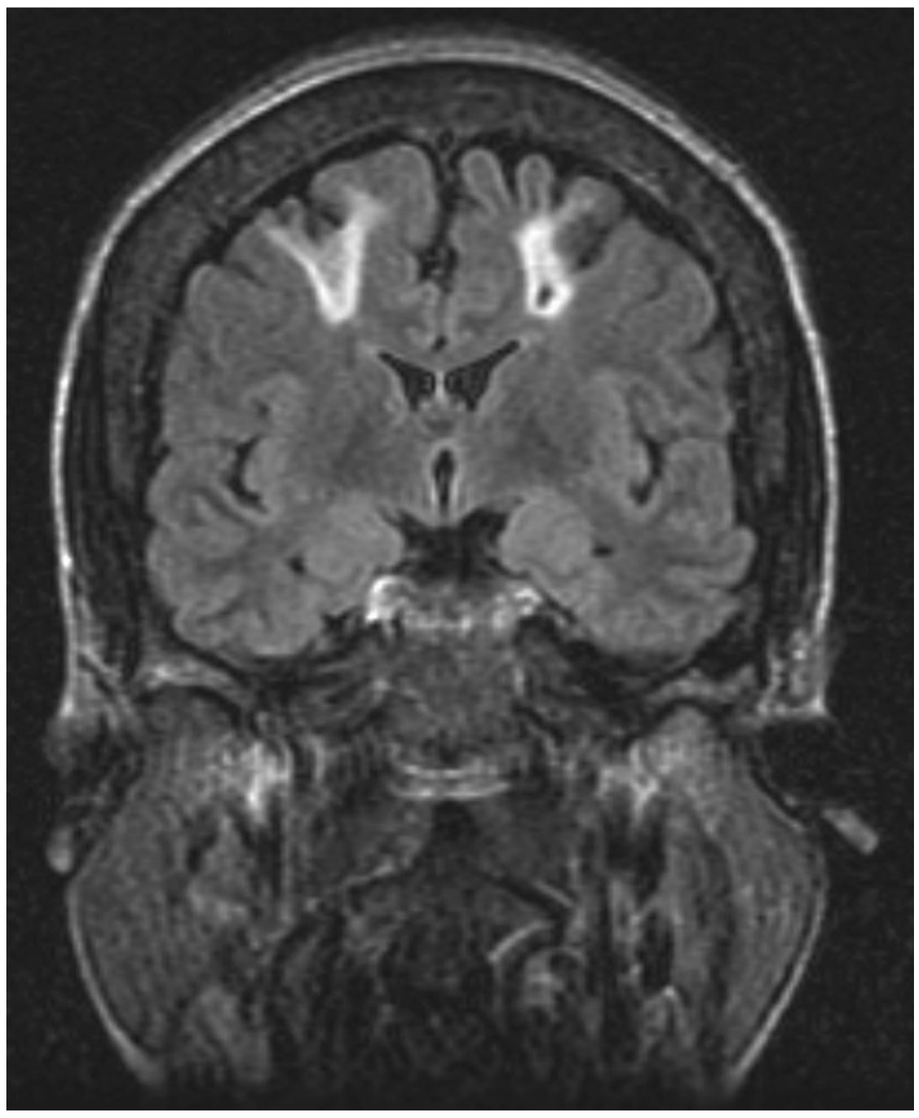


FIGURE 58-2
Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain in a patient presenting with altered mental status after an episode of hypotension during coronary artery bypass grafting (CABG). Increased signal is seen in the border zones bilaterally between the middle cerebral artery and anterior cerebral artery territories. Diffusion-weighted MRI sequences demonstrated restricted diffusion in these same locations, suggesting acute infarction.

www.ketabpezeshki.com (021) 66485457 - 66485438

of microemboli is lower, no acute syndrome is recognized, but the patient may suffer a chronic cognitive deficit. Cardiac surgery can be viewed, like delirium, as a "stress test for the brain." Some patients with a low cerebral reserve due to underlying cerebrovascular disease or an early neurodegenerative process will develop a chronic, cognitive deficit, whereas others with higher reserves may remain asymptomatic despite a similar dose of microemboli. In this manner, cardiac surgery may serve to unmask the early manifestations of neurodegenerative disorders such as Alzheimer's disease.

Since modern techniques have successfully minimized hypoperfusion complications during these surgeries, much attention is now focused on reducing this inevitable shower of microemboli. Off-pump CABG surgeries have the advantages of reducing length of stay and perioperative complications; however, off-pump CABG probably does not preserve cognitive function compared with on-pump CABG. Filters placed in the aortic arch may have some promise in capturing these emboli, although convincing evidence is lacking. Development of successful endovascular operative approaches may provide a reasonable alternative to conventional CABG procedures, especially for patients at high risk of developing cognitive dysfunction after surgery due to advanced age, previous stroke, underlying neurodegenerative disorders, or severe atheromatous disease of the carotid arteries or aortic arch.

POST-SOLID ORGAN TRANSPLANT BRAIN INJURY

Patients who have undergone solid organ transplantation are at risk for neurologic injury in the postoperative period and for months to years thereafter. Neurologic consultants should view these patients as a special population at risk for both unique neurologic complications as well as for the usual disorders found in any critically ill inpatient.

Immunosuppressive medications are administered in high doses to patients after solid organ transplant, and many of these compounds have well-described neurologic complications. In patients with headache, seizures, or focal neurologic deficits taking calcineurin inhibitors, the diagnosis of hyperperfusion syndrome should be considered, as discussed above. T is neurotoxicity occurs mainly with cyclosporine and tacrolimus and can present even in the setting of normal serum drug levels. Treatment primarily involves lowering the drug dosage or discontinuing the drug. Sirolimus has very few recorded cases of neurotoxicity and may be a reasonable alternative for some patients. Other examples of immunosuppressive medications and their neurologic complications include OKT3-associated akinetic mutism and the leukoencephalopathy seen with methotrexate, especially when it is administered intrathecally or with concurrent radiotherapy. In any solid organ transplant patient with neurologic complaints, a careful examination of the medication list is required to search for these possible drug effects.

Cerebrovascular complications of solid organ transplant are often first recognized in the immediate postoperative period. Border zone territory infarctions can occur, especially in the setting of systemic hypotension during cardiac transplant surgery. Embolic infarctions classically complicate cardiac transplantation, but all solid organ transplant procedures place patients at risk for systemic emboli. When cerebral embolization accompanies renal or liver transplantation surgery, a careful search for right-to-left shunting should include evaluation of the heart with agitated saline echocardiography (i.e., "bubble study"), as well as looking for intrapulmonary shunting. Renal and some cardiac transplant patients often have advanced atherosclerosis, providing yet another mechanism for stroke. Imaging with CT or MRI with diffusion is advised when cerebrovascular complications are suspected to confirm the diagnosis and to exclude intracerebral hemorrhage, which most often occurs in the setting of coagulopathy secondary to liver failure or after cardiac bypass procedures.

Given that patients with solid organ transplants are chronically immunosuppressed, infections are a common concern. In any transplant patient with new CNS signs or symptoms such as seizure, confusion, or focal deficit, the diagnosis of a CNS infection should be considered and evaluated through imaging (usually MRI) and possibly lumbar puncture. T e most common pathogens responsible for CNS infections in these patients vary based on time since transplant. In the first month posttransplant, common pathogens include the usual bacterial organisms associated with surgical procedures and indwelling catheters. Starting in the second month posttransplant, opportunistic infections of the CNS become more common, including Nocardia and Toxoplasma species as well as fungal infections such as aspergillosis. Viral infections that can affect the brain of the immunosuppressed patient, such as herpes simplex virus, cytomegalovirus, human herpesvirus type 6 (HHV-6), and varicella, also become more common after the first month posttransplant. After 6 months posttransplant, immunosuppressed patients still remain at risk for these opportunistic bacterial, fungal, and viral infections but can also suffer late CNS infectious complications such as progressive multifocal leukoencephalopathy (PML) associated with JC virus and Epstein-Barr virus–driven clonal expansions of B cells resulting in posttransplant lymphoproliferative disorder or CNS lymphoma.

www.ketabpezeshki.com (021) 66485457 - 66485438

COMMON NEUROLOGIC COMPLICATIONS OF ELECTROLYTE DISTURBANCES

A wide variety of neurologic conditions can result from abnormalities in serum electrolytes, and consideration of electrolyte disturbances should be part of any inpatient neurologic consultation. **A complete general discussion of fluid and electrolyte imbalance and homeostasis can be found in Chap. 63**.

HYPERNATREMIA AND HYPEROSMOLALITY

The normal range of serum osmolality is around 275–295 mOsm/kg, but neurologic manifestations are usually seen only at levels >325 mOsm/kg. Hyperosmolality is usually due to hypernatremia, hyperglycemia, azotemia, or the addition of extrinsic osmoles such as mannitol, which is commonly used in critically ill neurologic patients. Hyperosmolality itself can lead to a generalized encephalopathy that is nonspecific and without focal findings; however, an underlying lesion such as a mass can become symptomatic under the metabolic stress of a hyperosmolar state, producing focal neurologic signs. Some patients with hyperosmolality from severe hyperglycemia can present, for unclear reasons, with generalized seizures or unilateral movement disorders, which usually respond to lowering of the serum glucose. The treatment of all forms of hyperosmolality involves calculation of apparent water losses and slow replacement so that the serum sodium declines no faster than 2 mmol/L (2 meq/L) per hour.

Hypernatremia leads to the loss of intracellular water, leading to cell shrinkage. In the cells of the brain, solutes such as glutamine and urea are generated under these conditions in order to minimize this shrinkage. Despite this corrective mechanism, when hypernatremia is severe (serum sodium >160 mmol/L [>160 meq/L]) or occurs rapidly, cellular metabolic processes fail and encephalopathy will result. There are many etiologies of hypernatremia including, most commonly, renal and extrarenal losses of water. Causes of neurologic relevance include central diabetes insipidus, where hyperosmolality is accompanied by submaximal urinary concentration due to inadequate release of arginine vasopressin (AVP) from the posterior pituitary, resulting often from pituitary injury in the setting of surgery, hemorrhage, infiltrative processes, or cerebral herniation.

HYPONATREMIA

Hyponatremia is commonly defined as a serum sodium <135 mmol/L (<135 meq/L). Neurologic symptoms occur at different levels of low sodium, depending not only on the absolute value but also on the rate of fall. In patients with hyponatremia that develops over hours, life-threatening seizures and cerebral edema may occur at values as high as 125 mmol/L. In contrast, some patients with more chronic hyponatremia that has slowly developed over months to years may be asymptomatic even with serum levels <110 mmol/L. Correction of hyponatremia, especially when chronic, must take place slowly in order to avoid additional neurologic complications. Cells in the brain swell in hypotonic hyponatremic states but may compensate over time by excreting solute into the extracellular space, leading to restoration of cell volume when water follows the solute out of the cells. If treatment of hyponatremia results in a rapid rise in serum sodium, cells in the brain may quickly shrink, leading to osmotic demyelination, a process that previously was thought to be limited exclusively to the brainstem (central pontine myelinolysis; see **Fig. 33-6**), but now has been described elsewhere in the CNS.

Treatment of hyponatremia is dependent on the cause. Hypertonic hyponatremia treatment focuses on correcting the underlying condition, such as hyperglycemia. Isovolemic hyponatremia (syndrome of inappropriate antidiuretic hormone [SIADH]) is managed with water restriction or administration of AVP antagonists. The management of choice for patients with hypervolemic hypotonic hyponatremia is free-water restriction and treatment of the underlying edematous disorder, such as hepatic failure, nephrotic syndrome, or congestive heart failure. Finally, in hypovolemic hypotonic hyponatremia, volume is replaced with isotonic saline while underlying conditions of the kidneys, adrenals, and gastrointestinal tract are addressed.

One neurologic cause of hypovolemic hypotonic hyponatremia is the cerebral salt-wasting syndrome that accompanies subarachnoid hemorrhage and, less commonly, other cerebral processes such as meningitis, stroke, or traumatic brain injury. In these cases, the degree of renal sodium excretion can be remarkable, and large amounts of saline, hypertonic saline, or oral sodium may need to be given in a judicious fashion in order to avoid complications from cerebral edema.

HYPOKALEMIA

Hypokalemia, defined as a serum potassium level < 3.5 mmol/L (<3.5 meq/L), occurs either because of excessive potassium losses (from the kidneys or gut) or due to an abnormal potassium distribution between the intracellular and extracellular spaces. At very low levels (<1.5 mmol/L), hypokalemia may be life threatening due to the risk of cardiac arrhythmia and may present neurologically with severe muscle weakness and paralysis. Hypokalemic periodic paralysis is a rare disorder

www.ketabpezeshki.com (021) 66485457 - 66485438

caused by excessive intracellular potassium uptake in the setting of a calcium or sodium channel mutation. Treatment of hypokalemia is dependent on the etiology but usually includes replacement of potassium through oral or IV routes as well as correcting the cause of potassium balance problems (e.g., eliminating β_2-adrenergic agonist medications or treating the underlying cause of severe diarrhea).

HYPERKALEMIA

Hyperkalemia is defined as a serum potassium level >5.5 mmol/L (>5.5 meq/L) and can neurologically present as muscle weakness with or without paresthesias. Hyperkalemia becomes life threatening when it produces electrocardiographic abnormalities such as peaked T waves or a widened QRS complex. In these cases, prompt treatment is essential and consists of strategies that protect the heart against arrhythmias (calcium gluconate administration); promote potassium redistribution into cells (with glucose, insulin, and β_2-agonist medications); and increase potassium removal (through sodium polystyrene sulfonate, loop diuretics, or hemodialysis).

CALCIUM DISTURBANCES

Hypercalcemia usually occurs in the setting of either hyperparathyroidism or systemic malignancy. Neurologic manifestations include encephalopathy as well as muscle weakness due to reduced neuromuscular excitability. Seizures can occur but are more common in states of low calcium.

Hypocalcemia in adults often follows surgical treatment of the thyroid or parathyroid. Seizures and altered mental status dominate the neurologic picture and usually resolve with calcium repletion. Tetany is due to spontaneous, repetitive action potentials in peripheral nerves and remains the classic sign of symptomatic hypocalcemia.

MAGNESIUM DISTURBANCES

Disorders of magnesium are dif cult to correlate with serum levels because a very small amount of total-body magnesium is located in the extracellular space. Hypomagnesemia presents neurologically with seizures, tremor, and myoclonus. When intractable seizures occur in the setting of hypomagnesemia, only administration of magnesium will lead to their resolution.

High levels of magnesium, in contrast, lead to CNS depression. Hypermagnesemia usually only occurs in the setting of renal failure or magnesium administration and can lead to confusion and muscular paralysis when severe.

CONSULTATIONS REGARDING PERIPHERAL NERVOUS SYSTEM DYSFUNCTION

ENTRAPMENT NEUROPATHIES

Polyneuropathy is a common cause of outpatient neurologic consultation **(Chap. 53)**. In the inpatient setting, however, mononeuropathies are more frequent, especially the entrapment neuropathies that complicate many surgical procedures and medical conditions. Median neuropathy at the wrist (carpal tunnel syndrome) is the most frequent entrapment neuropathy by far, but it is rarely a cause for inpatient consultation. Mechanisms for perioperative mononeuropathy include traction, compression, and ischemia of the nerve. Imaging with MRI, including neurography, may allow these causes to be distinguished. In all cases of mononeuropathy, the diagnosis can be made through the clinical examination and then confirmed with electrodiagnostic studies in the subacute period, if necessary. Treatment consists mainly of avoidance of repetitive trauma but may also include surgical approaches to relieve pressure or repair the nerve.

RADIAL NEUROPATHY

Radial nerve injury classically presents with weakness of extension of the wrist and fingers ("wrist drop") with or without more proximal weakness of extensor muscles of the upper extremity, depending on the site of injury. Sensory loss is in the distribution of the radial nerve, which includes the dorsum of the hand **(Fig. 58-3A)**. Compression at the level of the axilla, e.g., resulting from use of crutches, leads to weakness of the triceps, brachioradialis, and supinator muscles in addition to wrist drop. A more common site of compression occurs in the spiral groove of the upper arm in the setting of a humerus fracture or from sleeping with the arm draped over a bench or chair ("Saturday night palsy"). Sparing of the triceps is the rule when the nerve is injured in this location. Because extensors of the upper extremity are injured preferentially in radial nerve injury, these lesions may be mistaken for the pyramidal distribution of weakness that accompanies upper motor neuron lesions from brain or spinal cord processes, prompting neuroimaging to exclude acute stroke or mass lesion.

ULNAR NEUROPATHY

Compression of the ulnar nerve is the second most common entrapment neuropathy after carpal tunnel syndrome. T e most frequent site of compression is at the elbow where the nerve passes superficially in the ulnar groove. Symptoms usually begin with tingling in

www.ketabpezeshki.com (021) 66485457 - 66485438

the ulnar distribution, including the fourth and fifth digits of the hand **(Fig. 58-3B)**. Sensory symptoms may be worsened by elbow flexion due to increased pressure on the nerve, hence the tendency of patients to complain of increasing paresthesias at night when the arm is flexed at the elbow during sleep. Motor dysfunction can be disabling and involves most of the intrinsic hand muscles, limiting dexterity and strength of grasp and pinch. Etiologies of ulnar entrapment include trauma to the nerve (hitting the "funny bone"), malpositioning during anesthesia for surgical procedures, and chronic arthritis of the elbow. When a perioperative ulnar nerve injury is considered, stretch injury or trauma to the lower trunk of the brachial plexus should be entertained as well since its symptoms can mimic those of an ulnar neuropathy. If the clinical examination is equivocal, electrodiagnostic studies can definitively distinguish between plexus and ulnar nerve lesions a few weeks after the injury. Conservative methods of treatment are often the first step including bracing of the elbow to prevent flexion while sleeping. A variety of surgical approaches may also be effective in refractory or recurrent cases, including anterior ulnar nerve transposition and release of the flexor carpi ulnaris aponeurosis.

PERONEAL NEUROPATHY

The peroneal (also known as the fibular) nerve winds around the head of the fibula in the leg below the lateral aspect of the knee, and its superficial location at this site makes it vulnerable to trauma. Patients present with weakness of foot dorsiflexion ("foot drop") as well as with weakness in eversion but not inversion at the ankle. Sparing of inversion, which is a function of

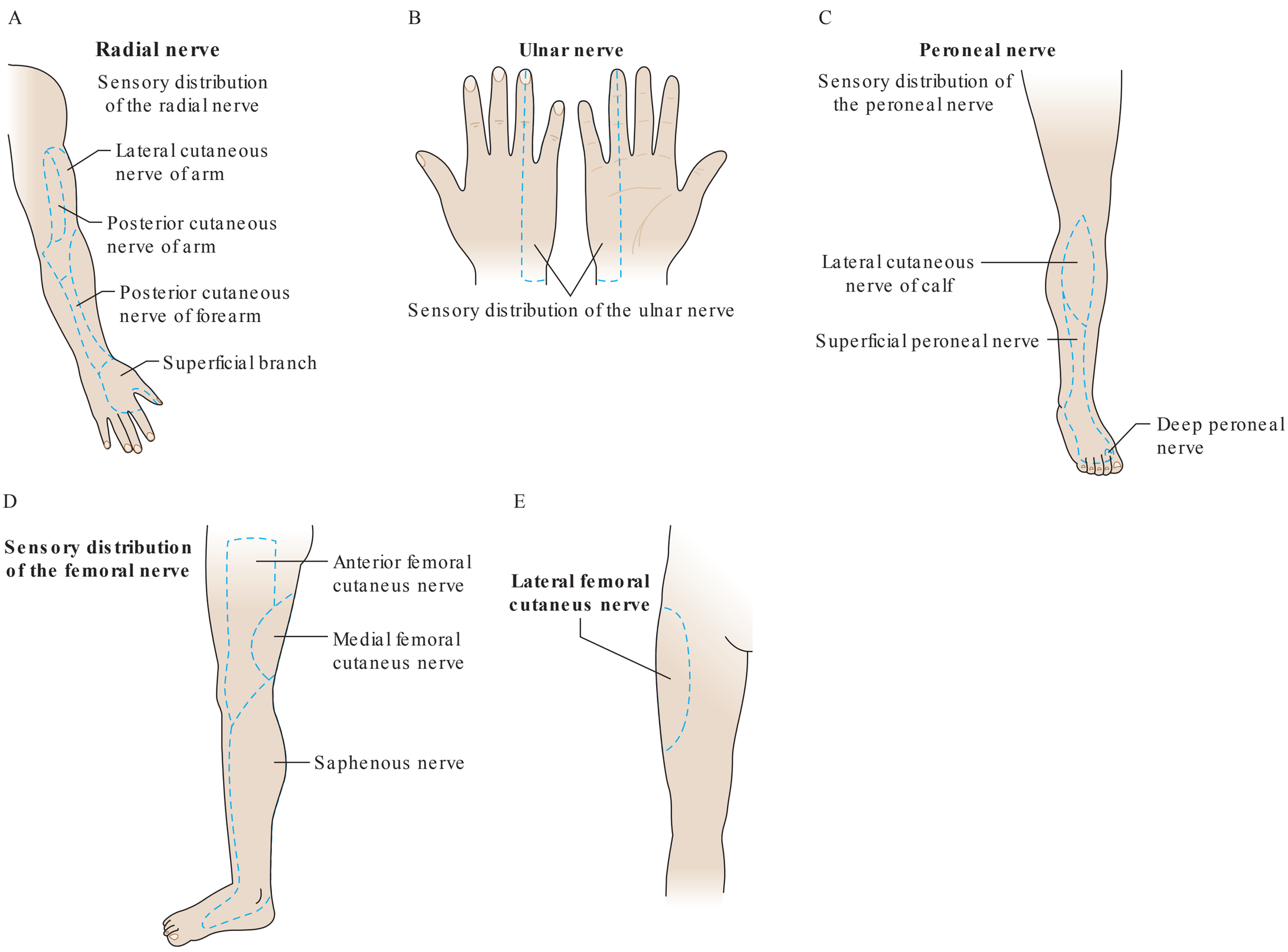


FIGURE 58-3
Sensory distribution of peripheral nerves commonly affected by entrapment neuropathies. A. Radial nerve. B. Ulnar nerve. C. Peroneal nerve. D. Femoral nerve. E. Lateral femoral cutaneous nerve.

www.ketabpezeshki.com (021) 66485457 - 66485438

muscles innervated by the tibial nerve, helps to distinguish peroneal neuropathies from L5 radiculopathies. Sensory loss involves the lateral aspect of the leg as well as the dorsum of the foot **(Fig. 58-3C)**. Fractures of the fibular head may be responsible for peroneal neuropathies, but in the perioperative setting, poorly applied braces exerting pressure on the nerve while the patient is unconscious, often in lithotomy position, are more often responsible. Tight-fitting stockings or casts of the upper leg can also cause a peroneal neuropathy, and thin individuals and those with recent weight loss are at increased risk.

PROXIMAL FEMORAL NEUROPATHY

Lesions of the proximal femoral nerve are relatively uncommon but may present dramatically with weakness of hip flexion, quadriceps atrophy, weakness of knee extension (often manifesting with leg-buckling falls), and an absent patellar reflex. Adduction of the thigh is spared as these muscles are supplied by the obturator nerve, thereby distinguishing a femoral neuropathy from a more proximal lumbosacral plexus lesion. The sensory loss found is in the distribution of the femoral nerve sensory branches including the anterior part of the thigh **(Fig. 58-3D)**. Compressive lesions from retroperitoneal hematomas or masses are common, and a CT of the pelvis should be obtained in all cases of femoral neuropathy to exclude these conditions. Bleeding into the pelvis resulting in hematoma can occur spontaneously, following trauma, or after intrapelvic surgeries such as renal transplantation. In intoxicated or comatose patients, stretch injuries to the femoral nerve are seen following prolonged, extreme hip flexion or extension. Rarely, attempts at femoral vein or arterial puncture can be complicated by injury to this nerve.

LATERAL FEMORAL CUTANEOUS NERVE

The symptoms of lateral femoral cutaneous nerve entrapment, commonly known as "meralgia paresthetica," include sensory loss, pain, and dysesthesia in part of the area supplied by the nerve **(Fig. 58-3E)**. There is no motor component to the nerve, and therefore weakness is not a part of this syndrome. Symptoms often are worsened by standing or walking. Compression of the nerve occurs where it enters the leg near the inguinal ligament, usually in the setting of tight-fitting belts, pants, corsets, or recent weight gain, including that of pregnancy. The differential diagnosis of these symptoms includes hip problems such as trochanteric bursitis.

OBSTETRIC NEUROPATHIES

Pregnancy and delivery place women at special risk for a variety of nerve injuries. Radiculopathy due to a herniated lumbar disc is not common during pregnancy, but compressive injuries of the lumbosacral plexus do occur secondary to either the fetal head passing through the pelvis or the use of forceps during delivery. These plexus injuries are more frequent with cephalopelvic disproportion and often present with a painless unilateral foot drop which must be distinguished from a peroneal neuropathy caused by pressure on the nerve while in lithotomy position during delivery. Other compressive mononeuropathies of pregnancy include meralgia paresthetica, carpal tunnel syndrome, femoral neuropathy when the thigh is abducted severely in an effort to facilitate delivery of the fetal shoulder, and isolated obturator neuropathy during lithotomy positioning. The latter presents with medial thigh pain that may be accompanied by weakness of thigh adduction. There is also a clear association between pregnancy and an increased frequency of idiopathic facial palsy (Bell's palsy).

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION IV

CHRONIC FATIGUE SYNDROME

CHAPTER 59

CHRONIC FATIGUE SYNDROME

Gijs Bleijenberg ■ Jos W. M. van der Meer

DEFINITION

Chronic fatigue syndrome (CFS) is a disorder characterized by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Besides intense fatigue, most patients with CFS report concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and abdominal cramps. Criteria for the diagnosis of CFS have been developed by the U.S. Centers for Disease Control and Prevention **(Table 59-1)**.

TABLE 59-1

DIAGNOSTIC CRITERIA FOR CHRONIC FATIGUE SYNDROME
Characteristic Persistent or Relapsing Unexplained Chronic Fatigue
Fatigue lasts for at least 6 months.
Fatigue is of new or definite onset.
Fatigue is not the result of an organic disease or of continuing exertion.
Fatigue is not alleviated by rest.
Fatigue results in a substantial reduction in previous occupational, educational, social, and personal activities.
Four or more of the following symptoms are concurrently present for 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep, or malaise after exertion.
Exclusion Criteria
Medical condition explaining fatigue
Major depressive disorder (psychotic features) or bipolar disorder
Schizophrenia, dementia, or delusional disorder
Anorexia nervosa, bulimia nervosa
Alcohol or substance abuse
Severe obesity (body mass index >40)

EPIDEMIOLOGY

CFS is seen worldwide, with adult prevalence rates varying between 0.2% and 0.4%. In the United States, the prevalence is higher among women (–75% of cases), members of minority groups (African and Native Americans), and individuals with lower levels of education and occupational status. T e mean age of onset is between 29 and 35 years. Many patients probably go undiagnosed and/or do not seek help.

ETIOLOGY

T ere are numerous hypotheses about the etiology of CFS; there is no definitively identified cause. Distinguishing between predisposing, precipitating, and perpetuating factors in CFS helps to provide a framework for understanding this complex condition **(Table 59-2)**.

Predisposing factors

Physical inactivity and trauma in childhood tend to increase the risk of CFS in adults. Neuroendocrine dysfunction may be associated with childhood trauma, reflecting a biological correlate of vulnerability. Psychiatric illness and physical hyperactivity in adulthood raise the risk of CFS in later life. Twin studies suggest a familial predisposition to CFS, but no causative genes have been identified.

Precipitating factors

Physical or psychological stress may elicit the onset of CFS. Most patients report an infection (usually a flu-like illness or infectious mononucleosis) as the trigger of their fatigue. Relatively high percentages of CFS cases follow Q fever and Lyme disease. However, no differences in Epstein-Barr virus load and immunologic reactivity were found between individuals who developed

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 59-2

PREDISPOSING, PRECIPITATING, AND PERPETUATING FACTORS IN CHRONIC FATIGUE SYNDROME

Predisposing Factors
Childhood trauma (sexual, physical, emotional abuse; emotional and physical neglect)
Physical inactivity during childhood
Premorbid psychiatric illness or psychopathology
Premorbid hyperactivity
↓
Precipitating Factors
Somatic events: infection (e.g., mononucleosis, Q fever, Lyme disease), surgery, pregnancy
Psychosocial stress, life events
↓
Perpetuating Factors
Non-acknowledgment by physician
Negative self-ef cacy
Strong physical attributions
Strong focus on bodily symptoms
Fear of fatigue
Lack of social support
Low physical activity pattern

CFS and those who did not. While antecedent infections are associated with CFS, a direct microbial causality is unproven and unlikely. One study identified a murine leukemia virus–related retrovirus (XMRV); however, several subsequent studies have established this virus as a laboratory artifact. Patients also of en report other precipitating somatic events such as serious injury, surgery, pregnancy, or childbirth. Serious life events, such as the loss of a loved one or a job, military combat, and other stressful situations, may also precipitate CFS. One-third of all patients cannot recall a trigger.

Perpetuating factors

Once CFS has developed, numerous factors may impede recovery. Physicians may contribute to chronicity by ordering unnecessary diagnostic procedures, by persistently suggesting psychological causes, and by not acknowledging CFS as a diagnosis.

A patient's focus on illness and avoidance of activities may perpetuate symptoms. A firm belief in a physical cause, a strong focus on bodily sensations, and a poor sense of control over symptoms may also prolong or exacerbate the fatigue and functional impairment. In most patients, inactivity is caused by negative illness perceptions rather than by poor physical fitness. Solicitous behavior of others may reinforce a patient's illness-related perceptions and behavior. A lack of social support is another known perpetuating factor.

PATHOPHYSIOLOGY

T e pathophysiology of CFS is unclear. Neuroimaging studies have found that CFS is associated with reduced gray matter volume, which in turn is associated with a decline in physical activity; these changes have been partially reversed following cognitive behavioral therapy (CBT). In addition, functional MRI data have suggested that abnormal patterns of activation correlate with self-reported problems with information processing. Neurophysiologic studies have shown altered CNS activation patterns during muscle contraction.

Evidence for immunologic dysfunction is inconsistent. Modest elevations in titers of antinuclear antibodies, reductions in immunoglobulin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine production, and shif s in lymphocyte subsets have been described. None of these immune findings appears in most patients, nor does any correlate with the severity of CFS. In theory, symptoms of CFS could result from excessive production of a cytokine, such as interleukin 1, that induces asthenia and other flulike symptoms; however, compelling data in support of this hypothesis are lacking. T ere is some evidence that CFS patients have mild hypocortisolism, the degree of which is associated with a poorer response to CBT. Discrepancies in perceived and actual cognitive performance are consistent findings in patients with CFS.

DIAGNOSIS

In addition to a thorough history, a systematic physical examination is warranted to exclude disorders causing fatigue (e.g., endocrine disorders, neoplasms, heart failure). T e heart rate of CFS patients is of en slightly above normal. Laboratory tests serve primarily to exclude other diagnoses; no test can diagnose CFS. T e following laboratory screen usually suffices: complete blood count; erythrocyte sedimentation rate; C-reactive protein; serum creatinine, electrolytes, calcium, and iron; blood glucose; creatine kinase; liver function tests; thyroid-stimulating hormone; anti-gliadin antibodies; and urinalysis. Serology for viral or bacterial infections usually is not helpful. No specific abnormalities have been identified on MRI or CT scans. T e decrease in gray matter volume observed at a population level by MRI is not useful for diagnosis in the individual patient. Extensive, unfocused, and expensive testing in a search for the "hidden" cause of the fatigue is not productive. CFS is a constellation of symptoms with no pathognomonic features and remains a diagnosis of exclusion.

Bipolar disorders, schizophrenia, and substance abuse exclude a diagnosis of CFS, as do eating disorders, unless

www.ketabpezeshki.com (021) 66485457 - 66485438

these issues have been resolved ≥5 years before symptom onset. In addition, CFS is excluded if the chronic fatigue developed immediately after a depressive episode. Depression developing in the course of the fatigue, however, does not preclude CFS. Concurrent psychiatric disorders, especially anxiety and mood disorders, are present in 30–60% of cases.

INITIAL MANAGEMENT

In cases of suspected CFS, the clinician should acknowledge the impact of the patient's symptoms on daily functioning. Disbelief or denial can provoke an exacerbation of genuine symptoms, which in turn strengthens the clinician's disbelief, leading to an unfortunate cycle of miscommunication. The possibility of CFS should be considered if a patient fulfils all criteria (Table 59-1) and if other diagnoses have been excluded.

The patient should be asked to describe the symptoms (fatigue and accompanying symptoms) and their duration as well as their consequences (reduction in daily activities). To assess symptom severity and the extent of daily-life impairment, the patient should describe a typical day, from waking to retiring, and, for comparison, an average day prior to symptom onset. Next, potential fatigue-precipitating factors are sought. The severity of fatigue is commonly difficult to assess quantitatively; a brief questionnaire is often helpful **(Fig. 59-1)**.

The patient should be informed of the current understanding of precipitating and perpetuating factors and effective treatments and should be offered general advice about disease management. If CBT for CFS is not available as an initial option (see below) and depression and anxiety are present, these symptoms should be treated. For patients with headache, diffuse pain, and feverishness, nonsteroidal anti-inflammatory drugs may be helpful. Even modest improvements in symptoms can make an important difference in the patient's degree of self-sufficiency and ability to appreciate life's pleasures.

Controlled therapeutic trials have established that acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents, offer no significant benefit in CFS. Countless anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from those therapeutic modalities that are toxic, expensive, or unreasonable.

The patient should be encouraged to maintain regular sleep patterns, to remain as active as possible, and to gradually return to previous levels of exercise and other activity (work).

TREATMENT Chronic Fatigue Syndrome

CBT and graded exercise therapy (GET) have been found to be the only beneficial interventions in CFS. Some patient groups argue against these approaches because of the implication that CFS is a purely mental disorder. CBT is a psychotherapeutic approach directed at changing unhealthy

How have you felt during the last two weeks?

Please rate all four statements and per statement check the box that reflects your situation best.

1.	I feel tired	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
2.	I tire easily	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
3.	I feel fit	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true
4.	Physically I feel exhausted	Yes, that is true	☐☐☐☐☐☐☐	No, that is not true

Scoring:
1, 2 and 4: Yes, that is true | 7 | 6 | 5 | 4 | 3 | 2 | 1 | No, that is not true — 3: Reversed

Sum scores >18 indicate severe fatigue

FIGURE 59-1
Shortened fatigue questionnaire.

www.ketabpezeshki.com (021) 66485457 - 66485438

disease-perpetuating patterns of thoughts and behaviors. It includes educating the patient about the etiologic model, setting goals, restoring fixed bedtimes and wake-up times, challenging and changing fatigue- and activity-related concerns, reducing a focus on symptoms, spreading activities evenly throughout the day, gradually increasing physical activity, planning a return to work, and resuming other activities. T e intervention, which typically consists of 12–14 sessions spread over 6 months, helps CFS patients gain control over their symptoms.

GET targets deconditioning and exercise intolerance and usually involves a home exercise program that continues for 3–5 months. Walking or cycling is systematically increased, with set goals for maximal heart rates. Evidence that deconditioning is the basis for symptoms in CFS is lacking, however. CBT and GET appear to improve fatigue primarily by changing the patient's perception of the fatigue and also by reducing the focus on symptoms. In general, CBT is the more multifaceted treatment, which may explain why CBT studies tend to yield better improvement rates than GET trials.

Not all patients benefit from CBT or GET. Predictors of poor outcome are medical (including psychiatric) comorbidities, current disability claims, and severe pain. CBT offered in an early stage of the illness reduces the burden of CFS for the patient as well as for society in terms of decreased medical and disability-related costs.

PROGNOSIS

Full recovery from untreated CFS is rare: the median annual recovery rate is 5% (range, 0–31%), and the median improvement rate is 39% (range, 8–63%). Patients with an underlying psychiatric disorder and those who continue to attribute their symptoms to an undiagnosed medical condition have poorer outcomes.

www.ketabpezeshki.com (021) 66485457 - 66485438

This page intentionally left blank

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION V

PSYCHIATRIC DISORDERS

CHAPTER 60

BIOLOGY OF PSYCHIATRIC DISORDERS

Robert O. Messing ■ Eric J. Nestler

Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. They are highly heritable, with genetic risk comprising 20–90% of disease vulnerability. As a result of their prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. All psychiatric disorders are broad heterogeneous syndromes that currently lack well-defined neuropathology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical observations using criteria in the Diagnostic and Statistical Manual *of* Mental Disorders (DSM) of the American Psychiatric Association, which is in its fifth edition as of 2013.

There is increasing agreement that the classification of psychiatric illnesses in DSM does not accurately reflect the underlying biology of these disorders. Uncertainties in diagnosis make it extremely difficult to study the neurobiologic and genetic basis of mental illness. This has led to the development of an alternative diagnostic scheme, termed Research Domain Criteria (RDoCs), which classifies mental illness on the basis of core abnormalities—e.g., psychosis (loss of reality) or anhedonia (decreased ability to experience pleasure), which are common symptoms of several illnesses—with the idea that such classifications will assist in defining the biologic basis of at least key symptoms. Other factors that have impeded progress in understanding mental illness include the lack of access to pathologic brain tissue except upon death and the inherent limitations of animal models for disorders defined largely by behavioral abnormalities (e.g., hallucinations, delusions, guilt, suicidality) that are inaccessible in animals.

Despite these limitations, the past decade has seen significant advances. Neuroimaging methods are beginning to provide evidence of brain pathology, genome-wide association studies and high-throughput sequencing are at last revealing genes that confer risk for severe forms of mental illness, and investigations using better validated animal models are offering new insight into the molecular, cellular, and circuit mechanisms of disease pathogenesis. There is also excitement in the potential utility of neuron-like cells induced in vitro from a patient's peripheral tissues (e.g., fibroblasts) providing novel ways of studying disease pathophysiology and screening for new treatments. There is consequently justified optimism that the field of psychiatry will transition from behaviorally defined syndromes to true biologic disease entities and that such advances will drive the development of improved treatments and eventually cures and preventive measures. This chapter describes several examples of recent discoveries in basic neuroscience that have informed our current understanding of disease mechanisms in psychiatry.

NEUROGENETICS

Because the human brain can only be examined indirectly during life, genome analyses have been extremely important for obtaining molecular clues about the pathogenesis of psychiatric disorders. A wealth of new information has been made possible by recent technological developments that have permitted affordable, large-scale genome-wide association studies and fine-scale sequencing. As an example, significant progress has been made in the genetics of autism spectrum disorders (ASDs), which are a heterogeneous group of neurodevelopmental diseases that share clinical features of impaired reciprocal social communication and interaction and restricted, repetitive patterns of behavior. ASDs are highly heritable; concordance rates in monozygotic twins (~60–90%) are roughly 10-fold higher than in dizygotic twins and siblings, whereas first-degree relatives show about 50-fold increased risk compared with the general population. ASDs are also genetically heterogeneous. More than 100 known mutations account for up to 20% of cases, although none individually accounts for more than 1% **(Table 60-1)**.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 60-1

EXAMPLES OF GENES IMPLICATED IN AUTISM

GENE SYMBOL	GENE NAME	FUNCTION
PTEN	Phosphatase and tensin homolog	Signal transduction Synaptic function
TSC1	Tuberous sclerosis 1	Signal transduction Translation and protein stability Synaptic function
TSC2	Tuberous sclerosis 2	Signal transduction Translation and protein stability Synaptic function
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase	Signal transduction
FMR1	Fragile X mental retardation 1	Translation and protein stability Synaptic function
UBE3A	Ubiquitin protein ligase E3A	Translation and protein stability Synaptic function
CNTN3	Contactin 3	Synaptic function
CNTN4	Contactin 4	Synaptic function
CNTNAP2	Contactin-associated protein-like 2	Synaptic function
NLGN3	Neuroligin 3	Synaptic function
NLGN4	Neuroligin 4	Synaptic function
NRXN1	Neurexin 1	Synaptic function
PCDH10	Protocadherin 10	Synaptic function
SHANK3	Shank 3	Synaptic function
SLC6A4	Serotonin transporter	Neurotransmitter signaling
AVPR1	Arginine vasopressin receptor 1	Neurotransmitter signaling
OXTR	Oxytocin receptor	Neurotransmitter signaling
CACNA1C	Voltage-gated calcium channel–alpha 1C subunit	Ion channel
CACNA1H	Voltage-gated calcium channel–alpha 1H subunit	Ion channel
SCN1A	Sodium channel, voltage-gated, type I, alpha subunit	Ion channel
SCN2A	Sodium channel, voltage-gated, type II, alpha subunit	Ion channel
SLC9A9	Sodium/hydrogen exchanger	Transporter
GRIN2B	Glutamate receptor, ionotropic, N-methyl-d-aspartate 2B	Neurotransmitter signaling
DHCR7	7-Dehydrocholesterol reductase	Metabolism
PAH	Phenylalanine hydroxylase	Metabolism
ARX	Arx transcription factor	Gene expression
EN2	Engrailed 2 transcription factor	Gene expression
MECP2	Methyl CpG–binding protein 2 (Rett's syndrome)	Gene expression
RNF8	Ring finger protein 8	Gene expression
CHD8	Chromodomain helicase DNA binding protein	Gene expression
TBR1	T-box, brain 1	Gene expression

It appears that most cases result from complex genetic mechanisms, including inheritance of multiple genetic risk variants and epigenetic modifications. For example, up to 10% of patients with autism have large (>500 kb) de novo copy number variations scattered across the genome, suggesting that hundreds of different genes can influence autism risk.

Amid this genetic heterogeneity, however, some common themes have emerged that inform pathogenesis of ASDs. For instance, many identified mutations are in genes that encode proteins involved in synaptic function and early transcriptional regulation (Table 60-1) and have a clear relationship to activity-dependent neural responses that can affect the development of neural

www.ketabpezeshki.com (021) 66485457 - 66485438

systems underlying cognition and social behaviors. Mutations in these genes may be detrimental by altering the balance of excitatory versus inhibitory synaptic signaling in local and extended circuits and by altering mechanisms that control brain growth. Some mutations affect genes (e.g., PTEN, TSC1, and TSC2) that negatively regulate signaling from several types of extracellular stimuli, including those transduced by receptor tyrosine kinases. Their dysregulation can alter neuronal growth as well as synaptic development and function.

With further understanding of pathogenesis and the definition of specific ASD subtypes, there is reason to believe that effective therapies will be identified. Work in mouse models has already demonstrated that some autism-like behaviors can be reversed, even in fully developed adult animals, by modifying the underlying pathology; these results encourage hope for many affected individuals. Treatments that target excitation-inhibition imbalance or altered mRNA translation appear to offer early promise. For example, the genes TSC1, TSC2, and PTEN are negative regulators of signaling through the target of rapamycin complex 1 (TORC1), which regulates protein synthesis. Rapamycin, a selective inhibitor of TORC1, can reverse several behavioral and synaptic defects in mice carrying null mutations in these genes. Another example is fragile X syndrome, which is the leading cause of inherited autism and mental disability and is due to mutations in FMR1 that result in loss of the encoded fragile X mental retardation protein (FMRP). FMRP is a polyribosome-associated mRNA-binding protein that represses the translation of a subset (~5%) of all mRNAs, several of which encode proteins that comprise the postsynaptic density, including the metabotropic glutamate receptor 5 (mGluR5). Treatment of Fmr1 knockout mice with mGluR5 antagonists reduces several behavioral and morphologic abnormalities in these mice; these promising preclinical results have led to ongoing trials of mGluR5 antagonists in humans with fragile X syndrome.

The ability to catalog common genetic variants and assay them on array-based platforms and, more recently, to carry out whole-exome sequencing has allowed investigators to collect sample sizes sufficient to detect genetic risk loci for schizophrenia with genome-wide significance. Several of the identified genes are parts of molecular complexes, such as voltage-gated calcium channels (in particular, CACNA1C and CACNB2) and the postsynaptic density of excitatory synapses. As in ASDs, copy number variants, single-nucleotide polymorphisms, and small insertions and deletions are common in schizophrenia. Genes that promote risk for drug addiction have also begun to emerge from large family and population studies. The best-established susceptibility loci are regions on chromosomes 4 and 5 containing $GABA_A$ receptor gene clusters linked to alcoholism and the CHRNA5-A3-B4 nicotinic acetylcholine receptor gene cluster on chromosome 15 associated with nicotine and alcohol addiction.

A recurrent theme that has emerged from genetic studies of psychiatric disorders is pleiotropy, namely, that many genes are associatedwith multiple psychiatric syndromes. For example, mutations in MECP2, FMR1, and TSC1 and TSC2 (see Table 60-1 for abbreviations) can cause mental retardation without ASD, others in MECP2 can cause obsessive-compulsive and attention-deficit hyperactivity disorders, some alleles of NRXN1 are associated with symptoms of both ASD and schizophrenia, and common polymorphisms in CACNA1C are strongly associated with both schizophrenia and bipolar disorder. Likewise, duplication of chromosome 16p is associated with both schizophrenia and autism, whereas DiGeorge's (velocardiofacial) syndrome region deletions and the DISC1 (disrupted in schizophrenia 1) locus on chromosome 22 are associated with schizophrenia, autism, and bipolar disorder. The association of genes with multiple syndromes attests to the complexity of psychiatric disorders and the influence of additional factors that combine to specify the ultimate phenotype, including regulatory variants that determine cell-type specificity and timing of gene expression, protective variants, and epigenetic effects.

SIGNAL TRANSDUCTION

Studies of signal transduction have revealed numerous intracellular signaling pathways that are perturbed in psychiatric disorders, and such research has provided insight into development of new therapeutic agents. For example, lithium is a highly effective drug for bipolar disorder and competes with magnesium to inhibit numerous magnesium-dependent enzymes, including the enzyme GSK3β and several enzymes involved in phosphoinositide signaling that lead to activation of protein kinase C. These findings have led to discovery programs focused on developing GSK3β or protein kinase C inhibitors as potential novel treatments for mood disorders.

The observations that tricyclic antidepressants (e.g., imipramine) inhibit serotonin and/or norepinephrine reuptake and that monoamine oxidase inhibitors (e.g., tranylcypromine) are effective antidepressants initially led to the view that depression is caused by a deficiency of these monoamines. However, this hypothesis has not been substantiated. A cardinal feature of these drugs is that long-term administration is needed for their antidepressant effects. This means that their short-term actions, namely promotion of serotonin or norepinephrine function, are not per se antidepressant but rather induce a cascade of adaptations in the brain that underlie their clinical effects. The nature of these therapeutic drug-induced adaptations has not been identified with certainty. One theory holds that, in a subset of depressed patients who display upregulation of the hypothalamic-pituitary-adrenal (HPA) axis

www.ketabpezeshki.com (021) 66485457 - 66485438

characterized by increased secretion of corticotropin-releasing factor (CRF) and glucocorticoids, excessive glucocorticoids cause atrophy of hippocampal neurons, which is associated with reduced hippocampal volumes seen clinically. Chronic antidepressant administration might reverse this atrophy by increasing brain-derived neurotrophic factor (BDNF) in hippocampus. A role for stress-induced decreases in the generation of newly born hippocampal granule cell neurons, and its reversal by antidepressants through BDNF and other growth factors, has also been suggested.

A major advance in recent years has been the identification of several rapidly acting antidepressants with non–monoamine-based mechanisms of action. T e best established is ketamine, a noncompetitive antagonist of N-methyl-d-aspartate (NMDA) glutamate receptors, which exerts rapid (hours) and robust antidepressant ef ects in severely depressed patients who have not responded to other treatments. Ketamine, which at higher doses is psychotomimetic and anesthetic, exerts these antidepressant ef ects at low doses with minimal side ef ects. However, the response to ketamine is transient, which has led to several approaches to maintain treatment response, such as repeated ketamine delivery. T e mechanism underlying ketamine's antidepressant action is not known, but its striking clinical efficacy has stimulated animal research on the role of glutamate neurotransmission and synaptic plasticity in key limbic regions. Recent evidence supports a role for TORC1 activation because administration of rapamycin blocks the antidepressant-like ef ects of ketamine in animal models. Mechanisms by which ketamine activates TORC1 are currently an active area of investigation.

A major goal in the field of drug abuse has been to identify neuroadaptive mechanisms that lead from recreational use to addiction. Such research has determined that repeated intake of abused drugs induces specific changes in cellular signal transduction, leading to changes in synaptic strength (long-term potentiation or depression) and neuronal structure (altered dendritic branching or cell soma size) within the brain's reward circuitry. T ese modifications are mediated in part by changes in gene expression, achieved by drug regulation of transcription factors (e.g., CREB [cAMP response element-binding protein] and ΔFosB [a Fos family protein]) and their target genes. Such alterations in gene expression are associated with lasting alterations in epigenetic modifications, including histone acetylation and methylation and DNA methylation. T ese adaptations provide opportunities for developing treatments targeted to drug-addicted individuals. T e fact that the spectrum of these adaptations partly dif ers depending on the particular addictive substance used creates opportunities for treatments that are specific for dif erent classes of addictive drugs and that may, therefore, be less likely to disturb basic mechanisms that govern normal motivation and reward.

Increasingly, causal relationships are being established between individual molecular and cellular adaptations and specific behavioral abnormalities that characterize the addicted state. For example, acute activation of μ-opioid receptors by morphine or other opiates activates $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase, resulting in reduced cyclic AMP (cAMP) production, protein kinase A (PKA) activation, and activation of the transcription factor CREB. Repeated administration of these drugs **(Fig. 60-1)**

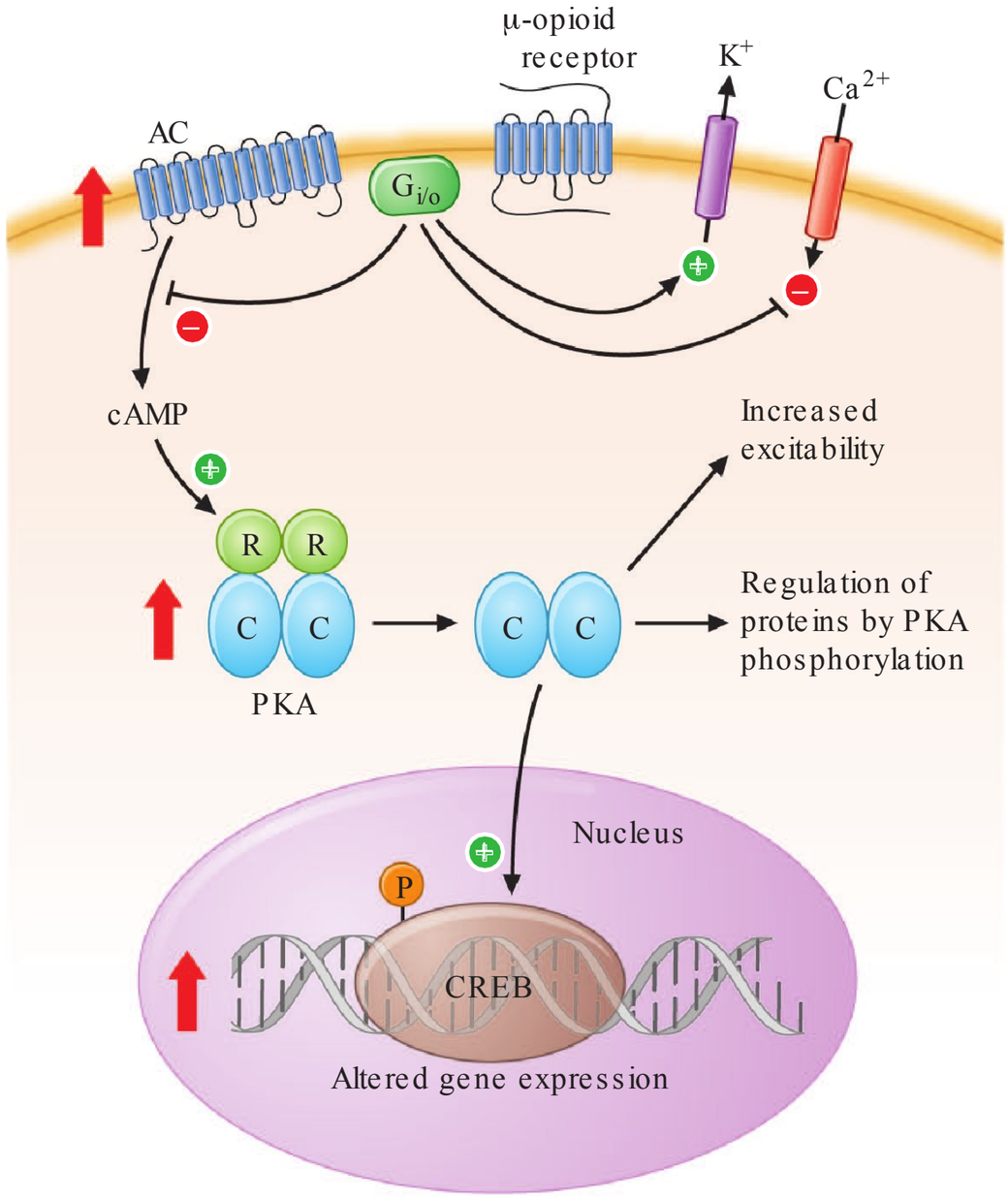


FIGURE 60-1

Opiate action in the locus coeruleus (LC). Binding of opiate agonists to μ-opioid receptors catalyzes nucleotide exchange on G_i and G_o proteins, leading to inhibition of adenylyl cyclase, neuronal hyperpolarization via activation of K^+ channels, and inhibition of neurotransmitter release via inhibition of Ca^{2+} channels. Inhibition of adenylyl cyclase (AC) reduces protein kinase A (PKA) activity and phosphorylation of several PKA substrate proteins, thereby altering their function. For example, opiates reduce phosphorylation of the cAMP response element-binding protein (CREB), which appears to initiate longer term changes in neuronal function. Chronic administration of opiates increases levels of AC isoforms, PKA catalytic (C) and regulatory (R) subunits, and the phosphorylation of several proteins, including CREB (indicated by red arrows). These changes contribute to the altered phenotype of the drug-addicted state. For example, the excitability of LC neurons is increased by enhanced cAMP signaling, although the ionic basis of this ef ect remains unknown. Activation of CREB causes upregulation of AC isoforms and tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis.

www.ketabpezeshki.com (021) 66485457 - 66485438

evokes a homeostatic response involving upregulation of adenylyl cyclases and PKA and increased activation of CREB. Such upregulation of cAMP-CREB signaling has been identified in the locus coeruleus, periaqueductal gray, ventral tegmental area (VTA), nucleus accumbens, and several other CNS regions, and contributes to opiate craving and signs of opiate withdrawal. The fact that endogenous opioid peptides do not produce tolerance and dependence, while morphine and heroin do, may relate to the observation that, unlike endogenous opioids, morphine and heroin are weak inducers of μ-opioid receptor desensitization and endocytosis. Therefore, these drugs cause prolonged receptor activation and inhibition of adenylyl cyclases, which provides a powerful stimulus for the upregulation of cAMP-CREB signaling that characterizes the opiate-dependent state.

SYSTEMS NEUROSCIENCE

The study of interconnected brain circuits that drive behavior has been greatly advanced through newer methods in brain imagining that have documented abnormalities in neural function and connectivity in psychiatric disorders. The past decade has also witnessed the development of revolutionary new techniques—optogenetics and designer receptors and ligands—that provide unprecedented temporal and spatial control of neural circuits and permit detection of neural activity in real time in awake, behaving animals.

Positron emission tomography (PET), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) have identified neural circuits that contribute to psychiatric disorders, for example, defining the neural circuitry of mood within the brain's limbic system **(Fig. 60-2)**. Integral to this system are the

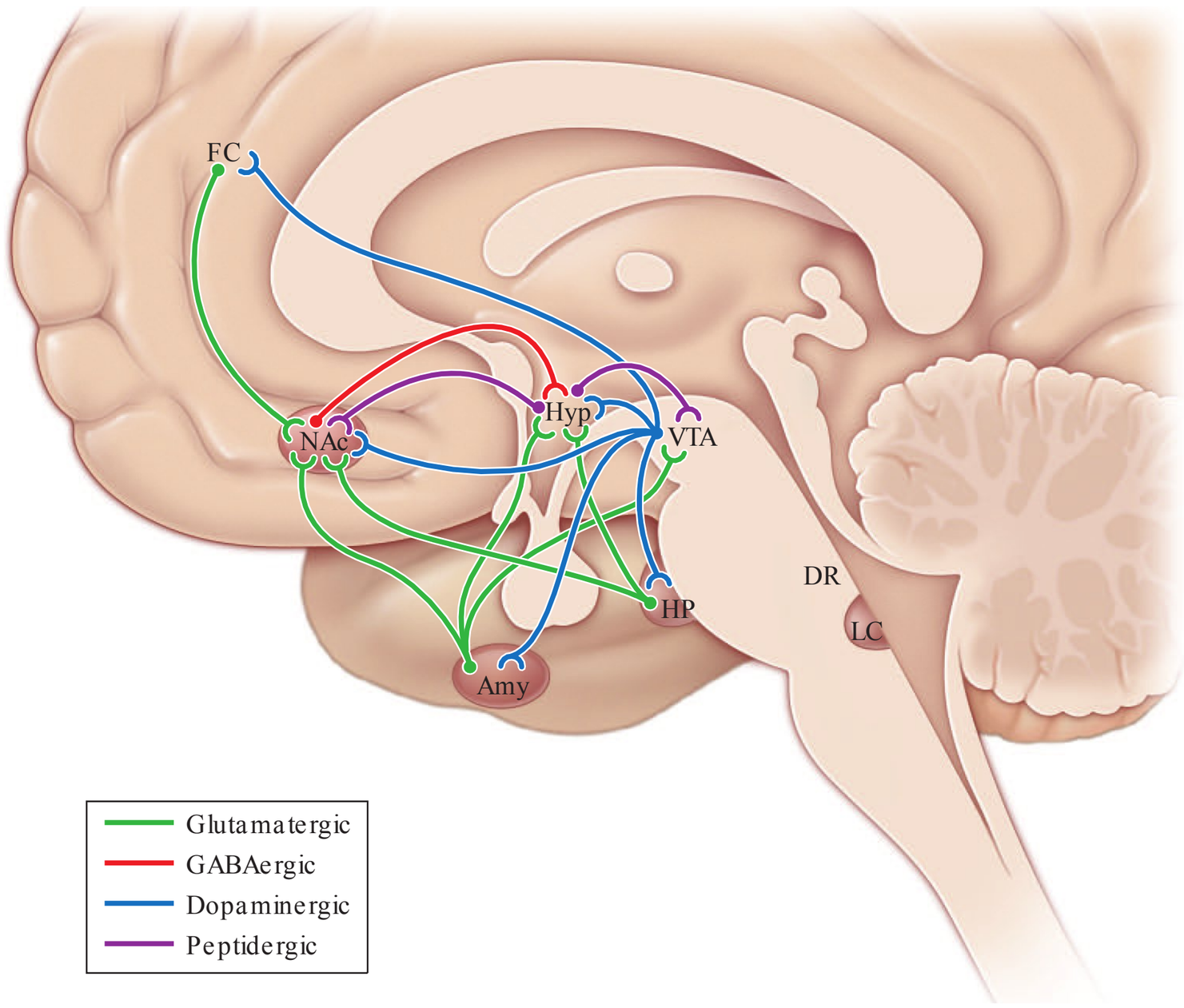


FIGURE 60-2

Neural circuitry of depression and addiction. The figure shows a simplified summary of a series of limbic circuits in brain that regulate mood and motivation and are implicated in depression and addiction. Shown in the figure are the hippocampus (HP) and amygdala (Amy) in the temporal lobe, regions of prefrontal cortex, nucleus accumbens (NAc), and hypothalamus (Hyp). Only a subset of the known interconnections among these brain regions is shown. Also shown is the innervation of several of these brain regions by monoaminergic neurons. The ventral tegmental area (VTA) provides dopaminergic input to each of the limbic structures. Norepinephrine (from the locus coeruleus [LC]) and serotonin (from the dorsal raphe [DR] and other raphe nuclei) innervate all of the regions shown. In addition, there are strong connections between the hypothalamus and the VTA-NAc pathway. Important peptidergic projections from the hypothalamus include those from the arcuate nucleus that release β-endorphin and melanocortin and from the lateral hypothalamus that release orexin.

www.ketabpezeshki.com (021) 66485457 - 66485438

nucleus accumbens (important also for brain reward—see below), amygdala, hippocampus, and regions of prefrontal cortex. Recent optogenetic research in animals, where the activity of specific types of neurons in defined circuits can be controlled with light, has confirmed the importance of this limbic circuitry in controlling depression-related behavioral abnormalities. Given that many symptoms of depression (so-called neurovegetative symptoms) involve physiologic functions, a key role for the hypothalamus is also presumed. A subset of depressed individuals shows a small reduction in hippocampal size, as noted above. In addition, brain imaging investigations have revealed increased activation of the amygdala by negative stimuli and reduced activation of the nucleus accumbens by rewarding stimuli. T ere is also evidence for altered activity in prefrontal cortex, such as hyperactivity of subgenual area 25 in anterior cingulate cortex. Such findings have led to trials of deep brain stimulation (DBS) of either the nucleus accumbens or subgenual area 25, which appears to be therapeutic in some severely depressed individuals.

In schizophrenia, structural and functional imaging studies have identified a 3% loss of brain volume, most of which is in gray matter. T is loss is progressive, and cortical gray matter appears to be particularly af ected over time. T e temporal lobes, particularly the left superior temporal gyrus, Heschl gyrus, and planum temporale, are often the most severely af ected. T e rate of loss in these regions as well as in frontal and parietal lobes appears to be greatest early in the course of the disease. Functional imaging studies provide evidence of reduced metabolic (presumably neural) activity in the dorsolateral prefrontal cortex at rest and when performing tests of executive function, including working memory. T ere is also evidence for impaired structural and task-related functional connectivity, mainly in frontal and temporal lobes.

T ese neuroimaging findings in schizophrenia have been confirmed in pathologic studies that show enlargement of the ventricular system and reduction of cortical and subcortical gray matter in frontal and temporal lobes and in the limbic system. T e reduction in cortical thickness is associated with increased cell packing density and reduced neuropil (defined as axons, dendrites, and glial cell processes) without an apparent change in neuronal cell number. Specific classes of interneurons in prefrontal cortex consistently show reduced expression of the gene encoding the enzyme glutamic acid decarboxylase 1 (GAD1), which synthesizes γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. Neuregulin 1 (NRG1), a member of the epidermal growth factor (EGF) family of growth factors, and its receptor ERBB4, have been implicated in schizophrenia, and they serve important roles in the maturation of GABAergic interneurons in cerebral cortex; loss of NRG1-ERBB4 in mice leads to a reduced neuropil, thus phenocopying a pathologic finding in schizophrenia. T ese findings are consistent with one working hypothesis of schizophrenia as a developmental neurodegenerative disorder due in part to loss of cortical interneurons in frontal and temporal lobes.

Work in rodent and nonhuman primate models of addiction has established the brain's reward regions as key neural substrates for the acute actions of drugs of abuse and for addiction induced by repeated drug administration (Fig. 60-2). Midbrain dopamine neurons in the VTA function normally as rheostats of reward: they are activated by natural rewards (food, sex, social interaction) or even by the expectation of such rewards, and many are suppressed by the absence of an expected reward or by aversive stimuli. T ese neurons thereby transmit crucial survival signals to the rest of the limbic brain to promote reward-related behavior, including motor responses to seek and obtain the rewards (nucleus accumbens), memories of reward-related cues (amygdala, hippocampus), and executive control of obtaining rewards (prefrontal cortex).

Drugs of abuse alter neurotransmission through initial actions at dif erent classes of ion channels, neurotransmitter receptors, or neurotransmitter transporters **(Table 60-2)**. Studies in animal models have demonstrated that although the initial targets dif er, the actions of these drugs converge on the brain's reward circuitry by promoting dopamine neurotransmission in the nucleus accumbens and other limbic targets of the VTA. In addition, some drugs promote activation of opioid and cannabinoid receptors, which modulate this reward circuitry. By these mechanisms, drugs of abuse produce powerful rewarding signals, which, after repeated drug administration, corrupt a vulnerable brain's reward circuitry in ways that promote addiction. T ree major pathologic adaptations have been described. First, drugs produce tolerance and dependence in reward circuits, which promote escalating drug intake and a negative emotional state during drug withdrawal that promotes relapse. Second, sensitization to the rewarding ef ects of the drugs and associated cues is seen during prolonged abstinence and also triggers relapse. T ird, executive function is impaired in such a way as to increase impulsivity and compulsivity, both of which promote relapse.

Imaging studies in humans confirm that addictive drugs, as well as craving for them, activate the brain's reward circuitry. In addition, patients who abuse alcohol or psychostimulants show reduced gray matter in the prefrontal cortex as well as reduced activity in anterior cingulate and orbitofrontal cortex during tasks of attention and inhibitory control. It is thought that

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 60-2

INITIAL ACTIONS OF DRUGS OF ABUSE

DRUG	NEUROTRANSMITTER AFFECTED	DRUG TARGET (ACTION)
Opiates	Endorphins, enkephalins	μ- and δ-opioid receptors (agonist)
Psychostimulants (cocaine, amphetamine, methamphetamine)	Dopamine	Dopamine transporter (antagonist—cocaine; reverse transport—amphetamine, methamphetamine)
Nicotine	Acetylcholine	Nicotinic cholinergic receptors (agonist)
Ethanol	GABA	$GABA_A$ receptors (positive allosteric modulator)
	Glutamate	NMDA glutamate receptors (antagonist)
	Acetylcholine	Nicotinic cholinergic receptors (allosteric modulator)
	Serotonin—	5HT-3 receptor (positive allosteric modulator) Calcium-activated K^+ channel (activator)
Marijuana	Endocannabinoids (anandamide, 2-arachidonoylglycerol)	CB_1 receptor (agonist)
Phencyclidine	Glutamate	NMDA glutamate receptor (antagonist)

damage to these cortical areas contributes to addiction by impairing decision-making and increasing impulsivity.

NEUROINFLAMMATION

There is increasing evidence for the involvement of inflammatory mechanisms in a subset of depressed patients. These individuals display elevated blood levels of interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and other cytokines. Moreover, rodents exposed to chronic stress exhibit similar increases in peripheral cytokines, and peripheral or central delivery of those cytokines to normal rodents increases their susceptibility to chronic stress. These findings have led to the novel idea of using peripheral cytokines as biomarkers of a subtype of depression and the potential utility of developing new antidepressants that oppose cytokine action.

Recent evidence has also linked proinflammatory signaling in the brain to addiction, particularly to alcohol. Human alcoholism is associated with impaired innate immunity, increases in circulating proinflammatory cytokines, and an increase in brain levels of the cytokine monocyte chemotactic protein-1 (MCP-1, also referred to as CCL2). Many of these cytokines are produced by astrocytes and microglia, and by neurons under certain pathologic conditions, where they play important roles in modifying neuronal function and plasticity. For example MCP-1 modulates the release of certain neurotransmitters and, when administered into the VTA, increases neuronal excitability, promotes dopamine release, and increases locomotor activity. Recent gene expression array studies of alcohol drinking in mice have identified a network of regulated cytokines in brain, and a role in regulation of alcohol consumption has been recently validated for several of them, including IL-6. A major focus of current research is to define the site and mechanism by which proinflammatory cytokines impair brain function to elicit a depressive episode or promote drug abuse.

CONCLUSIONS

This brief narrative illustrates the substantial progress that is being made in understanding the genetic and neurobiologic basis of mental illness. It is anticipated that biologic measures will be used increasingly to diagnosis and subtype a psychiatric disorder and that targeted therapeutics will become available to treat them.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 61

MENTAL DISORDERS

Victor I. Reus

Mental disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is approximately 30%, but only one-third of affected individuals are currently receiving treatment. Global burden of disease statistics indicate that 4 of the 10 most important causes of morbidity and attendant health care costs worldwide are psychiatric in origin.

Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into targeted assessment. The Primary Care Evaluation of Mental Disorders (PRIME-MD; and a self-report form, the Patient Health Questionnaire) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 min to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence.

A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to refer, because societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that he or she will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of posttraumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment. This chapter reviews the clinical assessment and treatment of some of the most common mental disorders presenting in primary care and is based on the Diagnostic and Statistical Manual *of* Mental Disorders, Fifth Edition (DSM-5), the framework for categorizing psychiatric illness used in the United States. **Eating disorders are discussed later in this chapter, and the biology of psychiatric and addictive disorders is discussed in Chap. 60.**

GLOBAL CONSIDERATIONS

The DSM-5 and the tenth revision of the International Classification of Diseases (ICD-10), which is used more commonly worldwide, have taken somewhat differing approaches to the diagnosis of mental illness, but considerable effort has been expended to provide an operational translation between the two nosologies. Both systems are in essence purely descriptive and emphasize clinical pragmatism, in distinction to the Research Domain Criteria (RDOC) proposed by National Institute of Mental Health, which aspires to provide a causal framework for classification of behavioral disturbance. None of these diagnostic systems has as yet achieved adequate validation. The Global Burden of Disease Study 2010, using available epidemiologic data, nevertheless has reinforced the conclusion that, regardless of nosologic differences, mental and substance abuse disorders are the major cause of life-years lost to disability among all medical illnesses. There is general agreement that high-income countries will need to build capacity in professional training in low- and middle-income countries in order to provide an adequate balanced care model for the

www.ketabpezeshki.com (021) 66485457 - 66485438

delivery of evidence-based therapies for mental disorders. Recent surveys that indicate a dramatic increase in mental disorder prevalence in rapidly developing countries, such as China, may reflect both an increased recognition of the issue, but also the consequence of social turmoil, stigma, and historically inadequate resources. T e need for improved prevention strategies and for more definitive and effective interventional treatments remains a global concern.

ANXIETY DISORDERS

Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15–20% of medical clinic patients. Anxiety, defined as a subjective sense of unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. T e primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants.

When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition.

PANIC DISORDER

Clinical manifestations

Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death. Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Diagnostic criteria require at least 1 month of concern or worry about the attacks or a change in behavior related to them. T e lifetime prevalence of panic disorder is 2–3%. Panic attacks have a sudden onset, developing within 10 min and usually resolving over the course of an hour, and they occur in an unexpected fashion. Some may occur when waking from sleep. T e frequency and severity of panic attacks vary, ranging from once a week to clusters of attacks separated by months of well-being. T e first attack is usually outside the home, and onset is typically in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. Agoraphobia, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape. It may, however, be diagnosed even if panic disorder is not present. Typically, it leads the patient into a progressive restriction in lifestyle and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus, physicians will fail to recognize the syndrome if direct questioning is not pursued.

Differential diagnosis

A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance abuse disorder, the most common being panic disorder. T e differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also satisfy criteria for major depression at some point in their illness.

When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out anxiety states resulting from medical disorders such as pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic such as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome.

Etiology and pathophysiology

T e etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsivity, and social learning. Panic disorder shows familial aggregation; the disorder is concordant in 30–45% of monozygotic twins, and genome-wide screens have identified suggestive risk loci. Acute panic attacks appear to be associated with increased noradrenergic discharges in the locus coeruleus.

www.ketabpezeshki.com (021) 66485457 - 66485438

Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the α_2-adrenergic antagonist yohimbine, cholecystokinin tetrapeptide (CCK-4), and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a pathway involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Agents that block serotonin reuptake can prevent attacks. Patients with panic disorder have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the panic attack; accordingly, therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

TREATMENT Panic Disorder

Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medication **(Tables 61-1 through 61-3)**. Selective serotonin reuptake inhibitors (SSRIs) benefit the majority of panic disorder patients and do not have the adverse effects of tricyclic antidepressants (TCAs). Fluoxetine, paroxetine, sertraline, and the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have received approval from the U.S. Food and Drug Administration (FDA) for this indication. These drugs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5–10 mg fluoxetine, 25–50 mg sertraline, 10 mg paroxetine, venlafaxine 37.5 mg). Monoamine oxidase inhibitors (MAOIs) are also effective and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2–6 weeks to become effective, and doses may need to be adjusted based on the clinical response.

Because of anticipatory anxiety and the need for immediate relief of panic symptoms, benzodiazepines are useful early in the course of treatment and sporadically thereafter **(Table 61-4)**. For example, alprazolam, starting at 0.5 mg qid and increasing to 4 mg/d in divided doses, is effective, but patients must be monitored closely, as some develop dependence and begin to escalate the dose of this medication. Clonazepam, at a final maintenance dose of 2–4 mg/d, is also helpful; its longer half-life permits twice-daily dosing, and patients appear less likely to develop dependence on this agent.

Early psychotherapeutic intervention and education aimed at symptom control enhance the effectiveness of drug treatment. Patients can be taught breathing techniques, be educated about physiologic changes that occur with panic, and learn to expose themselves voluntarily to precipitating events in a treatment program spanning 12–15 sessions. Homework assignments and monitored compliance are important components of successful treatment. Once patients have achieved a satisfactory response, drug treatment should be maintained for 1–2 years to prevent relapse. Controlled trials indicate a success rate of 75–85%, although the likelihood of complete remission is somewhat lower.

GENERALIZED ANXIETY DISORDER

Clinical manifestations

Patients with generalized anxiety disorder (GAD) have persistent, excessive, and/or unrealistic worry associated with muscle tension, impaired concentration, autonomic arousal, feeling "on edge" or restless, and insomnia **(Table 61-5)**. Onset is usually before age 20 years, and a history of childhood fears and social inhibition may be present. The lifetime prevalence of GAD is 5–6%; the risk is higher in first-degree relatives of patients with the diagnosis. Interestingly, family studies indicate that GAD and panic disorder segregate independently. More than 80% of patients with GAD also suffer from major depression, dysthymia, or social phobia. Comorbid substance abuse is common in these patients, particularly alcohol and/or sedative/hypnotic abuse. Patients with GAD worry excessively over minor matters, with life-disrupting effects; unlike in panic disorder, complaints of shortness of breath, palpitations, and tachycardia are relatively rare.

Etiology and pathophysiology

All anxiogenic agents act on the γ-aminobutyric acid $(GABA)_A$ receptor/chloride ion channel complex, implicating this neurotransmitter system in the pathogenesis of anxiety and panic attacks. Benzodiazepines are thought to bind two separate $GABA_A$ receptor sites: type I, which has a broad neuroanatomic distribution, and type II, which is concentrated in the hippocampus, striatum, and neocortex. The antianxiety effects of the various benzodiazepines are influenced by their relative binding to alpha 2 and 3 subunits of the $GABA_A$ receptor, and sedation and memory impairment to the alpha 1 subunit, Serotonin (5-hydroxytryptamine [5-HT]) and 3α-reduced neuroactive steroids (allosteric modulators of $GABA_A$) also appear to have a role in anxiety, and buspirone, a partial 5-HT_{1A} receptor agonist, and certain 5-HT_{2A} and 5-HT_{2C} receptor antagonists (e.g., nefazodone) may have beneficial effects.

TREATMENT Generalized Anxiety Disorder

A combination of pharmacologic and psychotherapeutic interventions is most effective in GAD, but complete symptomatic relief is rare. A short course of a benzodiazepine is

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-1

ANTIDEPRESSANTS

NAME	USUAL DAILY DOSE, mg	SIDE EFFECTS	COMMENTS
SSRIs			
Fluoxetine (Prozac)	10–80	Headache; nausea and other GI effects; jitteriness; insomnia; sexual dysfunction; can affect plasma levels of other medicines (except sertraline); akathisia rare	Once-daily dosing, usually in the morning; fluoxetine has very long half-life; must not be combined with MAOIs
Sertraline (Zoloft)	50–200		
Paroxetine (Paxil)	20–60		
Fluvoxamine (Luvox)	100–300		
Citalopram (Celexa)	20–60		
Escitalopram (Lexapro)	10–30		
TCAs			
Amitriptyline (Elavil)	150–300	Anticholinergic (dry mouth, tachycardia, constipation, urinary retention, blurred vision); sweating; tremor; postural hypotension; cardiac conduction delay; sedation; weight gain	Once-daily dosing, usually qhs; blood levels of most TCAs available; can be lethal in overdose (lethal dose = 2 g); nortriptyline best tolerated, especially by elderly
Nortriptyline (Pamelor)	50–200		
Imipramine (Tofranil)	150–300		
Desipramine (Norpramin)	150–300		
Doxepin (Sinequan)	150–300		
Clomipramine (Anafranil)	150–300		
Mixed Norepinephrine/Serotonin Reuptake Inhibitors (SNRI) and Receptor Blockers			
Venlafaxine (Effexor)	75–375	Nausea; dizziness; dry mouth; headaches; increased blood pressure; anxiety and insomnia	Bid-tid dosing (extended release available); lower potential for drug interactions than SSRIs; contraindicated with MAOIs
Desvenlafaxine (Pristiq)	50–400	Nausea, dizziness, insomnia	Primary metabolite of venlafaxine; no increased efficacy with higher dosing
Duloxetine (Cymbalta)	40–60	Nausea, dizziness, headache, insomnia, constipation	May have utility in treatment of neuropathic pain and stress incontinence
Mirtazapine (Remeron)	15–45	Somnolence, weight gain; neutropenia rare	Once a day dosing
Vilazodone (Viibryd)	40	Nausea, diarrhea, headache; dosage adjustment if given with CYP3A4 inhibitor/stimulator	Also 5-HT_{1a} receptor partial agonist
Vortioxetine (Brintellix)	5–20	Nausea, diarrhea, sweating, headache; low incidence of sedation or weight gain	No specific p450 effects; 5-HT_{3a} and 5-HT_7 receptor antagonist, 5-HT_{1b} partial agonist, and 5-HT_{1a} agonist
Levomilnacipran (Fetzima)	40–120	Nausea, constipation, sweating; rare increase in blood pressure/pulse	Most noradrenergic of SNRIs
Mixed-Action Drugs			
Bupropion (Wellbutrin)	250–450	Jitteriness; flushing; seizures in at-risk patients; anorexia; tachycardia; psychosis	Tid dosing, but sustained release also available; fewer sexual side effects than SSRIs or TCAs; may be useful for adult ADD
Trazodone (Desyrel)	200–600	Sedation; dry mouth; ventricular irritability; postural hypotension; priapism rare	Useful in low doses for sleep because of sedating effects with no anticholinergic side effects
Trazodone extended release (Oleptro)	150–375	Daytime somnolence, dizziness, nausea	
Amoxapine (Asendin)	200–600	Sexual dysfunction	Lethality in overdose; EPS possible
MAOIs			
Phenelzine (Nardil)	45–90	Insomnia; hypotension; edema; anorgasmia; weight gain; neuropathy; hypertensive crisis; toxic reactions with SSRIs; narcotics	May be more effective in patients with atypical features or treatment-refractory depression
Tranylcypromine (Parnate)	20–50		
Isocarboxazid (Marplan)	20–60		Less weight gain and hypotension than phenelzine
Transdermal selegiline (Emsam)	6–12	Local skin reaction hypertension	No dietary restrictions with 6 mg dose

Abbreviations: ADD, attention deficit disorder; EPS, extrapyramidal symptoms; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; MAOIs, monoamine oxidase inhibitors; OCD, obsessive-compulsive disorder; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-2

MANAGEMENT OF ANTIDEPRESSANT SIDE EFFECTS

SYMPTOMS	COMMENTS AND MANAGEMENT STRATEGIES
Gastrointestinal	
Nausea, loss of appetite	Usually short-lived and dose-related; consider temporary dose reduction or administration with food and antacids
Diarrhea	Famotidine, 20–40 mg/d
Constipation	Wait for tolerance; try diet change, stool softener, exercise; avoid laxatives
Sexual dysfunction	Consider dose reduction; drug holiday
Anorgasmia/impotence; impaired ejaculation	Bethanechol, 10–20 mg, 2 h before activity, or cyproheptadine, 4–8 mg 2 h before activity, or bupropion, 100 mg bid, or amantadine, 100 mg bid/tid
Orthostasis	Tolerance unlikely; increase fluid intake, use calf exercises/support hose; fludrocortisone, 0.025 mg/d
Anticholinergic	Wait for tolerance
Dry mouth, eyes	Maintain good oral hygiene; use artificial tears, sugar-free gum
Tremor/jitteriness	Antiparkinsonian drugs not effective; use dose reduction/slow increase; lorazepam, 0.5 mg bid, or propranolol, 10–20 mg bid
Insomnia	Schedule all doses for the morning; trazodone, 50–100 mg qhs
Sedation	Caffeine; schedule all dosing for bedtime; bupropion, 75–100 mg in afternoon
Headache	Evaluate diet, stress, other drugs; try dose reduction; amitriptyline, 50 mg/d
Weight gain	Decrease carbohydrates; exercise; consider fluoxetine
Loss of therapeutic benefit over time	Related to tolerance? Increase dose or drug holiday; add amantadine, 100 mg bid, buspirone, 10 mg tid, or pindolol, 2.5 mg bid

TABLE 61-3

POSSIBLE DRUG INTERACTIONS WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS

AGENT	EFFECT
Monoamine oxidase inhibitors	Serotonin syndrome—absolute contraindication
Serotonergic agonists, e.g., tryptophan, fenfluramine, tryptans	Potential serotonin syndrome
Drugs that are metabolized by P450 isoenzymes: tricyclics, other SSRIs, antipsychotics, beta blockers, codeine, triazolobenzodiazepines, calcium channel blockers	Delayed metabolism resulting in increased blood levels and potential toxicity
Drugs that are bound tightly to plasma proteins, e.g., warfarin	Increased bleeding secondary to displacement
Drugs that inhibit the metabolism of SSRIs by P450 isoenzymes, e.g., quinidine	Increased SSRI side effects

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.

usually indicated, preferably lorazepam, oxazepam, or alprazolam. (The first two of these agents are metabolized via conjugation rather than oxidation and thus do not accumulate if hepatic function is impaired; the latter also has limited active metabolites.) Treatment should be initiated at the lowest dose possible and prescribed on an as-needed basis as symptoms warrant. Benzodiazepines differ in their milligram per kilogram potency, half-life, lipid solubility, metabolic pathways, and presence of active metabolites. Agents that are absorbed rapidly and are lipid soluble, such as diazepam, have a rapid onset of action and a higher abuse potential. Benzodiazepines should generally not be prescribed for >4–6 weeks because of the development of tolerance and the risk of abuse and dependence. Withdrawal must be closely monitored as relapses can occur. It is important to warn patients that concomitant use of alcohol or other sedating drugs may exacerbate side effects and impair their ability to function. An optimistic approach that encourages the patient to clarify environmental precipitants, anticipate his or her reactions, and plan effective response strategies is an essential element of therapy.

Adverse effects of benzodiazepines generally parallel their relative half-lives. Longer-acting agents, such as diazepam, chlordiazepoxide, flurazepam, and clonazepam, tend to accumulate active metabolites, with resultant sedation, impairment of cognition, and poor psychomotor performance. Shorter-acting compounds, such as alprazolam, lorazepam, and oxazepam, can produce daytime anxiety, early morning insomnia, and, with discontinuation, rebound anxiety and insomnia. Although patients develop tolerance to the sedative effects of benzodiazepines, they are less likely to habituate to the adverse psychomotor effects. Withdrawal from the longer half-life benzodiazepines can be accomplished through gradual, stepwise dose reduction (by 10% every 1–2 weeks) over 6–12 weeks. It is usually more difficult to taper patients off shorter-acting benzodiazepines. Physicians may need to switch the patient to a benzodiazepine with a longer half-life or use an adjunctive medication such as a beta blocker or carbamazepine, before attempting to discontinue the benzodiazepine. Withdrawal reactions vary in severity and duration; they can include depression, anxiety, lethargy, diaphoresis, autonomic arousal, and, rarely, seizures.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-4

ANXIOLYTICS

NAME	EQUIVALENT PO DOSE, mg	ONSET OF ACTION	HALF-LIFE, H	COMMENTS
Benzodiazepines				
Diazepam (Valium)	5	Fast	20–70	Active metabolites; quite sedating
Flurazepam (Dalmane)	15	Fast	30–100	Flurazepam is a prodrug; metabolites are active; quite sedating
Triazolam (Halcion)	0.25	Intermediate	1.5–5	No active metabolites; can induce confusion and delirium, especially in elderly
Lorazepam (Ativan)	1	Intermediate	10–20	No active metabolites; direct hepatic glucuronide conjugation; quite sedating; FDA approved for anxiety with depression
Alprazolam (Xanax)	0.5	Intermediate	12–15	Active metabolites; not too sedating; FDA approved for panic disorder and anxiety with depression; tolerance and dependence develop easily; difficult to withdraw
Chlordiazepoxide (Librium)	10	Intermediate	5–30	Active metabolites; moderately sedating
Oxazepam (Serax)	15	Slow	5–15	No active metabolites; direct glucuronide conjugation; not too sedating
Temazepam (Restoril)	15	Slow	9–12	No active metabolites; moderately sedating
Clonazepam (Klonopin)	0.5	Slow	18–50	No active metabolites; moderately sedating; FDA approved for panic disorder
Clorazepate (Tranxene)	15	Fast	40–200	Low sedation; unreliable absorption
Nonbenzodiazepines				
Buspirone (BuSpar)	7.5	2 weeks	2–3	Active metabolites; tid dosing—usual daily dose 10–20 mg tid; nonsedating; no additive effects with alcohol; useful for controlling agitation in demented or brain-injured patients

Abbreviation: FDA, U.S. Food and Drug Administration.

Buspirone is a nonbenzodiazepine anxiolytic agent. It is nonsedating, does not produce tolerance or dependence, does not interact with benzodiazepine receptors or alcohol, and has no abuse or disinhibition potential. However, it requires several weeks to take effect and requires thrice-daily dosing. Patients who were previously responsive to a benzodiazepine are unlikely to rate buspirone as equally effective, but patients with head injury or dementia who have symptoms of anxiety and/or agitation may do well with this agent. Escitalopram, paroxetine, and venlafaxine are FDA approved for the treatment of GAD, usually at doses that are comparable to their efficacy in major depression, and may be preferable to usage of benzodiazepines in the treatment of chronic anxiety. Benzodiazepines are contraindicated during pregnancy and breast-feeding.

Anticonvulsants with GABAergic properties may also be effective against anxiety. Gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex have all shown some degree of benefit in a variety of anxiety-related syndromes in off-label usage. Agents that selectively target $GABA_A$ receptor subtypes are currently under development, and it is hoped that these will lack the sedating, memory-impairing, and addicting properties of benzodiazepines.

PHOBIC DISORDERS

Clinical manifestations

The cardinal feature of phobic disorders is a marked and persistent fear of objects or situations, exposure to which results in an immediate anxiety reaction. The patient avoids the phobic stimulus, and this avoidance usually impairs occupational or social functioning. Panic attacks may be triggered by the phobic stimulus or may occur spontaneously. Unlike patients with other anxiety disorders, individuals with phobias usually experience anxiety only in specific situations. Common phobias include fear of closed spaces (claustrophobia), fear of blood, and fear of flying. Social phobia is distinguished by a specific fear of social or performance situations in which the individual is exposed to unfamiliar individuals or to possible examination and evaluation by others. Examples include having to converse at a party, use public restrooms, and meet strangers. In each case, the affected individual is aware that the experienced fear is excessive and unreasonable given the circumstance. The specific content of a phobia may vary across gender, ethnic, and cultural boundaries.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-5

DIAGNOSTIC CRITERIA FOR GENERALIZED ANXIETY DISORDER

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months): (1) restlessness or feeling keyed up or on edge; (2) being easily fatigued; (3) difficulty concentrating or mind going blank; (4) irritability; (5) muscle tension; (6) sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, American Psychiatric Association, 2013.

Phobic disorders are common, affecting ~7–9% of the population. Twice as many females are affected than males. Full criteria for diagnosis are usually satisfied first in early adulthood, but behavioral avoidance of unfamiliar people, situations, or objects dating from early childhood is common.

In one study of female twins, concordance rates for agoraphobia, social phobia, and animal phobia were found to be 23% for monozygotic twins and 15% for dizygotic twins. A twin study of fear conditioning, a model for the acquisition of phobias, demonstrated a heritability of 35–45%. Animal studies of fear conditioning have indicated that processing of the fear stimulus occurs through the lateral nucleus of the amygdala, extending through the central nucleus and projecting to the periaqueductal gray region, lateral hypothalamus, and paraventricular hypothalamus.

TREATMENT Phobic Disorders

Beta blockers (e.g., propranolol, 20–40 mg orally 2 h before the event) are particularly effective in the treatment of "performance anxiety" (but not general social phobia) and appear to work by blocking the peripheral manifestations of anxiety such as perspiration, tachycardia, palpitations, and tremor. MAOIs alleviate social phobia independently of their antidepressant activity, and paroxetine, sertraline, and venlafaxine have received FDA approval for treatment of social anxiety. Benzodiazepines can be helpful in reducing fearful avoidance, but the chronic nature of phobic disorders limits their usefulness.

Behaviorally focused psychotherapy is an important component of treatment because relapse rates are high when medication is used as the sole treatment. Cognitive-behavioral strategies are based on the finding that distorted perceptions and interpretations of fear-producing stimuli play a major role in perpetuation of phobias. Individual and group therapy sessions teach the patient to identify specific negative thoughts associated with the anxiety-producing situation and help to reduce the patient's fear of loss of control. In desensitization therapy, hierarchies of feared situations are constructed, and the patient is encouraged to pursue and master gradual exposure to the anxiety-producing stimuli.

Patients with social phobia, in particular, have a high rate of comorbid alcohol abuse, as well as of other psychiatric conditions (e.g., eating disorders), necessitating the need for parallel management of each disorder if anxiety reduction is to be achieved.

STRESS DISORDERS

Clinical manifestations

Patients may develop anxiety after exposure to extreme traumatic events such as the threat of personal death or injury or the death of a loved one. The reaction may occur shortly after the trauma (acute stress disorder) or be delayed and subject to recurrence (PTSD) **(Table 61-6)**. In both syndromes, individuals experience associated symptoms of detachment and loss of emotional responsivity. The patient may feel depersonalized and unable to recall specific aspects of the trauma, although typically it is reexperienced through intrusions in thought, dreams, or flashbacks, particularly when cues of the original event are present. Patients often actively avoid stimuli that precipitate recollections of the trauma and demonstrate a resulting increase in vigilance, arousal, and startle response. Patients with stress disorders are at risk for the development of other disorders related to anxiety, mood,

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-6

DIAGNOSTIC CRITERIA FOR POSTTRAUMATIC STRESS DISORDER

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred as evidenced by two (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.
   6. Feelings of detachment or estrangement from others.
   7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
   2. Reckless or self-destructive behavior.
   3. Hypervigilance.
   4. Exaggerated startle response.
   5. Problems with concentration.
   6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).
F. Duration of the disturbance (criteria B, C, D, and E) is more than 1 month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, American Psychiatric Association, 2013.

and substance abuse (especially alcohol). Between 5 and 10% of Americans will at some time in their life satisfy criteria for PTSD, with women more likely to be affected than men.

Risk factors for the development of PTSD include a past psychiatric history and personality characteristics of high neuroticism and extroversion. Twin studies show a substantial genetic influence on all symptoms associated with PTSD, with less evidence for an environmental effect.

Etiology and pathophysiology

It is hypothesized that in PTSD there is excessive release of norepinephrine from the locus coeruleus in response to stress and increased noradrenergic activity at projection sites in the hippocampus and amygdala. These changes theoretically facilitate the encoding of fear-based memories. Greater sympathetic responses to cues associated with the traumatic event occur in PTSD, although pituitary adrenal responses are blunted.

www.ketabpezeshki.com (021) 66485457 - 66485438

TREATMENT Stress Disorders

Acute stress reactions are usually self-limited, and treatment typically involves the short-term use of benzodiazepines and supportive/expressive psychotherapy. The chronic and recurrent nature of PTSD, however, requires a more complex approach using drug and behavioral treatments. PTSD is highly correlated with peritraumatic dissociative symptoms and the development of an acute stress disorder at the time of the trauma. The SSRIs (paroxetine and sertraline are FDA approved for PTSD), venlafaxine, and topiramate can all reduce anxiety, symptoms of intrusion, and avoidance behaviors, as can prazosin, an α_1 antagonist. Propranolol and opiates such as morphine, given during the acute stress period, may have beneficial effects in preventing the development of PTSD, and adjunctive naltrexone can be effective when comorbid alcoholism is present. Trazodone, a sedating antidepressant, is frequently used at night to help with insomnia (50–150 mg qhs). Carbamazepine, valproic acid, and alprazolam have also independently produced improvement in uncontrolled trials. Psychotherapeutic strategies for PTSD help the patient overcome avoidance behaviors and demoralization and master fear of recurrence of the trauma; therapies that encourage the patient to dismantle avoidance behaviors through stepwise focusing on the experience of the traumatic event, such as trauma-focused cognitive-behavioral therapy, exposure therapy, and eye movement desensitization and reprocessing, are the most effective.

OBSESSIVE-COMPULSIVE DISORDER

Clinical manifestations

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors that impair everyday functioning. Fears of contamination and germs are common, as are handwashing, counting behaviors, and having to check and recheck such actions as whether a door is locked. The degree to which the disorder is disruptive for the individual varies, but in all cases, obsessive-compulsive activities take up >1 h per day and are undertaken to relieve the anxiety triggered by the core fear. Patients often conceal their symptoms, usually because they are embarrassed by the content of their thoughts or the nature of their actions. Physicians must ask specific questions regarding recurrent thoughts and behaviors, particularly if physical clues such as chafed and reddened hands or patchy hair loss (from repetitive hair pulling, or trichotillomania) are present. Comorbid conditions are common, the most frequent being depression, other anxiety disorders, eating disorders, and tics. OCD has a lifetime prevalence of 2–3% worldwide. Onset is usually gradual, beginning in early adulthood, but childhood onset is not rare. The disorder usually has a waxing and waning course, but some cases may show a steady deterioration in psychosocial functioning.

Etiology and pathophysiology

A genetic contribution to OCD is suggested by twin studies, but no susceptibility gene for OCD has been identified to date. Family studies show an aggregation of OCD with Tourette's disorder, and both are more common in males and in first-born children.

The anatomy of obsessive-compulsive behavior is thought to include the orbital frontal cortex, caudate nucleus, and globus pallidus. The caudate nucleus appears to be involved in the acquisition and maintenance of habit and skill learning, and interventions that are successful in reducing obsessive-compulsive behaviors also decrease metabolic activity measured in the caudate.

TREATMENT Obsessive-Compulsive Disorder

Clomipramine, fluoxetine, fluvoxamine, and sertraline are approved for the treatment of OCD in adults (fluvoxamine is also approved for children). Clomipramine is a TCA that is often tolerated poorly owing to anticholinergic and sedative side effects at the doses required to treat the illness (25–250 mg/d); its efficacy in OCD is unrelated to its antidepressant activity. Fluoxetine (5–60 mg/d), fluvoxamine (25–300 mg/d), and sertraline (50–150 mg/d) are as effective as clomipramine and have a more benign side effect profile. Only 50–60% of patients with OCD show adequate improvement with pharmacotherapy alone. In treatment-resistant cases, augmentation with other serotonergic agents such as buspirone, or with a neuroleptic or benzodiazepine, may be beneficial, and in severe cases, deep brain stimulation has been found to be effective. When a therapeutic response is achieved, long-duration maintenance therapy is usually indicated.

For many individuals, particularly those with time-consuming compulsions, behavior therapy will result in as much improvement as that afforded by medication. Effective techniques include the gradual increase in exposure to stressful situations, maintenance of a diary to clarify stressors, and homework assignments that substitute new activities for compulsive behaviors.

MOOD DISORDERS

Mood disorders are characterized by a disturbance in the regulation of mood, behavior, and affect. Mood disorders are subdivided into (1) depressive disorders, (2) bipolar disorders, and (3) depression in association with medical illness or alcohol and substance

www.ketabpezeshki.com (021) 66485457 - 66485438

abuse **(Chaps. 63, 64, 65, 66, and 62).** Major depressive disorder (MDD) is differentiated from bipolar disorder by the absence of a manic or hypomanic episode. T e relationship between pure depressive syndromes and bipolar disorders is not well understood; MDD is more frequent in families of bipolar individuals, but the reverse is not true. In the Global Burden of Disease Study conducted by the World Health Organization, unipolar major depression ranked fourth among all diseases in terms of disability-adjusted life-years and was projected to rank second by the year 2020. In the United States, lost productivity directly related to mood disorders has been estimated at $55.1 billion per year.

DEPRESSION IN ASSOCIATION WITH MEDICAL ILLNESS

Depression occurring in the context of medical illness is dif cult to evaluate. Depressive symptomatology may reflect the psychological stress of coping with the disease, may be caused by the disease process itself or by the medications used to treat it, or may simply coexist in time with the medical diagnosis.

Virtually every class of medication includes some agent that can induce depression. Antihypertensive drugs, anticholesterolemic agents, and antiarrhythmic agents are common triggers of depressive symptoms. Iatrogenic depression should also be considered in patients receiving glucocorticoids, antimicrobials, systemic analgesics, antiparkinsonian medications, and anticonvulsants. To decide whether a causal relationship exists between pharmacologic therapy and a patient's change in mood, it may sometimes be necessary to undertake an empirical trial of an alternative medication.

Between 20 and 30% of cardiac patients manifest a depressive disorder; an even higher percentage experience depressive symptomatology when self-reporting scales are used. Depressive symptoms following unstable angina, myocardial infarction, cardiac bypass surgery, or heart transplant impair rehabilitation and are associated with higher rates of mortality and medical morbidity. Depressed patients often show decreased variability in heart rate (an index of reduced parasympathetic nervous system activity), which may predispose individuals to ventricular arrhythmia and increased morbidity. Depression also appears to increase the risk of developing coronary heart disease, possibly through increased platelet aggregation. TCAs are contraindicated in patients with bundle branch block, and TCA-induced tachycardia is an additional concern in patients with congestive heart failure. SSRIs appear not to induce ECG changes or adverse cardiac events and thus are reasonable first-line drugs for patients at risk for TCA-related complications. SSRIs may interfere with hepatic metabolism of anticoagulants, however, causing increased anticoagulation.

In patients with cancer, the mean prevalence of depression is 25%, but depression occurs in 40–50% of patients with cancers of the pancreas or oropharynx. T is association is not due to the effect of cachexia alone, as the higher prevalence of depression in patients with pancreatic cancer persists when compared to those with advanced gastric cancer. Initiation of antidepressant medication in cancer patients has been shown to improve quality of life as well as mood. Psychotherapeutic approaches, particularly group therapy, may have some effect on short-term depression, anxiety, and pain symptoms.

Depression occurs frequently in patients with neurologic disorders, particularly cerebrovascular disorders, Parkinson's disease, dementia, multiple sclerosis, and traumatic brain injury. One in five patients with left-hemisphere stroke involving the dorsolateral frontal cortex experiences major depression. Late-onset depression in otherwise cognitively normal individuals increases the risk of a subsequent diagnosis of Alzheimer's disease. All classes of antidepressant agents are effective against these depressions, as are, in some cases, stimulant compounds.

T e reported prevalence of depression in patients with diabetes mellitus varies from 8 to 27%, with the severity of the mood state correlating with the level of hyperglycemia and the presence of diabetic complications. Treatment of depression may be complicated by effects of antidepressive agents on glycemic control. MAOIs can induce hypoglycemia and weight gain, whereas TCAs can produce hyperglycemia and carbohydrate craving. SSRIs and SNRIs, like MAOIs, may reduce fasting plasma glucose, but they are easier to use and may also improve dietary and medication compliance.

Hypothyroidism is frequently associated with features of depression, most commonly depressed mood and memory impairment. Hyperthyroid states may also present in a similar fashion, usually in geriatric populations. Improvement in mood usually follows normalization of thyroid function, but adjunctive antidepressant medication is sometimes required. Patients with subclinical hypothyroidism can also experience symptoms of depression and cognitive dif culty that respond to thyroid replacement.

T e lifetime prevalence of depression in HIV-positive individuals has been estimated at 22–45%. T e relationship between depression and disease progression is multifactorial and likely to involve psychological and social factors, alterations in immune function, and central nervous system (CNS) disease. Chronic hepatitis C infection is also associated with depression, which may worsen with interferon-α treatment.

www.ketabpezeshki.com (021) 66485457 - 66485438

Some chronic disorders of uncertain etiology, such as chronic fatigue syndrome **(Chap. 59)** and fibromyalgia, are strongly associated with depression and anxiety; patients may benefit from antidepressant treatment or anticonvulsant agents such as pregabalin.

DEPRESSIVE DISORDERS

Clinical manifestations

Major depression is defined as depressed mood on a daily basis for a minimum duration of 2 weeks **(Table 61-7)**. An episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired concentration and decision making; feelings of shame or guilt; and thoughts of death or dying. Patients with depression have a profound loss of pleasure in all enjoyable activities, exhibit early morning awakening, feel that the dysphoric mood state is qualitatively different from sadness, and often notice a diurnal variation in mood (worse in morning hours). Patients experiencing bereavement or grief may exhibit many of the same signs and symptoms of major depression, although the emphasis is usually on feelings of emptiness and loss, rather than anhedonia and loss of self-esteem, and the duration is usually limited. In certain cases, however, the diagnosis of major depression may be warranted even in the context of a significant loss.

TABLE 61-7

CRITERIA FOR A MAJOR DEPRESSIVE EPISODE

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition.
   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. The episode is not attributable to the physiologic effects of a substance or to another medical condition.
D. The occurrence of the major depressive episode is not better explained by seasonal affective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, American Psychiatric Association, 2013.

Approximately 15% of the population experiences a major depressive episode at some point in life, and 6–8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder. Depression is often undiagnosed, and even more frequently, it is treated inadequately. If a physician suspects the presence of a major depressive episode, the initial task is to determine whether it represents unipolar or bipolar depression or is one of the 10–15% of cases that are secondary to general medical illness or substance abuse. Physicians should also assess the risk of suicide by direct questioning, as patients are often reluctant to verbalize such thoughts without prompting. If specific plans are uncovered or if significant risk factors exist (e.g., a past history of suicide attempts, profound hopelessness, concurrent medical illness, substance abuse, or social isolation), the patient must be referred to a mental health specialist for immediate care. The physician should specifically probe each of these areas in an empathic and hopeful manner, being sensitive to denial and possible minimization of distress. The presence of anxiety, panic, or agitation significantly increases near-term suicidal risk. Approximately 4–5% of all depressed patients will commit suicide; most will have sought help from physicians within 1 month of their deaths.

In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual's usual experience in life. Persistent depressive disorder (dysthymic disorder) consists of a pattern of chronic (at least 2 years), ongoing depressive symptoms that are usually less severe and/or less numerous than those found in major depression, but the functional consequences may be equivalent to or even greater; the two conditions are sometimes difficult to separate and can occur together ("double depression"). Many patients who exhibit a profile of pessimism, disinterest, and low self-esteem respond

www.ketabpezeshki.com (021) 66485457 - 66485438

to antidepressant treatment. Persistent and chronic depressive disorders occur in approximately 2% of the general population.

Depression is approximately twice as common in women as in men, and the incidence increases with age in both sexes. Twin studies indicate that the liability to major depression of early onset (before age 25) is largely genetic in origin. Negative life events can precipitate and contribute to depression, but genetic factors influence the sensitivity of individuals to these stressful events. In most cases, both biologic and psychosocial factors are involved in the precipitation and unfolding of depressive episodes. T e most potent stressors appear to involve death of a relative, assault, or severe marital or relationship problems.

Unipolar depressive disorders usually begin in early adulthood and recur episodically over the course of a lifetime. T e best predictor of future risk is the number of past episodes; 50–60% of patients who have a first episode have at least one or two recurrences. Some patients experience multiple episodes that become more severe and frequent over time. T e duration of an untreated episode varies greatly, ranging from a few months to ≥1 year. T e pattern of recurrence and clinical progression in a developing episode are also variable. Within an individual, the nature of episodes (e.g., specific presenting symptoms, frequency and duration) may be similar over time. In a minority of patients, a severe depressive episode may progress to a psychotic state; in elderly patients, depressive symptoms may be associated with cognitive deficits mimicking dementia ("pseudodementia"). A seasonal pattern of depression, called seasonal af ective disorder, may manifest with onset and remission of episodes at predictable times of the year. T is disorder is more common in women, whose symptoms are anergy, fatigue, weight gain, hypersomnia, and episodic carbohydrate craving. T e prevalence increases with distance from the equator, and improvement may occur by altering light exposure.

Etiology and pathophysiology

Although evidence for genetic transmission of unipolar depression is not as strong as in bipolar disorder, monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%), with little support for any effect of a shared family environment.

Neuroendocrine abnormalities that reflect the neurovegetative signs and symptoms of depression include: (1) increased cortisol and corticotropin-releasing hormone (CRH) secretion, (2) an increase in adrenal size, (3) a decreased inhibitory response of glucocorticoids to dexamethasone, and (4) a blunted response of thyroid-stimulating hormone (TSH) level to infusion of thyroid-releasing hormone (TRH). Antidepressant treatment leads to normalization of these abnormalities. Major depression is also associated with changes in levels of proinflammatory cytokines and neurotrophins.

Diurnal variations in symptom severity and alterations in circadian rhythmicity of a number of neurochemical and neurohumoral factors suggest that biologic differences may be secondary to a primary defect in regulation of biologic rhythms. Patients with major depression show consistent findings of a decrease in rapid eye movement (REM) sleep onset (REM latency), an increase in REM density, and, in some subjects, a decrease in stage IV delta slow-wave sleep.

Although antidepressant drugs inhibit neurotransmitter uptake within hours, their therapeutic effects typically emerge over several weeks, implicating adaptive changes in second messenger systems and transcription factors as possible mechanisms of action.

T e pathogenesis of depression is discussed in detail in Chap. 60.

TREATMENT Depressive Disorders

Treatment planning requires coordination of short-term strategies to induce remission combined with longer term maintenance designed to prevent recurrence. T e most effective intervention for achieving remission and preventing relapse is medication, but combined treatment, incorporating psychotherapy to help the patient cope with decreased self-esteem and demoralization, improves outcome **(Fig. 61-1)**. Approximately 40% of primary care patients with depression drop out of treatment and discontinue medication if symptomatic improvement is not noted within a month, unless additional support is provided. Outcome improves with (1) increased intensity and frequency of visits during the first 4–6 weeks of treatment, (2) supplemental educational materials, and (3) psychiatric consultation as indicated. Despite the widespread use of SSRIs and other second-generation antidepressant drugs, there is no convincing evidence that these classes of antidepressants are more ef cacious than TCAs. Between 60 and 70% of all depressed patients respond to any drug chosen, if it is given in a suf cient dose for 6–8 weeks.

A rational approach to selecting which antidepressant to use involves matching the patient's preference and medical history with the metabolic and side effect profile of the drug (Tables 61-4 and 61-5). A previous response, or a family history of a positive response, to a specific antidepressant often suggests that that drug be tried first. Before initiating antidepressant therapy, the physician should evaluate the possible contribution of comorbid illnesses and consider their specific treatment. In individuals with suicidal ideation, particular attention should be paid to choosing a drug with low toxicity if taken in overdose. Newer antidepressant drugs are distinctly safer in this regard; nevertheless, the advantages of TCAs have

www.ketabpezeshki.com (021) 66485457 - 66485438

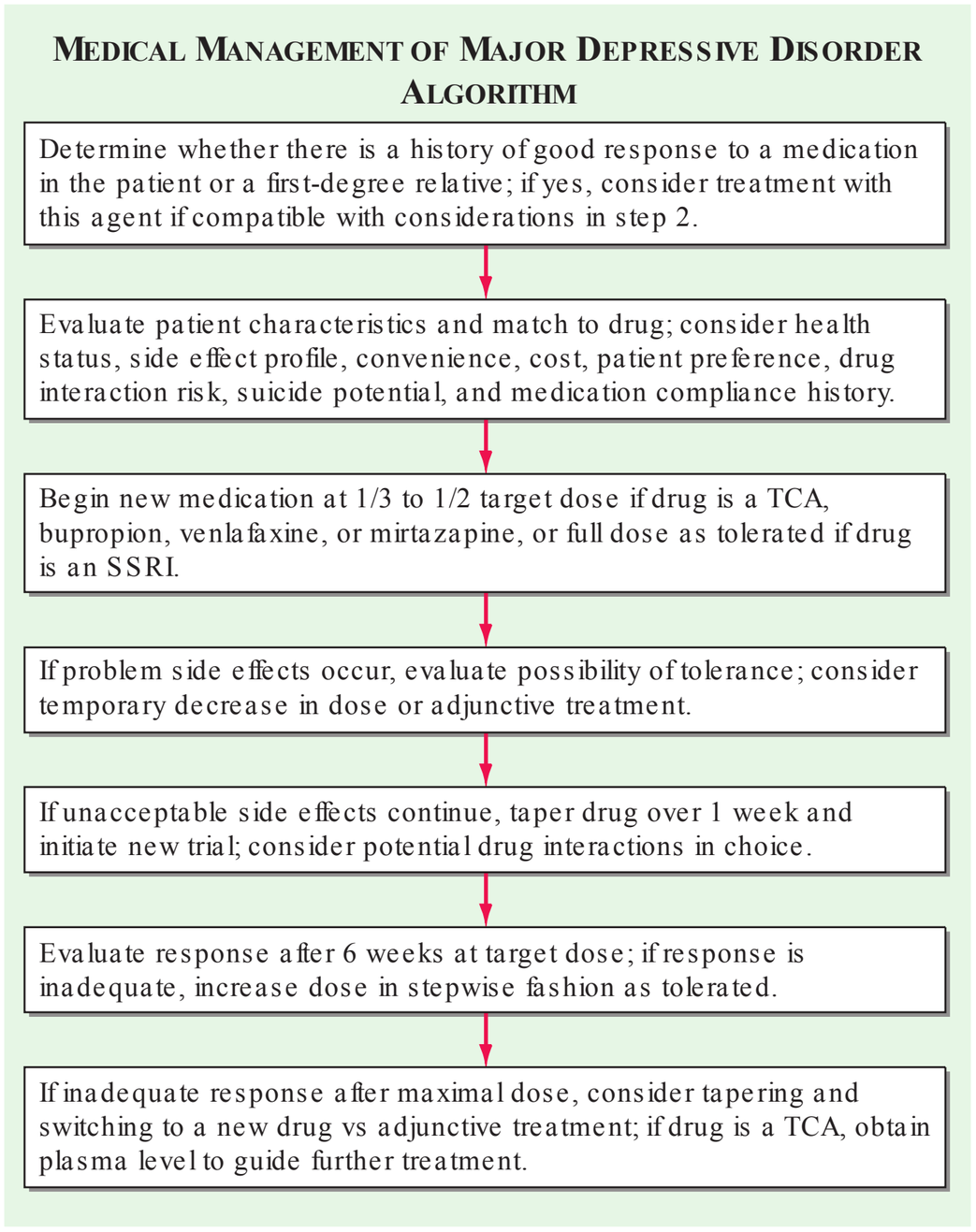


FIGURE 61-1
A guideline for the medical management of major depressive disorder. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

not been completely superseded. The existence of generic equivalents makes TCAs relatively cheap, and for secondary tricyclics, particularly nortriptyline and desipramine, well-defined relationships among dose, plasma level, and therapeutic response exist. The steady-state plasma level achieved for a given drug dose can vary more than 10-fold between individuals, and plasma levels may help in interpreting apparent resistance to treatment and/or unexpected drug toxicity. The principal side effects of TCAs are antihistamine (sedation) and anticholinergic (constipation, dry mouth, urinary hesitancy, blurred vision). TCAs are contraindicated in patients with serious cardiovascular risk factors, and overdoses of tricyclic agents can be lethal, with desipramine carrying the greatest risk. It is judicious to prescribe only a 10-day supply when suicide is a risk. Most patients require a daily dose of 150–200 mg of imipramine or amitriptyline or its equivalent to achieve a therapeutic blood level of 150–300 ng/mL and a satisfactory remission; some patients show a partial effect at lower doses. Geriatric patients may require a low starting dose and slow escalation. Ethnic differences in drug metabolism are significant, with Hispanic, Asian, and black patients generally requiring lower doses than whites to achieve a comparable blood level. P450 profiling using genetic chip technology may be clinically useful in predicting individual sensitivity.

Second-generation antidepressants are similar to tricyclics in their effect on neurotransmitter reuptake, although some also have specific actions on catecholamine and indolamine receptors as well. Amoxapine is a dibenzoxazepine derivative that blocks norepinephrine and serotonin reuptake and has a metabolite that shows a degree of dopamine blockade. Long-term use of this drug carries a risk of tardive dyskinesia. Maprotiline is a potent noradrenergic reuptake blocker that has little anticholinergic effect but may produce seizures. Bupropion is a novel antidepressant whose mechanism of action is thought to involve enhancement of noradrenergic function. It has no anticholinergic, sedating, or orthostatic side effects and has a low incidence of sexual side effects. It may, however, be associated with stimulant-like side effects, may lower seizure threshold, and has an exceptionally short half-life, requiring frequent dosing. An extended-release preparation is available.

SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram cause a lower frequency of anticholinergic, sedating, and cardiovascular side effects but a possibly greater incidence of gastrointestinal complaints, sleep impairment, and sexual dysfunction than do TCAs. Akathisia, involving an inner sense of restlessness and anxiety in addition to increased motor activity, may also be more common, particularly during the first week of treatment. One concern is the risk of "serotonin syndrome," which is thought to result from hyperstimulation of brainstem 5-HT_{1A} receptors and characterized by myoclonus, agitation, abdominal cramping, hyperpyrexia, hypertension, and potentially death. Serotonergic agonists taken in combination should be monitored closely for this reason. Considerations such as half-life, compliance, toxicity, and drug-drug interactions may guide the choice of a particular SSRI. Fluoxetine and its principal active metabolite, norfluoxetine, for example, have a combined half-life of almost 7 days, resulting in a delay of 5 weeks before steady-state levels are achieved and a similar delay for complete drug excretion once its use is discontinued. All the SSRIs may impair sexual function, resulting in diminished libido, impotence, or difficulty in achieving orgasm. Sexual dysfunction frequently results in noncompliance and should be asked about specifically. Sexual dysfunction can sometimes be ameliorated by lowering the dose, by instituting weekend drug holidays (two or three times a month), or by treatment with amantadine (100 mg tid), bethanechol (25 mg tid), buspirone (10 mg tid), or bupropion (100–150 mg/d). Paroxetine appears to be more anticholinergic than either fluoxetine or sertraline, and sertraline carries a lower risk of producing an adverse drug interaction than the other two. Rare side effects of SSRIs include angina due to vasospasm and prolongation of the prothrombin time. Escitalopram is the most specific of currently available SSRIs and appears to have no specific inhibitory effects on the P450 system.

Venlafaxine, desvenlafaxine, duloxetine, vilazodone, vortioxetine, and levomilnacipran block the reuptake of both norepinephrine and serotonin but produce relatively little in

www.ketabpezeshki.com (021) 66485457 - 66485438

the way of traditional tricyclic side effects. Unlike the SSRIs, venlafaxine and vortioxetine have relatively linear dose-response curves. Patients on immediate release venlafaxine should be monitored for a possible increase in diastolic blood pressure, and multiple daily dosing is required because of the drug's short half-life. An extended-release form is available and has a somewhat lower incidence of gastrointestinal side effects. Mirtazapine is a TCA that has a unique spectrum of activity. It increases noradrenergic and serotonergic neurotransmission through a blockade of central α_2-adrenergic receptors and postsynaptic 5-HT_2 and 5-HT_3 receptors. It is also strongly antihistaminic and, as such, may produce sedation. Levomilnacipran is the most noradrenergic of the SNRIs and theoretically may be appropriate for patients with more severe fatigue and anergia.

With the exception of citalopram and escitalopram, each of the SSRIs may inhibit one or more cytochrome P450 enzymes. Depending on the specific isoenzyme involved, the metabolism of a number of concomitantly administered medications can be dramatically affected. Fluoxetine and paroxetine, for example, by inhibiting 2D6, can cause dramatic increases in the blood level of type 1C antiarrhythmics, whereas sertraline, by acting on 3A4, may alter blood levels of carbamazepine or digoxin. Depending on drug specificity for a particular CYP enzyme for its own metabolism, concomitant medications or dietary factors, such as grapefruit juice, may in turn affect the ef cacy or toxicity of the SSRI.

T e MAOIs are highly effective, particularly in atypical depression, but the risk of hypertensive crisis following intake of tyramine-containing food or sympathomimetic drugs makes them inappropriate as first-line agents. Transdermal selegiline may avert this risk at low dose. Common side effects include orthostatic hypotension, weight gain, insomnia, and sexual dysfunction. MAOIs should not be used concomitantly with SSRIs, because of the risk of serotonin syndrome, or with TCAs, because of possible hyperadrenergic effects.

Electroconvulsive therapy is at least as effective as medication, but its use is reserved for treatment-resistant cases and delusional depressions. Transcranial magnetic stimulation (TMS) is approved for treatment-resistant depression and has been shown to have ef cacy in several controlled trials. Vagus nerve stimulation (VNS) has also recently been approved for treatment-resistant depression, but its degree of ef cacy is controversial. Deep brain stimulation and ketamine, a glutamatergic antagonist, are experimental approaches for treatment-resistant cases.

Regardless of the treatment undertaken, the response should be evaluated after ~2 months. T ree-quarters of patients show improvement by this time, but if remission is inadequate, the patient should be questioned about compliance, and an increase in medication dose should be considered if side effects are not troublesome. If this approach is unsuccessful, referral to a mental health specialist is advised. Strategies for treatment then include selection of an alternative drug, combinations of antidepressants, and/or adjunctive treatment with other classes of drugs, including lithium, thyroid hormone, atypical antipsychotic agents, and dopamine agonists. A large randomized trial (STAR-D) was unable to show preferential ef cacy, but the addition of certain atypical antipsychotic drugs (quetiapine extended-release; aripiprazole) has received FDA approval, as has usage of a combined medication, olanzapine and fluoxetine (Symbyax). Patients whose response to an SSRI wanes over time may benefit from the addition of buspirone (10 mg tid) or pindolol (2–5 mg tid) or small amounts of a TCA such as desipramine (25 mg bid or tid). Most patients will show some degree of response, but aggressive treatment should be pursued until remission is achieved, and drug treatment should be continued for at least 6–9 more months to prevent relapse. In patients who have had two or more episodes of depression, indefinite maintenance treatment should be considered.

It is essential to educate patients both about depression and the benefits and side effects of medications they are receiving. Advice about stress reduction and cautions that alcohol may exacerbate depressive symptoms and impair drug response are helpful. Patients should be given time to describe their experience, their outlook, and the impact of the depression on them and their families. Occasional empathic silence may be as helpful for the treatment alliance as verbal reassurance. Controlled trials have shown that cognitive-behavioral and interpersonal therapies are effective in improving psychological and social adjustment and that a combined treatment approach is more successful than medication alone for many patients.

BIPOLAR DISORDER

Clinical manifestations

Bipolar disorder is characterized by unpredictable swings in mood from mania (or hypomania) to depression. Some patients suffer only from recurrent attacks of mania, which in its pure form is associated with increased psychomotor activity; excessive social extroversion; decreased need for sleep; impulsivity and impairment in judgment; and expansive, grandiose, and sometimes irritable mood **(Table 61-8)**. In severe mania, patients may experience delusions and paranoid thinking indistinguishable from schizophrenia. One-half of patients with bipolar disorder present with a mixture of psychomotor agitation and activation with dysphoria, anxiety, and irritability. It may be dif cult to distinguish mixed mania from agitated depression. In some bipolar patients (bipolar II disorder), the full criteria for mania are lacking, and the requisite recurrent depressions are separated by periods of mild activation and increased energy (hypomania). In cyclothymic disorder, there are numerous hypomanic periods, usually of relatively short duration, alternating with clusters of depressive symptoms

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-8

CRITERIA FOR A MANIC EPISODE

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of the mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or another medical condition.

Source: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, American Psychiatric Association, 2013.

that fail, either in severity or duration, to meet the criteria of major depression. The mood fluctuations are chronic and should be present for at least 2 years before the diagnosis is made.

Manic episodes typically emerge over a period of days to weeks, but onset within hours is possible, usually in the early morning hours. An untreated episode of either depression or mania can be as short as several weeks or last as long as 8–12 months, and rare patients have an unremitting chronic course. The term rapid cycling is used for patients who have four or more episodes of either depression or mania in a given year. This pattern occurs in 15% of all patients, almost all of whom are women. In some cases, rapid cycling is linked to an underlying thyroid dysfunction, and in others, it is iatrogenically triggered by prolonged antidepressant treatment. Approximately one-half of patients have sustained difficulties in work performance and psychosocial functioning, with depressive phases being more responsible for impairment than mania.

Bipolar disorder is common, affecting ~1.5% of the population in the United States. Onset is typically between 20 and 30 years of age, but many individuals report premorbid symptoms in late childhood or early adolescence. The prevalence is similar for men and women; women are likely to have more depressive and men more manic episodes over a lifetime.

Differential diagnosis

The differential diagnosis of mania includes secondary mania induced by stimulant or sympathomimetic drugs, hyperthyroidism, AIDS, and neurologic disorders such as Huntington's or Wilson's disease and cerebrovascular accidents. Comorbidity with alcohol and substance abuse is common, either because of poor judgment and increased impulsivity or because of an attempt to self-treat the underlying mood symptoms and sleep disturbances.

Etiology and pathophysiology

Genetic predisposition to bipolar disorder is evident from family studies; the concordance rate for monozygotic twins approaches 80%. Patients with bipolar disorder also appear to have altered circadian rhythmicity, and lithium may exert its therapeutic benefit through a resynchronization of intrinsic rhythms keyed to the light/dark cycle.

TREATMENT Bipolar Disorder

(Table 61-9) Lithium carbonate is the mainstay of treatment in bipolar disorder, although sodium valproate and carbamazepine, as well as a number of second-generation antipsychotic agents (aripiprazole, asenapine, olanzapine, quetiapine, risperidone, ziprasidone), also have FDA approval for the treatment of acute mania. Oxcarbazepine is not FDA approved, but appears to enjoy carbamazepine's spectrum of efficacy. The response rate to lithium carbonate is 70–80% in acute mania, with beneficial effects appearing in 1–2 weeks. Lithium also has a prophylactic effect in prevention of recurrent mania and, to a lesser extent, in the prevention of recurrent depression. A simple cation, lithium is rapidly absorbed from the gastrointestinal tract and remains unbound to plasma or tissue proteins. Some 95% of a given dose is excreted unchanged through the kidneys within 24 h.

Serious side effects from lithium are rare, but minor complaints such as gastrointestinal discomfort, nausea, diarrhea, polyuria, weight gain, skin eruptions, alopecia, and edema are common. Over time, urine-concentrating ability may be decreased, but significant nephrotoxicity does not usually

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-9

CLINICAL PHARMACOLOGY OF MOOD STABILIZERS

AGENT AND DOSING	SIDE EFFECTS AND OTHER EFFECTS
Lithium	Common Side Effects
Starting dose: 300 mg bid or tid Therapeutic blood level: 0.8–1.2 meq/L	Nausea/anorexia/diarrhea, fine tremor, thirst, polyuria, fatigue, weight gain, acne, folliculitis, neutrophilia, hypothyroidism Blood level is increased by thiazides, tetracyclines, and NSAIDs Blood level is decreased by bronchodilators, verapamil, and carbonic anhydrase inhibitors Rare side effects: Neurotoxicity, renal toxicity, hypercalcemia, ECG changes
Valproic Acid	Common Side Effects
Starting dose: 250 mg tid Therapeutic blood level: 50–125 µg/mL	Nausea/anorexia, weight gain, sedation, tremor, rash, alopecia Inhibits hepatic metabolism of other medications Rare side effects: Pancreatitis, hepatotoxicity, Stevens-Johnson syndrome
Carbamazepine/ Oxcarbazepine	Common Side Effects
Starting dose: 200 mg bid for carbamazepine, 150 mg bid for oxcarbazepine Therapeutic blood level: 4–12 µg/mL for carbamazepine	Nausea/anorexia, sedation, rash, dizziness/ataxia Carbamazepine, but not oxcarbazepine, induces hepatic metabolism of other medications Rare side effects: Hyponatremia, agranulocytosis, Stevens-Johnson syndrome
Lamotrigine	Common Side Effects
Starting dose: 25 mg/d	Rash, dizziness, headache, tremor, sedation, nausea Rare side effect: Stevens-Johnson syndrome

Abbreviations: ECG, electrocardiogram; NSAIDs, nonsteroidal anti-inflammatory drugs.

occur. Lithium exerts an antithyroid effect by interfering with the synthesis and release of thyroid hormones. More serious side effects include tremor, poor concentration and memory, ataxia, dysarthria, and incoordination. There is suggestive, but not conclusive, evidence that lithium is teratogenic, inducing cardiac malformations in the first trimester.

In the treatment of acute mania, lithium is initiated at 300 mg bid or tid, and the dose is then increased by 300 mg every 2–3 days to achieve blood levels of 0.8–1.2 meq/L. Because the therapeutic effect of lithium may not appear until after 7–10 days of treatment, adjunctive usage of lorazepam (1–2 mg every 4 h) or clonazepam (0.5–1 mg every 4 h) may be beneficial to control agitation. Antipsychotics are indicated in patients with severe agitation who respond only partially to benzodiazepines. Patients using lithium should be monitored closely, since the blood levels required to achieve a therapeutic benefit are close to those associated with toxicity.

Valproic acid may be better than lithium for patients who experience rapid cycling (i.e., more than four episodes a year) or who present with a mixed or dysphoric mania. Tremor and weight gain are the most common side effects; hepatotoxicity and pancreatitis are rare toxicities.

The recurrent nature of bipolar mood disorder necessitates maintenance treatment. A sustained blood lithium level of at least 0.8 meq/L is important for optimal prophylaxis and has been shown to reduce the risk of suicide, a finding not yet apparent for other mood stabilizers. Combinations of mood stabilizers together or with atypical antipsychotic drugs are sometimes required to maintain mood stability. Quetiapine extended release, olanzapine, risperidone, and lamotrigine have been approved for maintenance treatment as sole agents, in combination with lithium and with aripiprazole and ziprasidone as adjunctive drugs. Lurasidone, olanzapine/fluoxetine, and quetiapine are also approved to treat acute depressive episodes in bipolar disorder. Compliance is frequently an issue and often requires enlistment and education of concerned family members. Efforts to identify and modify psychosocial factors that may trigger episodes are important, as is an emphasis on lifestyle regularity. Antidepressant medications are sometimes required for the treatment of severe breakthrough depressions, but their use should generally be avoided during maintenance treatment because of the risk of precipitating mania or accelerating the cycle frequency. Loss of efficacy over time may be observed with any of the mood-stabilizing agents. In such situations, an alternative agent or combination therapy is usually helpful.

SOMATIC SYMPTOM DISORDER

Many patients presenting in general medical practice, perhaps as many as 5–7%, will experience a somatic symptom(s) as particularly distressing and preoccupying, to the point that it comes to dominate their thoughts, feelings, and beliefs and interferes to a varying degree with everyday functioning. Although the absence of a medical explanation for these complaints was historically emphasized as a diagnostic element, it has been recognized that the patient's interpretation and elaboration of the experience is the critical defining factor and that patients with well-established medical causation may qualify for the diagnosis. Multiple complaints are typical, but severe single symptoms can occur as well.

www.ketabpezeshki.com (021) 66485457 - 66485438

Comorbidity with depressive and anxiety disorders is common and may affect the severity of the experience and its functional consequences. Personality factors may be a significant risk factor, as may a low level of educational or socioeconomic status or a history of recent stressful life events. Cultural factors are relevant as well and should be incorporated into the evaluation. Individuals who have persistent preoccupations about having or acquiring a serious illness, but who do not have a specific somatic complaint, may qualify for a related diagnosis—illness anxiety disorder. T e diagnosis of conversion disorder (functional neurologic symptom disorder) is used to specifically identify those individuals whose somatic complaints involve one or more symptoms of altered voluntary motor or sensory function that cannot be medically explained and that causes significant distress or impairment or requires medical evaluation.

In *f*actitious illnesses, the patient consciously and voluntarily produces physical symptoms of illness. T e term Munchausen's syndrome is reserved for individuals with particularly dramatic, chronic, or severe factitious illness. In true factitious illness, the sick role itself is gratifying. A variety of signs, symptoms, and diseases have been either simulated or caused by factitious behavior, the most common including chronic diarrhea, fever of unknown origin, intestinal bleeding or hematuria, seizures, and hypoglycemia. Factitious disorder is usually not diagnosed until 5–10 years after its onset, and it can produce significant social and medical costs. In malingering, the fabrication derives from a desire for some external reward such as a narcotic medication or disability reimbursement.

TREATMENT Somatic Symptom Disorder and Related Disorders

Patients with somatic symptom disorder are frequently subjected to many diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or treatment action. Although the literature is limited, some patients may benefit from antidepressant treatment.

Any attempt to confront the patient usually creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed. Specific medical treatments also may be indicated and effective in treating some of the functional consequences of conversion disorder.

FEEDING AND EATING DISORDERS

CLINICAL MANIFESTATIONS

Feeding and eating disorders constitute a group of conditions in which there is a persistent disturbance of eating or associated behaviors that significantly impair an individual's physical health or psychosocial functioning. In DSM-5 the described categories (with the exception of pica) are defined to be mutually exclusive in a given episode, based on the understanding that although they are phenotypically similar in some ways, they differ in course, prognosis, and effective treatment interventions. Compared with DSM-IV-TR, three disorders (i.e., avoidant/restrictive food intake disorder, rumination disorder, pica) that were previously classified as disorders of infancy or childhood have been grouped together with the disorders of anorexia and bulimia nervosa. Binge-eating disorder is also now included as a formal diagnosis; the intent of each of these modifications is to encourage clinicians to be more specific in their codification of eating and feeding pathology.

PICA

Pica is diagnosed when the individual, over age 2, eats one or more nonnutritive, nonfood substances for a month or more and requires medical attention as a result. T ere is usually no specific aversion to food in general but a preferential choice to ingest substances such as clay, starch, soap, paper, or ash. T e diagnosis requires the exclusion of specific culturally approved practices and has not been commonly found to be caused by a specific nutritional deficiency. Onset is most common in childhood but the disorder can occur in association with other major psychiatric conditions in adults. An association with pregnancy has been observed, but the condition is only diagnosed when medical risks are increased by the behavior.

RUMINATION DISORDER

In this condition, individuals who have no demonstrable associated gastrointestinal or other medical condition repeatedly regurgitate their food after eating and then either rechew or swallow it or spit it out. T e behavior typically occurs on a daily basis and must persist for at least 1 month. Weight loss and malnutrition

www.ketabpezeshki.com (021) 66485457 - 66485438

are common sequelae, and individuals may attempt to conceal their behavior, either by covering their mouth or through social avoidance while eating. In infancy, the onset is typically between 3 to 12 months, and the behavior may remit spontaneously, although in some it appears to be recurrent.

AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDER

T e cardinal feature of this disorder is avoidance or restriction of food intake, usually stemming from a lack of interest in or distaste of food and associated with weight loss, nutritional deficiency, dependency on nutritional supplementation, or marked impairment in psychosocial functioning, either alone or in combination. Culturally approved practices, such as fasting, or a lack of available food must be excluded as possible causes. T e disorder is distinguished from anorexia nervosa by the presence of emotional factors, such as a fear of gaining weight and distortion of body image in the latter condition. Onset is usually in infancy or early childhood, but avoidant behaviors may persist into adulthood. T e disorder is equally prevalent in males and females and is frequently comorbid with anxiety and cognitive and attention-deficit disorders and situations of familial stress. Developmental delay and functional deficits may be significant if the disorder is long-standing and unrecognized.

ANOREXIA NERVOSA

Individuals are diagnosed with anorexia nervosa if they restrict their caloric intake to a degree that their body weight deviates significantly from age, gender, health, and developmental norms and if they also exhibit a fear of gaining weight and an associated disturbance in body image. T e condition is further characterized by differentiating those who achieve their weight loss predominantly through restricting intake or by excessive exercise (restricting type) from those who engage in recurrent binge eating and/or subsequent purging, self-induced vomiting, and usage of enemas, laxatives, or diuretics (binge-eating/purging type). Such subtyping is more state than trait specific, as individuals may transition from one profile to the other over time. Determination of whether an individual satisfies the primary criterion of significant low weight is complex and must be individualized, using all available historical information and comparison of body habitus to international body mass norms and guidelines.

Individuals with anorexia nervosa frequently lack insight into their condition and are in denial about possible medical consequences; they often are not comforted by their achieved weight loss and persist in their behaviors despite having met previously self-designated weight goals. Recent research has identified alterations in the circuitry of reward sensitivity and executive function in anorexia and implicated disturbances in frontal cortex and anterior insula regulation of interoceptive awareness of satiety and hunger. Neurochemical findings, including the role of ghrelin, remain controversial.

Onset is most common in adolescence, although onset in later life can occur. Many more females than males are affected, with a lifetime prevalence in women of up to 4%. T e disorder appears most prevalent in postindustrialized and urbanized countries and is frequently comorbid with preexisting anxiety disorders. T e medical consequences of prolonged anorexia nervosa are multisystemic and can be life-threatening in severe presentations. Changes in blood chemistry include leukopenia with lymphocytosis, elevations in blood urea nitrogen, and metabolic alkalosis and hypokalemia when purging is present. History and physical examination may reveal amenorrhea in females, skin abnormalities (petechiae, lanugo hair, dryness), and signs of hypometabolic function, including hypotension, hypothermia, and sinus bradycardia. Endocrine effects include hypogonadism, growth hormone resistance, and hypercortisolemia. Osteoporosis is a longer-term concern.

T e course of the disorder is variable, with some individuals recovering after a single episode, while others exhibit recurrent episodes or a chronic course. Untreated anorexia has a mortality of 5.1/1000, the highest among psychiatric conditions. Maudsley family-based therapy has proven to be an effective therapy in younger individuals, with strict behavioral contingencies used when weight loss becomes critical. No pharmacologic intervention has proven to be specifically beneficial, but comorbid depression and anxiety should be treated. Weight gain should be undertaken gradually with a goal of 0.5 to 1 pound per week to prevent refeeding syndrome. Most individuals are able to achieve remission within 5 years of the original diagnosis.

BULIMIA NERVOSA

Bulimia nervosa describes individuals who engage in recurrent and frequent (at least once a week for 3 months) periods of binge eating and who then resort to compensatory behaviors, such as self-induced purging, enemas, use of laxatives, or excessive exercise to avoid weight gain. Binge eating itself is defined as excessive food intake in a prescribed period of time, usually <2 h. As in anorexia nervosa, disturbances in body image occur and promote the behavior, but unlike in anorexia, individuals are of normal weight or even somewhat overweight. Subjects typically describe a loss of control and express shame about their actions, and often relate that their episodes are triggered by feelings of negative

www.ketabpezeshki.com (021) 66485457 - 66485438

self-esteem or social stresses. T e lifetime prevalence in women is approximately 2%, with a 10:1 female-to-male ratio. T e disorder typically begins in adolescence and may be persistent over a number of years. Transition to anorexia occurs in only 10–15% of cases. Many of the medical risks associated with bulimia nervosa parallel those of anorexia nervosa and are a direct consequence of purging, including fluid and electrolyte disturbances and conduction abnormalities. Physical examination often results in no specific findings, but dental erosion and parotid gland enlargement may be present. Effective treatment approaches include SSRI antidepressants, usually in combination with cognitive-behavioral, emotion regulation, or interpersonal-based psychotherapies.

BINGE-EATING DISORDER

Binge-eating disorder is distinguished from bulimia nervosa by the absence of compensatory behaviors to prevent weight gain after an episode and by a lack of effort to restrict weight gain between episodes. Other features are similar, including distress over the behavior and the experience of loss of control, resulting in eating more rapidly or in greater amounts than intended or eating when not hungry. T e 12-month prevalence in females is 1.6%, with a much lower female-to-male ratio than bulimia nervosa. Little is known about the course of the disorder, given its recent categorization, but its prognosis is markedly better than for other eating disorders, both in terms of its natural course and response to treatment. Transition to other eating disorder conditions is thought to be rare.

PERSONALITY DISORDERS

CLINICAL MANIFESTATIONS

Personality disorders are characteristic patterns of thinking, feeling, and interpersonal behavior that are relatively inflexible and cause significant functional impairment or subjective distress for the individual. T e observed behaviors are not secondary to another mental disorder, nor are they precipitated by substance abuse or a general medical condition. T is distinction is often dif cult to make in clinical practice, because personality change may be the first sign of serious neurologic, endocrine, or other medical illness. Patients with frontal lobe tumors, for example, can present with changes in motivation and personality while the results of the neurologic examination remain within normal limits. Individuals with personality disorders are often regarded as "dif cult patients" in clinical medical practice because they are seen as excessively demanding and/or unwilling to follow recommended treatment plans. Although DSM-5 portrays personality disorders as qualitatively distinct categories, there is an alternative perspective that personality characteristics vary as a continuum between normal functioning and formal mental disorder.

Personality disorders have been grouped into three overlapping clusters. Cluster A includes paranoid, schizoid, and schizotypal personality disorders. It includes individuals who are odd and eccentric and who maintain an emotional distance from others. Individuals have a restricted emotional range and remain socially isolated. Patients with schizotypal personality disorder frequently have unusual perceptual experiences and express magical beliefs about the external world. T e essential feature of paranoid personality disorder is a pervasive mistrust and suspiciousness of others to an extent that is unjustified by available evidence. Cluster B disorders include antisocial, borderline, histrionic, and narcissistic types and describe individuals whose behavior is impulsive, excessively emotional, and erratic. Cluster C incorporates avoidant, dependent, and obsessive-compulsive personality types; enduring traits are anxiety and fear. T e boundaries between cluster types are to some extent artificial, and many patients who meet criteria for one personality disorder also meet criteria for aspects of another. T e risk of a comorbid major mental disorder is increased in patients who qualify for a diagnosis of personality disorder.

TREATMENT Personality Disorders

Dialectical behavior therapy (DBT) is a cognitive-behavioral approach that focuses on behavioral change while providing acceptance, compassion, and validation of the patient. Several randomized trials have demonstrated the ef cacy of DBT in the treatment of personality disorders. Antidepressant medications and low-dose antipsychotic drugs have some ef cacy in cluster A personality disorders, whereas anticonvulsant mood-stabilizing agents and MAOIs may be considered for patients with cluster B diagnoses who show marked mood reactivity, behavioral dyscontrol, and/or rejection hypersensitivity. Anxious or fearful cluster C patients often respond to medications used for axis I anxiety disorders (see above). It is important that the physician and the patient have reasonable expectations vis-à-vis the possible benefit of any medication used and its side effects. Improvement may be subtle and observable only over time.

SCHIZOPHRENIA

CLINICAL MANIFESTATIONS

Schizophrenia is a heterogeneous syndrome characterized by perturbations of language, perception, thinking, social activity, affect, and volition. T ere are no pathognomonic

www.ketabpezeshki.com (021) 66485457 - 66485438

features. The syndrome commonly begins in late adolescence, has an insidious (and less commonly acute) onset, and, often, a poor outcome, progressing from social withdrawal and perceptual distortions to recurrent delusions and hallucinations. Patients may present with positive symptoms (such as conceptual disorganization, delusions, or hallucinations) or negative symptoms (loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement) and must have at least two of these for a 1-month period and continuous signs for at least 6 months to meet formal diagnostic criteria. Disorganized thinking or speech and grossly disorganized motor behavior, including catatonia, may also be present. As individuals age, positive psychotic symptoms tend to attenuate, and some measure of social and occupational function may be regained. "Negative" symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical.

The term schizophreni*form* disorder describes patients who meet the symptom requirements but not the duration requirements for schizophrenia, and schizoaffective disorder is used for those who manifest symptoms of schizophrenia and independent periods of mood disturbance. The terms "schizotypal" and "schizoid" refer to specific personality disorders and are discussed in that section. The diagnosis of delusional disorder is used for individuals who have delusions of various content for at least 1 month but who otherwise do not meet criteria for schizophrenia. Patients who experience a sudden onset of a brief (<1 month) alteration in thought processing, characterized by delusions, hallucinations, disorganized speech, or gross motor behavior, are most appropriately designated as having a brief psychotic disorder. Catatonia is recognized as a nonspecific syndrome that can occur as a consequence of other severe psychiatric/medical disorders and is diagnosed by the documentation of three or more of a cluster of motor and behavioral symptoms, including stupor, cataplexy, mutism, waxy flexibility, and stereotypy, among others. Prognosis depends not on symptom severity but on the response to antipsychotic medication. A permanent remission without recurrence does occasionally occur. About 10% of schizophrenic patients commit suicide.

Schizophrenia is present in 0.85% of individuals worldwide, with a lifetime prevalence of ~1–1.5%. An estimated 300,000 episodes of acute schizophrenia occur annually in the United States, resulting in direct and indirect costs of $62.7 billion.

DIFFERENTIAL DIAGNOSIS

The diagnosis is principally one of exclusion, requiring the absence of significant associated mood symptoms, any relevant medical condition, and substance abuse. Drug reactions that cause hallucinations, paranoia, confusion, or bizarre behavior may be dose-related or idiosyncratic; parkinsonian medications, clonidine, quinacrine, and procaine derivatives are the most common prescription medications associated with these symptoms. Drug causes should be ruled out in any case of newly emergent psychosis. The general neurologic examination in patients with schizophrenia is usually normal, but motor rigidity, tremor, and dyskinesias are noted in one-quarter of untreated patients.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Epidemiologic surveys identify several risk factors for schizophrenia, including genetic susceptibility, early developmental insults, winter birth, and increasing parental age. Genetic factors are involved in at least a subset of individuals who develop schizophrenia. Schizophrenia is observed in ~6.6% of all first-degree relatives of an affected proband. If both parents are affected, the risk for offspring is 40%. The concordance rate for monozygotic twins is 50%, compared to 10% for dizygotic twins. Schizophrenia-prone families are also at risk for other psychiatric disorders, including schizoaffective disorder and schizotypal and schizoid personality disorders, the latter terms designating individuals who show a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions.

TREATMENT Schizophrenia

Antipsychotic agents **(Table 61-10)** are the cornerstone of acute and maintenance treatment of schizophrenia and are effective in the treatment of hallucinations, delusions, and thought disorders, regardless of etiology. The mechanism of action involves, at least in part, binding to dopamine D_2/D_3 receptors in the ventral striatum; the clinical potencies of traditional antipsychotic drugs parallel their affinities for the D_2 receptor, and even the newer "atypical" agents exert some degree of D_2 receptor blockade. All neuroleptics induce expression of the immediate-early gene c-*fos* in the nucleus accumbens, a dopaminergic site connecting prefrontal and limbic cortices. The clinical efficacy of newer atypical neuroleptics, however, may involve N-methyl-d-aspartate (NMDA) receptor blockade, α_1- and α_2-noradrenergic activity, altering the relationship between 5-HT_2 and D_2 receptor activity, and faster dissociation of D_2 binding and effects on neuroplasticity.

Conventional neuroleptics differ in their potency and side effect profile. Older agents, such as chlorpromazine and thioridazine, are more sedating and anticholinergic and more likely to cause orthostatic hypotension, whereas higher potency antipsychotics, such as haloperidol, perphenazine,

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 61-10

ANTIPSYCHOTIC AGENTS

NAME	USUAL PO DAILY DOSE, mg	SIDE EFFECTS	SEDATION	COMMENTS
First-Generation Antipsychotics				
Low potency				
Chlorpromazine (Thorazine)	100–1000 100–600	Anticholinergic effects; orthostasis; photosensitivity; cholestasis; QT prolongation	+++	EPSEs usually not prominent; can cause anticholinergic delirium in elderly patients
Thioridazine (Mellaril)				
Midpotency				
Trifluoperazine (Stelazine)	2–50	Fewer anticholinergic side effects	++	Well tolerated by most patients
Perphenazine (Trilafon)	4–64	Fewer EPSEs than with higher potency agents	++	
Loxapine (Loxitane)	30–100	Frequent EPSEs	++	
Molindone (Moban)	30–100	Frequent EPSEs	0	Little weight gain
High potency				
Haloperidol (Haldol)	5–20	No anticholinergic side effects; EPSEs often prominent	0/+	Often prescribed in doses that are too high; long-acting injectable forms of haloperidol and fluphenazine available
Fluphenazine (Prolixin)	1–20	Frequent EPSEs	0/+	
Thiothixene (Navane)	2–50	Frequent EPSEs	0/+	
Second-Generation Antipsychotics				
Clozapine (Clozaril)	150–600	Agranulocytosis (1%); weight gain; seizures; drooling; hyperthermia	++	Requires weekly WBC count for first 6 months, then biweekly if stable
Risperidone (Risperdal)	2–8	Orthostasis	+	Requires slow titration; EPSEs observed with doses >6 mg qd
Olanzapine (Zyprexa)	10–30	Weight gain	++	Mild prolactin elevation
Quetiapine (Seroquel)	350–800	Sedation; weight gain; anxiety	+++	bid dosing
Ziprasidone (Geodon)	120–200	Orthostatic hypotension	+/++	Minimal weight gain; increases QT interval
Aripiprazole (Abilify)	10–30	Nausea, anxiety, insomnia	0/+	Mixed agonist/antagonist
Paliperidone (Invega)	3–12	Restlessness, EPSEs, increased prolactin, headache	+	Active metabolite of risperidone
Iloperidone (Fanapt)	12–24	Dizziness, hypotension	0/+	Requires dose titration; long acting injectable available
Asenapine (Saphris)	10–20	Dizziness, anxiety, EPSEs, minimal weight gain	++	Sublingual tablets; bid dosing
Lurasidone (Latuda)	40–80	Nausea, EPSEs	++	Uses CYP3A4

Abbreviations: EPSEs, extrapyramidal side effects; WBC, white blood cell.

and thiothixene, are more likely to induce extrapyramidal side effects. The model "atypical" antipsychotic agent is clozapine, a dibenzodiazepine that has a greater potency in blocking the 5-HT_2 than the D_2 receptor and a much higher affinity for the D_4 than the D_2 receptor. Its principal disadvantage is a risk of blood dyscrasias. Paliperidone is a recently approved agent that is a metabolite of risperidone and shares many of its properties. Unlike other antipsychotics, clozapine does not cause a rise in prolactin level. Approximately 30% of patients who do not benefit from conventional antipsychotic agents will have a better response to this drug, which also has a demonstrated superiority to other antipsychotic agents in preventing suicide; however, its side effect profile makes it most appropriate for treatment-resistant cases. Risperidone, a benzisoxazole derivative, is more potent at 5-HT_2 than D_2 receptor sites, like clozapine, but it also exerts significant α_2 antagonism, a property that may contribute to its perceived ability to improve mood and increase motor activity. Risperidone is not as effective as clozapine in treatment-resistant cases but does not carry a risk of blood dyscrasias. Olanzapine is similar neurochemically to clozapine but has a significant risk of inducing weight gain.

www.ketabpezeshki.com (021) 66485457 - 66485438

Quetiapine is distinct in having a weak D_2 effect but potent α_1 and histamine blockade. Ziprasidone causes minimal weight gain and is unlikely to increase prolactin but may increase QT prolongation. Aripiprazole also has little risk of weight gain or prolactin increase but may increase anxiety, nausea, and insomnia as a result of its partial agonist properties. Asenapine is associated with minimal weight gain and anticholinergic effect but may have a higher than expected risk of extrapyramidal symptoms.

Antipsychotic agents are effective in 70% of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6–8 weeks. T e choice of agent depends principally on the side effect profile and cost of treatment or on a past personal or family history of a favorable response to the drug in question. Atypical agents appear to be more effective in treating negative symptoms and improving cognitive function. An equivalent treatment response can usually be achieved with relatively low doses of any drug selected (i.e., 4–6 mg/d of haloperidol, 10–15 mg of olanzapine, or 4–6 mg/d of risperidone). Doses in this range result in >80% D_2 receptor blockade, and there is little evidence that higher doses increase either the rapidity or degree of response. Maintenance treatment requires careful attention to the possibility of relapse and monitoring for the development of a movement disorder. Intermittent drug treatment is less effective than regular dosing, but gradual dose reduction is likely to improve social functioning in many schizophrenic patients who have been maintained at high doses. If medications are completely discontinued, however, the relapse rate is 60% within 6 months. Long-acting injectable preparations (risperidone, paliperidone, olanzapine, aripiprazole) are considered when noncompliance with oral therapy leads to relapses but should not be considered interchangeable, because the agents differ in their indications, injection intervals and sites/volumes, and possible adverse reactions, among other factors. In treatment-resistant patients, a transition to clozapine usually results in rapid improvement, but a prolonged delay in response in some cases necessitates a 6- to 9-month trial for maximal benefit to occur.

Antipsychotic medications can cause a broad range of side effects, including lethargy, weight gain, postural hypotension, constipation, and dry mouth. Extrapyramidal symptoms such as dystonia, akathisia, and akinesia are also frequent with first-generation agents and may contribute to poor adherence if not specifically addressed. Anticholinergic and parkinsonian symptoms respond well to trihexyphenidyl, 2 mg bid, or benztropine mesylate, 1–2 mg bid. Akathisia may respond to beta blockers. In rare cases, more serious and occasionally life-threatening side effects may emerge, including hyperprolactinemia, ventricular arrhythmias, gastrointestinal obstruction, retinal pigmentation, obstructive jaundice, and neuroleptic malignant syndrome (characterized by hyperthermia, autonomic dysfunction, muscular rigidity, and elevated creatine phosphokinase levels). T e most serious adverse effects of clozapine are agranulocytosis, which has an incidence of 1%, and induction of seizures, which has an incidence of 10%. Weekly white blood cell counts are required, particularly during the first 3 months of treatment.

T e risk of type 2 diabetes mellitus appears to be increased in schizophrenia, and second-generation agents as a group produce greater adverse effects on glucose regulation, independent of effects on obesity, than traditional agents. Clozapine, olanzapine, and quetiapine seem more likely to cause hyperglycemia, weight gain, and hypertriglyceridemia than other atypical antipsychotic drugs. Close monitoring of plasma glucose and lipid levels are indicated with the use of these agents.

A serious side effect of long-term use of first-generation antipsychotic agents is tardive dyskinesia, characterized by repetitive, involuntary, and potentially irreversible movements of the tongue and lips (bucco-linguo-masticatory triad) and, in approximately half of cases, choreoathetosis. Tardive dyskinesia has an incidence of 2–4% per year of exposure and a prevalence of 20% in chronically treated patients. The prevalence increases with age, total dose, and duration of drug administration. The risk associated with second-generation agents appears to be much lower. The cause may involve formation of free radicals and perhaps mitochondrial energy failure. Vitamin E may reduce abnormal involuntary movements if given early in the syndrome.

T e CATIE study, a large-scale investigation of the effectiveness of antipsychotic agents in "real-world" patients, revealed a high rate of discontinuation of treatment over 18 months. Olanzapine showed greater effectiveness than quetiapine, risperidone, perphenazine, or ziprasidone but also a higher discontinuation rate due to weight gain and metabolic effects. Surprisingly, perphenazine, a first-generation agent, showed little evidence of inferiority to newer drugs.

Drug treatment of schizophrenia is by itself insuf cient. Educational efforts directed toward families and relevant community resources have proved to be necessary to maintain stability and optimize outcome. A treatment model involving a multidisciplinary case-management team that seeks out and closely follows the patient in the community has proved particularly effective.

ASSESSMENT AND EVALUATION OF VIOLENCE

Primary care physicians may encounter situations in which family, domestic, or societal violence is discovered or suspected. Such an awareness can carry legal and moral obligations; many state laws mandate reporting of child, spousal, and elder abuse. Physicians are frequently the first point of contact for both victim and abuser. Approximately 2 million older Americans and 1.5 million U.S. children are thought to experience

www.ketabpezeshki.com (021) 66485457 - 66485438

some form of physical maltreatment each year. Spousal abuse is thought to be even more prevalent. An interview study of 24,000 women in 10 countries found a lifetime prevalence of physical or sexual violence that ranged from 15 to 71%; these individuals are more likely to suffer from depression, anxiety, and substance abuse and to have attempted suicide. In addition, abused individuals frequently express low self-esteem, vague somatic symptomatology, social isolation, and a passive feeling of loss of control. Although it is essential to treat these elements in the victim, the first obligation is to ensure that the perpetrator has taken responsibility for preventing any further violence. Substance abuse and/or dependence and serious mental illness in the abuser may contribute to the risk of harm and require direct intervention. Depending on the situation, law enforcement agencies, community resources such as support groups and shelters, and individual and family counseling can be appropriate components of a treatment plan. A safety plan should be formulated with the victim, in addition to providing information about abuse, its likelihood of recurrence, and its tendency to increase in severity and frequency. Antianxiety and antidepressant medications may sometimes be useful in treating the acute symptoms, but only if independent evidence for an appropriate psychiatric diagnosis exists.

MENTAL HEALTH PROBLEMS IN THE HOMELESS

T ere is a high prevalence of mental disorders and substance abuse among homeless and impoverished individuals. Depending on the definition used, estimates of the total number of homeless individuals in the United States range from 800,000 to 2 million, one-third of whom qualify as having a serious mental disorder. Poor hygiene and nutrition, substance abuse, psychiatric illness, physical trauma, and exposure to the elements combine to make the provision of medical care challenging. Only a minority of these individuals receives formal mental health care; the main points of contact are outpatient medical clinics and emergency departments. Primary care settings represent a critical site in which housing needs, treatment of substance dependence, and evaluation and treatment of psychiatric illness can most ef ciently take place. Successful intervention is dependent on breaking down traditional administrative barriers to health care and recognizing the physical constraints and emotional costs imposed by homelessness. Simplifying health care instructions and follow-up, allowing frequent visits, and dispensing medications in limited amounts that require ongoing contact are possible techniques for establishing a successful therapeutic relationship.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 62

NEUROPSYCHIATRIC ILLNESSES IN WAR VETERANS

Charles W. Hoge

Neuropsychiatric sequelae are common in combat veterans. Advances in personal protective body armor, armored vehicles, battlefield resuscitation, and the speed of evacuation to tertiary care have considerably improved the survivability of battlefield injuries, resulting in a greater awareness of the "silent wounds" associated with service in a combat zone. Although psychiatric and neurologic problems have been well documented in veterans of prior wars, the conflicts in Iraq and Afghanistan that began after September 11, 2001, were unique in terms of the level of commitment by the U.S. Department of Defense (DoD) and Department of Veterans Affairs (VA), Veterans Health Administration (VHA) to support research as the wars unfolded and to use that knowledge to guide population-level screening, evaluation, and treatment initiatives.

T e Iraq and Afghanistan conflicts produced over 2.5 million combat veterans, many of whom have received or will need care in government and civilian medical facilities in the future. Studies clearly showed that service in the Iraq and Afghanistan theaters was associated with significantly elevated rates of mental disorders. Two conditions in particular have been labeled the signature injuries related to these wars: posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI)—also known as concussion. Although particular emphasis will be given in this chapter to PTSD and concussion/mTBI, it is important to understand that the neuropsychiatric sequelae of war are much broader than these two conditions. Wartime service is associated with a number of health concerns that coexist and overlap, and a multidisciplinary patient-centered approach to care is necessary.

EPIDEMIOLOGY OF WAR-RELATED PSYCHOLOGICAL AND NEUROLOGIC CONDITIONS

Service members involved in the Iraq and Afghanistan wars faced multiple deployments to two very different high-intensity combat theaters, and for many veterans, the cumulative strain negatively impacted health, marriages, parenting, educational goals, and civilian occupations. T e stresses of service in these conflicts also led to a significant increase in rates of suicide in personnel from the two branches of service involved in the greatest level of ground combat (U.S. Army, Marines).

Service in a war zone can involve extreme physical stress in austere environments, prolonged sleep deprivation, physical injury, exposure to highly life-threatening events, and hazards such as explosive devices, sniper fire, ambushes, indirect fire from rockets and mortars, and chemical pollutants. Certain events, such as loss of a close friend in combat, leave indelible scars. All of these experiences have additive effects on health, likely mediated through physiologic mechanisms involving dysregulation of neuroendocrine and autonomic nervous system (ANS) functions.

Veterans of virtually all wars have reported elevated rates of generalized and multisystem physical, cognitive, and psychological health concerns that often become the focus of treatment months or years after returning home. T ese multisystem health concerns include sleep disturbance, memory and concentration problems, headaches, musculoskeletal pain, gastrointestinal symptoms (including gastroesophageal reflux), residual effects of wartime injuries, fatigue, anger, hyperarousal symptoms, high blood pressure, rapid heart rate (sometimes associated with panic symptoms), sexual problems,

www.ketabpezeshki.com (021) 66485457 - 66485438

and symptoms associated with PTSD and depression. In order to provide optimal care to veterans with these symptoms, it is important to understand how the symptoms interrelate and to consider the possibility that there may be underlying combat-related physiologic effects.

POSTWAR SYMPTOMS

The overlapping and multisystem health concerns reported by warriors from every generation have been given different labels and have led to debates among medical professionals as to whether these are mediated primarily by physical or psychological causes. For example, World War I produced extensive debate about whether "shell shock," diagnosed in more than 80,000 British soldiers, was neurologic ("commotional" from the brain being shaken in the skull by concussive blasts) or psychological ("emotional" or "neurasthenia") in origin. World War II veterans were said to suffer from "battle fatigue," Korean War veterans developed "combat stress reactions," and Vietnam veterans developed the "post-Vietnam syndrome." The role of environmental exposure (e.g., Agent Orange) and psychological causes (e.g., PTSD, depression, substance use disorders) continue to be debated.

Gulf War I (Operation Desert Storm), following the Iraqi invasion of Kuwait in 1990, led to extensive debates as to whether Gulf War syndrome, also known as multisystem illness, was best explained by environmental exposures (e.g., oil fires, depleted uranium, nerve gas, pesticides, multiple vaccinations) or the psychological stress of deployment to a war zone where there was anticipation of high casualty rates from chemical and biologic weapons, repeated stressful alerts, and training exercises involving the use of impermeable full-body protective uniforms (made from rubber, vinyl, charcoal-impregnated polyurethane, and other materials) in desert conditions under extreme temperatures. Although no clinical syndrome was ever definitively confirmed among the nearly 1 million service members who deployed in 1990–1991, studies consistently found that military personnel who served in the Gulf experienced elevations in generalized symptoms across all health domains (e.g., physical, cognitive, neurologic, psychological) compared with service members who deployed elsewhere or did not deploy. In addition, there is good evidence that deployment to the Persian Gulf region during this period was associated with subsequent development of PTSD; other psychiatric disorders including generalized anxiety disorder, depression, and substance use disorders **(Chap. 63)**; functional gastrointestinal symptoms such as irritable bowel syndrome; and chronic fatigue syndrome **(Chap. 59)**.

The conflicts in Iraq and Afghanistan led to similar debates as to whether postwar symptoms such as headaches, irritability, sleep disturbance, dizziness, and concentration problems are best attributed to concussion/mTBI or to PTSD. Numerous studies showed that either PTSD or depression explained the majority of the postdeployment "postconcussive" symptoms attributed to concussion/mTBI, a finding not well received by many experts in traumatic brain injury (TBI) but consistent with civilian studies on risk factors for developing persistent symptoms after concussion. As in past wars, the polarized nature of the debate largely focused on only the two conditions of PTSD and concussion/mTBI, which has interfered with full appreciation of how the large spectrum of deployment-related health concerns interrelate and of the clinical implications for designing effective evaluation and treatment strategies.

Veterans understandably may become angry at the suggestion that their postwar health concerns could be "stress-related" or psychological, and thus it is necessary for primary care professionals to be able to discuss the physical toll that war-zone service has on the body, the generalized nature of war-related health concerns, and the likely underlying physiologic neuroendocrine and ANS contributors. Mental health specialists also need to be able to reinforce this message and understand the important role they have in promoting physical health through addressing comorbid health concerns.

PTSD

PTSD **(Chap. 61)** is the most common mental disorder documented following war-zone service. Studies from the conflicts in Iraq and Afghanistan found PTSD prevalence rates of 2–6% before deployment (comparable to civilian general population samples) and rates of 6–20% after deployment, depending primarily on the level of combat frequency and intensity. Many other veterans experience subclinical PTSD symptoms after war-zone service, sometimes termed posttraumatic stress (PTS) or combat stress. These subclinical symptoms can contribute to distress and affect health, even if overall functioning is not as impaired as in the full disorder.

The definition of PTSD was modified in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual *of* Mental Disorders (2013), although most individuals who had PTSD diagnosed according to the previous criteria also meet the definition under the new criteria. PTSD is defined as persistent (>1 month) symptoms occurring after a traumatic event (involving exposure to actual or threatened death, serious injury, or sexual assault). The symptoms must be associated with significant distress or impairment in social or occupational functioning. Symptoms are

www.ketabpezeshki.com (021) 66485457 - 66485438

grouped into four categories: (1) intrusion/reexperiencing symptoms in which the person has nightmares, flashbacks, or intrusive (often involuntary) memories connected with the traumatic event; (2) avoidance symptoms where the person avoids distressing memories or people, places, situations, or other stimuli that serve as reminders of the traumatic event (for example, a crowded mall that triggers heightened alertness to threat); (3) negative alterations of cognitions or mood (for example, feeling detached or losing interest in things that previously brought enjoyment); and (4) hyperarousal symptoms in which the person is physiologically revved up, hyperalert, startles easily, and experiences sleep disturbance, anger, and/or concentration problems. Although PTSD is a clinical symptom-based case definition, it is best to think of PTSD not as an emotional or psychological/psychiatric condition, but rather as a physiologically-based response to life-threatening trauma that is associated with physical, cognitive, emotional, and psychological symptoms.

PTSD has strong biologic correlates, based in fear-conditioning responses to threat and responses to extreme stress involving neuroendocrine dysregulation and ANS reactivity. Numerous studies have shown that PTSD is highly correlated with generalized physical and cognitive symptoms—including hypertension, chronic pain, and cardiovascular disease—as well as cell-mediated immune dysfunction and shortened life expectancy. PTSD is frequently comorbid with other mental disorders such as major depressive disorder, generalized anxiety, substance use disorders, and risky behaviors (e.g., aggression, accidents); it has been estimated that up to 80% of patients with PTSD exhibit one or more comorbid conditions. Misuse of alcohol or substances is most prevalent, often reflecting self-medication. PTSD is also associated with tolerance and withdrawal symptoms related to prescription pain and sleep medications, as well as nicotine dependence **(Chap. 66)**.

Clinicians should understand how to provide meaningful psychological education in a way that resonates with veterans who may have PTSD symptoms as a result of their military service. T ere is an important occupational context to consider, which is also applicable to trauma exposures that occur in other first responder professions, such as law enforcement of - cers and firefighters. Service members and other first responders are trained to respond to traumatic events and effectively learn to override automatic fight-or-flight reflexes in order to carry out their duties. Reactions that are labeled as symptoms of PTSD are based on adaptive survival responses that are beneficial in a combat environment. For example, physiologic hyperarousal, use of anger, and being able to shut down other emotions are very useful skills in combat and can be present even prior to traumatic events during tough realistic training. It is natural for these responses to persist after returning home, and the label of a "disorder" only gets applied when the responses that persist significantly impair functioning.

CONCUSSION/mTBI

TBI **(Chap. 44)** gained increased recognition during the conflicts in Iraq and Afghanistan because of the widespread exposure of troops to improvised explosive devices. Many veterans of Iraq and Afghanistan reported experiencing multiple concussions during deployments, and many also reported ignoring concussions and not seeking treatment at the time of injury in order to remain with their unit. However, these legitimate concerns were also counterbalanced and challenged by high prevalence estimates of deployment-related TBI that did not distinguish concussion/mTBI from moderate or severe TBI; data from animal models of blast exposure that did not necessarily extrapolate to human experiences on the battlefield; neuroimaging studies (e.g., diffusion tensor imaging) that attributed putative abnormalities to blast exposure but lacked adequate control comparisons; and fear-provoking speculation that repetitive blast exposure may lead to future dementia, based largely on case series of professional athletes (e.g., boxers, football players) exposed to highly repetitive injuries linked to chronic traumatic encephalopathy (previously termed dementia pugilistica) **(Chap. 30)**.

TBI includes closed and penetrating head injuries; closed head injuries are categorized as mild (mTBI or concussion), moderate, or severe based on the duration of loss of consciousness, duration of posttraumatic amnesia, and the Glasgow coma score (GCS) **(see Table 44-2)**. Several studies have estimated that 10–20% of all military personnel deployed to Iraq or Afghanistan sustained one or more concussion/mTBI events during deployment, most commonly from exposure to blasts; however, concussion injuries are also common in non-deployed environments from sports, training (e.g., hand-to-hand combatives), and accidents.

Although there is a neurophysiologic continuum of injury, there are stark clinical and epidemiologic distinctions between concussion/mTBI and moderate or severe TBI **(Table 62-1)**. Concussion/mTBI is defined as a blow or jolt to the head that results in brief loss of consciousness (LOC) for <30 min (most commonly, only a few seconds to minutes), posttraumatic amnesia (PTA) of <24 h (most commonly <1 h), or transient alteration in consciousness (AOC) without LOC. T e majority of concussions in Iraq or Afghanistan involved AOC without LOC or PTA (which soldiers may refer to as getting their "bell rung"). GCSs in concussion/mTBI are usually normal (15 out of 15). Concussion is treated

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 62-1

COMPARISON BETWEEN CONCUSSION/MILD TRAUMATIC BRAIN INJURY (TBI) AND MODERATE/SEVERE TBI

	MILD TBI (CONCUSSION)	MODERATE/SEVERE TBI
Clinical case definition		
Loss of consciousness	<30 min (usually a few seconds to minutes)	≥30 min to indefinite
Altered consciousness	<24 h (usually <30 min)	≥24 h to indefinite
Posttraumatic amnesia	<24 h (usually <30 min)	≥24 h to indefinite
Glasgow coma score	13–15 (usually 15)	As low as 3
Focal neurologic signs	None or transient	Frequently present
Traditional neuroimaging (CT/MRI)	Usually negative	Diagnostic
Clinical usefulness of neurocognitive testing after acute injury period	Usually inconclusive	Essential and valuable
Neuronal cell damage	Metabolic/ionic processes associated with axonal swelling, which can lead to disconnection	Direct injury effects plus metabolic/ionic effects
Sequelae, natural history, and recovery	Full recovery expected in majority of individuals; no consensus on natural history; the percentage who develop persistent symptoms is debated	Based directly on injury characteristics; may be severely disabling
Predictors of persistent postconcussive symptoms or disability	Intensely debated; risk factors found to be most predictive include psychiatric conditions (e.g., depression, PTSD) and negative expectations	Not debated; predictors are directly related to injury severity and clinical progress with rehabilitation treatment

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder.

with rest to allow the brain time to heal, and it almost never resulted in air evacuation from Iraq or Afghanistan unless there were other associated injuries.

In contrast, moderate, severe, or penetrating TBI, which is estimated to account for <1% of all battlefield head injuries in Iraq and Afghanistan, is characterized by LOC ≥30 min (up to permanent coma), PTA ≥24 h (also may be permanent), and GCSs as low as 3 (the minimum value). T ese virtually always result in air evacuation from the battlefield and carry a significant risk of severe long-term neurologic impairment and requirement for rehabilitative care.

Symptoms following concussion/mTBI can include headache; fatigue; concentration, memory, or attention problems; sleep disturbance; irritability; balance dif - culties; and tinnitus, among other symptoms. Recovery is usually rapid, with symptoms usually resolving in a few hours to days, but in a small percentage of patients, symptoms may persist for a longer period or become chronic (referred to as persistent "postconcussive symptoms" [PCS]).

Establishing a clear causal connection between a deployment concussion injury and persistent PCS months or years after return from deployment has been dif cult and often confounded by other postwar conditions that are associated with the same symptoms, including injuries not involving the head, other medical disorders, sleep disorders, PTSD, depression, grief, substance use disorders, chronic pain, and the generalized physiologic effects of wartime service. Contributing to the dif culty in establishing causation is the fact that the concussion/mTBI case definition refers only to the acute injury event and lacks symptoms, time course, or impairment; case definitions for persistent postconcussion syndrome have failed tests of validation. Numerous studies found that PTSD and depression were much stronger predictors of PCS and objective neuropsychological impairment after combat deployment than concussions/mTBIs, and one study even found that bereavement (particularly related to the death of a team member) was as strong a predictor of postdeployment symptoms and poor general health as were symptoms of depression or PTSD. T ese data do not minimize the importance of concussion/mTBI per se, but highlight the complex interrelationships of war-related health problems and the relatively lower importance of concussion/mTBI in overall postdeployment health than is generally thought.

Studies of veterans who sustained concussions in Iraq or Afghanistan have suggested that blast mechanisms produce similar clinical outcomes as nonblast mechanisms, in contrast to expectations based on some animal models. An explosion can produce serious injury from rapid atmospheric pressure changes

www.ketabpezeshki.com (021) 66485457 - 66485438

(primary blast wave mechanism), as well as from munition fragments/flying debris (secondary blast mechanism) or being thrown into a hard object (tertiary blast mechanism). Secondary and tertiary mechanisms are similar to other mechanical mechanisms of concussions sustained during accidents. It is likely that blast physics explains differences between human clinical studies and experimental animal studies. Because the distribution of munition fragments usually extends well beyond the distribution of the primary blast wave in most explosions, the possibility of a unique head injury solely from the primary blast wave in otherwise uninjured service members appears to be very low.

Multisystem health problems that lack clear case definitions do not lend themselves well to uniform public health strategies such as screening. Nevertheless, mass population screening for concussion/mTBI was mandated for all U.S. service members returning from Iraq or Afghanistan and all veterans presenting for care at VA health care facilities. T ese screening processes attempt to apply the acute concussion case definition (lacking symptoms, time course, or impairment) months or years after injury, and often involve questions that encourage patients and clinicians to make a direct link between current symptoms and past head injuries that likely have very little to do with the current symptoms. T ese screening approaches led to sharp criticism that they were encouraging clinicians to misattribute common postwar symptoms to concussion/mTBI. Nevertheless, the screening processes have persisted and are part of an extensive specialty structure of care erected in both the DoD and VA to address health concerns attributed to concussions/mTBIs.

Management of postwar physical and cognitive health concerns is largely symptom focused and ideally carried out within primary care–based structures of care. Studies suggest that optimal strategies for treatment of multisymptom health concerns include regularly scheduled primary care visits with brief physical exam at each visit, protecting patients from unnecessary diagnostic tests and non-evidence-based interventions, judicious use of consultations that protects patients from unnecessary specialty referrals, care/case management, and communication that enhances positive expectations for recovery. Concussion research has shown that negative expectations are one of the most important risk factors for persistent symptoms.

Although many questions remain regarding the long-term health effects of concussions (particularly multiple concussions) sustained during deployment, these are important battlefield injuries that require careful attention. However, they need to be addressed within the context of a much broader approach to other war-related health concerns.

STIGMA AND BARRIERS TO CARE

Stigma and other barriers to care add to the complexity of treating veterans. Despite extensive education efforts among military leaders and service members, perceptions of stigma showed little change over the many years of war; warriors are often concerned that they will be perceived as weak by peers or leaders if they seek care. Studies have shown that less than one-half of service members and veterans with serious mental health problems receive needed care, and upwards of half of those who begin treatment drop out before receiving an adequate number of encounters. Many factors contribute to this, including the pervasive nature of stigma in society in general (particularly among men), the critical importance of group cohesiveness of military teams, the nature of avoidance symptoms in PTSD, perceptions of self-suf ciency (e.g., “I can handle problems on my own”), and sometimes negative perceptions of mental health care and skepticism that mental health professionals will be able to help.

APPROACH TO THE PATIENT: Evaluation of Veterans with Neuropsychiatric Health Concerns

Evaluation should begin with a careful occupational history as part of the routine medical evaluation; this includes the number of years served, military occupation, deployment locations and dates, illnesses or injuries resulting from service, and significant combat traumatic experiences that may be continuing to affect the individual **(Table 62-2)**. T e clinician should evaluate the degree to which the patient’s current dif culties reflect the normal course of readjusting after the intense occupational experience of combat. It is helpful to reinforce the many strengths associated with being a professional in the military: courage, honor, service to country, resiliency in combat, leadership, ability to work in a cohesive workgroup with peers, and demonstrated skills in handling extreme stress, as well as the fact that reactions that interfere with functioning back home may have their roots in beneficial adaptive physiologic processes.

One of the challenges with current medical practice is that there may be multiple providers with different clinical perspectives. Care should be coordinated through the primary care clinician, with the assistance of a care manager if needed. It is particularly important to continually evaluate all medications prescribed by other practitioners and assess each for possible long-term side effects, dependency, or drug-drug interactions. Particular attention should be given to the level of chronic pain and sleep disturbance, self-medication with alcohol or substances, chronic use of nonsteroidal anti-inflammatory agents

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 62-2

SPECIFIC CONSIDERATIONS IN THE MEDICAL EVALUATION OF VETERANS	
Occupational context of health concerns	Deployment locations and dates, combat experiences or other deployment stressors, frequent moves, separations from family, impact of deployment on civilian occupation (for reservists)
Medical problems during deployment	History of deployment-related injuries (including concussions), environmental exposures, sleep pattern during deployment, use of caffeine/energy drinks, use of other substances
Current medical history	Current symptoms, level of chronic pain, sleep problems, evidence of persistent physiologic hyperarousal (hypertension, tachycardia, panic symptoms, concentration/memory problems, irritability/anger, sleep disturbance), chronic use of caffeine or energy drinks, chronic use of nonsteroidal anti-inf ammatory medications, chronic use of narcotic pain medications, chronic use of nonbenzodiazepine sedative-hypnotic medications, chronic use of benzodiazepines for sleep or anxiety
Mental health assessment	Screen for PTSD, major depressive disorder; ask about suicidal or homicidal ideation, intent, or plans, as well as access to firearms
Alcohol/substance use	Screen for alcohol and substance use disorders, quantity and frequency of use, and evidence of tolerance; inquire about "self-medication"(e.g., use of alcohol to sleep, "calm down," or "forget" war-zone experiences)
Functional impairment	Impact of current symptoms on social and occupational functioning; high-risk behaviors (e.g., drinking and driving, reckless driving, aggression)
Social support, impact of military service on marriage and family	Level of social support; readjustment stress on spouse, children, or other family members

Abbreviation: PTSD, posttraumatic stress disorder.

(which can contribute to rebound headaches or pain), chronic use of sedative-hypnotic agents, chronic use of narcotic pain medications, and the impact of war-related health concerns on social and occupational functioning.

Screening for PTSD, depression, and alcohol misuse should be performed routinely in all combat veterans. T ree screening tools, which are in the public domain, have been validated for use in primary care, and have been used frequently in veterans: the four-question Primary Care PTSD Screen (PC-PTSD), the two-question Patient Health Questionnaire (PHQ-2), and the three-question Alcohol Use Disorders Identification Test-Consumption module (AUDIT-C) **(Table 62-3)**.

Because the clinical definition of an acute concussion/mTBI does not include symptoms, time course, or impairment, there is currently no clinically validated screening process for use months or years after injury. However, it is important to gather information about all injuries sustained during deployment, including any that resulted in loss or alteration of consciousness or loss of memory around the time of the event. If concussion injuries have occurred, the clinician should assess the number of such injuries, the duration of time unconscious, and injury mechanisms. T is should be followed by an assessment of any PCS immediately following the injury event (e.g., headaches, dizziness, tinnitus, nausea, irritability, insomnia, and concentration or memory problems) and the severity and duration of such symptoms.

TREATMENT Neuropsychiatric Illnesses in War Veterans

Given the interrelationship of postwar health concerns, care needs to be carefully coordinated. Specific techniques that have been found to be helpful include scheduling regular primary care visits instead of as-needed visits, establishing care management, using good risk-communication principles, establishing a consultative step care approach that draws on the expertise of specialists in a collaborative manner (instead of immediately referring the patient to a specialist and relying on the specialist to provide care), and having behavioral health support directly within primary care clinics (both for referrals and to provide education and support to primary care professionals prescribing treatment for depression or PTSD).

It is important not to implicitly or explicitly convey the message that physical or cognitive symptoms are psychological or due to "stress." Even if depression or anxiety plays a large role in the etiology of physical health symptoms, the treatment approach should be designed within a patient-centered primary care structure, and referrals should be managed from within this framework. For example, it might help to explain that the primary goal of referral to a mental health professional is to improve sleep and reduce physiologic hyperarousal, which in turn will help with treatment of war-related chronic headaches, concentration problems, or chronic fatigue. If, however, the primary care professional conveys the message that the cause of headaches or concentration problems is anxiety or depression, and this conflicts

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 62-3

PRIMARY CARE MENTAL HEALTH SCREENING TOOLS

PC-PTSD Screen

1. Have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you:		
Have had nightmares about it or thought about it when you did not want to?	Yes	No
Tried hard not to think about it or went out of your way to avoid situations that remind you of it?	Yes	No
Were constantly on guard, watchful, or easily startled?	Yes	No
Felt numb or detached from others, activities, or your surroundings?	Yes	No

Note: Two or more "yes" responses (three or more a more specific cutoff) are considered a positive screen.
Source: A Prins et al: The Primary Care PTSD Screen (PC-PTSD): Development and operating characteristics. Prim Care Psychiatr 9:9, 2004.

PHQ-2 Depression Screen

2. Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all (0)**	**Few or several days (1)**	**More than half the days (2)**	**Nearly every day (3)**
Little interest or pleasure in doing things.	0	1	2	3
Feeling down, depressed, or hopeless.	0	1	2	3

Note: If either (or both) questions are marked 2 or 3 (more than half the days or higher), this is considered a positive screen for depression.
Source: K Kroenke et al: The Patient Health Questionnaire-2: Validity of a two-item depression screener. Med Care 41:1284, 2003.

AUDIT-C Alcohol Screen

3a. How often do you have a drink containing alcohol?				
Never (0)	Monthly or less (1)	Two or four times a month (2)	Two to three times per week (3)	Four or more times a week (4)
3b. How many drinks containing alcohol do you have on a typical day when you are drinking?				
1 or 2 (0)	3 or 4 (1)	5 or 6 (2)	7 or 9 (3)	10 or more (4)
3c. How often do you have six or more drinks on one occasion?				
Never (0)	Less than Monthly (1)	Monthly (2)	Two to three times per week (3)	Four or more times a week (4)

Note: A positive AUDIT-C screen is defined as a total score for men ≥4; for women ≥3. A report of drinking 6 or more drinks on one occasion should prompt an in-depth assessment of drinking.
Source: K Bush et al: The AUDIT Alcohol Consumption Questions (AUDIT-C): An effective brief screening test for problem drinking. Arch Intern Med 158:1789, 1998.

with the patient's own viewpoint, then this could damage therapeutic rapport and in turn exacerbate the symptoms.

Specific questions related to military service (Table 62-2) combined with screening for depression, PTSD, and alcohol use disorders (Table 62-3) should be a routine part of care for all veterans. A positive screen for depression or PTSD should prompt follow-up questions related to these disorders (or use of a longer screening tool such as the nine-question Patient Health Questionnaire or National Center for PTSD Checklist), as well as risk assessment for suicide or homicide. It is important to assess the impact of depression or PTSD symptoms on occupational functioning and interpersonal relationships.

A positive screen for alcohol misuse should prompt a brief motivational intervention that includes bringing attention to the elevated level of drinking, informing the veteran about the effects of alcohol on health, recommending limiting use or abstaining, exploring and setting goals related to drinking behavior, and follow-up and referral to specialty care if needed. T is type of brief primary care intervention has been found to be effective and should be incorporated into routine practice. One way to facilitate dialogue about this topic with veterans is to point out how hyperarousal associated with combat service can lead to increased craving for alcohol as the body searches for ways to modulate this. Veterans may

www.ketabpezeshki.com (021) 66485457 - 66485438

consciously or unconsciously drink more to help with sleep, reduce arousal, or avoid thinking about events that happened "downrange." A key educational strategy is to help the veteran to learn that drinking to get to sleep actually damages sleep architecture and makes sleep worse (e.g., reduces rapid eye movement [REM] sleep initially followed by rebound REM activity and early morning wakening).

SPECIFIC TREATMENT STRATEGIES FOR PTSD AND COMORBID DEPRESSION

PTSD and depression are highly comorbid in combat veterans, and the evidence-based treatments are similar, involving antidepressant medications, cognitive behavioral therapy (CBT), or both. Psychoeducation that assists veterans to understand that their symptoms of PTSD have a basis in adaptive survival mechanisms and skills they exhibited in combat can facilitate therapeutic rapport. Remaining hypervigilant to threat, being able to shut down emotions, being able to function on less sleep, and using anger to help focus and control fear are all adaptive beneficial survival skills in a combat environment. Therefore, PTSD for warriors is both a medical disorder and a set of reactions that have their roots in the physiologic adaptation and skills they successfully applied in combat.

It is important to know that combat is not the only important trauma in a war-zone environment. Rape, assault, and accidents also occur. Rape or assault by a fellow service member, which affects a greater number of women veterans, but also occurs in men, can be particularly devastating because it destroys the vital feeling of safety that individuals derive from their own unit peers in a war environment.

The treatments for PTSD considered by most consensus guideline committees to have an A level of evidence include CBTs and medications, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), with the strongest evidence from double-blind, placebo-controlled studies for sertraline, paroxetine, fluoxetine, and venlafaxine (of which paroxetine and sertraline received U.S. Food and Drug Administration approval for PTSD). **(See Table 61-3 for recommended dosages.)** Prazosin has also gained very strong evidence recently through randomized placebo-controlled studies for its effectiveness in controlling nightmares as well as global PTSD symptoms, through modulation of the physiologic processes associated with PTSD.

CBT interventions include narrative therapy (often called "imaginal exposure"), in vivo exposure focused on retraining the body not to react to stimuli related to traumatic reminders (e.g., a crowded mall), and techniques to modulate physiologic hyperarousal (e.g., diaphragmatic breathing, progressive muscle relaxation). A number of complementary alternative medicine approaches including acupuncture, mindfulness meditation, yoga, and massage are also being used in PTSD. Although not evidence-based treatments per se, if they facilitate a relaxation response and alleviation of hyperarousal or sleep symptoms, they can be considered useful adjunctive modalities.

There have been no head-to-head comparisons of medication compared with psychotherapy for treatment of PTSD. It is reasonable for primary care clinicians to consider initiating treatment for mild to moderate PTSD symptoms with an SSRI and to refer patients to a mental health professional if there are more severe symptoms, significant comorbidity, safety concerns, or limited response to initial treatment. All PTSD treatments are associated with a sizable proportion of individuals who fail to respond adequately, and it is often necessary to add modalities or switch treatment. SNRIs may be useful alternatives to SSRIs if there has been nonresponse or side effects with SSRIs or if there is comorbid pain (duloxetine, in particular, has indications for pain). Both SSRIs and SNRIs can increase anxiety initially; patients should be warned about this possibility, and treatment should be initiated with the lowest recommended dose (or even one-half of the lowest dose for a few days) and gradually increased thereafter. Antidepressants also are likely to be useful in comorbid depression, which is common in veterans with PTSD. All antidepressants have potential drug-drug interactions that must be considered.

Many other medications have been used in PTSD, including tricyclic antidepressants, benzodiazepines, atypical antipsychotics, and anticonvulsants. In general, these should be prescribed in conjunction with psychiatric consultation because of their greater side effects and risks. Benzodiazepines, in particular, should be avoided in the treatment of PTSD. Studies have shown that they do not reduce core PTSD symptoms, are likely to exacerbate substance use disorders that are common in veterans with PTSD, and may produce significant rebound anxiety and anger. Individuals with PTSD often report symptomatic relief upon initiation of a benzodiazepine, but this is generally short lived and associated with a high risk of tolerance and dependence that can worsen recovery. Atypical antipsychotics, which have gained widespread popularity as adjunctive treatment for depression, anxiety, or sleep problems, have significant long-term side effects, including metabolic effects (e.g., glucose dysregulation), weight gain, and cardiovascular risks.

Sleep disturbance should be addressed initially with sleep hygiene education, followed by consideration of an antihistamine, trazodone, low-dose mirtazapine, or nonbenzodiazepine sedative-hypnotic such as zolpidem, eszopiclone, or zaleplon. However, the nonbenzodiazepine sedative-hypnotics should be used with caution in veterans because they can lead to tolerance and rebound sleep problems similar to those seen with benzodiazepine use.

TREATMENT STRATEGIES FOR CONCUSSION/mTBI AND POSTDEPLOYMENT POSTCONCUSSIVE SYMPTOMS

Concussion/mTBI is best treated at the time of injury with education and rest to allow time for the brain to heal and protect against a second impact syndrome (a rare but life-threatening event involving brain swelling that can occur when a second concussion occurs before the brain has adequately healed from an initial event). Randomized trials have shown that education regarding

www.ketabpezeshki.com (021) 66485457 - 66485438

concussion that informs the patient of what to expect and promotes the expectation of recovery is the most effective treatment in preventing persistent symptoms.

Once service members return from deployment and seek care for postwar health problems, treatment is largely symptom focused, following the principles of patient-centered and collaborative care models. Cognitive rehabilitation, which is very useful in moderate and severe TBI to improve memory, attention, and concentration, has generally not been shown to be effective for mTBI in randomized clinical studies, although consensus groups have supported its use.

General recommendations for the clinical management of persistent, chronic PCS include treating physical and cognitive health problems based on symptom presentation, coexisting health problems, and individual preferences; and addressing coexisting depression, PTSD, substance use disorders, or other factors that may be contributing to symptom persistence. Headache is the most common symptom associated with concussion/mTBI, and the evaluation and treatment of headache parallels that for other causes of headache **(Chaps. 9 and 34)**. Stimulant medications for alleviating neurocognitive effects attributed to concussion/mTBI are not recommended. Clinicians should be aware of the potential for cognitive or sedative side effects of certain medications that may be prescribed for depression, anxiety, sleep, or chronic pain.

Treatment of neuropsychiatric problems must be coordinated with care for other war-related health concerns, with the goal of treatment to reduce the severity of symptoms, improve social and occupational functioning, and prevent long-term disability. Understanding the occupational context of war-related health concerns is important in communicating with veterans and developing a comprehensive treatment strategy.

Disclosure

The opinions or assertions contained herein are the private views of the author and are not to be construed as official, or as reflecting the views of the Department of the Army or the Department of Defense.

www.ketabpezeshki.com (021) 66485457 - 66485438

SECTION VI

ALCOHOLISM AND DRUG DEPENDENCY

CHAPTER 63

ALCOHOL AND ALCOHOLISM

Marc A. Schuckit

Alcohol (beverage ethanol) distributes throughout the body, affecting almost all systems and altering nearly every neurochemical process in the brain. T is drug is likely to exacerbate most medical problems, affect medications metabolized in the liver, and temporarily mimic many medical (e.g., diabetes) and psychiatric (e.g., depression) conditions. T e lifetime risk for repetitive alcohol problems is almost 20% for men and 10% for women, regardless of a person's education or income. Although low doses of alcohol might have healthful benefits, greater than three standard drinks per day enhances the risk for cancer and vascular disease, and alcohol use disorders decrease the life span by about 10 years. Unfortunately, most clinicians have had only limited training regarding alcohol-related disorders. T is chapter presents a brief overview of clinically useful information about alcohol use and problems.

PHARMACOLOGY AND NUTRITIONAL IMPACT OF ETHANOL

Ethanol blood levels are expressed as milligrams or grams of ethanol per deciliter (e.g., 100 mg/dL = 0.10 g/dL), with values of ~0.02 g/dL resulting from the ingestion of one typical drink. In round figures, a standard drink is 10–12 g, as seen in 340 mL (12 oz) of beer, 115 mL (4 oz) of nonfortified wine, and 43 mL (1.5 oz) (a shot) of 80-proof beverage (e.g., whisky); 0.5 L (1 pint) of 80-proof beverage contains ~160 g of ethanol (about 16 standard drinks), and 750 mL of wine contains ~60 g of ethanol. T ese beverages also have additional components (congeners) that affect the drink's taste and might contribute to adverse effects on the body. Congeners include methanol, butanol, acetaldehyde, histamine, tannins, iron, and lead. Alcohol acutely decreases neuronal activity and has similar behavioral effects and cross-tolerance with other depressants, including benzodiazepines and barbiturates.

Alcohol is absorbed from mucous membranes of the mouth and esophagus (in small amounts), from the stomach and large bowel (in modest amounts), and from the proximal portion of the small intestine (the major site). T e rate of absorption is increased by rapid gastric emptying (as seen with carbonation); by the absence of proteins, fats, or carbohydrates (which interfere with absorption); and by dilution to a modest percentage of ethanol (maximum at ~20% by volume).

Between 2% (at low blood alcohol concentrations) and 10% (at high blood alcohol concentrations) of ethanol is excreted directly through the lungs, urine, or sweat, but most is metabolized to acetaldehyde, primarily in the liver. T e most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is then rapidly destroyed by aldehyde dehydrogenase (ALDH) in the cytosol and mitochondria **(Fig. 63-1)**. A second pathway occurs in the microsomes of the smooth endoplasmic reticulum (the microsomal ethanol-oxidizing system, or MEOS) that is responsible for ≥10% of ethanol oxidation at high blood alcohol concentrations.

Although a drink contains ~300 kJ, or 70–100 kcal, these are devoid of minerals, proteins, and vitamins. In addition, alcohol interferes with absorption of vitamins in the small intestine and decreases their storage in the liver with modest effects on folate (folacin or folic acid), pyridoxine (B_6), thiamine (B_1), nicotinic acid (niacin, B_3), and vitamin A.

Heavy drinking in a fasting, healthy individual can produce transient hypoglycemia within 6–36 h, secondary to the acute actions of ethanol on gluconeogenesis. T is can result in temporary abnormal glucose tolerance tests (with a resulting erroneous diagnosis of diabetes mellitus) until the alcoholic has abstained for 2–4 weeks. Alcohol ketoacidosis, probably reflecting a decrease in fatty acid oxidation coupled with poor diet or recurrent vomiting, can be misdiagnosed as diabetic ketosis. With the former, patients show an increase in

www.ketabpezeshki.com (021) 66485457 - 66485438

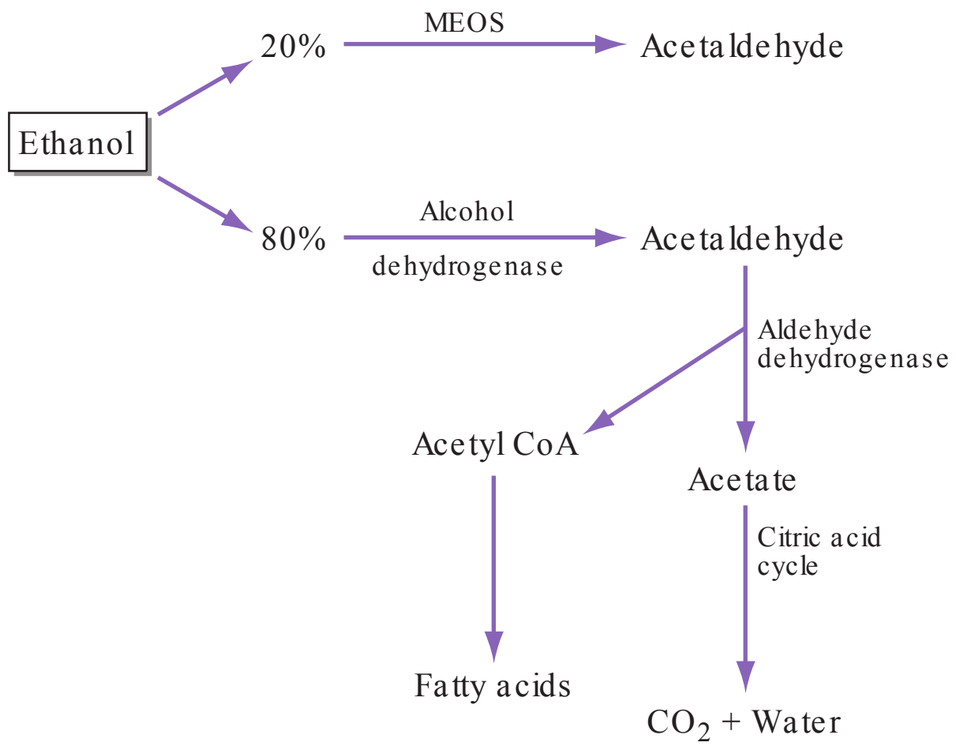


FIGURE 63-1
The metabolism of alcohol. CoA, coenzyme A; MEOS, microsomal ethanoloxidizing system.

serum ketones along with a mild increase in glucose but a large anion gap, a mild to moderate increase in serum lactate, and a β-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 (with normal being 1:1).

In the brain, alcohol affects almost all neurotransmitter systems, with acute effects that are often the opposite of those seen following desistance after a period of heavy drinking. The most prominent actions relate to boosting γ-aminobutyric acid (GABA) activity, especially at $GABA_A$ receptors. Enhancement of this complex chloride channel system contributes to anticonvulsant, sleep-inducing, antianxiety, and muscle relaxation effects of all GABA-boosting drugs. Acutely administered alcohol produces a release of GABA, and continued use increases density of $GABA_A$ receptors, whereas alcohol withdrawal states are characterized by decreases in GABA-related activity. Equally important is the ability of acute alcohol to inhibit postsynaptic N-methyl-d-aspartate (NMDA) excitatory glutamate receptors, whereas chronic drinking and desistance are associated with an upregulation of these excitatory receptor subunits. The relationships between greater GABA and diminished NMDA receptor activity during acute intoxication and diminished GABA with enhanced NMDA actions during alcohol withdrawal explain much of intoxication and withdrawal phenomena.

As with all pleasurable activities, alcohol acutely increases dopamine levels in the ventral tegmentum and related brain regions, and this effect plays an important role in continued alcohol use, craving, and relapse. The changes in dopamine pathways are also linked to increases in "stress hormones," including cortisol and adrenocorticotropic hormone (ACTH) during intoxication and withdrawal. Such alterations are likely to contribute to both feelings of reward during intoxication and depression during falling blood alcohol concentrations. Also closely linked to alterations in dopamine (especially in the nucleus accumbens) are alcohol-induced changes in opioid receptors, with acute alcohol causing release of beta endorphins.

Additional neurochemical changes include increases in synaptic levels of serotonin during acute intoxication and subsequent upregulation of serotonin receptors. Acute increases in nicotinic acetylcholine systems contribute to the impact of alcohol in the ventral tegmental region, which occurs in concert with enhanced dopamine activity. In the same regions, alcohol impacts on cannabinol receptors, with resulting release of dopamine, GABA, and glutamate as well as subsequent effects on brain reward circuits.

BEHAVIORAL EFFECTS, TOLERANCE, AND WITHDRAWAL

The acute effects of a drug depend on the dose, the rate of increase in plasma, the concomitant presence of other drugs, and past experience with the agent. "Legal intoxication" with alcohol in most states requires a blood alcohol concentration of 0.08 g/dL, but levels of 0.04 are cited in some other countries. However, behavioral, psychomotor, and cognitive changes are seen at 0.02–0.04 g/dL (i.e., after one to two drinks) **(Table 63-1)**. Deep but disturbed sleep can be seen at twice the legal intoxication level, and death can occur with levels between 0.30 and 0.40 g/dL. Beverage alcohol is probably responsible for more overdose deaths than any other drug.

Repeated use of alcohol contributes to acquired tolerance, a phenomenon involving at least three compensatory mechanisms. (1) After 1–2 weeks of daily drinking, metabolic or pharmacokinetic tolerance can be seen, with up to 30% increases in the rate of hepatic ethanol metabolism. This is alteration disappears almost

TABLE 63-1
EFFECTS OF BLOOD ALCOHOL LEVELS IN THE ABSENCE OF TOLERANCE

BLOOD LEVEL, G/DL	USUAL EFFECT
0.02	Decreased inhibitions, a slight feeling of intoxication
0.08	Decrease in complex cognitive functions and motor performance
0.20	Obvious slurred speech, motor incoordination, irritability, and poor judgment
0.30	Light coma and depressed vital signs
0.40	Death

www.ketabpezeshki.com (021) 66485457 - 66485438

as rapidly as it develops. (2) Cellular or pharmacodynamic tolerance develops through neurochemical changes that maintain relatively normal physiologic functioning despite the presence of alcohol. Subsequent decreases in blood levels contribute to symptoms of withdrawal. (3) Individuals learn to adapt their behavior so that they can function better than expected under influence of the drug (learned or behavioral tolerance).

T e cellular changes caused by chronic ethanol exposure may not resolve for several weeks or longer following cessation of drinking. Rapid decreases in blood alcohol levels before that time can produce a withdrawal syndrome, which is most intense during the first 5 days, but some symptoms (e.g., disturbed sleep and anxiety) can take up to 4–6 months to resolve.

THE EFFECTS OF ETHANOL ON ORGAN SYSTEMS

Relatively low doses of alcohol (one or two drinks per day) have potential beneficial effects of increasing high-density lipoprotein cholesterol and decreasing aggregation of platelets, with a resulting decrease in risk for occlusive coronary disease and embolic strokes. Red wine has additional potential health-promoting qualities at relatively low doses due to flavinols and related substances. Modest drinking might also decrease the risk for vascular dementia and, possibly, Alzheimer's disease. However, any potential healthful effects disappear with the regular consumption of three or more drinks per day, and knowledge about the deleterious effects of alcohol can both help the physician to identify patients with an alcohol use disorder and to supply them with information that might help motivate a change in behavior.

NERVOUS SYSTEM

Approximately 35% of drinkers (and a much higher proportion of alcoholics) experience a blackout, an episode of temporary anterograde amnesia, in which the person forgets all or part of what occurred during a drinking evening. Another common problem, one seen after as few as one or two drinks shortly before bedtime, is disturbed sleep. Although alcohol might initially help a person fall asleep, it disrupts sleep throughout the rest of the night. T e stages of sleep are altered, and time spent in rapid eye movement (REM) and deep sleep is reduced. Alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea; symptoms of the latter occur in 75% of alcoholic men older than age 60 years. Patients may also experience prominent and sometimes disturbing dreams later in the night. All of these sleep problems are more pronounced in alcoholics, and their persistence may contribute to relapse.

Another common consequence of alcohol use is impaired judgment and coordination, increasing the risk of injury. In the United States, ~40% of drinkers have at some time driven while intoxicated. Heavy drinking can also be associated with headache, thirst, nausea, vomiting, and fatigue the following day, a hangover syndrome that is responsible for much missed time and temporary cognitive deficits at work and school.

Chronic high doses cause peripheral neuropathy in ~10% of alcoholics: similar to diabetes, patients experience bilateral limb numbness, tingling, and paresthesias, all of which are more pronounced distally. Approximately 1% of alcoholics develop cerebellar degeneration or atrophy, producing a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus; neuroimaging studies reveal atrophy of the cerebellar vermis. Fortunately, very few alcoholics (perhaps as few as 1 in 500 for the full syndrome) develop Wernicke's (ophthalmoparesis, ataxia, and encephalopathy) and Korsakof 's (retrograde and anterograde amnesia) syndromes, although a higher proportion have one or more neuropathologic findings related to these conditions. T ese result from low levels of thiamine, especially in predisposed individuals with transketolase deficiencies. Alcoholics can manifest cognitive problems and temporary memory impairment lasting for weeks to months after drinking heavily for days or weeks. Brain atrophy, evident as ventricular enlargement and widened cortical sulci on magnetic resonance imaging (MRI) and computed tomography (CT) scans, occurs in ~50% of chronic alcoholics; these changes are usually reversible if abstinence is maintained. T ere is no single alcoholic dementia syndrome; rather, this label describes patients who have irreversible cognitive changes (possibly from diverse causes) in the context of chronic alcoholism.

Psychiatric comorbidity

As many as two-thirds of individuals with alcohol use disorders meet the criteria for another psychiatric syndrome in the fifth edition of the Diagnostic and Statistical Manual *of* Mental Disorders (DSM-5) of the American Psychiatric Association **(Chap. 61)**. Half of these relate to a preexisting antisocial personality manifesting as impulsivity and disinhibition that contribute to both alcohol and drug use disorders. T e lifetime risk is 3% in males, and ≥80% of such individuals demonstrate alcohol- and/or drug-related conditions. Another common comorbidity occurs with problems regarding illicit substances. T e remainder of alcoholics with psychiatric syndromes have preexisting conditions such as schizophrenia or manic-depressive disease and anxiety syndromes such as panic disorder. T e comorbidities of alcoholism with independent psychiatric disorders might represent an overlap in genetic vulnerabilities,

www.ketabpezeshki.com (021) 66485457 - 66485438

impaired judgment in the use of alcohol from the independent psychiatric condition, or an attempt to use alcohol to alleviate symptoms of the disorder or side effects of medications.

Many psychiatric syndromes can be seen temporarily during heavy drinking and subsequent withdrawal. T ese alcohol-induced conditions include an intense sadness lasting for days to weeks in the midst of heavy drinking seen in 40% of alcoholics, which tends to disappear over several weeks of abstinence (alcohol-induced mood disorder); temporary severe anxiety in 10–30% of alcoholics, often beginning during alcohol withdrawal, which can persist for a month or more after cessation of drinking (alcohol-induced anxiety disorder); and auditory hallucinations and/or paranoid delusions in a person who is alert and oriented, seen in 3–5% of alcoholics (alcohol-induced psychotic disorder).

Treatment of all forms of alcohol-induced psychopathology includes helping patients achieve abstinence and offering supportive care, as well as reassurance and "talk therapy" such as cognitive-behavioral approaches. However, with the exception of short-term antipsychotics or similar drugs for substance-induced psychoses, substance-induced psychiatric conditions only rarely require medications. Recovery is likely within several days to 4 weeks of abstinence. Conversely, because alcohol-induced conditions are temporary and do not indicate a need for long-term pharmacotherapy, a history of alcohol intake is an important part of the workup for any patient with one of these psychiatric symptoms.

THE GASTROINTESTINAL SYSTEM

Esophagus and stomach

Alcohol can cause inflammation of the esophagus and stomach causing epigastric distress and gastrointestinal bleeding, making alcohol one of the most common causes of hemorrhagic gastritis. Violent vomiting can produce severe bleeding through a Mallory-Weiss lesion, a longitudinal tear in the mucosa at the gastroesophageal junction.

Pancreas and liver

T e incidence of acute pancreatitis (~25 per 1000 per year) is almost threefold higher in alcoholics than in the general population, accounting for an estimated 10% or more of the total cases. Alcohol impairs gluconeogenesis in the liver, resulting in a fall in the amount of glucose produced from glycogen, increased lactate production, and decreased oxidation of fatty acids. T is contributes to an increase in fat accumulation in liver cells. In healthy individuals these changes are reversible, but with repeated exposure to ethanol, especially daily heavy drinking, more severe changes in the liver occur, including alcohol-induced hepatitis, perivenular sclerosis, and cirrhosis, with the latter observed in an estimated 15% of alcoholics. Perhaps through an enhanced vulnerability to infections, alcoholics have an elevated rate of hepatitis C, and drinking in the context of that disease is associated with more severe liver deterioration.

CANCER

As few as 1.5 drinks per day increases a woman's risk of breast cancer 1.4-fold. For both genders, four drinks per day increases the risk for oral and esophageal cancers approximately threefold and rectal cancers by a factor of 1.5; seven to eight or more drinks per day produces an approximately fivefold increased risk for many cancers. T ese consequences may result directly from cancer-promoting effects of alcohol and acetaldehyde or indirectly by interfering with immune homeostasis.

HEMATOPOIETIC SYSTEM

Ethanol causes an increase in red blood cell size (mean corpuscular volume [MCV]), which reflects its effects on stem cells. If heavy drinking is accompanied by folic acid deficiency, there can also be hypersegmented neutrophils, reticulocytopenia, and a hyperplastic bone marrow; if malnutrition is present, sideroblastic changes can be observed. Chronic heavy drinking can decrease production of white blood cells, decrease granulocyte mobility and adherence, and impair delayed-hypersensitivity responses to novel antigens (with a possible false-negative tuberculin skin test). Associated immune deficiencies can contribute to vulnerability toward infections, including hepatitis and HIV, and interfere with their treatment. Finally, many alcoholics have mild thrombocytopenia, which usually resolves within a week of abstinence unless there is hepatic cirrhosis or congestive splenomegaly.

CARDIOVASCULAR SYSTEM

Acutely, ethanol decreases myocardial contractility and causes peripheral vasodilation, with a resulting mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in cardiac oxygen consumption are higher after alcohol intake. T ese acute effects have little clinical significance for the average healthy drinker but can be problematic when persisting cardiac disease is present.

T e consumption of three or more drinks per day results in a dose-dependent increase in blood pressure, which returns to normal within weeks of abstinence. T us, heavy drinking is an important factor in mild to moderate hypertension. Chronic heavy drinkers also

www.ketabpezeshki.com (021) 66485457 - 66485438

have a sixfold increased risk for coronary artery disease, related, in part, to increased low-density lipoprotein cholesterol, and carry an increased risk for cardiomyopathy through direct effects of alcohol on heart muscle. Symptoms of the latter include unexplained arrhythmias in the presence of left ventricular impairment, heart failure, hypocontractility of heart muscle, and dilation of all four heart chambers with associated mural thrombi and mitral valve regurgitation. Atrial or ventricular arrhythmias, especially paroxysmal tachycardia, can also occur temporarily after heavy drinking in individuals showing no other evidence of heart disease—a syndrome known as the "holiday heart."

GENITOURINARY SYSTEM CHANGES, SEXUAL FUNCTIONING, AND FETAL DEVELOPMENT

Drinking in adolescence can affect normal sexual development and reproductive onset. At any age, modest ethanol doses (e.g., blood alcohol concentrations of 0.06 g/dL) can increase sexual drive but also decrease erectile capacity in men. Even in the absence of liver impairment, a significant minority of chronic alcoholic men show irreversible testicular atrophy with shrinkage of the seminiferous tubules, decreases in ejaculate volume, and a lower sperm count.

T e repeated ingestion of high doses of ethanol by women can result in amenorrhea, a decrease in ovarian size, absence of corpora lutea with associated infertility, and an increased risk of spontaneous abortion. Heavy drinking during pregnancy results in the rapid placental transfer of both ethanol and acetaldehyde, which may contribute to a range of consequences known as fetal alcohol spectrum disorder (FASD). One severe result is the *f*etal alcohol syndrome (FAS), seen in ~5% of children born to heavy-drinking mothers, which can include any of the following: facial changes with epicanthal eye folds; poorly formed ear concha; small teeth with faulty enamel; cardiac atrial or ventricular septal defects; an aberrant palmar crease and limitation in joint movement; and microcephaly with mental retardation. Less pervasive FASD conditions include combinations of low birth weight, a lower intelligence quotient (IQ), hyperactive behavior, and some modest cognitive deficits. T e amount of ethanol required and the time of vulnerability during pregnancy have not been defined, making it advisable for pregnant women to abstain completely.

OTHER EFFECTS

Between one-half and two-thirds of alcoholics have skeletal muscle weakness caused by acute alcoholic myopathy, a condition that improves but which might not fully remit with abstinence. Effects of repeated heavy drinking on the skeletal system include changes in calcium metabolism, lower bone density, and decreased growth in the epiphyses, leading to an increased risk for fractures and osteonecrosis of the femoral head. Hormonal changes include an increase in cortisol levels, which can remain elevated during heavy drinking; inhibition of vasopressin secretion at rising blood alcohol concentrations and enhanced secretion at falling blood alcohol concentrations (with the final result that most alcoholics are likely to be slightly overhydrated); a modest and reversible decrease in serum thyroxine (T_4); and a more marked decrease in serum triiodothyronine (T_3). Hormone irregularities should be reevaluated because they may disappear after a month of abstinence.

ALCOHOLISM (ALCOHOL USE DISORDER)

Because many drinkers occasionally imbibe to excess, temporary alcohol-related problems are common in nonalcoholics, especially in the late teens to the late twenties. However, repeated problems in multiple life areas can indicate an alcohol use disorder as defined in DSM-5.

DEFINITIONS AND EPIDEMIOLOGY

An alcohol use disorder is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period **(Table 63-2)**. Ten of the 11 items were taken directly from the 7 dependence and 4 abuse criteria in DSM-IV, after deleting legal problems and adding craving. Severity of an alcohol use disorder is based on the number of items endorsed: mild is two or three items; moderate is four or five; and severe is six or more of the criterion items. T e new diagnostic approach is similar enough to DSM-IV that the following descriptions of associated phenomena are still accurate.

T e lifetime risk for an alcohol use disorder in most Western countries is about 10–15% for men and 5–8% for women. Rates are similar in the United States, Canada, Germany, Australia, and the United Kingdom, tend to be lower in most Mediterranean countries, such as Italy, Greece, and Israel, and may be higher in Ireland, France, and Scandinavia. An even higher lifetime prevalence has been reported for most native cultures, including American Indians, Eskimos, Maori groups, and aboriginal tribes of Australia. T ese differences reflect both cultural and genetic influences, as described below. In Western countries, the typical alcoholic is more often a blue- or white-collar worker or homemaker. T e lifetime risk for alcoholism among physicians is similar to that of the general population.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 63-2

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FIFTH EDITION, CLASSIFICATION OF ALCOHOL USE DISORDER (AUD)

CRITERIA
Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an alcohol use disorder[a]:
Drinking resulting in recurrent failure to fulfill role obligations
Recurrent drinking in hazardous situations
Continued drinking despite alcohol-related social or interpersonal problems
Tolerance
Withdrawal, or substance use for relief/avoidance of withdrawal
Drinking in larger amounts or for longer than intended
Persistent desire/unsuccessful attempts to stop or reduce drinking
Great deal of time spent obtaining, using, or recovering from alcohol
Important activities given up/reduced because of drinking
Continued drinking despite knowledge of physical or psychological problems caused by alcohol
Alcohol craving

[a]Mild AUD: 2–3 criteria required; Moderate AUD: 4–5 items endorsed; severe AUD: 6 or more items endorsed.

GENETICS

Approximately 60% of the risk for alcohol use disorders is attributed to genes, as indicated by the fourfold higher risk in children of alcoholics (even if adopted early in life and raised by nonalcoholics) and a higher risk in identical twins compared to fraternal twins of alcoholics. The genetic variations operate primarily through intermediate characteristics that subsequently combine with environmental influences to alter the risk for heavy drinking and alcohol problems. These include genes relating to a high risk for all substance use disorders that operate through impulsivity, schizophrenia, and bipolar disorder. Another characteristic, an intense flushing response when drinking, decreases the risk for only alcohol use disorders through gene variations for several alcohol-metabolizing enzymes, especially aldehyde dehydrogenase (a mutation only seen in Asians), and to a lesser extent, variations in ADH.

An additional genetically influenced characteristic, a low sensitivity to alcohol, affects the risk for heavy drinking and may operate, in part, through variations in genes relating to calcium and potassium channels, GABA, nicotinic, and serotonin systems. A low response per drink is observed early in the drinking career and before alcohol use disorders develop. All follow-up studies have demonstrated that this need for higher doses of alcohol to achieve effects predicts future heavy drinking, alcohol problems, and alcohol use disorders. The impact of a low response to alcohol on adverse drinking outcomes is partially mediated by a range of environmental influences, including the selection of heavier-drinking friends, more positive expectations of the effects of high doses of alcohol, and suboptimal ways of coping with stress.

NATURAL HISTORY

Although the age of the first drink (~15 years) is similar in most alcoholics and nonalcoholics, a slightly earlier onset of regular drinking and drunkenness, especially in the context of conduct problems, is associated with a higher risk for later alcohol use disorders. By the midtwenties, most nonalcoholic men and women moderate their drinking (perhaps learning from problems), whereas alcoholics are likely to escalate their patterns of drinking despite difficulties. The first major life problem from alcohol often appears in the late teens to early twenties, and a pattern of multiple alcohol difficulties by the midtwenties. Once established, the course of alcoholism is likely to include exacerbations and remissions, with little difficulty in temporarily stopping or controlling alcohol use when problems develop, but without help, desistance usually gives way to escalations in alcohol intake and subsequent problems. Following treatment, between half and two-thirds of alcoholics maintain abstinence for years, and often permanently. Even without formal treatment or self-help groups, there is at least a 20% chance of spontaneous remission with long-term abstinence. However, should the alcoholic continue to drink heavily, the life span is shortened by ~10 years on average, with the leading causes of death being heart disease, cancer, accidents, and suicide.

TREATMENT

The approach to treating alcohol-related conditions is relatively straightforward: (1) recognize that at least 20% of all patients have an alcohol use disorder; (2) learn how to identify and treat acute alcohol-related conditions; (3) know how to help patients begin to address their alcohol problems; and (4) know enough about treating alcoholism to appropriately refer patients for additional help.

IDENTIFICATION OF THE ALCOHOLIC

Even in affluent locales, ~20% of patients have an alcohol use disorder. These men and women can be identified by asking questions about alcohol problems and noting laboratory test results that can reflect regular consumption of six to eight or more drinks per day. The two blood tests with ≥60% sensitivity and specificity for heavy alcohol consumption are γ-glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient transferrin (CDT) (>20 U/L or >2.6%); the combination of the two

www.ketabpezeshki.com (021) 66485457 - 66485438

is likely to be more accurate than either alone. The values for these serologic markers are likely to return toward normal within several weeks of abstinence. Other useful blood tests include high-normal MCVs (≥91 μm^3) and serum uric acid (>416 mol/L, or 7 mg/dL).

The diagnosis of an alcohol use disorder ultimately rests on the documentation of a pattern of repeated difficulties associated with alcohol (Table 63-2). Thus, in screening, it is important to probe for marital or job problems, legal difficulties, histories of accidents, medical problems, evidence of tolerance, and so on, and then attempt to tie in use of alcohol or another substance. Some standardized questionnaires can be helpful, including the 10-item Alcohol Use Disorders Identification Test (AUDIT) **(Table 63-3)**, but these are only screening tools, and a face-to-face interview is still required for a meaningful diagnosis.

TABLE 63-3

THE ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)[a]

ITEM	5-POINT SCALE (LEAST TO MOST)
1. How often do you have a drink containing alcohol?	Never (0) to 4+ per week (4)
2. How many drinks containing alcohol do you have on a typical day?	1 or 2 (0) to 10+ (4)
3. How often do you have six or more drinks on one occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

[a]The AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥8 may indicate harmful alcohol use.

TREATMENT Alcohol-Related Conditions

ACUTE INTOXICATION The first priority in treating severe intoxication is to assess vital signs and manage respiratory depression, cardiac arrhythmias, or blood pressure instability, if present. The possibility of intoxication with other drugs should be considered by obtaining toxicology screens for other central nervous system (CNS) depressants such as benzodiazepines and for opioids. Aggressive behavior should be handled by offering reassurance but also by considering a possible show of force with an intervention team. If the aggressive behavior continues, relatively low doses of a short-acting benzodiazepine such as lorazepam (e.g., 1–2 mg PO or IV) may be used and can be repeated as needed, but care must be taken not to destabilize vital signs or worsen confusion. An alternative approach is to use an antipsychotic medication (e.g., 0.5–5 mg of haloperidol PO or IM every 4–8 h as needed, or olanzapine 2.5–10 mg IM repeated at 2 and 6 h, if needed).

INTERVENTION There are two main elements to intervention in a person with alcoholism: motivational interviewing and brief interventions. During motivational interviewing, the clinician helps the patient to think through the assets (e.g., comfort in social situations) and liabilities (e.g., health- and interpersonal-related problems) of the current pattern of drinking. The patient's responses are key, and the clinician should listen empathetically, helping to weigh options and encouraging the patient to take responsibility for needed changes. Patients should be reminded that only they can decide to avoid the consequences that will occur without changes in drinking. The process of brief intervention has been summarized by the acronym FRAMES: Feedback to the patient; Responsibility to be taken by the patient; Advice, rather than orders, on what needs to be done; Menus of options that might be considered; Empathy for understanding the patient's thoughts and feelings; and Self-efficacy, i.e., offering support for the capacity of the patient to make changes.

Once the patient begins to consider change, the emphasis shifts to brief interventions designed to help them understand more about potential actions. Discussions focus on consequences of high alcohol consumption, suggested

www.ketabpezeshki.com (021) 66485457 - 66485438

approaches to stopping drinking, and help in recognizing and avoiding situations likely to lead to heavy drinking. Both motivational interviewing and brief interventions can be carried out in 15-min sessions, but because patients do not always change behavior immediately, multiple meetings are often required to explain the problem, discuss optimal treatments, and explain the benefits of abstinence.

ALCOHOL WITHDRAWAL If the patient agrees to stop drinking, sudden decreases in alcohol intake can produce withdrawal symptoms, many of which are the opposite of those produced by intoxication. Features include tremor of the hands (shakes); agitation and anxiety; autonomic nervous system overactivity including an increase in pulse, respiratory rate, sweating, and body temperature; and insomnia. These symptoms usually begin within 5–10 h of decreasing ethanol intake, peak on day 2 or 3, and improve by day 4 or 5, although mild levels of these problems may persist for 4–6 months as a protracted abstinence syndrome.

About 2% of alcoholics experience a withdrawal seizure, with the risk increasing in the context of concomitant medical problems, misuse of additional drugs, and higher alcohol quantities. The same risk factors also contribute to a similar rate of delirium tremens (DTs), where the withdrawal includes delirium (mental confusion, agitation, and fluctuating levels of consciousness) associated with a tremor and autonomic overactivity (e.g., marked increases in pulse, blood pressure, and respirations). The risks for seizures and DTs can be diminished by identifying and treating any underlying medical conditions early in the course of withdrawal.

Thus, the first step is a thorough physical examination in all alcoholics considering abstinence, including a search for evidence of liver failure, gastrointestinal bleeding, cardiac arrhythmia, infection, and glucose or electrolyte imbalances. It is also important to offer adequate nutrition and oral multiple B vitamins, including 50–100 mg of thiamine daily for a week or more. Because most alcoholics who enter withdrawal are either normally hydrated or mildly overhydrated, IV fluids should be avoided unless there is a relevant medical problem or significant recent bleeding, vomiting, or diarrhea.

The next step is to recognize that because withdrawal symptoms reflect the rapid removal of a CNS depressant, alcohol, the symptoms can be controlled by administering any depressant in doses that decrease symptoms (e.g., a rapid pulse and tremor) and then tapering the dose over 3–5 days. Although most depressants are effective, benzodiazepines **(Chap. 61)** have the highest margin of safety and lowest cost and are, therefore, the preferred class of drugs. Short-half-life benzodiazepines can be considered for patients with serious liver impairment or evidence of significant brain damage, but they must be given every 4 h to avoid abrupt blood-level fluctuations that may increase the risk for seizures. Therefore, most clinicians use drugs with longer half-lives (e.g., chlordiazepoxide), adjusting the dose if signs of withdrawal escalate, and withholding the drug if the patient is sleeping or has orthostatic hypotension. The average patient requires 25–50 mg of chlordiazepoxide or 10 mg of diazepam given PO every 4–6 h on the first day, with doses then decreased to zero over the next 5 days. Although alcohol withdrawal can be treated in a hospital, patients in good physical condition who demonstrate mild signs of withdrawal despite low blood alcohol concentrations and who have no prior history of DTs or withdrawal seizures can be considered for outpatient detoxification. For the next 4 or 5 days, these patients should return daily for evaluation of vital signs and can be hospitalized if signs and symptoms of withdrawal escalate.

Treatment of patient with DTs can be challenging, and the condition is likely to run a course of 3–5 days regardless of the therapy used. The focus of care is to identify and correct medical problems and to control behavior and prevent injuries. Many clinicians recommend the use of high doses of a benzodiazepine (as much as 800 mg/d of chlordiazepoxide has been reported), a treatment that will decrease agitation and raise the seizure threshold but probably does little to improve the confusion. Other clinicians recommend the use of antipsychotic medications, such as haloperidol or olanzapine as discussed above, although these drugs have not been directly evaluated for DTs. Antipsychotics are less likely to exacerbate confusion but may increase the risk of seizures; they have no place in the treatment of mild withdrawal symptoms.

Generalized withdrawal seizures rarely require more than giving an adequate dose of benzodiazepines. There is little evidence that anticonvulsants such as phenytoin or gabapentin are more effective in drug-withdrawal seizures, and the risk of seizures has usually passed by the time effective drug levels are reached. The rare patient with status epilepticus must be treated aggressively **(Chap. 31)**.

REHABILITATION OF ALCOHOLICS

An overview After completing alcoholic rehabilitation, ≥60% of alcoholics, especially middle-class patients, maintain abstinence for at least a year, and many achieve lifetime sobriety. The core of treatment uses cognitive-behavioral approaches to help patients recognize the need to change, while working with them to alter their behaviors to enhance compliance. A key step is to optimize motivation toward abstinence through education about alcoholism and instructions to family members to stop protecting the patient from problems caused by alcohol. After years of heavy drinking, many patients also need counseling, some require vocational or avocational help to structure their days, and all should try self-help groups such as Alcoholics Anonymous (AA) to help them develop a sober peer group and learn how to deal with life's stresses while sober. A third component, relapse prevention, helps the patient identify situations in which a return to drinking is likely, formulate ways of managing these risks, and develop coping strategies that increase the chances of a return to abstinence if a slip occurs.

Although many can be treated as outpatients, more intense interventions are more effective, and some alcoholics do not respond to AA or outpatient groups. Whatever

www.ketabpezeshki.com (021) 66485457 - 66485438

the setting, subsequent contact with outpatient treatment staff should be maintained for at least 6 months and preferably a year after abstinence. Counseling focuses on areas of improved functioning in the absence of alcohol (i.e., why it is a good idea to continue abstinence) and helping the patient to manage free time without alcohol, develop a nondrinking peer group, and handle stresses.

The physician serves an important role in identifying the alcoholic, diagnosing and treating associated medical and psychiatric syndromes, overseeing detoxification, referring the patient to rehabilitation programs, providing counseling, and, if appropriate, selecting which (if any) medication might be needed. For insomnia, patients should be reassured that troubled sleep is normal after alcohol withdrawal and will improve over subsequent weeks. They should be taught the elements of "sleep hygiene" including maintaining consistent schedules for bedtime and awakening. Sleep medications have the danger of being misused and of rebound insomnia when stopped. Sedating antidepressants (e.g., trazodone) should not be used because they interfere with cognitive functioning the next morning and disturb the normal sleep architecture, but occasional use of over-the-counter sleeping medications (sedating antihistamines) can be considered. Anxiety can be addressed by increasing the patient's insight into the temporary nature of the symptoms and helping the patient to develop strategies to achieve relaxation by using forms of cognitive therapy.

Medications for rehabilitation Several medications have modest benefits when used for the first 6 months of recovery. The opioid antagonist, naltrexone, 50–150 mg/d orally, may shorten subsequent relapses, whether used in the oral form or as a once-per-month 380-mg injection, especially in individuals with the G allele of the AII8G polymorphism of the μ opioid receptor. By blocking opioid receptors, naltrexone decreases activity in the dopamine-rich ventral tegmental reward system and decreases the feeling of pleasure if alcohol is imbibed. A second medication, acamprosate (Campral) at ~2 g/d divided into three oral doses, has similar modest effects; acamprosate inhibits NMDA receptors, decreasing mild symptoms of protracted withdrawal. Several trials of combined naltrexone and acamprosate have reported that the combination may be superior to either drug alone, although not all studies agree.

It is more difficult to establish the asset-to-liability ratio of a third drug, disulfiram, an ALDH inhibitor, used at doses of 250 mg/d. This drug produces vomiting and autonomic nervous system instability in the presence of alcohol as a result of rapidly rising blood levels of acetaldehyde. This reaction can be dangerous, especially for patients with heart disease, stroke, diabetes mellitus, or hypertension. The drug itself carries potential risks of depression, psychotic symptoms, peripheral neuropathy, and liver damage. Disulfiram is best given under supervision by someone (such as a spouse), especially during high-risk drinking situations (such as the Christmas holiday). Other drugs under investigation include another opioid antagonist nalmefene, the nicotinic receptor agonist varenicline, the serotonin antagonist ondansetron, the α-adrenergic agonist prazosin, the $GABA_B$ receptor agonist baclofen, the anticonvulsant topiramate, and cannabinol receptor antagonists. At present, there are insufficient data to determine the asset-to-liability ratio for these medications in treating alcoholism and, therefore, no data to offer solid support for their use in routine clinical settings.

GLOBAL CONSIDERATIONS

As described above, rates of alcohol use disorders differ across sex, age, ethnicity, and country. There are also differences across countries regarding the definition of a standard drink (e.g., 10–12 g of ethanol in the United States and 8 g in the United Kingdom) and the definition of being legally drunk. The preferred alcoholic beverage also varies across groups, even within countries. That said, regardless of sex, ethnicity, or country, the actual drug in the drink is still ethanol, and the risks for problems, course of alcohol use disorders, and approaches to treatment are similar across the world.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 64

OPIOID-RELATED DISORDERS

Thomas R. Kosten ■ Colin N. Haile

Opiate analgesics have been abused since at least 300 b.c. Nepenthe (Greek "free from sorrow") helped the hero of T e Odyssey, but widespread opium smoking in China and the Near East has caused harm for centuries. Since the first chemical isolation of opium and codeine 200 years ago, a wide range of synthetic opioids have been developed, and opioid receptors were cloned in the 1990s. Two of the most important adverse effects of all these agents are the development of opioid use disorder and overdose. T e 0.1% annual prevalence of heroin dependence in the United States is only about one-third the rate of prescription opiate use and is substantially lower than the 2% rate of morphine users in Southeast and Southwest Asia. Prescription opiates are primarily used for pain management, but due to ease of availability, adolescents procure and use these drugs with dire consequences. In 2011, for example, 11 million individuals in the United States used nonmedically prescribed pain killers that were linked to over 420,000 emergency department visits and nearly 17,000 overdose deaths. Although these rates are low relative to other abused substances, their disease burden is substantial, with high rates of morbidity and mortality; disease transmission; increased health care, crime, and law enforcement costs; and less tangible costs of family distress and lost productivity.

T e terms "dependence" and "addiction" are no longer used to describe substance use disorders. Opioid-related disorders encompass opioid use disorder, opioid intoxication, and opioid withdrawal. T e diagnosis of opioid use disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) requires the repeated use of the opiate while producing problems in two or more areas in a 12-month period. T e areas include tolerance, withdrawal, use of greater amounts of opiates than intended, craving, and use despite adverse consequences. T is new definition of opiate use disorder, reducing the criteria for diagnosis from three problem areas to two, is not expected to change the rates of these disorders because most individuals using these substances meet more than three criteria.

A striking recent aspect of illicit opiate use has been its marked increase as the gateway to illicit drugs in the United States. Since 2007, prescription opiates have surpassed marijuana as the most common illicit drug that adolescents initially use, although overall rates of opiate dependence are far lower than marijuana. T e most commonly used opiates are diverted prescriptions for oxycodone and hydrocodone, followed by heroin and morphine, and—among health professionals—meperidine and fentanyl. Heroin is derived from morphine and acts as a prodrug that more readily penetrates the brain and is converted rapidly to morphine in the body. Two opiate maintenance treatment agents—methadone and buprenorphine—are also misused, but at substantially lower rates, and the partial opiate agonists such as butorphanol, tramadol, and pentazocine are misused even less frequently. Because the chemistry and general pharmacology of these agents are covered in major pharmacology texts, this chapter focuses on the neurobiology and pharmacology relevant to dependence and its treatments. Although the neurobiology of abuse involves all four of the known opiate receptors—mu, kappa, delta, and nociceptin/orphanin—this discussion focuses on the mu receptor, at which most of the clinically used opiates are active.

NEUROBIOLOGY

T e neurobiology of opiates and their effects not only include opiate receptors, but also the downstream intracellular messenger systems and ion channels that the receptors regulate. T e different functional activities of opiate receptors are summarized in **Table 64-1**. Abuse liability of opiates is primarily associated with the mu receptor. All opiate receptors are G protein–linked and coupled to the cyclic adenosine monophosphate (cAMP) second messenger system and to G protein–coupled,

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 64-1

ACTIONS OF OPIOID RECEPTORS

RECEPTOR TYPE	ACTIONS
Mu (μ) (e.g., morphine, buprenorphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa (κ) (e.g., butorphanol)	Dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta (δ) (e.g., etorphine)	Analgesia, euphoria, physical dependence, Hormone changes, appetite suppression, dopamine release
Nociceptin/orphanin (e.g., buprenorphine)	Analgesia, appetite, anxiety, tolerance to opioids, hypotension, decreased GI motility, 5-HT and NE release

Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine.

inwardly rectifying potassium channels (GIRKs). Opiates activate GIRKs, increasing permeability to potassium ions to cause hyperpolarization, which inhibits the production of action potentials. T us, opiates inhibit the activity of diverse and widely distributed neuronal types. T e major effects of opiates, such as analgesia, sedation, and drug reinforcement are produced through this inhibition of neurons that belong to specific brain pathways.

Many opiate actions are related to the specific neuroanatomic locations of mu receptors. Reinforcing and euphoric effects of opiates occur in the mesolimbic dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), where opiates increase synaptic levels of dopamine. T is increase is due to inhibition of GABAergic neurons that inhibit both the activity of neurons within the VTA and the NAc. T e positive subjective effects of opioid drugs also include mu receptor desensitization and internalization, potentially related to stimulation of beta-arrestin signalizing pathways. However, the "high" only occurs when the rate of change in dopamine is fast. Large, rapidly administered doses of opiates block γ-aminobutyric acid (GABA) inhibition and produce a burst of VTA dopamine neuron activity that is associated with "high" in all abused drugs. T erefore, routes of administration that slowly increase opiate blood and brain levels, such as oral and transdermal routes, are effective for analgesia and sedation but do not produce an opiate "high" that follows smoking and intravenous routes. Other acute effects such as analgesia and respiratory depression involve opiate receptors located in other brain areas such as the locus coeruleus (LC).

Opiate tolerance and withdrawal are chronic effects related to the cAMP-protein kinase A (PKA)-cAMP response-element binding protein (CREB) intracellular cascade **(Fig. 64-1)**. T ese effects are also reflective of

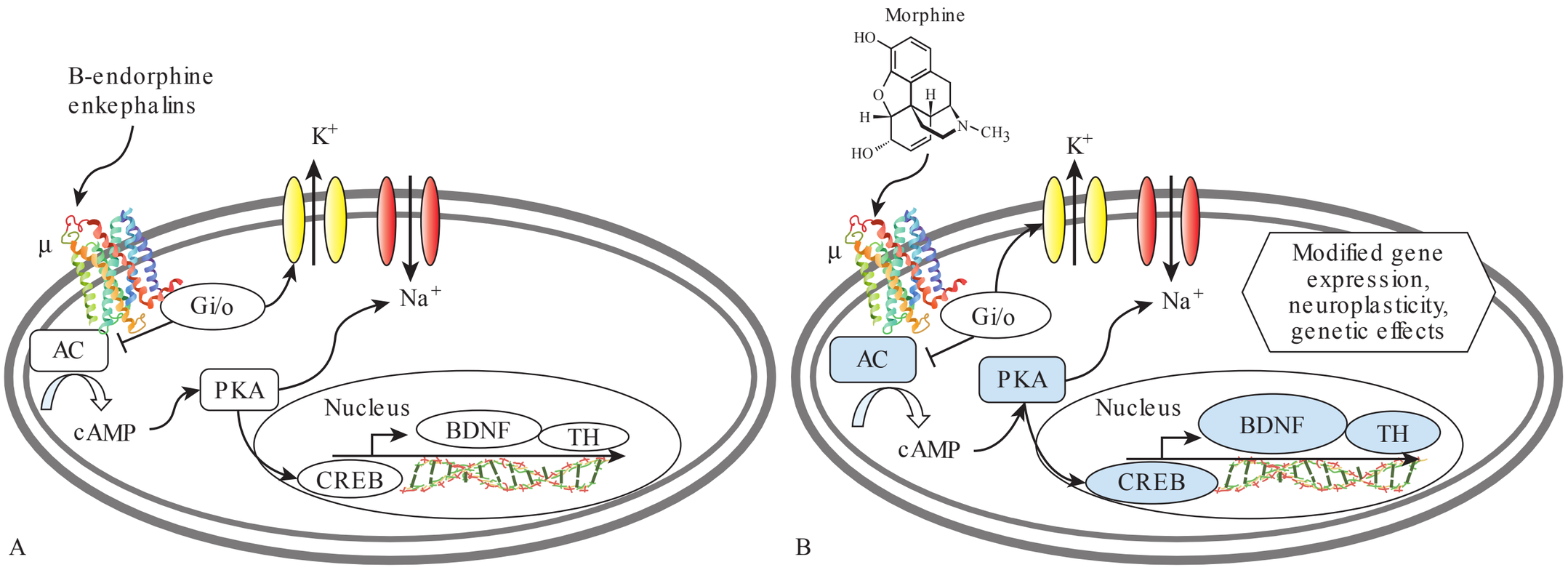


FIGURE 64-1

Normal mu-receptor activation by endogenous opioids inhibits the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response-element binding protein (CREB) cascade in noradrenergic neurons within the locus coeruleus (A) through inhibitory Gi/o protein infuence on adenylyl cyclase (AC). Similarly, acute exposure to opiates (e.g., morphine) inhibits this system, whereas chronic exposure to opiates (B) leads to upregulation of the cAMP pathway in an attempt to oppose opiate-induced inhibitory infuence. Upregulation of this system is involved in opiate tolerance, and when the opiate is removed, unopposed noradrenergic neurotransmission is involved in opiate withdrawal. Upregulated PKA phosphorylates CREB, initiating the expression of various genes such as tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF). BDNF is implicated in long-term neuroplastic changes in response to chronic opiates.

www.ketabpezeshki.com (021) 66485457 - 66485438

genetic risk factors for developing opiate use disorder, with estimates of up to 50% of the risk for dependence due to polygenic inheritance. Specific functional polymorphisms in the mu opiate receptor gene appear to be associated with this risk for opiate abuse, including one producing a threefold increase in this receptor's af nity for opiates and the endogenous ligand beta endorphin. Epigenetic methylation changes also occur on the DNA of the mu receptor gene of opiate addicts, inhibiting gene transcription. T is molecular cascade links acute intoxication and sedation to opiate tolerance and withdrawal mediated by the LC. Noradrenergic neurons in the LC mediate activation of the cortical hemispheres. When large opiate doses saturate and activate all of its mu receptors, action potentials cease. When this direct inhibitory effect is sustained over weeks and months of opiate use, a secondary set of adaptive changes occur that lead to tolerance and withdrawal symptoms (Fig. 64-1). Withdrawal symptoms reflect, in part, overactivity of norepinephrine (NE) neurons in the LC. T is molecular model of NE neuronal activation during withdrawal has had important treatment implications, such as the use of the alpha-2 agonist clonidine to treat opioid withdrawal. Other contributors to withdrawal include deficits within the dopamine reward system.

PHARMACOLOGY

Tolerance and withdrawal commonly occur with chronic daily use, developing as quickly as 6–8 weeks depending on dose concentration and dosing frequency. Tolerance appears to be primarily a pharmacodynamic rather than pharmacokinetic effect, with relatively limited induction of cytochrome P450 or other liver enzymes. T e metabolism of opiates occurs in the liver primarily through the cytochrome P450 systems of 2D6 and 3A4. T ey then are conjugated to glucuronic acid and excreted in small amounts in feces. T e plasma half-lives generally range from 2.5 to 3 h for morphine and more than 22 h for methadone. T e shortest half-lives of several minutes are for fentanyl-related opiates and the longest are for buprenorphine and its active metabolites, which can block opiate withdrawal for up to 3 days after a single dose. Tolerance to opioids leads to the need for increasing amounts of drugs to sustain the desired euphoric effects—as well as to avoid the discomfort of withdrawal. T is combination has the expected consequence of strongly reinforcing dependence once it has started. Methadone taken chronically at maintenance doses is stored in the liver, which may reduce the occurrence of withdrawal between daily doses. T e role of endogenous opioid peptides in tolerance and withdrawal is uncertain.

T e clinical features of abuse are tied to route of administration and the rapidity of an opiate bolus in reaching the brain. Intravenous and smoked administration rapidly produces a bolus of high drug concentration in the brain. T is bolus produces a "rush," followed by euphoria, a feeling of tranquility, and sleepiness ("the nod"). Heroin produces effects that last 3–5 h, and several doses a day are required to forestall manifestations of withdrawal in chronic users. Symptoms of opioid withdrawal begin 8–10 h after the last dose; lacrimation, rhinorrhea, yawning, and sweating appear first. Restless sleep followed by weakness, chills, gooseflesh ("cold turkey"), nausea and vomiting, muscle aches, and involuntary movements ("kicking the habit"), hyperpnea, hyperthermia, and hypertension occur in later stages of the withdrawal syndrome. T e acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.

Besides the brain effects of opioids on sedation and euphoria and the combined brain and peripheral nervous system effects on analgesia, a wide range of other organs can be affected. T e cough reflex is inhibited through the brain, leading to the use of some opiates as an antitussive, and nausea and vomiting are due to effects on the medulla. T e release of several pituitary hormones is inhibited, including corticotropin-releasing factor (CRF) and luteinizing hormone, which reduces levels of cortisol and sex hormones and can lead to impaired stress responses and reduced libido. An increase in prolactin also contributes to the reduced sex drive in males. Two other hormones affected are thyrotropin, which is reduced, and growth hormone, which is increased. Respiratory depression results from opiate-induced insensitivity of brainstem neurons to increases in carbon dioxide, and in patients with pulmonary disease, this can result in clinically significant complications. In overdoses, aspiration pneumonia is common due to loss of the gag reflex. Opiates reduce gut motility, which is helpful for treating diarrhea, but can lead to nausea, constipation, and anorexia with weight loss. Deaths occurred in early methadone maintenance programs due to severe constipation and toxic megacolon. Opiates such as methadone may prolong QT intervals and lead to sudden death in some patients. Orthostatic hypotension may occur due to histamine release and peripheral blood vessel dilation, which is an opiate effect usefully applied to managing acute myocardial infarction. During opiate maintenance, interactions with other medications are of concern; these include inducers of the cytochrome P450 system (usually CYP3A4) such as rifampin and carbamazepine.

Heroin users in particular tend to use opiates intravenously and are likely to be polydrug users, also using alcohol, sedatives, cannabinoids, and stimulants. None

www.ketabpezeshki.com (021) 66485457 - 66485438

of these other drugs are substitutes for opioids, but they have desired additive effects. T erefore, one needs to be sure that the person undergoing a withdrawal reaction is not also withdrawing from alcohol or sedatives, which might be more dangerous and more dif cult to manage.

Intravenous opiate use carries with it the risk of serious complications. T e common sharing of hypodermic syringes can lead to infections with hepatitis B and HIV/AIDS, among others. Bacterial infections can lead to septic complications such as meningitis, osteomyelitis, and abscesses in various organs. Off-target effects of opiates synthesized in illicit drug labs can lead to serious toxicity. For example, attempts to illicitly manufacture meperidine in the 1980s resulted in the production of a highly specific neurotoxin, MPTP, which produced parkinsonism in users **(Chap. 36)**.

Lethal overdose is a relatively common complication of opiate use disorder. Rapid recognition and treatment with naloxone, a highly specific reversal agent that is relatively free of complications, is essential. T e diagnosis is based on recognition of characteristic signs and symptoms, including shallow and slow respirations, pupillary miosis (mydriasis does not occur until significant brain anoxia supervenes), bradycardia, hypothermia, and stupor or coma. Blood or urine toxicology studies can confirm a suspected diagnosis, but immediate management must be based on clinical criteria. If naloxone is not administered, progression to respiratory and cardiovascular collapse leading to death occurs. At autopsy, cerebral edema and sometimes frothy pulmonary edema are generally found. Opiates generally do not produce seizures except for unusual cases of polydrug use with the opiate meperidine, with high doses of tramadol, or in the newborn.

TREATMENT Opioid Overdose

Beyond the acute treatment of opiate overdose with naloxone, clinicians have two general treatment options: opioid maintenance or detoxification. Opioid agonist and partial agonist medications are commonly used for both maintenance and detoxification purposes. Alpha-2-adrenergic agonists are primarily used for detoxification. Antagonists are used to accelerate detoxification and then continued after detoxification to prevent relapse. Only the residential medication-free programs have had success that comes close to matching that of the medication-based programs. Success of the various treatment approaches is assessed as retention in treatment and reduced opioid and other drug use; secondary outcomes, such as reduced HIV risk behaviors, crime, psychiatric symptoms, and medical comorbidity, also indicate successful treatment.

Stopping opiates is much easier than preventing relapse. Long-term relapse prevention for opioid-dependent persons requires combined pharmacologic and psychosocial approaches. Chronic users tend to prefer pharmacologic approaches; those with shorter histories of drug abuse are more amenable to detoxification and psychosocial interventions.

OPIATE OVERDOSE Managing overdose requires naloxone and support of vital functions, including intubation if needed **(Table 64-2)**. If the overdose is due to buprenorphine, then naloxone might be required at total doses of 10 mg or greater, but primary buprenorphine overdose is nearly impossible because this agent is a partial opiate agonist, meaning that as the dose of buprenorphine is increased it has greater opiate antagonist than agonist activity. T us, a 0.2-mg buprenorphine dose leads to analgesia and sedation, while a hundred times greater 20-mg dose produces profound opiate antagonism, precipitating opiate withdrawal in a person who was opiate dependent on morphine or methadone. It is important to recognize that the goal is to reverse the respiratory depression and not to administer so much naloxone that it precipitates opiate withdrawal. Because naloxone only lasts a few hours and most opiates last considerably longer, an IV naloxone drip with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 h depending on the opiate used in the overdose (e.g., morphine vs methadone). Whenever naloxone has only a limited effect, other sedative drugs that produce significant overdoses must be considered. T e most common are benzodiazepines, which have produced overdoses and deaths in combination with buprenorphine. A specific antagonist for benzodiazepines—flumazenil at 0.2 mg/min—can be given to a maximum of 3 g/h, but it may precipitate seizures and increase intracranial pressure. Like naloxone, administration for a prolonged period is usually required because most benzodiazepines remain active for considerably longer than flumazenil. Support of vital functions may include oxygen and positive-pressure breathing, IV fluids, pressor agents for hypotension, and cardiac monitoring to detect QT prolongation, which might require specific treatment. Activated charcoal and gastric lavage may be helpful for oral ingestions, but intubation will be needed if the patient is stuporous.

OPIATE WITHDRAWAL T e principles of detoxification are the same for all drugs: to substitute a longer-acting, orally active,

TABLE 64-2

MANAGEMENT OF OPIOID OVERDOSE
Establish airway. Intubation and mechanical ventilation may be necessary.
Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is approximately 1–2 min.
Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.
One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis. (**Note:** naloxone dosing is not necessary if the patient has been intubated.)

www.ketabpezeshki.com (021) 66485457 - 66485438

pharmacologically equivalent medication for the substance being used, stabilize the patient on that medication, and then gradually withdraw the substituted medication. Methadone or buprenorphine are the two medications used to treat opioid use disorder. Clonidine, a centrally acting sympatholytic agent, has also been used for detoxification in the United States. By reducing central sympathetic outflow, clonidine mitigates many of the signs of sympathetic overactivity but typically requires augmentation with other agents. Clonidine has no narcotic action and is not addictive. Lofexidine, a clonidine analogue with less hypotensive effect, is not yet approved in the United States.

Methadone for detoxification Dose-tapering regimens for detoxification using methadone range from 2–3 weeks to as long as 180 days, but this approach is controversial given the relative effectiveness of methadone maintenance and the low success rates of detoxification. Unfortunately, the vast majority of patients tend to relapse to heroin or other opiates during or after the detoxification period, indicative of the chronic and relapsing nature of opioid use disorder.Buprenorphine for Detoxification

Buprenorphine does not appear to lead to better outcomes than methadone but is superior to clonidine in reducing symptoms of withdrawal, retaining patients in a withdrawal protocol, and in completing treatment.Alpha-2-Adrenergic Agonists for Detoxification

Several alpha-2-adrenergic agonists have relieved opioid withdrawal by suppressing brain noradrenergic hyperactivity. Clonidine relieves some signs and symptoms of opiate withdrawal such as lacrimation, rhinorrhea, muscle pain, joint pain, restlessness, and gastrointestinal symptoms. Related agents are lofexidine, guanfacine, and guanabenz acetate. Lofexidine can be dosed up to ~2 mg/d and appears to be associated with fewer adverse effects. Clonidine or lofexidine is typically administered orally, in three or four doses per day, with dizziness, sedation, lethargy, and dry mouth as the primary adverse side effects. Outpatient-managed withdrawal will require close follow-up often with naltrexone maintenance to prevent relapse.Rapid and Ultrarapid Opiate Detoxification

T e opioid antagonist naltrexone typically combined with an alpha-2-adrenergic agonist has been purported to shorten the duration of withdrawal without significantly increasing patient discomfort. Completion rates using naltrexone and clonidine range from 75 to 81% compared to 40 to 65% for methadone or clonidine alone. Ultrarapid opiate detoxification is an extension of this approach using anesthetics but is highly controversial due to the medical risks and mortality associated with it.

Opioid agonist medications for maintenance

Methadone maintenance substitutes a once-daily oral opioid dose for three- to four-times daily heroin. Methadone saturates the opioid receptors and, by inducing a high level of opiate tolerance, blocks the euphoria from additional opiates. Buprenorphine, a partial opioid agonist, also can be given once daily at sublingual doses of 4–32 mg daily, and in contrast to methadone, it can be given in an of ce-based primary care setting.

Methadone maintenance

Methadone's slow onset of action when taken orally, long elimination half-life (24–36 h), and production of cross-tolerance at doses from 80 to 150 mg are the basis for its ef cacy in treatment retention and reductions in IV drug use, criminal activity, and HIV risk behaviors and mortality. Methadone can prolong the QT interval at rates as high as 16% above the rates in non-methadone-maintained, drug-injecting patients, but it has been used safely in the treatment of opioid dependence for 40 years.

Buprenorphine maintenance

While France and Australia have had sublingual buprenorphine maintenance since 1996, it was first approved by the U.S. Food and Drug Administration (FDA) in 2002 as a Schedule III drug for managing opioid use disorder. Unlike the full agonist methadone, buprenorphine is a partial agonist of mu-opioid receptors with a slow onset and long duration of action. Its partial agonism reduces the risk of unintentional overdose but limits its ef cacy to patients who need the equivalent of only 60–70 mg of methadone, and many patients in methadone maintenance require higher doses up to 150 mg daily. Buprenorphine is combined with naloxone at a 4:1 ratio in order to reduce its abuse liability. Because of pediatric exposures and diversion of buprenorphine to illicit use, a new formulation, using mucosal films rather than sublingual pills that were crushed and snorted, is now marketed. A subcutaneous buprenorphine implant that lasts up to 6 months has also been tested and is pending FDA approval as a formulation improvement to prevent pediatric exposures and illicit diversion and enhance compliance.

In the United States, the ability of primary care physicians to prescribe buprenorphine for opioid use disorder represents an important opportunity to improve access and quality of treatment as well as reduce social harm. Europe, Asia, and Australia have found reduced opioid-related deaths and drug-injection-related medical morbidity with buprenorphine available in primary care. Retention in of ce-based buprenorphine treatment has been high as 70% at 6-month follow-ups.

Opioid antagonist medications

T e rationale for using narcotic antagonist therapy is that blocking the action of self-administered opioids should eventually extinguish the habit, but this therapy is poorly accepted by patients. Naltrexone, a long-acting

www.ketabpezeshki.com (021) 66485457 - 66485438

orally active pure opioid antagonist, can be given three times a week at doses of 100–150 mg. Because it is an antagonist, the patient must first be detoxified from opioid dependence before starting naltrexone. It is safe even when taken chronically for years, is associated with few side effects (headache, nausea, abdominal pain), and can be given to patients infected with hepatitis B or C without producing hepatotoxicity. However, most providers refrain from prescribing naltrexone if liver function tests are three times above normal levels. Naltrexone maintenance combined with psychosocial therapy is effective in reducing heroin use, but medication adherence is low. Depot injection formulations lasting up to 4 weeks markedly improve adherence, retention, and drug use. Subcutaneous naltrexone implants in Russia, China, and Australia have doubled treatment retention and reduced relapse to half that of oral naltrexone. In the United States, a depot naltrexone formulation is available for monthly use and maintains blood levels equivalent to 25 mg of daily oral use.

Medication-free treatment

Most opiate addicts enter medication-free treatments in inpatient, residential, or outpatient settings, but 1- to 5-year outcomes are very poor compared to pharmacotherapy except for residential settings lasting 6 to 18 months. The residential programs require full immersion in a regimented system with progressively increasing levels of independence and responsibility within a controlled community of fellow drug abusers. These medication-free programs, as well as the pharmacotherapy programs, also include counseling and behavioral treatments designed to teach interpersonal and cognitive skills for coping with stress and for avoiding situations leading to easy access to drugs or to craving. Relapse is prevented by having the individual very gradually reintroduced to greater responsibilities and to the working environment outside of the protected therapeutic community.

PREVENTION

Preventing opiate abuse represents a critically important challenge for physicians. Opiate prescriptions are the most common source of drugs accessed by adolescents who begin a pattern of illicit drug use. The major sources of these drugs are family members, not drug dealers or the Internet. Pain management involves providing sufficient opiates to relieve the pain over as short a period of time as the pain warrants **(Chap. 8)**. The patient then needs to dispose of any remaining opiates, not save them in the medicine cabinet, because this behavior leads to diversion by adolescents. Finally, physicians should never prescribe opiates for themselves.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 65

COCAINE AND OTHER COMMONLY ABUSED DRUGS

Nancy K. Mello[1] ■ Jack H. Mendelson[1]

The abuse of cocaine and other psychostimulants reflects a complex interaction between the pharmacology of the drug, the personality and expectations of the user, and the environmental context in which the drug is used. Polydrug abuse involving the concurrent use of several drugs with different pharmacologic effects is increasingly common. Sometimes one drug is used to enhance the effects of another, as with the combined use of cocaine and nicotine, benzodiazepines and methadone, or cocaine and heroin in methadone-maintained patients. Some forms of polydrug abuse, such as the combined use of IV heroin and cocaine, are especially dangerous and account for many hospital emergency room visits.

Chronic cocaine and psychostimulant abuse may cause a number of adverse health consequences and may exacerbate preexisting disorders such as hypertension and cardiac disease. The combined use of two or more drugs may accentuate medical complications associated with abuse of one drug. Chronic drug abuse is often associated with immune system dysfunction and increased vulnerability to infections, including risk for HIV infection. In addition, concurrent use of cocaine and opiates (the "speedball") is frequently associated with needle sharing by IV drug users. IV drug abusers continue to be the largest single group of persons with HIV infection in several major metropolitan areas in the United States as well as in many parts of Europe and Asia.

Stimulants and hallucinogens have been used to induce euphoria and alter consciousness for centuries. Cocaine and marijuana are two of the most commonly abused drugs today. Synthetic variations of marijuana and a variety of hallucinogens have become popular recently, and new drugs are continually being developed. This chapter describes the subjective and adverse medical effects of cocaine, marijuana, and lysergic acid diethylamide (LSD), as well as methamphetamine, 3,4-methylenedioxy-N-methamphetamine (MDMA), synthetic cathinones (bath salts), phencyclidine (PCP), Salvia divinorum, and other drugs of abuse (flunitrazepam, γ-hydroxybutyric acid [GHB], ketamine). Some options for medical management of severe adverse effects are also described.

COCAINE

Cocaine is a stimulant and a local anesthetic with potent vasoconstrictor properties. The leaves of the coca plant (Erythroxylum coca) contain ~0.5–1% cocaine. The drug produces physiologic and behavioral effects after oral, intranasal, IV, or inhalation/smoking routes of administration. The reinforcing effects of cocaine are related to activation of dopaminergic neurons in the mesolimbic system **(Chap. 60)**. Cocaine increases synaptic concentrations of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin by binding to transporter proteins in presynaptic neurons and blocking reuptake.

PREVALENCE OF COCAINE USE

Cocaine is widely available and is abused in virtually all social and economic strata of society. In 2012, an estimated 1.6 million persons in the United States used cocaine, and 1.1 million abused or were dependent on cocaine. Emergency room admissions involving cocaine totaled 505,224 in 2011. Cocaine abuse is prevalent in the general population and in heroin-dependent persons, including those in methadone maintenance programs. IV cocaine is often used concurrently with IV heroin in a combination called a "speedball." This combination purportedly attenuates the postcocaine "crash" and substitutes a cocaine "high" for the heroin "high" blocked by methadone.

[1]Deceased

www.ketabpezeshki.com (021) 66485457 - 66485438

ACUTE AND CHRONIC INTOXICATION

T ere has been an increase in both IV administration and inhalation of pyrolyzed cocaine via smoking. Following intranasal administration, changes in mood and sensation are perceived within 3–5 min, and peak effects occur at 10–20 min. T ese effects rarely last more than 1 h. Inhalation of pyrolyzed materials includes inhaling crack/cocaine or smoking coca paste, a product made by extracting cocaine preparations with flammable solvents, and cocaine free-base smoking. Free-base cocaine, including the free-base prepared with sodium bicarbonate (crack), has become increasingly popular because of its relative high potency and rapid onset of action (8–10 seconds following smoking).

Cocaine produces a brief, dose-related stimulation and euphoria and an increase in cardiac rate and blood pressure. Body temperature usually increases following cocaine administration, and high doses of cocaine may induce lethal pyrexia or hypertension. Because cocaine inhibits reuptake of catecholamines at adrenergic nerve endings, it potentiates sympathetic nervous system activity. Cocaine has a short plasma half-life of approximately 45–60 min. Cocaine is metabolized by plasma esterases, and cocaine metabolites are excreted in urine. T e brief duration of the euphorigenic effects of cocaine reported by chronic abusers is probably due to both acute and chronic tolerance. Cocaine may be used as often as two to three times per hour. Alcohol is often used to modulate both the cocaine high and the dysphoria associated with the abrupt disappearance of cocaine's effects. A metabolite of cocaine, cocaethylene, has been detected in blood and urine of persons who concurrently abuse alcohol and cocaine. Cocaethylene induces changes in cardiovascular function similar to those of cocaine alone, and the pathophysiologic consequences of the concurrent abuse of alcohol plus cocaine may be additive.

Cocaine may cause serious medical consequences by any route of administration. T e prevalent assumption that cocaine inhalation or IV administration is relatively safe is contradicted by reports of death from respiratory depression, cardiac arrhythmias, and convulsions associated with cocaine use. In addition to generalized seizures, neurologic complications may include headache, ischemic or hemorrhagic stroke, or subarachnoid hemorrhage. Disorders of cerebral blood flow and perfusion in cocaine-dependent persons have been detected with magnetic resonance spectroscopy (MRS). Inhalation of crack cocaine may lead to severe pulmonary disease due to the direct effects of cocaine and to residual contaminants in the smoked material. Hepatic necrosis may occur following chronic crack/cocaine use. Protracted cocaine abuse may also cause paranoid ideation and visual and auditory hallucinations, a state that resembles alcoholic hallucinosis.

Although men and women who abuse cocaine may report that the drug enhances libidinal drive, chronic cocaine use causes significant loss of libido and adversely affects sexual function. Impotence and gynecomastia have been observed in male cocaine abusers, and these abnormalities often persist for long periods following cessation of drug use. Cocaine abuse may produce major derangements in menstrual cycle function including galactorrhea, amenorrhea, and infertility in women and in a rhesus monkey model of cocaine self-administration. Chronic cocaine abuse may cause persistent hyperprolactinemia as a consequence of disordered dopaminergic inhibition of prolactin secretion by the anterior pituitary. Cocaine abuse by pregnant women, particularly crack smoking, has been associated with both an increased risk of congenital malformations in the fetus and perinatal cardiovascular and cerebrovascular disease in the mother. However, cocaine abuse per se is probably not the sole cause of these perinatal disorders, because maternal cocaine abuse is often associated with poor nutrition and prenatal health care as well as polydrug abuse that may contribute to the risk for perinatal disease.

Psychological dependence on cocaine, indicated by inability to abstain from frequent compulsive use, has been reported. Although the occurrence of withdrawal syndromes involving psychomotor agitation and autonomic hyperactivity remains controversial, severe depression ("crashing") following cocaine intoxication may accompany drug withdrawal.

TREATMENT Cocaine Overdose and Chronic Abuse

Treatment of cocaine overdose is a medical emergency that is best managed in an intensive care unit. Cocaine toxicity produces a hyperadrenergic state characterized by hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias. IV diazepam in doses up to 0.5 mg/kg administered over an 8-h period has been shown to be effective for control of seizures. Ventricular arrhythmias have been managed successfully by administration of 0.5–1.0 mg of propranolol IV. Because many instances of cocaine-related mortality have been associated with concurrent use of other illicit drugs (particularly heroin), the physician must be prepared to institute effective emergency treatment for multiple drug toxicities.

Treatment of chronic cocaine abuse requires the combined efforts of primary care physicians, psychiatrists, and psychosocial care providers. Early abstinence from cocaine use is often complicated by symptoms of depression and guilt, insomnia, and anorexia, which may be as severe as those observed in major affective disorders. Individual and group psychotherapy, family therapy, and peer group assistance programs are often useful for inducing prolonged remission

www.ketabpezeshki.com (021) 66485457 - 66485438

from drug use. Although psychotherapy may be helpful, no specific form of psychotherapy or behavioral modification is uniquely beneficial.

A number of medications used for the treatment of various medical and psychiatric disorders have been administered to reduce the duration and severity of cocaine abuse and dependence. T e search for a medication that is both safe and highly effective for cocaine detoxification or maintenance of abstinence is continuing. Clinical trials of buspirone (BuSpar), a nonbenzodiazepine anxiolytic with dopamine D_3 and D_4 receptor antagonist properties, are ongoing. Buspirone reduced use of cocaine, nicotine, and cocaine plus nicotine in combination in a nonhuman primate model of stimulant addiction.

Another approach to reducing cocaine abuse is the development of vaccines to actively immunize against cocaine or to functionally antagonize cocaine by preventing it from reaching the brain. Cocaine is converted into inactive metabolites by the plasma enzyme, butyrylcholinesterase (BChE). When this enzyme is modified to increase its catalytic ef ciency and accelerate cocaine metabolism, it can both prevent and reverse cocaine-induced toxicity in animals. Importantly, it remains effective even when high doses of cocaine are administered. Ongoing development of this approach includes cocaine hydrolase gene therapy. Vaccines for both cocaine and nicotine have been designed and shown to be safe and somewhat effective in clinical trials. Individual variability in antibody titers and dif culties in determining the optimally effective antibody titer that will neutralize responses to increasing doses of cocaine and have a relatively long duration of action are among the challenges that remain to be resolved.

MARIJUANA AND CANNABIS COMPOUNDS

Cannabis sativa contains >400 compounds in addition to the psychoactive substance, delta-9-tetrahydrocannabinol (THC). Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5–1 g of plant material. T e usual THC concentration varies between 10 and 40 mg, but concentrations <100 mg per cigarette have been detected. Hashish is prepared from concentrated resin of C. sativa and contains a THC concentration of between 8 and 12% by weight. "Hash oil," a lipid-soluble plant extract, may contain THC between 25 and 60% and may be added to marijuana or hashish to enhance its THC concentration. Smoking is the most common mode of marijuana or hashish use. During pyrolysis, <150 compounds in addition to THC are released in the smoke. Although most of these compounds do not have psychoactive properties, they may have physiologic effects.

THC is quickly absorbed from the lungs into blood and then rapidly sequestered in tissues. THC is metabolized primarily in the liver, where it is converted to 11-hydroxy-THC, a psychoactive compound, and >20 other metabolites. Many THC metabolites are excreted through the feces at a relatively slow rate of clearance compared with most other psychoactive drugs.

Specific cannabinoid receptors (CB_1 and CB_2) have been identified in the central and peripheral nervous system. High densities of cannabinoid receptors have been found in the cerebral cortex, basal ganglia, and hippocampus. T and B lymphocytes also contain cannabinoid receptors, and these appear to mediate the anti-inflammatory and immunoregulatory properties of cannabinoids. A naturally occurring THC-like ligand has been identified and is widely distributed in the nervous system.

Herbal marijuana alternatives are also available. T ese are usually a combination of several herbs and synthetic cannabinoids. "Spice" and "K2" are among the best known, but many formulations exist, and marijuana is undetectable by the usual methods. T ese compounds are marketed on the Internet as containing no illegal ingredients. However a number of synthetic cannabinoids are now classified as Schedule I by the Drug Enforcement Administration due to reports of toxicity.

PREVALENCE OF USE

Marijuana is the most commonly used illegal drug in the United States. In 2012, an estimated 18.9 million people reported using marijuana within the past month. An estimated 7.2% of adolescents age 12 to 17 years reported current use of marijuana. Marijuana is relatively inexpensive and is often considered to be less hazardous than other controlled drugs and substances. Very potent forms of marijuana (sinsemilla) are widely available, and concurrent use of marijuana with other drugs such as cocaine is not uncommon. Due in part to the dif culty of detecting herbal marijuana alternatives, the prevalence of use is unknown.

ACUTE AND CHRONIC INTOXICATION

Acute intoxication from marijuana and cannabis compounds is related to both the dose of THC and the route of administration. THC is absorbed more rapidly from marijuana smoking than from orally ingested cannabis compounds. Acute marijuana intoxication may produce a perception of relaxation and mild euphoria resembling mild to moderate alcohol intoxication. T is condition is usually accompanied by some impairment in thinking, concentration, and perceptual and psychomotor function. Higher doses of cannabis may produce more pronounced impairment in concentration

www.ketabpezeshki.com (021) 66485457 - 66485438

and perception, as well as greater sedation. Although the acute effects of marijuana intoxication are relatively benign in normal users, the drug can precipitate severe emotional disorders in individuals who have antecedent psychotic or neurotic problems. Like other psychoactive compounds, both the user's expectations and the environmental context are important determinants of the type and severity of the effects of marijuana intoxication.

As with abuse of cocaine, opioids, and alcohol, chronic marijuana abusers may lose interest in common socially desirable goals and devote progressively more time to drug acquisition and use. However, THC does not cause a specific and unique "amotivational syndrome." T e range of symptoms sometimes attributed to marijuana use is dif cult to distinguish from mild to moderate depression and the maturational dysfunctions often associated with protracted adolescence. Chronic marijuana use has also been reported to increase the risk of psychotic symptoms in individuals with a past history of schizophrenia. Persons who begin marijuana smoking before the age of 17 may have more pronounced cognitive deficits and also may be at higher risk for polydrug and alcohol abuse problems in later life, but the role of marijuana in this sequence is uncertain.

T e acute effects of herbal marijuana alternatives are based primarily on case reports and include anxiety, agitation, delusions, paranoia, and psychosis. T e extent to which these symptoms reflect drug effects or exacerbation of an underlying psychiatric disorder is often difficult to determine.

PHYSICAL EFFECTS

Conjunctival injection and tachycardia are the most frequent immediate physical concomitants of smoking marijuana. Tolerance for marijuana-induced tachycardia develops rapidly among regular users. However, marijuana smoking may precipitate angina in persons with a history of coronary insuf ciency. Exercise-induced angina may increase after marijuana use to a greater extent than after tobacco cigarette smoking. Patients with cardiac disease should be strongly advised not to smoke marijuana or use cannabis compounds.

Significant decrements in pulmonary vital capacity have been found in regular daily marijuana smokers. Because marijuana smoking typically involves deep inhalation and prolonged retention of marijuana smoke, chronic bronchial irritation may develop. Impairment of single-breath carbon monoxide diffusion capacity (Dl_{CO}) is greater in persons who smoke both marijuana and tobacco than in tobacco smokers.

Although marijuana has also been associated with a number of other adverse effects, many of these studies await replication and confirmation. A reported correlation between chronic marijuana use and decreased testosterone levels in males has not been confirmed. Decreased sperm count and sperm motility and morphologic abnormalities of spermatozoa following marijuana use have been reported. Prospective studies found a correlation between impaired fetal growth and development and heavy marijuana use during pregnancy. Marijuana has also been implicated in derangements of the immune system; in chromosomal abnormalities; and in inhibition of DNA, RNA, and protein synthesis; however, these findings have not been confirmed or related to any specific physiologic effect in humans. Herbal marijuana alternatives produce many of the effects of marijuana including conjunctival injection and tachycardia.

TOLERANCE AND PHYSICAL DEPENDENCE

Habitual marijuana users may develop tolerance to the psychoactive effects of marijuana, and then smoke more frequently and try to acquire more potent cannabis compounds. Tolerance for the physiologic effects of marijuana develops at different rates; e.g., tolerance develops rapidly for marijuana-induced tachycardia but more slowly for marijuana-induced conjunctival injection. Tolerance for both behavioral and physiologic effects of marijuana decreases rapidly upon cessation of marijuana use.

A distinct withdrawal syndrome has been documented in chronic cannabis users, and the severity of symptoms is related to dosage and duration of use. T ese symptoms typically reach their peak several days after cessation of chronic use and include irritability, anorexia, and sleep disturbances. Withdrawal signs and symptoms observed in chronic marijuana users are usually relatively mild in comparison to those observed in heavy opioid or alcohol users and rarely require medical or pharmacologic intervention. However, more severe and protracted abstinence syndromes may occur after sustained use of high-potency cannabis compounds. As yet there have been no systematic studies of tolerance and physical dependence to the herbal marijuana alternatives. T e large number of synthetic cannabinoids available for combination with about 20 herbs presents a daunting challenge for analysis.

THERAPEUTIC USE OF MARIJUANA

Marijuana, administered as cigarettes or as a synthetic oral cannabinoid (dronabinol), is thought to have a number of clinically useful medicinal properties. T ese include antiemetic effects in chemotherapy recipients, appetite-promoting effects in AIDS patients, reduction of intraocular pressure in glaucoma, and reduction

www.ketabpezeshki.com (021) 66485457 - 66485438

of spasticity in multiple sclerosis and other neurologic disorders. With the possible exception of AIDS-related cachexia, none of these attributes of marijuana compounds is clearly superior to other readily available therapies.

METHAMPHETAMINE

Methamphetamine is also referred to as "meth," "speed," "crank," "chalk," "ice," "glass," or "crystal." Methamphetamine is a mixed-action monoamine releaser with activity at dopamine, serotonin, and norepinephrine systems. Methamphetamine was considered second only to cocaine as a drug threat to society by the U.S. Department of Justice in 2009. Hospital admissions for methamphetamine treatment more than doubled between 1998 and 2007, and young adults (age 18–25) have the highest use rates. In 2011, an estimated 439,000 people reported current use of methamphetamine in the United States, and emergency room admissions involving amphetamines/methamphetamine totaled 160,000. Persistent abuse of methamphetamine continues despite drug seizures, closures of clandestine laboratories that produce methamphetamine illegally, and an increase in methamphetamine abuse prevention programs.

Methamphetamine can be used by smoking, snorting, IV injection, or oral administration. Methamphetamine abusers report that drug use induces feelings of euphoria and decreased fatigue. Adverse consequences of methamphetamine use include headache, dif culty concentrating, diminished appetite, abdominal pain, vomiting or diarrhea, disordered sleep, paranoid or aggressive behavior, and psychosis. Chronic methamphetamine abuse can result in severe dental caries, described as blackened, rotting, crumbling teeth. Severe, life-threatening methamphetamine toxicity may include hypertension, cardiac arrhythmia or cardiac failure, subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, convulsions, or coma.

Methamphetamines increase the release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) from presynaptic neurons. It is thought that the euphoric and reinforcing effects of this class of drugs are mediated through dopamine and the mesolimbic system, whereas the cardiovascular effects are related to norepinephrine. MRS studies of the brain suggest that chronic abusers have neuronal damage in the frontal areas and basal ganglia.

Treatment of acute methamphetamine overdose is largely symptomatic. Ammonium chloride may be useful to acidify the urine and enhance clearance of the drug. Hypertension may respond to sodium nitroprusside or α-adrenergic antagonists. Sedatives may reduce agitation and other signs of central nervous system hyperactivity. Treatment of chronic methamphetamine dependence may be accomplished in either an inpatient or outpatient setting using strategies similar to those described earlier for cocaine abuse.

MDMA is a derivative of methamphetamine also called Ecstasy or Molly. Reported use of MDMA in the United States has increased from 615,000 persons in 2005, to an estimated 869,000 people in 2012. Emergency ward admissions involving MDMA totaled more than 22,000 in 2011. Ecstasy is usually taken orally but may be injected or inhaled, and its effects last for 3–6 h. MDMA has amphetamine-like effects including vivid visual and auditory hallucinations and other perceptual distortions. Recent studies indicate that MDMA use is associated with cognitive and memory impairment. MDMA can induce hyperthermia and elevated blood pressure, seizures, comma, and death. Withdrawal symptoms after cessation of use may include teeth grinding, anxiety, loss of appetite, insomnia, and fever. T e long-term consequences of recreational use of MDMA by young persons are poorly understood.

SYNTHETIC CATHINONES (BATH SALTS)

T e rapid emergence of synthetic cathinone abuse during 2010 was accompanied by numerous reports of adverse medical and psychiatric effects, suicides, and deaths. Reports to poison centers and health agencies increased from about 300 in 2010 to over 6000 in 2011. In 2011, the Drug Enforcement Administration classified three commonly abused synthetic cathinones (mephedrone [4-methyl methcathinone], MDPV [3,4-methylenedioxy pyrovalerone], and methylone) as Schedule I compounds with no accepted medical use and a high potential for abuse. However, synthetic cathinones are readily available on the Internet as well as in convenience stores, gas stations, and head shops. T ese drugs are merchandised under a variety of names such as Vanilla Sky, Purple Wave, Blue Silk, White Lightening, and Snow Leopard. Regulatory constraints are evaded by labeling the products as plant food, insecticides, pond cleaner, and bath salts with the qualifier, "not for human consumption."

Cathinone is the primary psychoactive ingredient in khat leaves. Chewing the leaves of the khat shrub (Catha edulis) produces mild stimulant and euphoric effects and remains a common practice in east Africa that has persisted for centuries. Cathinone is structurally similar to amphetamine, and mephedrone is structurally similar to methamphetamine. Cathinones, like amphetamines, inhibit dopamine, serotonin, and norepinephrine transporters to varying degrees, and this probably accounts for variations in the behavioral

www.ketabpezeshki.com (021) 66485457 - 66485438

effects observed. T e effects of cathinone derivatives are often described as similar to the effects of MDMA or Ecstasy. Synthetic cathinones can be inhaled, snorted, injected, or taken orally. T ese drugs may be taken repeatedly over several hours in episodes lasting for hours or days. T e onset of effects after oral ingestion is relatively rapid for MDPV (15–30 min) and slightly slower for mephedrone and methylone (30–45 min). T e duration of action varies from 2 to 5 or 7 h. After mephedrone inhalation, effects occur within minutes and only last for 1 h or less, but mood changes may persist for several days. Evaluation of the neurotoxic effects of prolonged synthetic cathinone abuse is just beginning, and the long-term consequences are unknown.

T e reported positive subjective effects of synthetic cathinones include euphoria, improved energy, alertness, sociability, and increased sensitivity to music and other sensory experiences. T e reported negative subjective effects include agitation, visual and auditory hallucinations, anxiety and panic attacks, paranoid delusions, disorientation, depression, and suicidal ideation. Observers report irritability, aggression, violent behavior, tremors, and seizures. Medical evidence of adverse effects includes cardiovascular dysfunction and cardiac arrest, hypertension, hyperthermia, nausea and vomiting, and anorexia. T ere is no specific antagonist for synthetic cathinone intoxication. Patients with severe hyperthermia, seizures, and arrhythmia are medical emergencies and should be treated in a hospital. Sedation with benzodiazepines can be useful for managing agitation, seizures, aggression, and other related symptoms. Antipsychotic medications may be necessary for management of severe and persistent psychiatric symptoms.

LYSERGIC ACID DIETHYLAMIDE (LSD)

Discovery of the psychedelic effects of LSD led to an epidemic of LSD abuse during the 1960s. Imposition of stringent constraints on the manufacture and distribution of LSD (classified as a Schedule I substance by the U.S. Food and Drug Administration [FDA]) and public recognition that psychedelic experiences induced by LSD were a health hazard have resulted in a reduction in LSD abuse. LSD still remains popular among adolescents and young adults, and there are indications that LSD use among young persons has been increasing in some areas in the United States. In 2011, an estimated 358,000 persons used LSD, whereas 200,000 and 271,000 persons reported LSD use in 2003 and 2007, respectively.

LSD is a very potent hallucinogen; oral doses as low as 20 μg may induce profound psychological and physiologic effects. Tachycardia, hypertension, pupillary dilation, tremor, and hyperpyrexia occur within minutes following oral administration of 0.5–2 μg/kg. A variety of bizarre and often conflicting perceptual and mood changes, including visual illusions, synesthesias, and extreme lability of mood, usually occur within 30 min after LSD intake. T ese effects of LSD may persist for 12–18 h, even though the half-life of the drug is only 3 h.

Emergency ward visits involving LSD totaled nearly 5000 in 2011. T e most frequent acute medical emergency associated with LSD use is a panic episode (the "bad trip"), which may persist up to 24 h. Management of this problem is best accomplished by supportive reassurance ("talking down") and, if necessary, administration of small doses of anxiolytic drugs. Adverse consequences of chronic LSD use include an enhanced risk for schizophreniform psychosis and derangements in memory function, problem solving, and abstract thinking. Treatment of these disorders is best carried out in specialized psychiatric facilities.

Tolerance develops rapidly for LSD-induced changes in psychological function when the drug is used one or more times per day for >4 days. Abrupt abstinence following continued use does not produce withdrawal signs or symptoms. T ere have been no clinical reports of death caused by the direct effects of LSD.

PHENCYCLIDINE (PCP)

PCP, a cyclohexylamine derivative, is widely used in veterinary medicine to briefly immobilize large animals and is sometimes described as a dissociative anesthetic. PCP binds to ionotropic N-methyl-d-aspartate (NMDA) receptors in the nervous system, blocking ion current through these channels. PCP is easily synthesized and is abused primarily by young people and polydrug users. It is used orally, by smoking, by snorting, or by IV injection. It is also used as an adulterant in THC, LSD, amphetamine, or cocaine. T e most common street preparation, angel dust, is a white granular powder that contains 50–100% of the drug. Low doses (5 mg) produce agitation, excitement, impaired motor coordination, dysarthria, and analgesia. Physical signs of intoxication may include horizontal or vertical nystagmus, flushing, diaphoresis, and hyperacusis. Behavioral changes include distortions of body image, disorganization of thinking, and feelings of estrangement. Higher doses of PCP (5–10 mg) may produce profuse salivation, vomiting, myoclonus, fever, stupor, or coma. PCP doses of ≥10 mg cause convulsions, opisthotonus, and decerebrate posturing that may be followed by prolonged coma.

In 2011, more than 75,000 emergency ward admissions involved PCP. T e diagnosis of PCP overdose is

www.ketabpezeshki.com (021) 66485457 - 66485438

dif cult because the patient's initial symptoms (anxiety, paranoia, delusions, and hallucinations) may suggest an acute schizophrenic reaction. Confirmation of PCP use is possible by determination of PCP levels in serum or urine. PCP assays are available at most toxicologic centers. PCP remains in urine for 1–5 days following high-dose intake.

PCP overdose requires emergency life-support measures that may involve treatment of coma, convulsions, and respiratory depression in an intensive care unit. T ere is no specific antidote or antagonist for PCP. PCP excretion from the body can be enhanced by gastric lavage and acidification of urine. Death from PCP overdose may occur as a consequence of some combination of pharyngeal hypersecretion, hyperthermia, respiratory depression, severe hypertension, seizures, hypertensive encephalopathy, and intracerebral hemorrhage.

Acute psychosis associated with PCP use is a psychiatric emergency because patients may be at high risk for suicide or extreme violence toward others. Phenothiazines should not be used for treatment because these drugs potentiate PCP's anticholinergic effects. Haloperidol (5 mg IM) has been administered on an hourly basis to induce suppression of psychotic behavior. PCP, like LSD and mescaline, produces vasospasm of cerebral arteries at relatively low doses. Chronic PCP use has been shown to induce insomnia, anorexia, severe changes in behavior, and, in some cases, chronic schizophrenia.

SALVIA DIVINORUM

T is naturally occurring herb is a recent entry into the spectrum of hallucinogens. Like PCP and ecstasy, this drug can produce profound alterations in mood, hallucinations, and distorted perceptions. T is drug is available on the Internet and is known by a variety of names including magic mint, mystic sage, Mariana Pastora, and purple sticky. T e drug was first added to the annual National Surveys on Drug Use and Health in 2006, and its use is increasing. Between 2006 and 2011, the number of estimated users in the United States nearly tripled to more than 5000.

T e active ingredient is salvinorin A, a selective kappa opioid receptor agonist that has a range of effects including hallucinations, sedation, analgesia, and depression. T e hallucinatory symptoms may be associated with intense anxiety and severe agitation that can be managed with benzodiazepines. Importantly, this kappa opioid receptor agonist does not produce respiratory depression, and no significant change in blood pressure or heart rate was reported in a clinical study with healthy subjects.

Salvinorin A extract or crushed leaves of the Salvia divinorum plant can be chewed and absorbed through the buccal membrane or inhaled during smoking. T e onset of the acute "high" is within 5–10 min after chewing and 30 s after inhalation. T e duration of the effect is relatively brief, usually 15–20 min. However, if the drug is taken with alcohol or other hallucinogens, the duration and intensity of adverse effects may be increased. T e effects of the drug are reported to be similar to those of ketamine, LSD, and marijuana.

OTHER DRUGS OF ABUSE

A number of other pharmacologically diverse drugs of abuse are often referred to as "club drugs" because these are frequently used in bars, at concerts, and at rave parties. Commonly abused club drugs include flunitrazepam, GHB, and ketamine and are described below. Methamphetamine, MDMA, and LSD are also considered club drugs and were described earlier in this chapter. Abuse of club drugs at high doses, especially in combination with alcohol, can be lethal and should be treated as a medical emergency. GHB and ketamine can be identified in blood, and flunitrazepam can be identified in urine and hair samples. Flunitrazepam and GHB toxicity can be treated with antagonists at benzodiazepine and γ-aminobutyric acid B ($GABA_B$) receptors, respectively.

Flunitrazepam (Rohypnol) is a benzodiazepine derivative primarily used to treat insomnia, but it has significant abuse potential because of its strong hypnotic, anxiolytic, and amnesia-producing effects. It is a club drug commonly referred to as a "date-rape drug" or "roofies." T e drug enhances $GABA_A$ receptor activity, and overdose can be treated with flumazenil, a benzodiazepine receptor antagonist. Flunitrazepam is typically used orally but can be snorted or injected. Concomitant use of alcohol or opioids is common, and this enhances the sedative and hypnotic effects of flunitrazepam and also the risk of motor vehicle accidents. Overdose can produce life-threatening respiratory depression and coma. Abrupt cessation after chronic use may result in a benzodiazepine withdrawal syndrome consisting of anxiety, insomnia, disordered thinking, and seizures.

GHB (Xyrem) is a sedative drug that is approved by the FDA for the treatment of narcolepsy. It is classified as a club drug, is sometimes used in combination with alcohol or other drugs of abuse, and has been implicated in cases of date rape. It is also used by body builders as a growth hormone stimulant. GHB is usually available as a liquid, is taken orally, and has no distinctive color or odor. Its stimulant properties are attributed to agonist activity at the GHB receptor, but it also has sedative effects at high doses that reflect its

www.ketabpezeshki.com (021) 66485457 - 66485438

activity at $GABA_B$ receptors. $GABA_B$ antagonists can reverse GHB's sedative effects, and opioid antagonists (naloxone, naltrexone) can attenuate GHB effects on dopamine release. Low doses of GHB may produce euphoria and disinhibition, whereas high doses result in nausea, agitation, convulsions, and sedation that can lead to unconsciousness and death from respiratory depression. In 2011, more than 2400 emergency ward admissions involved GHB.

Ketamine (Ketaset, Ketalar) is a dissociative anesthetic, similar to PCP. In veterinary medicine, it is used for brief immobilization. In clinical medicine, it is used for sedation, analgesia, and to supplement anesthesia. Ketamine increases heart rate and blood pressure, with less respiratory depression than other anesthetics. Ketamine's popularity as a club drug appears to reflect its ability to induce a dissociative state and feelings of depersonalization, accompanied by intense hallucinations and subsequent amnesia. It can be administered orally, by smoking (usually in combination with tobacco and/or marijuana), or by IV or IM injection. Like PCP, it binds to NMDA receptors and acts as a noncompetitive NMDA antagonist. In 2011, ketamine accounted for 1550 emergency ward admissions. Ketamine has a complex profile of action and appears to be useful as an antidepressant in treatment-resistant patients and as an analgesic in patients with chronic pain. T e extent to which chronic recreational use leads to memory impairment remains controversial.

POLYDRUG ABUSE

Although some drug abusers may prefer a particular drug, the concurrent use of multiple drugs is common. Polydrug abuse often involves substances that may have different pharmacologic effects from the preferred drug. For example, concurrent use of such dissimilar compounds as stimulants and opioids or stimulants and alcohol is common. T e diversity of reported drug use combinations suggests that achieving a change in subjective state, rather than any particular direction of change (stimulation or sedation), may be the primary reinforcer in polydrug abuse. T ere is also evidence that intoxication with alcohol, opiates, and cocaine is associated with increased tobacco smoking. Nicotine and cocaine enhance each other's effects in clinical laboratory studies, and this drug combination maintains significantly higher levels of self-administration than either drug alone in preclinical models of addiction. T ere are relatively few controlled studies of multiple drug interactions. However, the combined use of cocaine, heroin, and alcohol increases the risk for toxic effects and adverse medical consequences. Similarly, some hallucinogens (MDMA, LSD) and club drugs (GHB, ketamine, flunitrazepam) are used in various combinations with an associated increase in toxic consequences.

One determinant of polydrug use patterns is the relative availability and cost of the drugs. For example, alcohol abuse, with its attendant medical complications, is one of the most serious problems encountered in former heroin addicts participating in methadone maintenance programs. Cocaine abuse often increases during methadone maintenance.

T e physician must recognize that perpetuation of polydrug abuse and drug dependence is not necessarily a symptom of an underlying emotional disorder. Neither alleviation of anxiety nor reduction of depression accounts for initiation and perpetuation of polydrug abuse. Severe depression and anxiety are the consequences of polydrug abuse as frequently as they are the antecedents. Interestingly, some adverse consequences of drug use may be reinforcing and contribute to the continuation of polydrug abuse.

Adequate treatment of polydrug abuse, as well as other forms of drug abuse, requires innovative intervention programs. T e first step in successful treatment is detoxification, a process that may be dif cult when several drugs with different pharmacologic actions (e.g., alcohol, opiates, and cocaine) have been abused. Because patients may not recall or may deny simultaneous multiple drug use, diagnostic evaluation should always include urinalysis for qualitative detection of psychoactive substances and their metabolites. Treatment of polydrug abuse often requires hospitalization or inpatient residential care during detoxification and the initial phase of drug abstinence. When possible, specialized facilities for the care and treatment of drug-dependent persons should be used. Outpatient detoxification of polydrug abuse patients is unlikely to be effective and may increase risk for dangerous medical consequences.

Drug abuse disorders often respond to effective treatment, but periods of relapse may occur unpredictably. T e physician should continue to assist patients during episodes of relapse with compassion and understanding. T e physician and the patient must recognize that occasional recurrent drug use is not unusual in this complex behavioral disorder.

www.ketabpezeshki.com (021) 66485457 - 66485438

CHAPTER 66

NICOTINE ADDICTION

David M. Burns

The use of tobacco leaf to create and satisfy nicotine addiction was introduced to Columbus by Native Americans and spread rapidly to Europe. Use of tobacco as cigarettes, however, only became popular in the twentieth century and so is a modern phenomenon, as is the epidemic of disease caused by this form of tobacco use.

Nicotine is the principal constituent of tobacco responsible for its addictive character, but other smoke constituents and behavioral associations contribute to the strength of the addiction. Addicted smokers regulate their nicotine intake by adjusting the frequency and intensity of their tobacco use both to obtain the desired psychoactive effects and avoid withdrawal.

Unburned cured tobacco used orally contains nicotine, carcinogens, and other toxicants capable of causing gum disease, oral and pancreatic cancers, and an increase in the risk of heart disease. When tobacco is burned, the resultant smoke contains, in addition to nicotine, more than 7000 other compounds that result from volatilization, pyrolysis, and pyrosynthesis of tobacco and various chemical additives used in making different tobacco products. The smoke is composed of a fine aerosol and a vapor phase; aerosolized particles are of a size range that results in deposition in the airways and alveolar surfaces of the lungs. The aggregate of particulate matter, after subtracting nicotine and moisture, is referred to as tar.

The alkaline pH of smoke from blends of tobacco used for pipes and cigars allows sufficient absorption of nicotine across the oral mucosa to satisfy the smoker's need for this drug. Therefore, smokers of pipes and cigars tend not to inhale the smoke into the lung, confining the toxic and carcinogenic exposure (and the increased rates of disease) largely to the upper airway for most users of these products. The acidic pH of smoke generated by the tobacco used in cigarettes dramatically reduces absorption of nicotine in the mouth, necessitating inhalation of the smoke into the larger surface of the lungs in order to absorb quantities of nicotine sufficient to satisfy the smoker's addiction. The shift to using tobacco as cigarettes, with resultant increased deposition of smoke in the lung, has created the epidemic of heart disease, lung disease, and lung cancer that dominates the current disease manifestations of tobacco use.

Several genes have been associated with nicotine addiction. Some reduce the clearance of nicotine, and others have been associated with an increased likelihood of becoming dependent on tobacco and other drugs as well as a higher incidence of depression. Rates of smoking cessation have increased, and rates of nicotine addiction have decreased dramatically, since the mid-1950s, suggesting that factors other than genetics are important. It is likely that genetic susceptibility can influence the probability that adolescent experimentation with tobacco will lead to addiction as an adult.

Adult cigarette smoking prevalence has declined to about 19% in the United States, with 20–40% of those smokers not smoking every day. Male smoking prevalence is falling but remains high in most Asian countries, with increasing smoking prevalence among women in those countries. The highest rates of smoking and least cessation are observed in eastern European countries. Of particular concern is the rapidly rising smoking rate observed in the developing world. The World Health Organization Framework Convention on Tobacco Control is encouraging effective tobacco control approaches in these countries with the hope of preventing a future epidemic of tobacco-related illness.

DISEASE MANIFESTATIONS OF CIGARETTE SMOKING

More than 400,000 individuals die prematurely each year in the United States from cigarette use; this represents almost one of every five deaths in the United States. Approximately 40% of cigarette smokers will die prematurely due to cigarette smoking unless they are able to quit.

www.ketabpezeshki.com (021) 66485457 - 66485438

The major diseases caused by cigarette smoking are listed in **Table 66-1**. The ratio of smoking-related disease rates in smokers compared to never smokers (relative risk) is greater at younger ages, particularly for coronary artery disease and stroke. At older ages, the background rate of disease in nonsmokers increases, diminishing the fractional contribution of smoking and the relative risk; however, absolute excess rates of disease mortality found in smokers compared to nonsmokers increase with increasing age. The organ damage caused by smoking and the number of smokers who die from smoking are both greater among the elderly, as one would expect from a process of cumulative injury.

CARDIOVASCULAR DISEASES

Cigarette smokers are more likely than nonsmokers to develop both large-vessel atherosclerosis and small-vessel disease. Approximately 90% of peripheral vascular disease in the nondiabetic population can be attributed to cigarette smoking, as can ~50% of aortic aneurysms. In contrast, 20–30% of coronary artery disease and ~10% of ischemic and hemorrhagic strokes are caused by cigarette smoking. There is a multiplicative interaction between cigarette smoking and other cardiac risk factors such that the increment in risk produced by smoking among individuals with hypertension or elevated serum lipids is substantially greater than the increment in risk produced by smoking for individuals without these risk factors.

In addition to its role in promoting atherosclerosis, cigarette smoking also increases the likelihood of myocardial infarction and sudden cardiac death by promoting platelet aggregation and vascular occlusion. Reversal of these effects on coagulation may explain the rapid benefit of smoking cessation for a new coronary event demonstrable among those who have survived a first myocardial infarction. This effect may also explain the substantially higher rates of graft occlusion among continuing smokers following vascular bypass surgery for cardiac or peripheral vascular disease.

Cessation of cigarette smoking reduces the risk of a second coronary event within 6–12 months; rates of first myocardial infarction and death from coronary heart disease also decline within the first few years following cessation among those with no prior cardiovascular history. After 15 years of abstinence, the risk of a new myocardial infarction or death from coronary heart disease in former smokers is similar to that for those who have never smoked.

TABLE 66-1

RELATIVE RISKS FOR CURRENT SMOKERS OF CIGARETTES

	CURRENT SMOKERS	
DISEASE OR CONDITION	MALES	FEMALES
Coronary heart disease		
Age 35–64	2.8	3.1
Age ≥65	1.5	1.6
Cerebrovascular disease		
Age 35–64	3.3	4
Age ≥65	1.6	1.5
Aortic aneurysm	6.2	7.1
Chronic airway obstruction	10.6	13.1
Cancer		
Lung	23.3	12.7
Larynx	14.6	13
Lip, oral cavity, pharynx	10.9	5.1
Esophagus	6.8	7.8
Bladder, other urinary organs	3.3	2.2
Kidney	2.7	1.3
Pancreas	2.3	2.3
Stomach	2	1.4
Liver	1.7	1.7
Colorectal	1.2	1.2
Cervix		1.6
Acute myeloid leukemia	1.4	1.4
Sudden infant death syndrome		2.3
Infant respiratory distress syndrome		1.3
Low birth weight at delivery		1.8

CANCER

Tobacco smoking causes cancer of the lung; oral cavity; naso-, oro-, and hypopharynx; nasal cavity and paranasal sinuses; larynx; esophagus; stomach; pancreas; liver (hepatocellular); colon and rectum; kidney (body and pelvis); ureter; urinary bladder; and uterine cervix, and also causes myeloid leukemia. There is evidence suggesting that cigarette smoking may play a role in increasing the risk of breast cancer. There does not appear to be a causal link between cigarette smoking and cancer of the endometrium, and there is a lower risk of uterine cancer among postmenopausal women who smoke. The risks of cancer increase with the increasing number of cigarettes smoked per day and with increasing duration of smoking. Additionally, there are synergistic interactions between cigarette smoking and alcohol use for cancer of the oral cavity and esophagus. Several occupational exposures synergistically increase lung cancer risk among cigarette smokers, most notably occupational asbestos and radon exposure.

Cessation of cigarette smoking reduces the risk of developing cancer relative to continuing smoking, but even 20 years after cessation, there is a modest persistent increased risk of developing lung cancer.

www.ketabpezeshki.com (021) 66485457 - 66485438

RESPIRATORY DISEASE

Cigarette smoking is responsible for 90% of chronic obstructive pulmonary disease. Within 1–2 years of beginning to smoke regularly, many young smokers will develop inf ammatory changes in their small airways, although lung function measures of these changes do not predict development of chronic airf ow obstruction. After 20 years of smoking, pathophysiologic changes in the lungs develop and progress proportional to smoking intensity and duration. Chronic mucous hyperplasia of the larger airways results in a chronic productive cough in as many as 80% of smokers >60 years of age. Chronic inf ammation and narrowing of the small airways and/or enzymatic digestion of alveolar walls resulting in pulmonary emphysema can result in reduced expiratory airf ow sufficient to produce clinical symptoms of respiratory limitation in ~15–25% of smokers.

Changes in the small airways of young smokers will reverse after 1–2 years of cessation. T ere may also be a small increase in measures of expiratory airf ow following cessation among individuals who have developed chronic airf ow obstruction, but the major change following cessation is a slowing of the rate of decline in lung function with advancing age rather than a return of lung function toward normal.

PREGNANCY

Cigarette smoking is associated with several maternal complications of pregnancy: premature rupture of membranes, abruptio placentae, and placenta previa; there is also a small increase in the risk of spontaneous abortion among smokers. Infants of smoking mothers are more likely to experience preterm delivery, have a higher perinatal mortality rate, be small for their gestational age, and have higher rates of infant respiratory distress syndrome; they are more likely to die of sudden infant death syndrome and appear to have a developmental lag for at least the first several years of life.

OTHER CONDITIONS

Smoking delays healing of peptic ulcers; increases the risk of developing diabetes, active tuberculosis, rheumatoid arthritis, osteoporosis, senile cataracts, and neovascular and atrophic forms of macular degeneration; and results in premature menopause, wrinkling of the skin, gallstones and cholecystitis in women, and male impotence.

ENVIRONMENTAL TOBACCO SMOKE

Long-term exposure to environmental tobacco smoke increases the risk of lung cancer and coronary artery disease among nonsmokers. It also increases the incidence of respiratory infections, chronic otitis media, and asthma in children and causes exacerbation of asthma in children. Some evidence suggests that environmental tobacco smoke exposure may increase the risk of premenopausal breast cancer. Patients who continue to smoke during treatment for cancer with chemotherapy or radiation have poorer outcomes and reduced survival.

PHARMACOLOGIC INTERACTIONS

Cigarette smoking may interact with a variety of other drugs **(Table 66-2)**. Cigarette smoking induces the cytochrome P450 system, which may alter the metabolic clearance of drugs such as theophylline. T is may result in inadequate serum levels in smokers as outpatients when the dosage is established in the hospital under nonsmoking conditions. Correspondingly, serum levels may rise when smokers are hospitalized and not allowed to smoke. Smokers may also have higher first-pass clearance for drugs such as lidocaine, and the stimulant effects of nicotine may reduce the effect of benzodiazepines or beta blockers.

OTHER FORMS OF TOBACCO USE

Other major forms of tobacco use are moist snuff deposited between the cheek and gum, chewing tobacco, pipes and cigars, and recently bidi (tobacco wrapped in tendu or temburni leaf; commonly used in India), clove cigarettes, and water pipes. Oral tobacco use leads to gum disease and can result in oral and pancreatic cancer as well as heart disease, with dramatic differences in the risks evident for products used in Africa and Asia as compared to those in the United States and Europe.

All forms of burned tobacco generate toxic and carcinogenic smoke similar to that of cigarette smoke. T e differences in disease consequences of use relate to frequency of use and depth of inhalation. T e risk of upper airway cancers is similar among cigarette, pipe, and cigar smokers, whereas those who have smoked only pipes and cigars have a much lower risk of lung cancer, heart disease, and chronic obstructive pulmonary disease. However, cigarette smokers who switch to pipes or cigars do tend to inhale the smoke, increasing their risk; and it is likely that comparable inhalation and frequency of exposure to tobacco smoke from any of these forms of tobacco use will lead to comparable disease outcomes.

A resurgence of cigar, bidi, and water pipe use among adolescents of both genders has raised concerns that these older forms of tobacco use are once again

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 66-2

INTERACTIONS OF SMOKING AND PRESCRIPTION DRUGS

DRUG	INTERACTION
Amitriptyline	Increased clearance
Benzodiazepines	Less sedation
Beta blockers	Reduced lowering of heart rate and blood pressure
Caffeine	Faster metabolic clearance
Chlorpromazine	Decreased serum concentrations[a]
Clomipramine	Decreased serum concentrations[a]
Clozapine	Decreased serum concentrations[a]
Dextropropoxyphene	Less analgesia
Estrogens (oral)	Increased hepatic clearance
Flecainide	Increased first-pass clearance
Fluphenazine	Decreased serum concentrations[a]
Fluvoxamine	Decreased serum concentrations[a]
Haloperidol	Decreased serum concentrations[a]
Heparin	Faster clearance
Imipramine	Decreased serum concentrations[a]
Insulin	Delayed absorption due to skin vasoconstriction
Lidocaine	Increased first-pass clearance
Mexiletine	Increased first-pass clearance
Naratriptan	Increased clearance
Olanzapine	Faster clearance
Pentazocine	Less analgesia, possible increased clearance
Propranolol	Increased first-pass clearance
Propoxyphene	Increased hepatic metabolism
Rivastigmine	Increased clearance
Tacrine	Increased clearance
Tacrine	Faster metabolic clearance
Theophylline	Faster metabolic clearance
Thiothixene	Faster metabolic clearance
Trazodone	Decreased serum concentrations[a]
Verapamil	Increased clearance

[a]Clinical implications uncertain.

causing a public health problem. A variety of devices are currently sold that deliver nicotine by electronically heating materials containing nicotine—so-called electronic cigarettes. Although these devices are marketed as substitutes for cigarettes and as cessation tools, the composition of the vapor and nicotine delivery varies widely among products, raising questions of both safety and efficacy in the absence of regulatory oversight.

LOWER TAR AND NICOTINE CIGARETTES

Filtered cigarettes with lower machine-measured yields of tar and nicotine commonly use ventilation holes in the filters and other engineering designs to artificially lower the machine measurements. Smokers compensate for the lowered nicotine delivery by changing the manner in which they puff on the cigarette or the number of cigarettes smoked per day, and tar and nicotine deliveries are not reduced with use of these products. Cigarette design changes that reduce machine-measured tar and nicotine lead to deeper inhalation of the smoke and an increase in the carcinogenicity of the smoke inhaled by smokers. The presentation of more carcinogenic smoke to the alveolar portions of the lung has resulted in an increase in the risk of lung cancer, and possibly chronic obstructive pulmonary disease, among smokers over the past six decades. This change in cigarette product is also one cause of the dramatic rise in rates of adenocarcinoma of the lung observed over the past half century. There has been no increase in risk of lung cancer or adenocarcinoma of the lung in never smokers over time.

CESSATION

The process of stopping smoking is commonly a cyclical one, with the smoker sometimes making multiple attempts to quit and failing before finally being successful. Approximately 70–80% of smokers would like to quit smoking. More than one-half of current smokers attempted to quit in the last year, but only 6% quit for 6 months, and only 3% remain abstinent for 2 years. Clinician-based smoking interventions should repeatedly encourage smokers to try to quit and to use different forms of cessation assistance with each new cessation attempt rather than focusing exclusively on immediate cessation at the time of the first visit.

Advice from a physician to quit smoking, particularly at the time of an acute illness, is a powerful trigger for cessation attempts, with up to half of patients who are advised to quit making a cessation effort. Other triggers include the cost of cigarettes, media campaigns, and changes in rules to restrict smoking in the workplace.

PHYSICIAN INTERVENTION

All patients should be asked whether they smoke, how much they smoke, how long they have smoked, their past experience with quitting, and whether they are currently interested in quitting **(Table 66-3)**. Intensity of smoking and smoking within 30 min of waking are useful measures of the intensity of nicotine addiction. Even those who are not interested in quitting should be encouraged and motivated to quit; provided a clear,

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 66-3

CLINICAL PRACTICE GUIDELINES
Physician Actions
Ask: Systematically identify all tobacco users at every visit
Advise: Strongly urge all smokers to quit
Identify smokers willing to quit
Assist the patient in quitting
Arrange follow-up contact
Effective Pharmacologic Interventions[a]
First-line therapies
Nicotine gum (1.5)
Nicotine patch (1.9)
Nicotine nasal inhaler (2.7)
Nicotine oral inhaler (2.5)
Nicotine lozenge (2.0)
Bupropion (2.1)
Varenicline (2.7)
Second-line therapies
Clonidine (2.1)
Nortriptyline (3.2)
Other Effective Interventions[a]
Physician or other medical personnel counseling (10 min) (1.3)
Intensive smoking cessation programs (at least 4–7 sessions of 20- to 30-min duration lasting at least 2 and preferably 8 weeks) (2.3)
Clinic-based smoking status identification system (3.1)
Counseling by nonclinicians and social support by family and friends
Telephone counseling (1.2)

[a]Numerical value following the intervention is the multiple for cessation success compared to no intervention.

strong, and personalized message by the clinician that smoking is an important health concern; and offered assistance if they become interested in quitting in the future. Many of those not currently expressing an interest in quitting may nevertheless make an attempt to quit in the subsequent year. For those interested in quitting, a quit date should be negotiated, usually not the day of the visit but within the next few weeks, and a follow-up contact by office staff around the time of the quit date should be provided. There is a relationship between the amount of assistance a patient is willing to accept and the success of the cessation attempt.

There are a variety of nicotine-replacement products, including over-the-counter nicotine patches, gum, and lozenges, as well as nicotine nasal and oral inhalers available by prescription. These products can be used for up to 3–6 months, and some products are formulated to allow a gradual step-down in dosage with increasing duration of abstinence. Antidepressants such as bupropion (300 mg in divided doses for up to 6 months) have also been shown to be effective, as has varenicline, a partial agonist for the nicotinic acetylcholine receptor (initial dose 0.5 mg daily increasing to 1 mg twice daily at day 8; treatment duration up to 6 months). Severe psychiatric symptoms, including suicidal ideation, have been reported with varenicline, resulting in a U.S. Food and Drug Administration–mandated warning and a recommendation for closer therapeutic supervision, but evidence to establish the frequency of these responses and the specificity of their association with varenicline remains unclear. Some evidence supports the combined use of nicotine-replacement therapy (NRT) and antidepressants as well as the use of gum or lozenges for acute cravings in patients using patches. Pretreatment with antidepressants or varenicline is recommended for 1–2 weeks prior to the quit date, and pretreatment with nicotine-replacement products is also being explored, as is longer duration of nicotine replacement as a maintenance therapy for those who are unsuccessful in quitting with a shorter duration of use. NRT is provided in different dosages, with higher doses being recommended for more intense smokers. Clonidine or nortriptyline may be useful for patients who have failed on first-line pharmacologic treatment or who are unable to use other therapies. Antidepressants are more effective in those with a history of depression symptoms.

Current recommendations are to offer pharmacologic treatment, usually with NRT or varenicline, to all who will accept it and to provide counseling and other support as a part of the cessation attempt. There are some data to suggest that longer term use of NRT may enable cessation in some smokers who are unable to quit with shorter duration use and that some individuals are able to achieve abstinence from tobacco through use of NRT chronically. Cessation advice alone by a physician or his or her staff is likely to increase success compared with no intervention; a more comprehensive approach with advice, pharmacologic assistance, and counseling can increase cessation success nearly threefold.

Incorporation of cessation assistance into a practice requires a change of the care delivery infrastructure. Simple changes include (1) adding questions about smoking and interest in cessation on patient-intake questionnaires, (2) asking patients whether they smoke as part of the initial vital sign measurements made by office staff, (3) listing smoking as a problem in the medical record, and (4) automating follow-up contact with the patient on the quit date. These changes are essential to institutionalizing smoking intervention within the practice setting; without this institutionalization,

www.ketabpezeshki.com (021) 66485457 - 66485438

the best intentions of physicians to intervene with their patients who smoke are often lost in the time crush of a busy practice.

PREVENTION

Approximately 85% of individuals who become cigarette smokers initiate the behavior during adolescence. Factors that promote adolescent initiation are parental or older-sibling cigarette smoking, tobacco advertising and promotional activities, the availability of cigarettes, and the social acceptability of smoking. T e need for an enhanced self-image and to imitate adult behavior is greatest for those adolescents who have the least external validation of their self-worth, which may explain in part the enormous differences in adolescent smoking prevalence by socioeconomic and school performance strata.

Prevention of smoking initiation must begin early, preferably in the elementary school years. Physicians who treat adolescents should be sensitive to the prevalence of this problem even in the pre-teen population. Physicians should ask all adolescents whether they have experimented with tobacco or currently use tobacco, reinforce the fact that most adolescents and adults do not smoke, and explain that all forms of tobacco are both addictive and harmful.

www.ketabpezeshki.com (021) 66485457 - 66485438

APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Robert C. Basner ■ Andrew J. Einstein

This Appendix contains tables of reference values for common laboratory tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for collection of the specimen. The reference or "normal" ranges given in this Appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be used in interpretation of laboratory data. Values supplied in this Appendix reflect typical reference ranges in nonpregnant adults. Pediatric reference ranges and values in pregnant patients may vary significantly from the data presented in the Appendix.

In preparing the Appendix, the authors have taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. Therefore, both systems are provided in the Appendix. The dual system is also used in the text except for those instances in which the numbers remain the same and only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given.

TABLE 1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
$Alpha_2$ antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Beta-2 glycoprotein 1 antibodies	S		
IgG		0–20 arbitrary units	0–20 SGU
IgM		0–20 arbitrary units	0–20 SMU
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
C4 binding protein	P	305–695 mg/L	30.5–69.5 mg/dL
	S	275–604 mg/L	27.5–60.4 mg/dL
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts:			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts:			
Neutrophils		$1.42–6.34 \times 10^9$/L	1420–6340/mm^3
Bands		$0–0.45 \times 10^9$/L	0–450/mm^3
Lymphocytes		$0.71–4.53 \times 10^9$/L	710–4530/mm^3
Monocytes		$0.14–0.72 \times 10^9$/L	140–720/mm^3
Eosinophils		$0–0.54 \times 10^9$/L	0–540/mm^3
Basophils		$0–0.18 \times 10^9$/L	0–180/mm^3
Erythrocyte count	WB		
Adult males		$4.30–5.60 \times 10^{12}$/L	$4.30–5.60 \times 10^6$/mm^3
Adult females		$4.00–5.20 \times 10^{12}$/L	$4.00–5.20 \times 10^6$/mm^3
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Females		0–20 mm/h	0–20 mm/h
Males		0–15 mm/h	0–15 mm/h

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Euglobulin lysis time	P	7200–14,400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150%
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda units	<0.5 Bethesda units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 μg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative
Hematocrit	WB		
Adult males		0.388–0.464	38.8–46.4
Adult females		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood	WB		
Adult males		133–162 g/L	13.3–16.2 g/dL
Adult females		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A_2		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A_2, or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fuid crystal	JF	Not applicable	No crystals seen
Joint fuid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 μkat/L	13–100 μ/L
Count (WBC)	WB	$3.54–9.06 \times 10^9$/L	$3.54–9.06 \times 10^3$/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 µg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10^9/L	165–415 × 10^3/mm^3
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 µm^3
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s
Protoporphyrin, free erythrocyte	WB	0.28–0.64 µmol/L of red blood cells	16–36 µg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult males		0.008–0.023 red cells	0.8–2.3% red cells
Adult females		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Thrombin-antithrombin (TAT) complex	P	<4 µg/L	<4 ng/mL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Total eosinophils	WB	150–300 × 10^6/L	150–300/mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (vWF) antigen (factor VIII:R antigen)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor collagen binding	P	590–2490 units/L	59–249 units/dL
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see "Leukocytes"			

Abbreviations: JF, joint fuid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 µmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 µkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 µg/L	0–8.5 ng/mL
Alpha-1-acid glycoprotein	S	0.50–1.2 g/L	50–120 mg/dL
$Alpha_1$ antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH_3	P	11–35 µmol/L	19–60 µg/dL
Amylase (method dependent)	S	0.34–1.6 µkat/L	20–96 U/L
Androstenedione (adult)	S		
Males		0.81–3.1 nmol/L	23–89 ng/dL
Females			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 µkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
(HCO_3^-)		22–30 mmol/L	22–30 meq/L
Pco_2 (Sea Level, Fio_2 0.21)		4.7–6.0 kPa	35–45 mmHg
pH		7.35–7.45	7.35–7.45
Po_2 (Sea Level, Fio_2 0.21, age related)		8.9–13.8 kPa	67–104 mmHg
Carboxyhemoglobin and methemoglobin at pH 7.40 and 37°C		≤0.01	≤1%
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 μkat/L	12–38 U/L
Autoantibodies	S		
Anti-centromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Anti-double-strand (native) DNA		<25 IU/L	<25 IU/L
Anti-glomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Anti-histone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Anti-mitochondrial antibody		Not applicable	<20 Units
Anti-neutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Anti-parietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Anti-smooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Anti-thyroglobulin antibody		<40 kIU/mL	<40 IU/mL
Anti-thyroid peroxidase antibody		<35 kIU/L	<35 IU/L
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Bile acids	S		
Cholic acid		0–1.9 µmol/L	0–1.9 µmol/L
Chenodeoxycholic acid		0–3.4 µmol/L	0–3.4 µmol/L
Deoxycholic acid		0–2.5 µmol/L	0–2.5 µmol/L
Ursodeoxycholic acid		0–1.0 µmol/L	0–1.0 µmol/L
Total		0–7.0 µmol/L	0–7.0 µmol/L
Bilirubin	S		
Total		5.1–22 µmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 µmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 µmol/L	0.2–0.9 mg/dL
C peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
C1-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO_2)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers (in a nonsmoking environment)		0.0–0.025	0–2.5% of total hemoglobin (Hgb) value
Smokers		0.04–0.09	4–9% of total Hgb value
Loss of consciousness and death		>0.50	>50% of total Hgb value
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol (LCL, Total, HDL): Ranges depend on individual patient factors; see 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–95 µg/L	0–95 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol			
Fasting, 8 a.m.–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 p.m.		138–414 nmol/L	5–15 µg/dL
8 p.m.–8 a.m.		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.87−5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cyclic citrullinated peptide (CCP) antibody (IgG)	S	Negative: <20 Units Weak positive: 20–39 Units Moderate positive: 40–59 Units Strong positive: ≥60 Units	Negative: <20 Units Weak positive: 20–39 Units Moderate positive: 40–59 Units Strong positive: ≥60 Units
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L
Deamidated gliadin peptide (DGP) antibody, IgA	S		
Negative Weak positive Positive		≤19 Units 20–30 Units ≥31 Units	≤19 Units 20–30 Units ≥31 Units
Deamidated gliadin peptide (DGP) antibody, IgG	S		
Negative Weak positive Positive		≤19 Units 20–30 Units ≥31 Units	≤19 Units 20–30 Units ≥31 Units
Dehydroepiandrosterone (DHEA) (adult)			
Male	S	6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult)			
premenopausal		120–5350 µ/L	12–535 µg/dL
post menopausal		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult) (compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone			
Male	S, P	1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Endomysial antibody, IgA	S	<1:10	<1:10
Endomysial antibody, IgG	S	<1:10	<1:10

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29−248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 µmol/L	<285 µmol/L
Galectin-3	S		
Low risk		≤17.8 µg/L	≤17.8 ng/mL
Intermediate risk		17.9–25.9 µg/L	17.9–25.9 ng/mL
Higher risk		>25.9 µg/L	>25.9 ng/mL
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Diabetes mellitus		Fasting ≥7.0 mmol/L	Fasting ≥126 mg/dL
		A 2-h level of ≥11.1 mmol/L during an oral glucose tolerance test	A 2-h level of ≥200 mg/dL during an oral glucose tolerance test
		A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia	A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 µg/L	0–5 ng/mL
Hemoglobin A_{lc}	WB	0.04–0.06 Hgb fraction	4.0–5.6%
Prediabetes		0.057–0.064 Hgb fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A_{1c} level of ≥0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association
Hemoglobin A_{1c} with estimated average glucose (eAG)	WB	eAg mmoL/L = 1.59 × HbA_{1c} – 2.59	eAg (mg/dL) = 28.7 × HbA_{1c} – 46.7
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		<5 IU/L	<5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks postconception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
Human epididymis protein 4 (HE-4)	S	0–150 pmol/L	0–150 pmol/L
β-Hydroxybutyrate	P	60–170 µmol/L	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		<4.17 nmol/L	<139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 kIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Inhibin A	S		
Males		≤2.0 ng/L	≤2.0 pg/mL
Females			
Early follicular phase		1.8–17.3 ng/L	1.8–17.3 pg/mL
Mid follicular phase		3.5–31.7 ng/L	3.5–17.3 pg/mL
Late follicular phase		9.8–90.3 ng/L	9.8–90.3 pg/mL
Midcycle		16.9–91.8 ng/L	16.9–91.8 pg/mL
Early luteal phase		16.1–97.5 ng/L	16.1–97.5 pg/mL
Mid luteal phase		3.9–87.7 ng/L	3.9–87.7 pg/mL
Late luteal phase		2.7–47.1 ng/L	2.7–47.1 pg/mL
Postmenopausal		<1.0–2.1 ng/L	<1.0–2.1 pg/mL
Insulin	S, P	14.35–143.5 pmol/L	2–20 µU/mL
Iron	S	7–25 µmol/L	41–141 µg/dL
Iron-binding capacity	S	45–73 µmol/L	251–406 µg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia modified albumin	S	<85 kU/L	<85 U/mL
Joint fuid crystal	JF	Not applicable	No crystals seen
Joint fuid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial	0.5–1.6 mmol/L	4.5–14.4 mg/dL
	P, venous	0.5–2.2 mmol/L	4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 µkat/L	115–221 U/L
Lamellar body count	AMF		
Immature		<15,000/µL	<15,000/µL
Indeterminate		15,000–50,000/µL	15,000-50,000/µL
Mature		>50,000/µL	>50,000/µL
Lecithin/sphingomyelin (L/S) ratio	AMF		
Immature		≤1.5	≤1.5
Transitional		1.5–1.9	1.5–1.9
Mature		2.0–2.5 or greater	2.0–2.5 or greater
Lipase	S	0.51–0.73 µkat/L	3–43 U/L
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Lipoprotein-associated phospholipase A2	S, P	0–234 µg/L	0–234 ng/mL
Luteinizing hormone (LH)	S, P		
Female			
Menstruating			
Follicular phase		2.0–15.0 U/L	2.0–15.0 mIU/mL
Ovulatory phase		22.0–105.0 U/L	22.0–105.0 mIU/mL
Luteal phase		0.6–19.0 U/L	0.6–19.0 mIU/mL
Postmenopausal		16.0–64.0 U/L	16.0–64.0 mIU/mL
Male		2.0–12.0 U/L	2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1% of total Hgb value
Myoglobin	S		
Male		20–71 µg/L	20–71 µg/L
Female		25–58 µg/L	25–58 µg/L

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Norepinephrine	P		
Supine (30 min)		650–2423 pmol/L	110–410 pg/mL
Sitting		709–4019 pmol/L	120–680 pg/mL
Standing (30 min)		739–4137 pmol/L	125–700 pg/mL
N-telopeptide (cross-linked), NTx	S		
Female, premenopausal		6.2–19.0 nmol BCE	6.2–19.0 nmol BCE
Male		5.4–24.2 nmol BCE	5.4–24.2 nmol BCE
BCE = bone collagen equivalent			
NT-proBNP	S, P	<125 ng/L up to 75 years <450 ng/L >75 years	<125 pg/mL up to 75 years <450 pg/mL >75 years
5' Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content (age and gender related)	WB		
Arterial (sea level)		17–21 mL/dL	17–21 vol%
Venous (sea level)		10–16 mL/dL	10–16 vol%
Oxygen saturation (sea level)	WB	Fraction:	Percent:
Arterial		0.91–1.0	91–100
Venous, arm		0.60–0.85	60–85
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL
Phosphatase, alkaline	S	0.56–1.63 µkat/L	33–96 U/L
Phosphatase, alkaline bone	S		
Male		≤20 µg/L	≤20 ng/mL
Female			
Premenopausal Postmenopausal		≤14 µg/L ≤22 µg/L	≤14 ng/mL ≤22 ng/mL
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin (transthyretin)	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 µg/L	<0.1 ng/mL
Progesterone	S, P		
Female			
Follicular Midluteal		<3.18 nmol/L 9.54–63.6 nmol/L	<1.0 ng/mL 3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 µg/L	0.0–4.0 ng/mL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Prostate-specific antigen, free	S	With total PSA between 4 and 10 µg/L and when the free PSA is:	With total PSA between 4 and 10 ng/mL and when the free PSA is:
		>0.25 decreased risk of prostate cancer	>25% decreased risk of prostate cancer
		<0.10 increased risk of prostate cancer	<10% increased risk of prostate cancer
Protein fractions	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
Alpha$_1$		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
Alpha$_2$		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 µmol/L	0.35–1.14 mg/dL
Retinol-binding protein	S	0.71–2.9 µmol/L	1.5–6.0 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 µmol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 µg/L	226–903 ng/mL
17 years		193–731 µg/L	193–731 ng/mL
18 years		163–584 µg/L	163–584 ng/mL
19 years		141–483 µg/L	141–483 ng/mL
20 years		127–424 µg/L	127–424 ng/mL
21–25 years		116–358 µg/L	116–358 ng/mL
26–30 years		117–329 µg/L	117–329 ng/mL
31–35 years		115–307 µg/L	115–307 ng/mL
36–40 years		119–204 µg/L	119–204 ng/mL
41–45 years		101–267 µg/L	101–267 ng/mL
46–50 years		94–252 µg/L	94–252 ng/mL
51–55 years		87–238 µg/L	87–238 ng/mL
56–60 years		81–225 µg/L	81–225 ng/mL
61–65 years		75–212 µg/L	75–212 ng/mL
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free			
Female, adult	S	10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	13–318 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone (thyrotropin)	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyrotropin receptor antibody	S	≤1.75 IU/L	≤1.75 mIU/mL
Thyroxine, free (fT_4)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T_4)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Tissue transglutaminase (tTG) antibody, IgA	S		
Negative		<4.0 Units/mL	<4.0 Units/mL
Weak positive		4.0–10.0 Units/mL	4.0–10.0 Units/mL
Positive		>10.0 Units/mL	>10.0 Units/mL
Tissue transglutaminase (tTG) antibody, IgG	S		
Negative		<6.0 Units/mL	<6.0 Units/mL
Weak positive		6.0–9.0 Units/mL	6.0–9.0 Units/mL
Positive		>9.0 Units/mL	>9.0 Units/mL
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Transferrin, carbohydrate deficient, for alcohol use	S	0.017	1.7%
Triglycerides	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT_3)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T_3)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I	S, P		
99th percentile of a healthy population		Method-dependent	Method-dependent
Troponin T	S, P		
99th percentile of a healthy population		0–14 ng/L	0–14 ng/L
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Females		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Males		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin (ZPP)	WB	0–400 µg/L	0–40 µg/dL
ZPP-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: AMF, amniotic fluid; P, plasma; S, serum; WB, whole blood.
Source: NJ Stone et al. J Am Coll Cardiol 63:2889–2934, 2014.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/mL	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	> 85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17 µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL(lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7 –3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4– 6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–1.6 nmol/L	0.5–1.2 ng/mL	>3.1 nmol/L	>2.4 ng/mL

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus (trough)				
Kidney transplant	3.1–8.34 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Oncology	5.2–10.4 nmol/L	5.0–10.0 ng/mL	>12.5 nmol/L	>12 ng/mL
Felbamate (trough)	126–252 µmol/L	30–60 µg/mL	Toxic range not well established	
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gabapentin (trough)	11.7–116.8 µmol/L	2–20 µg/mL	Toxic range not well established	
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolites)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Isopropanol			>8.3 mmol/L	>50 mg/dL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Levetiracetam (Keppra)	29–176 µmol/L	5–30 µg/mL	Toxic range not well established	
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5 µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 µmol/L	>0.1 µmol/L
High-dose (24h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (N-acetylprocainamide)	22–72 µmol/L	6–20 µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver transplant				
Initiation	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart transplant				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Topiramate (trough)	5.9–58.9 µmol/L	2.0–20.0 µg/mL	Toxic range not well established	
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL
Zonisamide (trough)	47–188 µmol/L	10–40 µg/mL	Toxic range not well established	

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 4

VITAMINS AND SELECTED TRACE MINERALS

		REFERENCE RANGE	
SPECIMEN	ANALYTE	SI UNITS	CONVENTIONAL UNITS
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.0–0.17 µmol/L	0–13 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/L cells	150–450 ng/mL cells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead	S		
Adult		<0.5 µmol/L	<10 µg/dL
Children		<0.25 µmol/L	<5 µg/dL
Mercury	WB	0–50 µmol/L	0–10 µg/L
Selenium	S	0.8–2.0 µmol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B_1 (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B_2 (riboflavin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B_6	P	20–121 nmol/L	5–30 ng/mL
Vitamin B_{12}	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D 1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D 25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 5

CEREBROSPINAL FLUID[a]

	REFERENCE RANGE	
CONSTITUENT	SI UNITS	CONVENTIONAL UNITS
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO_2 content	20–24 mmol/L	20–24 meq/L
P_{CO_2}	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
Creatinine	44–168 µmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 µg/L	
CSF pressure		50–180 mmH_2O
CSF volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per µL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Since cerebrospinal fuid (CSF) concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fuctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase.

[b]IgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d
Aluminum	0.19–1.11 µmol/L	5–30 µg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio ($[Cl_{am}/Cl_{cr}] \times 100$)	1–5	1–5
Arsenic	0.07–0.67 µmol/d	5–50 µg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d
Copper	<0.95 µmol/d	<60 µg/d
Coproporphyrins (types I and III)	0–20 µmol/mol creatinine	0–20 µmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 µg/d
Creatine, as creatinine		
Female	<760 µmol/d	<100 mg/d
Male	<380 µmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 µg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/d	0–20 µg/d
Glomerular filtration rate	>60 mL/min/1.73 m^2 For African Americans, multiply the result by 1.21	>60 mL/min/1.73 m^2 For African Americans, multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid (5-HIAA)	0–78.8 µmol/d	0–15 mg/d
Hydroxyproline	53–328 µmol/d	53–328 µmol/d
Iodine, spot urine		
WHO classification of iodine deficiency		
Not iodine deficient	>100 µg/L	>100 µg/L
Mild iodine deficiency	50–100 µg/L	50–100 µg/L
Moderate iodine deficiency	20–49 µg/L	20–49 µg/L
Severe iodine deficiency	<20 µg/L	<20 µg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Metanephrines		
Metanephrine	30–350 µg/d	30–350 µg/d
Normetanephrine	50–650 µg/d	50–650 µg/d
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
β_2-Microglobulin	0–160 µg/L	0–160 µg/L
Norepinephrine	89–473 nmol/d	15–80 µg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 µmol/d	7–44 mg/d
Female	45–350 µmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	

(continued)

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity:		
After 12-h fuid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 µmol/d	<6 mg/d

Abbreviation: BCE = bone collagen equivalent.

acknowledgment

T e contributions *of* Drs. Daniel J. Fink, Patrick M. Sluss, James L. Januzzi, Kent B. Lewandrowski, Amudha Palanisamy, and Scott Fink to this chapter in previous editions are grate*fully* acknowledged. We also express our gratitude to Drs. Alex Rai and Jef rey Jhang *for* help*ful* suggestions.

www.ketabpezeshki.com (021) 66485457 - 66485438

REVIEW AND SELF-ASSESSMENT*

Charles M. Wiener ■ Cynthia D. Brown ■ Brian Houston

Questions

DIRECTIONS: Choose the one best response to each question.

1. A 78-year-old man with a history of prostate cancer presents to the emergency department with weakness affecting his right arm and leg and left face. T e weakness began abruptly earlier during the day and is associated with numbness and paresthesias. On physical examination, strength is 4/5 in the right leg and arm. T e upper and lower facial muscles fail to move on the left. Babinski sign is positive. Sensation is decreased in the right extremities and on the left face. Based on this information, what is the most likely site of the lesion causing the patient's symptoms?

A. Brainstem
B. Cerebrum
C. Cervical spinal cord
D. Multiple spinal cord levels
E. Neuromuscular junction

2. During a neurologic examination, you ask a patient to stand with both arms fully extended and parallel to the ground with his eyes closed for 10 seconds. What is the name of this test?

A. Babinski sign
B. Dysdiadochokinesis
C. Lhermitte symptom
D. Pronator drift
E. Romberg sign

3. T e test described in Question 2 is considered positive if there is flexion at the elbows or forearms or if there is pronation of the forearms. A positive test is a sign of which of the following?

A. Abnormal sensation
B. Early dementia
C. Localized brainstem disease
D. Potential weakness
E. Underlying cerebellar dysfunction

4 through 8. For each of the following clinical findings on neurologic examination, identify the most likely anatomic location:

4. Anal sphincter dysfunction
5. Bilateral ptosis and diplopia
6. Diminished sensation bilaterally at the ankles and feet in a patient with diabetes
7. Left homonymous hemianopia
8. Right lateral extraocular muscle paresis

A. Brainstem
B. Cerebrum
C. Neuromuscular junction
D. Peripheral nerve
E. Spinal cord

9. A 54-year-old woman presents to the emergency department complaining of the abrupt onset of what she describes as the worst headache of her life. You are concerned about the possibility of subarachnoid hemorrhage. What is the most appropriate initial test for diagnosis?

A. Cerebral angiography
B. Computed tomography (CT) of the head with intravenous contrast
C. CT of the head without intravenous contrast
D. Lumbar puncture
E. Transcranial Doppler ultrasound

10. A 74-year-old woman has a recent diagnosis of small-cell lung cancer. She is now complaining of headaches, and her family has noticed confusion as well. Metastatic disease to the brain is suspected. A mass lesion on magnetic resonance imaging (MRI) is demonstrated in the right parietal lobe. Which MRI technique would best identify the extent of the edema surrounding the lesion?

A. Magnetic resonance angiography
B. Fluid-attenuated inversion recovery (FLAIR)
C. T1-weighted
D. T2-weighted
E. B and D

*Questions and answers were taken from Wiener CM et al. (eds). Harrison's Principles of Internal Medicine Self-Assessment and Board Review. 19th ed. New York: McGraw-Hill; 2017.

www.ketabpezeshki.com (021) 66485457 - 66485438

11. Which of the following is a possible complication of administration of gadolinium to a patient with chronic kidney disease?

A. Acute renal failure
B. Hyperthyroidism
C. Hypocalcemia
D. Lactic acidosis
E. Nephrogenic systemic sclerosis

12. A 45-year-old woman is admitted to the emergency department after a first episode of witnessed generalized tonic-clonic seizure. She is administered lorazepam 2 mg with cessation of seizure activity. All of the following are likely possible causes of her seizure EXCEPT:

A. Alcohol withdrawal
B. Autoantibodies
C. Brain tumor
D. Genetic disorder
E. Hyperglycemia

13. A 48-year-old woman is evaluated for seizure-like episodes. She has a history of major depression and borderline personality disorder. She is currently taking escitalopram 10 mg daily. She smokes one pack of cigarettes daily and drinks one to two glasses of wine daily. You are called to the bedside during an episode. You observe her head turning vigorously side to side with large-amplitude limb shaking and upward thrusting of the pelvis. You are concerned about psychogenic seizures. Which of the following findings could assist in this diagnosis?

A. A normal creatine kinase level within 30 minutes of the episode
B. A normal prolactin level within 30 minutes of the episode
C. An elevated creatine kinase within 30 minutes of the episode
D. An elevated prolactin level within 30 minutes of the episode
E. Decreased arousability in the period immediately following the episode

14. A 56-year-old man with glioblastoma multiforme in the right parietal lobe experiences his first generalized tonic-clonic seizure. What is the best course of action for this patient?

A. Initiate therapy with ethosuximide
B. Initiate therapy with lamotrigine
C. Initiate therapy with phenytoin

14. (Continued)

D. Observe for additional seizures and initiate therapy only if additional seizures occur
E. Refer for electroencephalogram (EEG) and treat only if an epileptogenic focus is identified

15. A 24-year-old man presents to your office requesting to be taken off of his antiepileptic drugs. He was in an automobile accident at the age of 12, resulting in significant head trauma. He was in a medically induced coma for 6 weeks and had intracranial edema with generalized tonic-clonic seizures at that time. T ese persisted for several years afterward. His last seizure that he is aware of occurred at the age of 18 and was generalized. He continues to take valproic acid 1000 mg bid. On physical examination, he demonstrates normal cognition and affect. He has ongoing focal weakness involving his left lower extremity with spasticity. You refer him for a sleep-deprived EEG, which shows no evidence of focal abnormalities. Which of the following factors is of greatest concern regarding his risk of recurrent seizures?

A. Focal defect on neurologic examination
B. Generalized seizure disorder
C. Head trauma
D. Seizure within the past 7 years

16. A 38-year-old man with a history of seizure disorder presents with generalized convulsive status epilepticus. He had been having persistent seizure activity for 20 minutes when emergency medical services were activated. He was given paralytic agents in the field to allow for intubation as well as lorazepam 8 mg intravenously (IV). Upon arrival in the emergency department 20 minutes later, the neuromuscular blockade has worn off and generalized seizure activity is again apparent. His initial temperature is 39.2°C with blood pressure of 182/92 mmHg, heart rate of 158 bpm, respiratory rate of 38 breaths/min, and SaO_2 of 95% on mechanical ventilation with an assist control mode with a set rate of 15, tidal volume of 420 mL, positive end-expiratory pressure of 5 cmH_2O, and FiO_2 of 0.6. What is the next step in the management of this patient?

A. Additional dosing of neuromuscular blockers
B. Isoflurane anesthesia
C. Fosphenytoin 20 mg/kg IV
D. Pentobarbital 5 mg/kg bolus followed by an infusion at 1 mg/kg/hr
E. Propofol 2 mg/kg bolus followed by an infusion at 2 mg/kg/hr

www.ketabpezeshki.com (021) 66485457 - 66485438

17. A 68-year-old man presents to the emergency department with right-sided face, arm, and leg weakness that began abruptly 1 hour prior to arrival. T e patient is accompanied by his wife. He exhibits Broca aphasia and dysarthria. Physical examination confirms a dense hemiparesis of the right face, arm, and leg with decreased sensation. In addition, there is a gaze preference to the left. T e patient's initial blood pressure on presentation to the emergency department is 195/115 mmHg. Multiple follow-up blood pressures have been sustained between 160–170/100–110 mmHg without treatment. An emergent noncontrast head CT shows no evidence of intracranial hemorrhage or edema with only mild loss of gray-white matter differentiation. On further review of the patient's medical history, he had a prior embolic stroke affecting the posterior circulation 12 months ago. He also has a history of colon cancer that was diagnosed 3 months ago when he presented with a lower gastrointestinal (GI) bleed requiring transfusion of 4 units of packed red blood cells. He successfully underwent left hemicolectomy of a stage I adenocarcinoma. In the postoperative period, he developed a deep venous thrombosis of the superficial femoral vein on the right. He is currently being treated with warfarin at 5 mg daily. His last international normalized ratio (INR) was therapeutic at 2.2. It was checked 4 days ago. Which of the following factors is a contraindication to use of IV recombinant tissue plasminogen activator in this patient?

A. GI bleeding within the past 3 months
B. Initial blood pressure elevation >180/110 mmHg
C. Major surgery within the past 3 months
D. Prior embolic stroke
E. Use of warfarin with elevated INR

18. A 54-year-old woman is seen in your office for a new patient visit. She is very concerned about her risk of stroke and wants to do whatever she can to prevent it. Her mother died following a stroke related to untreated hypertension at the age of 62. T e patient has hypertension and diabetes mellitus. She currently is taking hydrochlorothiazide 25 mg daily and metformin 500 mg twice daily. She smokes one pack of cigarettes daily. Her blood pressure today is 158/92 mmHg. Fasting lipids show a total cholesterol of 232 mg/dL, triglyceride level of 168 mg/dL, high-density lipoprotein of 32 mg/dL, and low-density lipoprotein of 166 mg/dL. T e hemoglobin A1C is 7.5%. What advice is LEAST helpful in primary prevention of stroke in this individual?

18. (Continued)
A. Add aspirin 81 mg daily as an antiplatelet agent
B. Add atorvastatin 10 mg daily to lower cholesterol
C. Add lisinopril 20 mg daily to decrease blood pressure to a target blood pressure of 130/80 mmHg
D. Increase metformin to 1000 mg twice daily and change diet to obtain a goal hemoglobin A1C level of less than 7%
E. Recommend smoking cessation and offer counseling and nicotine replacement

19. A 76-year-old man was seen in the emergency department for left-sided arm weakness that rapidly improved over the course of 4 hours. He has a past medical history positive for hypertension, dyslipidemia, and coronary artery disease. He previously has undergone coronary angioplasty with stenting to both his left anterior descending artery and right coronary artery on two occasions. He is currently being treated with aspirin 81 mg daily, metoprolol 100 mg bid, benazepril 20 mg daily, rosuvastatin 10 mg daily, and clopidogrel 75 mg daily. Evaluation demonstrates a 75% occlusion of the right internal carotid artery. T e patient is considering whether he would like to undergo carotid endarterectomy. What information is needed for him to make an informed decision about the risks and benefits of the surgery for him?

A. Perioperative mortality rate for the surgeon performing his surgery
B. Perioperative stroke rate for the surgeon performing his surgery
C. Risk of stroke in the next 90 days
D. Risk of stroke in the next year
E. T e surgeon cannot schedule his surgery for 6 weeks

20. A 48-year-old man presents to the emergency department with stupor. He was feeling well until 30 minutes ago when he complained of headache and right-sided weakness. He has a history of hypertension and cocaine use. He is prescribed hydrochlorothiazide 25 mg daily, but it is unknown whether he is taking his medication. On presentation, he is drowsy and minimally responsive to questioning. His blood pressure is 242/148 mmHg, heart rate is 124 bpm, respiratory rate is 24 breaths/min, SaO2 is 98% on room air, and temperature is 37.0°C. He is not moving his right arm and leg. He does withdraw to pain. His noncontrast head CT is shown in **Figure 20**. What is the diagnosis?

www.ketabpezeshki.com (021) 66485457 - 66485438

20. (Continued)

FIGURE 20

A. Brain mass
B. Epidural hematoma
C. Intracranial hemorrhage
D. Ischemic stroke in the left middle cerebral artery territory
E. Subdural hematoma

21. A 26-year-old woman has throbbing right-sided headaches that are centered around her right eye. T ey are worse with movement and aggravated by loud noises. T ere are no premonitory warning features. Triggers for the headaches include lack of sleep, stress, and red wine. A mild attack can be treated by ibuprofen, but nonsteroidal anti-inflammatory drugs have no effect on more severe pain. Which of the following best characterizes what is understood about the pathogenesis of the patient's headache syndrome?

A. Diffuse muscular contraction of the neck and scalp
B. Disinhibition of the central pacemaker neurons in the posterior hypothalamic region
C. Dysfunction of monoaminergic sensory control systems in brainstem and hypothalamus
D. Focal cerebral vasodilation in the region of the brain that is the focus of the pain
E. Vascular compression of the trigeminal nerve as it enters the pons

22. A 34-year-old woman is evaluated for migraine headaches. She has had migraines since her early 20s, and they are worse with recovery from sleep loss, menstrual cycles, stress, and certain foods that she tries to avoid. She describes the pain as left occipital in nature, throbbing, and severe. She has photophobia with episodes and occasionally vomits. With an acute episode, she takes rizatriptan 10 mg. It works within 1–2 hours in about 75% of attacks. However, recently, she has been having about six episodes per month. She has missed some days of work due to attacks. She would like to escalate her therapy and is asking for your advice. What is your advice about medications for migraine prevention?

A. Methysergide and phenelzine are first-line medications for this indication.
B. No drugs have a Food and Drug Administration–approved indication for migraine prevention.
C. Preventive therapy would not be recommended unless she has more than seven attacks per month.
D. T e probability of success with use of a preventive medication is 90%.
E. T ere is a lag of 2–12 weeks after starting a new medication before an effect is seen.

23. A 42-year-old man is evaluated for severe headaches that have occurred several times over the past 5–7 years. He describes the headaches as occurring behind his left eye and coming on suddenly. T e headaches have a stabbing quality and are associated with tearing of his eye and nasal congestion. He says the pain is a "12" out of 10 when it occurs, and he finds that he can't even sit still due to pain. T e headaches last about 20 minutes and then subside. He says that the headaches seem to occur at the same time every day, around 5 am, but he can go months without having any headache at all. He has a difficult time identifying a trigger for the headaches. What is the most likely cause of his headaches?

A. Cluster headache
B. Migraine
C. Paroxysmal hemicrania
D. Short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT)
E. Tension headache

24. A 72-year-old woman is evaluated for memory problems. She and her husband first noticed some mild problems about 2 or 3 years ago, but attributed her symptoms to "old age." T ey decided to seek an evaluation when she became lost while returning home from the grocery store last week. She had

www.ketabpezeshki.com (021) 66485457 - 66485438

24. (Continued)
driven back and forth from this same store weekly for the past 20 years, and this incident frightened them both. She does not know what happened and had to call her husband for help. She has shown no changes to her personality. Her medical history is significant for hypertension and stage II breast cancer treated 10 years ago. She is taking ramipril 5 mg bid. She smoked one pack of tobacco daily from the age of 20 until she was 64. She drinks a glass of wine nightly. She retired from her position as an accountant at the age of 60. On examination, she appears well-groomed and pleasant. Her blood pressure is 158/90 mmHg, and heart rate is 82 bpm. Her neurologic examination is normal without focal defect. Gait is normal. No rigidity is present. Neuropsychological testing shows impairment 1.5 standard deviations below the norm. What would be the most likely pathologic finding in the brain?

A. Deposition of amyloid within cerebral blood vessels
B. Loss of cortical serotonergic innervation with atrophy of the frontal, insular, and/or temporal cortex
C. Neuritic plaques and neurofibrillary tangles in the medial temporal lobes
D. Presence of intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff and ubiquitin in the substantia nigra, amygdala, cingulate gyrus, and neocortex

25. A 78-year-old man has been diagnosed with mild cognitive impairment after complaining of decreased memory. He asks you to prescribe something that will decrease his likelihood to progress to Alzheimer disease. What treatment do you recommend?

A. Brain training exercises
B. Donepezil
C. Gingko biloba
D. Memantine
E. No treatment at this time has been demonstrated to delay the progression of mild cognitive impairment to Alzheimer disease.

26. A 62-year-old man presents with memory and behavior problems. Until 1 year ago, he had worked as a senior account manager at a local bank, but he had to retire after he had an angry outburst with a client and was inappropriate with a female colleague in a departmental meeting. His family reports that this behavior was entirely out of character for him, and since then, he is increasingly brusque and easily angered. He also has been overly sexual and has said many inappropriate things within the hearing

26. (Continued)
of his teenaged grandchildren. At the same time, it has been noted that his memory has been worsening. He has an MBA degree, but his wife has recently begun managing the money after he could no longer be relied on to do this. T e financial records were highly disorganized when she began to look into them. T e patient also recently had a near-miss accident while driving the wrong way down a one-way street. On examination, he is gruff and says that he doesn't want to do "this damn thing." He needs to "get the hell out of here." He is quite rude and insults his wife several times. He has a positive glabellar reflex. Mini Mental State Examination score is 20/30. T ere is no rigidity. Gait is normal. Deep tendon reflexes are 3+ and symmetric. Strength is 5/5 throughout, and there are no sensory deficits. Cerebellar function is normal. What is the most likely diagnosis?

A. Alzheimer disease
B. Dementia with Lewy bodies
C. Frontotemporal dementia
D. Progressive supranuclear palsy
E. Vascular dementia

27. Which of the following statements regarding Parkinson disease is true?

A. Cigarette smoking reduces the risk of developing the disease.
B. Older age at presentation is more likely to be associated to genetic predisposition.
C. Parkinson disease has been identified as a monogenetic disorder related to mutations in the α-synuclein protein.
D. T e typical age of onset of symptoms is about 70 years.
E. T e hallmark pathologic feature of Parkinson disease is presence of neurofibrillary tangle and tau protein in the substantia nigra pars compacta.

28. A 64-year-old man presents with symptoms of tremor and a generalized feeling of slowing down. His tremor bothers him most on his left side. His past medical history is significant for depression, hypertension, and hyperlipidemia. He is taking fluoxetine 40 mg daily, lisinopril 40 mg daily, and atorvastatin 20 mg daily. On physical examination, he has a resting tremor with presence of cogwheel rigidity. When observing his gait, you note slow, shuf ing steps with difficulty maneuvering to turn around. His facial features show decreased range of emotion and appear somewhat flat. Eye movements are full. Mental status examination shows normal mentation. You suspect Parkinson disease. What is your first choice of therapy?

www.ketabpezeshki.com (021) 66485457 - 66485438

28. (Continued)

A. Defer therapy until further diagnostic studies are performed
B. Levodopa-carbidopa
C. Rotigotine
D. Selegiline
E. Either B or C can be used
F. Any of the above can be used

29. Which of the following patients with Parkinson disease is the best candidate for deep brain stimulation?

A. A 64-year-old woman on levodopa-carbidopa who continues to experience episodes of freezing while walking
B. A 68-year-old man with recurrent falls due to orthostatic hypotension
C. A 70-year-old woman with severe tremor unresponsive to dopaminergic therapy
D. A 71-year-old man with worsening symptoms of dementia
E. All of the above patients will respond to deep brain stimulation.

30. A 54-year-old man presents complaining of weakness. He has a difficult time pinpointing an onset. He believes he first noticed weakness in his right foot and leg about 6 months ago. He reports that he frequently trips over his toes and drags his foot. He also gets frequent cramps when he stretches in bed in the mornings. T e weakness is progressing to involve both legs now. On examination, you note tongue fasciculations. Deep tendon reflexes are 3+ at the knees and ankles. Strength is 4– at the extensors and flexors of the right foot and 4+ at the left foot. Hand grip strength is also 4+. Which of the following is the suspected pathologic cause of this patient's symptoms?

A. Degeneration of the corticospinal tracts
B. Demyelinating plaques
C. Loss of anterior horn cells in the spinal cord
D. Loss of large pyramidal cells in the precentral gyrus
E. Lymphocytic infiltrate of spinal roots and nerves
F. A and C

31. A 62-year-old woman is evaluated for symptoms of "slowing down." She used to be very active and ran 2–4 miles at least 3 days per week. For the past 6 months, she has not been able to complete even 1 mile, and her husband feels she has been moving more slowly and with a shuf ing gait. She reports no tremor. She frequently feels lightheaded upon standing and has been evaluated in the emergency

31. (Continued)

department twice for falls that occurred soon after standing. After one fall, she did require sutures for a scalp laceration. She has also been experiencing significant constipation requiring daily treatment with polyethylene glycol and bisacodyl suppositories. On physical examination, she has a blood pressure of 122/78 mmHg and a heart rate of 72 bpm while seated. Upon standing, her blood pressure falls to 92/60 mmHg with a heart rate of 102 bpm. She does report dizziness with the maneuver. She has bradykinesia and walks with a shuf ing gait. Cranial nerves are intact with full eye movements. Deep tendon reflexes are 2+ and symmetric. T ere is rigidity with passive motion of the forearms. She has no tremor. Mental status examination is normal. What is the most likely diagnosis?

A. Diffuse Lewy body disease
B. Multiple system atrophy
C. Parkinson disease
D. Postural orthostatic tachycardia syndrome
E. Progressive supranuclear palsy

32. A 58-year-old woman is seen for complaints of very sharp pain lasting about 1 minute over her right cheek and lips. T ese pain episodes occur in clusters with intense pain during the episode. When an episode occurs, it is present both day and night and can recur over a period of about a week. Paroxysms of pain can be elicited by washing her face. On physical examination, there is no sensory or motor loss in the right face. T ere are no masses. Touching the right face does bring about an episode of pain for the patient. What is the next best step in management of this patient?

A. Initiate treatment with carbamazepine 100 mg with a goal dose of 200 mg qid
B. Perform an MRI/magnetic resonance angiography (MRA) of the brain
C. Refer patient for a temporal artery biopsy
D. Refer patient for electromyography and nerve conduction study
E. Refer patient for microvascular decompression surgery

33. A 65-year-old woman with a prior history of stage IIB carcinoma of the right breast presents with a 1-week history of sharp mid-back pain. She reports that it becomes worse with movement and coughing. She has not slept well because the pain awakens her. On the day of presentation, she developed weakness in her lower extremities such that she is

www.ketabpezeshki.com (021) 66485457 - 66485438

33. (Continued)
not able to bear weight. She has had incontinence of the bladder. On examination, the patient has tenderness to palpation over the lower thoracic spine. T e strength in the lower extremities is 3 out of 5 with decreased deep tendon reflexes. Anal sphincter tone is decreased. Sensation to light touch and pinprick also demonstrates a decrease in perception to the level of T8. Metastatic disease to the spine is demonstrated in multiple thoracic and lumbar vertebral bodies with cord compression at T8 on T1-weighted MRI. What is the next best step in the management of this patient?

A. Administer dexamethasone 10 mg IV every 6 hours
B. Consult neurosurgery for surgical decompression
C. Consult medical oncology for additional chemotherapy
D. Consult radiation oncology for urgent radiotherapy
E. A and D
F. A, C, and D
G. A, B, C, and D

34. A 32-year-old African American man presents to the emergency department with progressive lower extremity weakness that has been present for the past month. It has now progressed to the point that he is unable to bear weight. He also has been experiencing loss of sensation and aching pains in his mid-back and a sensation of incomplete voiding with mild urinary incontinence. Today, he also had incontinence of stool. His past medical history is significant for a stab wound to the left chest 9 months prior. He required surgical repair. A CT scan was negative at that time for any lymph node abnormalities. He is on no medications and does not smoke or drink alcohol. Physical examination confirms lower extremity paresis with strength of only 3/5 and decreased deep tendon reflexes. Sensation to light touch and pinprick is absent in the lower extremities. He develops sensory perception at the umbilicus. An MRI shows multilevel enhancement of the spinal cord consistent with edema. It has a predominance in the mid-thoracic spinal cord. Gadolinium administration shows enhancement in a nodular fashion of the surface of the cord. Lumbar puncture is performed. T ere are 32 white blood cells (WBC)/μL in the first tube and 24 WBC/μL in the fourth tube. T ese are 90% lymphocytes. T e cerebrospinal fluid protein level is 75 mg/dL. T e glucose level is normal. A chest radiograph demonstrates enlargement of the hilar lymph nodes without pulmonary infiltrates. On chest CT, bilateral hilar, subcarinal, and precarinal lymphadenopathy is observed with

34. (Continued)
the largest lymph node measuring 2 × 1.8 cm. Serum calcium is 12.5 mg/dL. A biopsy of the hilar lymph nodes is planned. What is the most likely finding on biopsy?

A. Abundant atypical lymphocytes that demonstrate clonality on flow cytometry
B. Caseating granulomatous inflammation
C. Noncaseating granulomatous inflammation
D. Nonspecific chronic inflammatory changes
E. Sheets of small, round cells with dark nuclei, scant cytoplasm, and salt-and-pepper chromatin with indistinct nucleoli; frequent mitotic figures are also seen

35. A 32-year-old woman presents for neurologic evaluation after experiencing a severe burn on the palm of her right hand. She had placed her hand onto the hot surface of a smooth electric range. She did not feel the burn when it occurred, and only when she picked her hand up did she notice the burn. After that, it was discovered that the patient unknowingly has bilateral loss of pain and temperature sensation in both hands. However, she does have touch and vibratory sense. Mapping of her loss of sensation shows decreased pain sensation in the nape of her neck, shoulders, and upper arms as well in a cape-like distribution. Deep tendon reflexes are absent at the biceps and triceps, and there is visible muscle wasting of the right biceps and shoulder musculature. What is the most likely diagnosis?

A. Arteriovenous malformation of the spine
B. Neoplastic spinal cord compression
C. Subacute combined degeneration
D. Syringomyelia
E. Transverse myelitis

36. A 31-year-old white woman is evaluated for symptoms of blurred vision and weakness. She is not really sure how long the symptoms have been occurring. She has had intermittent blurring of her vision for the past 2 months, although it has been more persistent for the past 2 weeks. She states that she also notes that colors seem less vivid and that her symptoms are worse in the right eye. T ree months ago, she did notice some sharp pains in the right eye that were worse when she looked around. T ey subsided after about a week, and since then, her vision has worsened. At the same time, she feels as though she is stiff in her legs and also feels that her left leg is weak. She sometimes feels as if her left leg will give out on her if she stands on it for a prolonged

www.ketabpezeshki.com (021) 66485457 - 66485438

36. (Continued)
period. Her past medical history is significant for type 1 diabetes mellitus for which she uses an insulin pump. She has smoked one pack of cigarettes daily since the age of 18. On physical examination, there is spasticity in both of her lower extremities with passive motion. Deep tendon reflexes are 3+ bilaterally with strength at the quadriceps on the right at 4/5. All other strength in the lower extremity is 5/5 bilaterally. Sensation to light touch and pinprick is decreased in the lower extremities. A dilated funduscopic examination shows swelling of the optic disc. Which of the following findings is most likely to be demonstrated?

A. Elevated protein levels in the cerebrospinal fluid to more than 100 mg/dL
B. Hyperintensity on T1-weight images consistent with a mass lesion in the occipital lobe with hydrocephalus
C. Hyperintensity on T2-weighted MRI images in multiple areas of the brain, brainstem, and spinal cord
D. Marked increased in transmission of somatosensory evoked potentials of lower limbs
E. Presence of 15 polymorphonuclear cells/μL in the cerebrospinal fluid

37. In the patient in Question 36, the expected finding is demonstrated on testing. On further historical review, the patient reports that she had one prior episode of blurred vision that resolved spontaneously about 8 months ago. She never sought treatment for it, although it lasted for about 2 weeks. You make the correct diagnosis. All of the following are epidemiologic risks factors for her disease EXCEPT:

A. Age between 20 and 40
B. Cigarette smoking
C. Female sex
D. History of an autoimmune disorder (type 1 diabetes mellitus)
E. White race

38. A 38-year-old woman has relapsing/remitting multiple sclerosis. She has experienced two attacks of disease previously that have left her with residual lower extremity weakness. She was initially treated with glucocorticoids with some improvement in her symptoms. However, she is currently only able to walk with a rolling walker about 100 m. A prior antibody test shows that she is positive for reactivity to the JC virus. You are planning to start a disease-modifying therapy. Which of the following is LEAST appropriate for this individual?

38. (Continued)
A. Dimethyl fumarate (DMF)
B. Interferon-β-1a
C. Fingolimod
D. Natalizumab
E. Teriflunomide

39. You are evaluating a 42-year-old woman for complaints of muscle weakness and tingling in her lower extremities. You suspect a peripheral neuropathy. All of the following questions are important for the history and physical examination EXCEPT:

A. Are there any important comorbid conditions?
B. Is there evidence of upper motor neuron involvement?
C. What do the electromyogram and nerve conduction study demonstrate?
D. What is the distribution of the weakness?
E. Which systems are involved—motor, sensory, autonomic, or combination?

40. A 24-year-old man presents for evaluation of foot drop. He has noted that for the last several months, he has had difficulty picking his feet up to walk up stairs and over thresholds. His right leg is more affected than his left leg. He has not noted any sensory changes. His father and paternal aunt each have had some weakness in their lower extremities. However, his father is currently 50 years of age and only began to develop some weakness in the past 2 years. His paternal aunt has always had a limp for as long as he can recall. He does not remember his grandparents having any symptoms, although his paternal grandfather died in a car accident at the age of 46 prior to his birth. T e patient's examination is notable for distal leg weakness with reduced sensation to light touch in both lower extremities. Knee and ankle jerk reflexes are unobtainable. Calves are reduced in size bilaterally. Upper extremity examination is normal. Which of the following is the most likely diagnosis?

A. Charcot-Marie-Tooth syndrome
B. Fabry disease
C. Guillain-Barré syndrome
D. Hereditary neuralgic amyotrophy
E. Hereditary sensory and autonomic neuropathy

41. A 57-year-old immigrant from Vietnam is evaluated by his primary care giver for dysesthesias that have been present in his hands and feet for the past several weeks. He also reports some difficulty walking. His past medical history is notable for

www.ketabpezeshki.com (021) 66485457 - 66485438

41. (Continued)
hypertriglyceridemia, tobacco abuse, and a recently discovered positive purified protein derivative (PPD) with sputum that is smear-negative for Mycobacterium tuberculosis. His medications include niacin, aspirin, and isoniazid. Which of the following is likely to reverse his symptoms?

A. Cobalamin
B. Levothyroxine
C. Neurontin
D. Pregabalin
E. Pyridoxine

42. A 52-year-old woman with long-standing poorly controlled type 2 diabetes mellitus is evaluated for a sensation of numbness in her fingers and toes, as if she is wearing gloves and socks all the time. She also reports tingling and burning in the same location, but no weakness. Her symptoms have been intermittently present for the last several months. After a thorough evaluation, nerve biopsy is obtained and demonstrates axonal degeneration, endothelial hyperplasia, and perivascular inflammation. Which of the following statements regarding this condition is true?

A. Autonomic neuropathy is rarely seen in combination with sensory neuropathy.
B. T e presence of retinopathy or nephropathy does not portend increased risk for diabetic neuropathy.
C. T is is the most common cause of peripheral neuropathy in developed countries.
D. Tight glucose control will reverse her neuropathy.
E. None of the above is true.

43. A 52-year-old man presents to the emergency department complaining of weakness that has developed over the past 2 days. He first noticed that he had generalized fatigue and felt like he was having a hard time moving his feet. Over the past 24 hours, the weakness has progressed to the point that he can barely stand with assistance. He was brought into the emergency department in a wheelchair. He is beginning to feel that it is difficult to lift his arms. He also complains of a sharp pain in his shoulders and along his spine. Both his hands and feet are tingling. On physical examination, his initial blood pressure is 138/82 mmHg. On repeat 1 hour later, it is 92/50 mmHg. His heart rate is 108 bpm, respiratory rate is 24 breaths/min, temperature is 37.0°C, and SaO_2 is 96% on room air. He appears anxious and weak. Deep tendon reflexes are absent at the knee, ankle, and wrist. T e brachioradialis reflex is 1+. Strength throughout the lower extremities is diminished as

43. (Continued)
the patient is unable to lift either leg against gravity. In the arms, strength is 4/5 in the deltoids, biceps, and triceps. However, he is unable to maintain a grip, and wrist flexion and extension are 3/5. Which of the following features would most commonly accompany this patient's history?

A. A diagnosis of "walking pneumonia" that was treated with azithromycin 2 weeks prior to presentation
B. An acute diarrheal illness 2 weeks prior to presentation
C. Presence of a massive mediastinal lymphadenopathy on chest radiograph
D. Presence of a monoclonal gammopathy of unknown significance on laboratory testing
E. Recent immunization with the H1N1 vaccine

44. You make the correct diagnosis for the patient in Question 43 and transfer him to the intensive care unit for close monitoring. Forced vital capacity on admission is 1.5 L (20 mL/kg), and maximum negative inspiratory force is 30 cmH_2O. You are very concerned about impending respiratory failure. Cerebrospinal fluid analysis shows a protein level of 100 mg/dL. T ere is 1 WBC in the first tube and none in the fourth tube. What is the next step in the management of this patient?

A. Azithromycin
B. IV immunoglobulin
C. Oseltamivir
D. Prednisone
E. Pyridostigmine

45. A 34-year-old woman is seen for complaints of weakness for the past month. She notes this to be particularly worse in the late afternoon and evening. Initially, she attributed the weakness to stress from her job, but she feels that the weakness is worsening despite taking several days off work. She also is now noticing some occasional double vision, and her husband has noticed that her voice sounds weak. T e patient denies pain. On physical examination, you note the appearance of mild ptosis and a nasal, breathy tone to her voice. Which of the following tests would be most sensitive and specific for making a diagnosis in this patient?

A. Acetylcholine receptor (AChR) antibodies
B. Edrophonium test
C. Muscle-specific kinase (MuSK) antibodies
D. Repetitive nerve stimulation test
E. Voltage-gated calcium channel antibodies

www.ketabpezeshki.com (021) 66485457 - 66485438

46. A 26-year-old woman is diagnosed with myasthenia gravis in the setting of complaints of diplopia, dysphagia, and weakness with fatigability. Acetylcholine receptor antibodies are positive. She is initially treated with pyridostigmine 60 mg three times daily with improvement. She is further evaluated for concomitant conditions. A CT scan of the neck reveals a "thymic shadow" but no evidence of thymoma. She is not found to have hyperthyroidism or any other autoimmune disorder. Her forced vital capacity after treatment with pyridostigmine is 2.9 L (73% predicted). What is the next best approach for treatment of this patient?

A. Continue pyridostigmine at current dose only
B. Continue pyridostigmine at current dose and add mycophenolate mofetil 1 g twice daily
C. Continue pyridostigmine at current dose and add prednisone 20 mg daily
D. Refer for treatment with plasmapheresis
E. Refer for thymectomy

47. A 56-year-old man with facial and ocular weakness has just been diagnosed with myasthenia gravis. All of the following tests are necessary before instituting therapy EXCEPT:

A. CT of mediastinum
B. Lumbar puncture
C. Pulmonary function tests
D. Purified protein derivative skin test
E. T yroid-stimulating hormone

48. All of the following lipid-lowering agents are associated with muscle toxicity EXCEPT:

A. Atorvastatin
B. Ezetimibe
C. Gemfibrozil
D. Niacin
E. All of the above are associated with muscle toxicity.

49. All of the following endocrine conditions are associated with myopathy EXCEPT:

A. Hypothyroidism
B. Hyperparathyroidism
C. Hyperthyroidism
D. Acromegaly
E. All of the above are associated with myopathy.

50. A 34-year-old woman seeks evaluation for weakness. She has noted tripping when walking, particularly in her left foot, for the past 2 years. She also

50. (Continued)
has recently begun to drop things, once allowing a full cup of coffee to spill onto her legs. T e patient also feels as if the appearance of her face has changed over the course of many years, stating that she feels as if her face is becoming more hollow and elongated although she hasn't lost any weight recently. She has not seen a physician in many years and has no past medical history. Her only medications are a multivitamin and calcium with vitamin D. Her family history is significant for similar symptoms of weakness in her brother who is 2 years older. Her mother, who is 58 years old, was diagnosed with mild weakness after her brother was evaluated but is not symptomatic. On physical examination, the patient's face appears long and narrow with wasting of the temporalis and masseter muscles. Her speech is mildly dysarthric, and the palate is high and arched. Strength is 4/5 in the intrinsic muscles of the hand, wrist extensors, and ankle dorsiflexors. After testing handgrip strength, you notice that there is a delayed relaxation of the muscles of the hand. What is the most likely diagnosis?

A. Acid maltase deficiency (Pompe disease)
B. Becker muscular dystrophy
C. Duchenne muscular dystrophy
D. Myotonic dystrophy
E. Nemaline myopathy

51. A 33-year-old woman seeks an additional medical opinion after seeing multiple physicians in the past 3 years. She describes unrelenting fatigue that has lasted for approximately 2 years to the point where she no longer exercises and is in danger of losing her job as a copy editor. Her sleep is typically unsettled, and no matter how much she sleeps, she reports never feeling refreshed. She dates the onset of the fatigue to an episode of serologically confirmed mononucleosis 3 years prior. Her husband agrees that "she has never recovered from that episode." She has tried antidepressants and various supplements with no benefit. Her past medical history is unremarkable other than having anorexia and depression as a teenager. She says she is fully recovered from that since college. Her physical examination is unremarkable other than a resting heart rate of 95 bpm. She has a normal body mass index (BMI). Which of the following is an exclusion to the diagnosis of chronic fatigue syndrome?

A. History of anorexia and depression
B. History of mononucleosis
C. Normal BMI

www.ketabpezeshki.com (021) 66485457 - 66485438

51. (Continued)
D. Resting heart rate >90 bpm
E. None of the above

52. In the patient described in Question 51, which of the following has been shown to improve symptoms?

A. Acyclovir
B. Cognitive behavioral therapy
C. Gabapentin
D. Psychoanalysis
E. Venlafaxine

53. A 34-year-old woman seeks evaluation because of insomnia. She reports difficulty both falling and staying asleep because she cannot calm her mind. When questioned, she says she has always been a worrier. You are considering a diagnosis of generalized anxiety disorder. All of the following characteristics are common in this disorder EXCEPT:

A. She has episodic palpitations and shortness of breath lasting 10–30 minutes associated with feelings of impending doom.
B. She particularly worries about her job as a data analyst at a major telecommunications company, and she frequently avoids social outings because she "freezes" in social situations.
C. She reports concomitant feelings of hopelessness and sadness and worries about death.
D. She reports drinking four glasses of wine or more nightly to calm herself prior to bed.
E. Symptoms began during her teenage years.

54. You are paged by the clinic staff covering the sleep laboratory. A 24-year-old man has walked into the sleep laboratory asking if a sleep study will help him understand where the voices in his head are coming from. T e staff says he appears somewhat agitated and is talking to himself. You arrive at the sleep laboratory to find a disheveled-appearing young man pacing in the lobby. When you attempt to speak with him, he says that he has been hearing an angry voice telling him that he is a worthless pig. It gets loudest whenever he is lying in bed. Sometimes it tells him he is a demon and to hurt himself. He says these voices are being sent into his brain by an alien satellite and thinks a sleep study will help show the abnormal brain waves that are not his since the voices are worse at night. His speech is pressured, and he speaks rapidly, pacing the entire time. He refuses to go to the emergency department for help. You call 911 because it is obvious that the patient is having active hallucinations. T e man is unwilling

54. (Continued)
to provide any medical history or even his last name. He is admitted involuntarily to a psychiatric facility and diagnosed with acute psychosis and eventually schizophrenia, as this was his first episode of psychosis. He is treated appropriately with antipsychotics. Which of the following statements regarding his prognosis is true?

A. Antipsychotics are effective in treating 95% of patients with a first episode of psychosis.
B. Full remission from an episode of psychosis typically takes 3–6 months.
C. If medications are discontinued, the relapse rate is 60% at 6 months.
D. More than 25% of schizophrenia patients commit suicide.
E. Prognosis depends on severity of symptoms at initial presentation.

55. A 26-year-old woman presents to the emergency department complaining of shortness of breath and chest pain. T ese symptoms began abruptly while at a shopping mall and became progressively worse over 10 minutes, prompting her to call 911. Over this same period, the patient describes feeling her heart pounding, and she states that she felt like she was dying. She feels lightheaded and dizzy. It is currently about 20 minutes since the onset of symptoms, and the severity has abated, although she is not back to her baseline. She denies any immediate precipitating cause, although she has been under increased stress because her mother has been hospitalized recently with advanced breast cancer. She has never had any episode like this previously. She does not take any medications and has no medical history. She denies tobacco, alcohol, or drug use. On initial examination, she appears somewhat anxious and diaphoretic. Her initial vital signs show a heart rate of 108 bpm, blood pressure of 122/68 mmHg, and respiratory rate of 20 breaths/min. She is afebrile. Her examination is normal. Her arterial blood gas shows a pH of 7.52, $PaCO_2$ of 28 mmHg, and PaO_2 of 116 mmHg. T e electrocardiogram (ECG) shows sinus tachycardia. A D-dimer is normal. What is the next best step in the management of this patient?

A. Initiate therapy with alprazolam 0.5 mg as needed
B. Initiate therapy with fluoxetine 20 mg daily
C. Perform a CT pulmonary angiogram
D. Reassure the patient and suggest medical and/or psychological therapy if symptoms recur on a frequent basis
E. Refer for cognitive behavioral therapy

www.ketabpezeshki.com (021) 66485457 - 66485438

56. All of the following antidepressant medications are correctly paired with their class of medication EXCEPT:

A. Duloxetine—Selective serotonin reuptake inhibitor
B. Fluoxetine—Selective serotonin reuptake inhibitor
C. Nortriptyline—Tricyclic antidepressant
D. Phenelzine—Monoamine oxidase inhibitor
E. Venlafaxine—Mixed norepinephrine/serotonin reuptake inhibitor and receptor blocker

57. A 42-year-old woman seeks your advice regarding symptoms concerning for posttraumatic stress disorder. She was the victim of a home invasion 6 months previously where she was robbed by a man at gunpoint and beaten. She thought she was going to die and was hospitalized with multiple blunt force injuries including a broken nose and zygomatic arch. She now states that she is unable to be alone in her home and frequently awakens with dreams of the event. She is irritable with her husband and children and cries frequently. She has worsening insomnia and often stays awake most of the night watching out her window because she is afraid her assailant will return. She has begun drinking a bottle of wine nightly to help her fall asleep, although she notes that this has worsened her nightmares in the early morning hours. You concur that posttraumatic stress disorder is likely. What treatment do you recommend for this patient?

A. Avoidance of alcohol
B. Cognitive behavioral therapy
C. Paroxetine 20 mg daily
D. Trazodone 50 mg nightly
E. All of the above

58. A 36-year-old man is being treated with venlafaxine 150 mg twice daily for major depression. He has currently been on the medication for 4 months. After 2 months, his symptoms were inadequately controlled, necessitating an increase in the dose of venlafaxine from 75 mg twice daily. He has had one prior episode of major depression when he was 25. At that time, he was treated with fluoxetine 80 mg daily for 12 months, but found the sexual side effects difficult to tolerate. He asks when he can safely discontinue his medication. What is your advice to the patient?

A. He should continue on the medication indefinitely because his depression is likely to recur.
B. T e current medication should be continued for a minimum of 6–9 months following control of his symptoms.

58. (Continued)
C. T e medication can be discontinued safely if he establishes a relationship with a psychotherapist who will monitor his progress and symptoms.
D. T e medication can be discontinued safely now because his symptoms are well controlled.
E. T e medication should be switched to fluoxetine to complete 12 months of therapy because this was previously effective for him.

59. You are seeing a 28-year-old man in your primary care clinic. He reports drinking alcohol on most days. Typically, he drinks 3–4 beers daily, but on weekends, he will drink as many as 8–12 beers per night. He has not missed work due to his drinking, although he does state that he has been hungover at work at least twice in the past month. He also has blacked out from binge drinking at least once in the past 6 months. However, he does not feel that he has any problem with alcohol. He states he never drinks and drives and has not ever felt guilt related to his drinking. You suspect he may be minimizing his level of alcohol consumption. Which of the following laboratory tests has the greatest sensitivity and specificity in identifying heavy alcohol consumption?

A. Aspartate aminotransferase (AST) elevated >2× alanine aminotransferase (ALT)
B. Carbohydrate-deficient transferrin (CDT) >20 U/L or >2.6%
C. γ-Glutamyl transferase >35 U/L
D. Mean corpuscular volume (MCV) >91 μm^3
E. A and D
F. B and C

60. Which of the following will lead to a faster rate of absorption of alcohol from the gut into the blood?

A. Coadministration with a carbonated beverage
B. Concentration of alcohol of more than 20% by volume
C. Concurrent intake of a high-carbohydrate meal
D. Concurrent intake of a high-fat meal
E. Concurrent intake of a high-protein meal

61. Which of the following statements best reflects the effect of alcohol on neurotransmitters in the brain?

A. Decreases dopamine activity
B. Decreases serotonin activity
C. Increases γ-aminobutyric acid activity
D. Stimulates muscarinic acetylcholine receptors
E. Stimulates N-methyl-D-aspartate excitatory glutamate receptors

www.ketabpezeshki.com (021) 66485457 - 66485438

62. In an individual without any prior history of alcohol intake, what serum concentration of ethanol (in g/dL) would likely result in death?

A. 0.02
B. 0.08
C. 0.28
D. 0.40
E. 0.60

63. All of the following statements regarding the epidemiology and genetics of alcoholism are true EXCEPT:

A. Approximately 60% of the risk for alcohol abuse disorders is attributed to genetics.
B. At least 20% of all patients seen in primary care offices have an alcohol use disorder.
C. Children of alcoholics have a 10-fold higher risk of alcohol abuse and dependence even if adopted early in life and raised by nonalcoholics.
D. Presence of a mutation of aldehyde dehydrogenase that results in intense flushing with alcohol consumption confers a decreased risk of alcohol dependence.
E. T e lifetime risk of alcohol dependence in most Western countries is about 10%–15% for men and 5%–8% for women.

64. A 42-year-old man with alcohol dependence is admitted to the hospital for acute pancreatitis. Upon admission, he has an abdominal CT that shows pancreatic edema without necrosis or hemorrhage. He is treated with IV dextrose-containing fluids, multivitamins, thiamine 50 mg daily, pain control, and bowel rest. He typically drinks 24 12-ounce beers daily. Forty-eight hours after admission, you are called because the patient is febrile and combative with the nursing staff. His vital signs demonstrate a heart rate of 132 bpm, blood pressure of 184/96 mmHg, respiratory rate of 32 breaths/min, temperature of 38.7°C, and oxygen saturation of 94% on room air. He is agitated, diaphoretic, and pacing his room. He is oriented to person only. His neurologic examination appears nonfocal, although he does not cooperate. He is tremulous. What is the next step in the management of this patient?

A. Administration of a bolus of 1 L of normal saline and thiamine 100 mg IV
B. Administration of diazepam 10–20 mg IV followed by bolus doses of 5–10 mg as needed until the patient is calm but arousable
C. Perform an emergent head CT

64. (Continued)
D. Perform two peripheral blood cultures and begin treatment with imipenem 1 g IV every 8 hours
E. Place the patient in four-point restraints and treat with haloperidol 5 mg IV

65. A 48-year-old woman is recovering from alcohol dependence and requests medication to help prevent relapse. She has a medical history of stroke occurring during a hypertensive crisis. Which of the following medications could be considered?

A. Acamprosate
B. Disulfiram
C. Naltrexone
D. A and C
E. A, B, or C

66. Which of the following statements about cigarette smoking is true?

A. Approximately 75% of cigarette smokers will die prematurely due to cigarette smoking unless they are able to quit.
B. Approximately 90% of peripheral vascular disease in nondiabetic individuals is attributable to cigarette smoking.
C. Cigarette smoking causes small airway inflammation and alveolar destruction sufficient to cause clinical symptoms in about 40% of smokers.
D. More than one-half of smokers have attempted to quit in the past year, and of these, 25% remain quit for 6 months or more.
E. Two of every five deaths in the United States can be attributed to cigarette use.

67. A 42-year-old woman presents for a yearly office visit. She is in general good health and takes no medications. Her BMI is 32 kg/m^2. She was previously treated for depression with sertraline 100 mg daily for 12 months. She last took the medication 6 months ago. She is feeling mentally healthy now. She has smoked since the age of 21 and smokes one pack of cigarettes daily. You advise her to quit smoking. She tells you she has been thinking about this a lot lately since her father died at the age of 74 from complications of lung cancer and was a smoker. He died 2 years ago this month. She previously has tried on her own, both "cold turkey" and using nicotine patches. She was unable to sustain abstinence longer than 1 month. T e only time she had sustained abstinence was when she was pregnant 18 years ago, but she quickly started again after delivery. What do you recommend for this patient?

www.ketabpezeshki.com (021) 66485457 - 66485438

67. (Continued)

A. Close follow-up with ongoing counseling
B. Nicotine replacement therapy with patches or nasal inhaler
C. Varenicline orally
D. A and B only
E. A combined with either B or C is an acceptable option.

68. A 32-year-old man is seen in your office to discuss smoking cessation. He has been smoking since the age of 16 years. He typically smokes 1.5 to 2 packs of cigarettes each day. At the age of 21, he was hospitalized in a psychiatric facility for severe depression with psychotic features. He was originally treated with venlafaxine and quetiapine. After 6 months, the quetiapine was tapered off without recurrence of the psychosis. His depression has waxed and waned over time, but generally has been well controlled. He has had no suicide attempts and denies suicidal ideations. He has had multiple quit attempts in the past with nicotine replacement therapy but has failed each attempt. He says he would like to try varenicline and asks your opinion about its safety given his psychiatric history. What advice do you give him?

A. Varenicline has been recommended by the U.S. Food and Drug Administration for further monitoring and supervision because it is unclear how frequently severe psychiatric responses occur.
B. A recent publication did not demonstrate an increased risk of suicide or psychosis with varenicline use even though varenicline was used more frequently in individuals with a preexisting psychiatric diagnosis.
C. Alternative therapies such as bupropion and/or nicotine replacement therapy should be considered.
D. All of the above.

69. You are counseling your patient on the need to quit smoking cigarettes. She has been smoking for over two decades and wants to quit in order to avoid the harmful physical effects of smoking. Wanting to take "baby steps," she has switched to low-tar, low-nicotine cigarettes. Which of the following statements is true about the potential benefit of switching to these low-yield cigarettes?

A. Fewer smoking–drug interactions are found among smokers of low-yield cigarettes.
B. Most smokers inhale the same amount of nicotine and tar even if they switch to low-yield cigarettes.
C. Smokers of low-yield cigarettes tend to inhale less deeply and smoker fewer cigarettes daily.
D. Smoking low-yield cigarettes decreases the harmful cardiovascular effects of cigarette smoking.
E. Smoking low-yield cigarettes is a reasonable alternative to complete smoking cessation for chronic smokers.

www.ketabpezeshki.com (021) 66485457 - 66485438

Answers

1. The answer is A.
(Chap. 1) This patient is presenting with symptoms of metastatic neurologic disease, and a careful neurologic examination can localize the site of disease in most patients. The patient has "crossed" weakness and sensory abnormalities, which localizes the lesion to the brainstem. In this setting, the limbs exhibit weakness and sensory symptoms opposite from the facial symptoms. Moreover, the facial weakness localizes to lower motor neuron as it involves both the upper and lower facial muscles. If the upper facial muscles had preserved movement, this might suggest multiple areas of metastatic disease in both the cerebrum and spinal cord.

2 and 3. The answers are D and D, respectively.
(Chap. 1) The ability to perform a thorough neurologic examination is an important skill for all internists to master. A careful neurologic examination can localize the site of the lesion and is important in directing further workup. The components of the neurologic examination include mental status, cranial nerves, motor function, sensory function, gait, and coordination. The motor examination is further characterized by appearance, tone, strength, and reflexes. Pronator drift is a useful tool for determining if upper extremity weakness is present. In this test, an individual is asked to stand with both arms fully extended and parallel to the floor while closing his or her eyes. If the arms flex at the elbows or fingers or there is pronation of the forearm, this is considered a positive test. Other tests of motor strength include tests of maximal effort in a specific muscle or muscle group. Most commonly, this type of strength testing is graded from 0 (no movement) to 5 (full power) with varying degrees of weakness noted against resistance. However, many individuals find it more practical to use qualitative grading of strength, such as paralysis, severe weakness, moderate weakness, mild weakness, or full strength. Babinski sign is a sign of upper motor neuron disease above the level of the S1 vertebra and is characterized by paradoxical extension of the great toe with fanning and extension of the other toes as well. Dysdiadochokinesis refers to the inability to perform rapid alternating movements and is a sign of cerebellar disease. Lhermitte symptom causes electric shock–like sensations in the extremities associated with neck flexion. It has many causes including cervical spondylosis and multiple sclerosis. Romberg sign is performed with an individual standing with feet together and arms at the side. An individual is then asked to close his or her eyes. If the individual begins to sway or fall, this is considered a positive test and is a sign of abnormal proprioception.

4 to 8. The answers are E, C, D, B, and A, respectively.
The clinical data obtained from the history and examination are interpreted to arrive at a possible anatomic localization that best explains the clinical findings, helps to narrow the list of diagnostic possibilities, and helps to select the laboratory tests most likely to be informative **(Table 8)**.

TABLE 8

GLOBAL DISABILITY-ADJUSTED LIFE-YEARS (DALYS) AND NUMBER OF ANNUAL DEATHS FOR SELECTED NEUROLOGIC DISORDERS IN 2010

DISORDER	DALYS	DEATHS
Low back and neck pain	116,704,000	—
Cerebrovascular diseases	102,232,000	5,874,000
Meningitis and encephalitis	26,540,000	541,000
Migraine	22,362,000	—
Epilepsy	17,429,000	177,000
Dementia	11,349,000	485,000
Parkinson disease	1,918,000	111,000
% of total DALYs or deaths for all causes that are neurologic	**12.0**	**13.6**
% change of DALYs for neurologic disorders between 2000 and 2010	**51.6**	**114.3**

Source: R Lozano et al. Lancet 380:2095, 2012.

9. The answer is C.
(Chap. 4) Appropriate and timely evaluation is needed to determine whether a subarachnoid hemorrhage is present because it can be rapidly fatal if undetected. The procedure of choice for initial diagnosis is a computed tomography (CT) of the head without intravenous (IV) contrast. On the CT, blood in the subarachnoid space would appear whiter compared to the surrounding brain tissue. The head CT is most sensitive when it is performed shortly after the onset of symptoms, but sensitivity declines over several hours. It can also demonstrate significant mass effect and midline shift, factors that increase the severity of the underlying hemorrhage. In the situation where the head CT is negative but clinical suspicion is high, a lumbar puncture can be performed. This may demonstrate increased numbers of red blood cells that do not clear with successive aliquots

www.ketabpezeshki.com (021) 66485457 - 66485438

of cerebrospinal fluid (CSF). If the lumbar puncture is performed more than 12 hours after a small subarachnoid hemorrhage, then the red blood cells may begin to decompose, leading to xanthochromia—a yellow to pink coloration of CSF that can be measured spectrographically. A basic head CT with IV contrast is rarely useful in subarachnoid hemorrhage because the brightness of the contrast material may make it difficult to identify blood in the subarachnoid space. However, a CT angiography that is performed with IV contrast can be useful in identifying the aneurismal vessel leading to the bleeding. Classic angiography is a more direct way to visualize the anatomy of the cranial vasculature and is now often combined with interventional procedures to coil a bleeding vessel. Transcranial Doppler ultrasound is a test that measures the velocity of blood flow through the cranial vasculature. It is used in some centers following subarachnoid hemorrhage to assess for the development of vasospasm, which can worsen ischemia, leading to increased damage to brain tissue following subarachnoid hemorrhage.

10. T e answer is E.

(Chap. 4) Magnetic resonance imaging (MRI) is generated from the interaction between the hydrogen protons in biologic tissues, the magnetic field, and the radiofrequency (Rf) of waves generated by the coil placed next to the body part of interest. T e Rf pulses transiently excite the protons of the body with a subsequent return to the equilibrium energy state, a process known as relaxation. During relaxation, the protons release Rf energy, creating an echo that is then transformed via Fourier analysis to generate the MRI. T e two relaxation rates that influence the signal intensity of the image are T1 and T2. T1 refers to the time in milliseconds that it takes for 63% of protons to return to their baseline state. T2 relaxation is the time for 63% of protons to become dephased due to interactions among nearby protons. T e intensity of the signal is also influenced by the interval between Rf pulses (TR) and the time between the Rf pulse and the signal reception (TE). T1-weighted images are produced by keeping both TR and TE relatively short, whereas T2-weighted images require long TR and TE times. Fat and subacute hemorrhage have relatively short TR and TE times and thus appear more bright on T1-weighted images. Conversely, structures with more water such as CSF or edema have long T1 and T2 relaxation times, resulting in higher signal intensity on T2-weighted images. T2 images are also more sensitive for detecting demyelination, infarction, and chronic hemorrhage.

Fluid-attenuated inversion recovery (FLAIR) is a type of T2-weighted image that suppresses the high-intensity signal of CSF. As a result, images created by the FLAIR technique are more sensitive to detecting water-containing lesions or edema than the standard spin images.

Magnetic resonance angiography refers to several different techniques that are useful for assessing vascular structures but do not provide details of the underlying brain parenchyma.

11. T e answer is E.

(Chap. 4) For many years, MRI was considered the modality of choice for patients with renal insufficiency because it does not lead to acute renal failure. However, gadolinium was recently linked to a rare disorder called nephrogenic systemic fibrosis. T is newly described disorder results in widespread fibrosis in skin, skeletal muscle, bone, lungs, pleura, pericardium, myocardium, and many other tissues. Histologically, thickened collagen bundles are seen in the deep dermis of the skins with increased numbers of fibrocytes and elastic fibers. T ere is no known medical treatment for nephrogenic systemic fibrosis, although improvement may be seen following kidney transplantation. It has only recently been linked to the receipt of gadolinium-containing contrast agents with a typical onset between 5 and 75 days following administration of the contrast. T e incidence of nephrogenic systemic fibrosis following administration of gadolinium in individuals with a glomerular filtration rate of <30 mL/min may be as high as 4%, and thus, gadolinium is absolutely contraindicated in individuals with severe renal dysfunction.

Pseudohypocalcemia can occur following administration of gadolinium in individuals with renal dysfunction, but not true hypocalcemia. T is occurs because of an interaction of the contrast dye with standard colorimetric assays for serum calcium that are commonly used. If ionized calcium is measured, it would be normal, often in the face of very low levels of serum calcium.

The other reported complications can be seen following administration of iodinated contrast that is used for CT imaging. The most common complication of CT imaging outside of allergic reactions is the development of worsening renal function or acute renal failure. This risk can be minimized if the patient is adequately hydrated. Lactic acidosis is a rare but dreaded side effect of iodinated contrast that has been linked to the coadministration of metformin in diabetic

www.ketabpezeshki.com (021) 66485457 - 66485438

patients. Typically a patient is asked to hold metformin for 48 hours before and after a CT scan. The reason for the development of lactic acidosis is actually related to development of renal insufficiency and a subsequent buildup of lactic acid. In very rare instances, administration of iodinated contrast can unmask hyperthyroidism.

12. The answer is D.
(Chap. 31) Age of presentation is an important consideration when an individual presents with a new onset of seizure because certain causes of seizures are more likely to present within certain age ranges **(Table 12)**, ranging from the neonatal period throughout older adulthood (age >35 years). In individuals >35 years old, the most likely causes of new-onset seizures include alcohol withdrawal, cerebrovascular disease, brain tumor, autoantibodies, Alzheimer disease or other neurodegenerative disease, and a range of metabolic disorders. These disorders can include either hyper- or hypoglycemia, uremia, hepatic failure, and a host of electrolyte abnormalities or acid-base disorders. Inherited disorders of ion channels have been implicated in a variety of rare epilepsy syndromes. These genetic disorders typically present in childhood and rarely after the age of 18.

TABLE 12

CAUSES OF SEIZURES	
Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer disease and other degenerative CNS diseases Autoantibodies

Abbreviation: CNS, central nervous system.

13. The answer is B.
(Chap. 31) Psychogenic seizures are nonepileptic behaviors that resemble seizures and may be conversion reactions that occur under psychological distress. Psychogenic seizures may occur in individuals with underlying seizure disorder and may be difficult to distinguish. Clinical features prominent in psychogenic seizures include side-to-side turning of the head, asymmetric and large-amplitude movements of the limbs, twitching of all four extremities without loss of consciousness, and pelvic thrusting. Psychogenic seizures also often last longer than epileptic seizures and may wax and wane over minutes to hours. Video electroencephalogram (EEG) monitoring can be quite helpful in this situation as EEG monitoring during the episode is normal. In addition, there is no postictal period. Measurement of prolactin levels may also help to distinguish generalized and some focal seizures from psychogenic seizures because prolactin levels rise in these disorders but remain normal in psychogenic seizures. Serum creatine kinase may rise following a seizure, but this is not sensitive for detection of seizure disorder.

14. The answer is B.
(Chap. 31) Determination of when to initiate epileptic drug therapy can be difficult in clinical practice given the variability in presentation of seizure disorders and the large number of antiepileptic drugs available. In general, antiepileptic drugs should be initiated when an individual presents with either recurrent seizures of unknown etiology or known cause that cannot be reversed. Individuals with a single seizure and a clear cause such as a brain tumor, infection, or trauma should also be treated. Currently, lamotrigine and valproic acid are considered the best initial therapies for individuals with generalized seizures. Although used with good efficacy for many years, phenytoin is no longer first-line therapy for generalized seizures due to its long-term side

www.ketabpezeshki.com (021) 66485457 - 66485438

effect profile including gingival hyperplasia. Ethosuximide is generally only used for absence seizures.

15. The answer is A.
(Chap. 31) Overall, 70% of children and 60% of adults will be able to successfully discontinue antiepileptic drugs without recurrence of seizures. However, the data regarding the time frame to attempt weaning of antiepileptic drugs are scarce. Once the determination to discontinue antiepileptic drugs has been made, the dosage of medication is typically decreased over a 2–3 month period, gradually weaning to off. If a recurrence of seizure were to happen, it is most likely during the first 3 months after discontinuation of therapy. Four factors predict the greatest likelihood of remaining seizure-free upon discontinuation of antiepileptic drugs: (1) complete control of seizures for 1–5 years; (2) single seizure type—focal or generalized; (3) normal EEG; and (4) normal neurologic examination, including intelligence. Given that this patient continues to have an abnormal neurologic examination following closed head trauma, he would have a greater likelihood to have a poorer outcome after withdrawal of his seizure medication.

16. The answer is C.
(Chap. 31) Status epilepticus is a medical emergency that can result in severe metabolic derangements, hyperthermia, cardiorespiratory collapse, and irreversible neuronal injury. Prompt recognition and appropriate treatment are necessary to prevent long-term sequelae of this neuronal injury. Status epilepticus is defined as continuous seizures or repetitive discrete seizures with impaired consciousness in the interictal period. Status epilepticus has many subtypes, with the most common subtype leading to presentation and critical care admission being generalized convulsive status epilepticus (GCSE). The duration of seizure activity that leads to a diagnosis of GCSE is typically defined as 15–30 minutes, but practically, if intervention with anticonvulsant medication is required to stop the seizure activity, then one must be concerned about GCSE. Likewise, if a seizure is of sufficient duration to cause significant metabolic or cardiorespiratory consequence, GCSE must be considered. Once GCSE is diagnosed, initial treatment should include basic cardiopulmonary support, including maintaining an appropriate airway, establishing venous access, and obtaining samples of laboratory analysis to identify contributing laboratory abnormalities. It is important to understand that suppression of convulsive activity through the use of paralytic agents does not suppress the epileptic activity in the central nervous system and does not prevent ongoing neuronal injury and death. Thus, when these agents are used for rapid-sequence intubation, the treating team should also continue treatment for GCSE through appropriate use of IV benzodiazepines initially followed by loading doses of either IV phenytoin or fosphenytoin, valproic acid, or levetiracetam. In many cases, continuous EEG monitoring may be required to determine when the seizure activity has ceased. If the seizure activity fails to break with these agents, further therapy with propofol or pentobarbital may be required. In more severe cases, inhaled anesthetics may be required. In addition, it is important to treat any underlying infection or metabolic derangements.

17. The answer is E.
(Chap. 32) This is patient is presenting with symptoms of an acute ischemic stroke affecting the middle cerebral artery territory. All patients older than age 18 should be evaluated promptly upon arrival to determine if they are candidates for administration of recombinant tissue plasminogen activator (rtPA). A large trial showed a significant improvement in patients with only minimal disability (32% on placebo vs. 44% on rtPA) and a nonsignificant reduction in mortality (21% on placebo vs. 17% on rtPA) when IV rtPA was administered within 3 hours of the onset of symptoms. However, rtPA was associated with a significant increase in the risk of symptomatic intracranial hemorrhage (6.4% on rtPA vs. 0.6% on placebo). A more recent trial has confirmed this benefit and that rtPA is both cost-effective and cost-saving. Carefully choosing the correct patients for administration of rtPA is key to best achieve benefits while minimizing risk of adverse events. Thrombolytic administration should be considered in all patients ≥18 years old with a clinical diagnosis of stroke presenting with symptom onset of ≤4.5 hours. A noncontrast head CT should be performed promptly to ensure there is no intracranial hemorrhage or edema of more than one-third of the middle cerebral artery territory. If a patient meets these criteria, then a careful assessment for possible contraindications should be undertaken. Hypertension is common in acute stroke. A sustained blood pressure >185/110 mmHg despite treatment is a contraindication to administration of rtPA. However, a single blood pressure reading higher than this value would not prevent treatment with thrombolytics. Individuals with rapidly improving symptoms more indicative of a transient ischemic attack or mild cerebrovascular accident should not be treated with rtPA

www.ketabpezeshki.com (021) 66485457 - 66485438

because the risk outweighs the potential benefits. At the opposite end of the spectrum, individuals presenting with stupor or coma should not be treated with thrombolytics. Findings on past medical history that would be contraindications to the use of rTPA include prior stroke or head injury within 3 months, any prior history of intracranial hemorrhage, major surgery in the preceding 14 days, gastrointestinal (GI) bleeding in the preceding 21 days, and recent myocardial infarction. Individuals with platelets <100,000, hematocrit <25%, use of heparin within 48 hours, prolonged activated partial thromboplastin time, or elevated international normalized ratio should also not receive rtPA.

18. T e answer is D.

(Chap. 32) Multiple atherosclerotic risk factors contribute to the risk for stroke. Among these are hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and atrial fibrillation. Primary prevention of stroke is largely targeted at these modifiable risk factors. Untreated or undertreated hypertension is the most significant risk factor for stroke. All hypertension should be treated to a goal blood pressure of <140–150/90 mmHg. Data are strongest for thiazide diuretics and angiotensin-converting enzyme inhibitors for secondary prevention of stroke. T is patient also has an elevated total cholesterol, elevated triglycerides, low high-density lipoprotein (HDL), and high low-density lipoprotein (LDL). T erefore, she should be treated with a statin for primary stroke prevention. However, even in the absence of elevated LDL or low HDL, there is evidence that statins can be useful for stroke prevention, decreasing the incidence of stroke by 51%. Tobacco smoking should be discouraged in all patients, and the patient should be given assistance in quitting smoking. T e use of antiplatelet agents for primary prevention of stroke is somewhat controversial. T e most recent guidelines for primary stroke prevention recommend aspirin for individuals who are at high risk for stroke. In those with diabetes, additional risk factors for stroke must also be present. T is patient also has the risk factors of hypertension, smoking, and dyslipidemia. Although diabetes is a risk factor for stroke, no trial has ever demonstrated that improving glucose control decreases stroke risk.

19. T e answer is B.

(Chap. 32) T e choice to perform a carotid endarterectomy for a carotid stenosis depends on many factors, including the degree of stenosis and whether the patient is symptomatic. In general, carotid endarterectomy has been demonstrated to have the greatest benefit in those who are symptomatic and have stenosis of ≥70%. In individuals with asymptomatic carotid artery stenosis, the risk of stroke is ~2% per year, and the potential benefits of the procedure may be outweighed by the risks. A more measured approach with risk factor modification may be more prudent. In symptomatic individuals such as the patient in this case, several trials have attempted to address the value of carotid endarterectomy. T ere is a significant absolute risk reduction favoring surgery of 17%. In the symptomatic patient, the annual risk of stroke is ~13%. A recent meta-analysis showed that carotid endarterectomy is most beneficial when performed within 2 weeks of symptoms onset and has greater benefits in men and those ≥75 years old. However, the procedure should be performed only in institutions familiar with the procedure. T e benefit of the procedure is questionable for any surgeon whose perioperative stroke rate is ≥6%.

20. T e answer is C.

(Chap. 32) T e noncontrast head CT shows blood within the left putamen in this patient presenting with marked hypertension and abrupt onset of right hemiparesis. T is is consistent with intracranial hemorrhage. On a noncontrast head CT, blood is demonstrated as a hyperdense white area, and this is an emergent finding. Most patients have symptoms that begin abruptly and acutely worsen over the first 30–90 minutes. Diminished level of consciousness is common, and signs of increased intracranial pressure may occur. Intracranial hemorrhage is associated with a 40% mortality rate. T e patient should be admitted to a neurologic intensive care unit, if available, and monitored. Any coagulopathy should be corrected. T e goal for blood pressure management at this level of blood pressure is unclear. A recent clinical trial enrolled patients with blood pressure between 150 and 220 mmHg and demonstrated improved outcomes with lowering of blood pressure to 140 mmHg over 6 hours. However, it is not known how individuals with higher blood pressures would respond. T e patient should be carefully monitored for development of increased intracranial pressure and treated appropriately. Intracranial pressure monitoring is sometimes required with a goal cerebral perfusion pressure of >60 mmHg.

21. T e answer is C.

(Chap. 34) T e patient describes a typical history for migraine headaches, the second most common cause of headache and most common cause of headache-related disability worldwide. Migraine affects approximately 15% of women and 6% of men

www.ketabpezeshki.com (021) 66485457 - 66485438

in any given year. Diagnostic criteria for migraine have been simplified recently. To diagnose migraine, an individual should complain of repeated attacks of headache lasting from 4–72 hours, with a normal physical examination and no other clear cause. T e headache should be associated with two of the following four features: unilateral pain, throbbing pain, aggravation by movement, and moderate to severe intensity. In addition, the individual should complain of either nausea/vomiting or phonophobia and photophobia. Most individuals with migraine headaches can identify triggers associated with an attack. Common triggers include lack of sleep or excessive sleep, stress, hormonal fluctuations, alcohol, and barometric pressure changes. T e pathophysiology that underlies migraine is increasingly understood as a dysfunction of the monoaminergic sensory control systems located in the brainstem and hypothalamus. Activation of cells in the trigeminal nucleus leads to release of vasoactive neuropeptides at vascular terminations of the trigeminal nerve and within the trigeminal nucleus. T ese neurons also project centrally, crossing the midline, to project to ventrobasal and posterior nuclei of the posterior thalamus. T e primary vasoactive peptide that has been implicated is calcitonin gene-related peptide (CGRP). A new class of medication called gepants is being developed to act as an antagonist at the CGRP receptor and has been demonstrated to be effective against migraine in early clinical trials. T e most common medications used for acute relief of severe migraine pain are the triptans, potent agonists of the 5-hydroxytryptamine (serotonin) receptor, implicating serotonin in pathogenesis of migraine as well. It is thought that serotonin is necessary for nociceptive signaling in the trigeminovascular system and that triptans arrest this pathway. Finally, dopamine may also play a role in pathogenesis of migraine because migraine symptoms can be induced by dopamine stimulation, and individuals with migraine have been demonstrated to have hypersensitivity to dopamine agonists at doses that do not affect non–migraine-affected persons. In the past, the "vascular theory" of migraine was frequently espoused, with the cause of migraine thought to be related to abnormal cerebral vasodilation. T is theory has been discounted as the pathogenesis has become more widely understood.

22. T e answer is E.
(Chap. 34) Patients who have increasing frequency of migraines or attacks that are poorly responsive to abortive treatment should be considered for preventive therapy. T e typical patient considered for preventive therapy has four or more attacks per month. T e U.S. Food and Drug Administration (FDA)-approved medications for migraine prevention include propranolol, timolol, sodium valproate, topiramate, and methysergide (not currently available). In addition, many medications are commonly used for migraine prevention off-label including amitriptyline, nortriptyline, flunarizine, phenelzine, gabapentin, and cyproheptadine. When considering which medication to choose for a particular patient, one must carefully consider the potential side effects that may limit use. T e appropriate dose for migraine prevention may also be unclear as the dosing for these drugs was determined for an indication other than migraine. Patients should be started on a low dose and titrated upward to limit side effects. T e efficacy in decreasing migraine attacks is 50%–75%. However, the treatment effect is delayed 2–12 weeks. Once efficacy is achieved, the drug is continued for 6 months before tapering downward. Many patients exhibit fewer and milder attacks after cessation of medications, indicating that these drugs may potentially alter the natural history of migraine.

23. T e answer is A.
(Chap. 34) Cluster headache is a rare disorder affecting only about 0.1% of the population. T is episodic headache disorder is characterized by severe unilateral headache of relatively short duration that occurs over 8–10 weeks a year, followed by prolonged pain-free intervals that average a little less than a year. As opposed to migraine, men are more likely to have cluster headache, but cluster headache does share some features common to migraine including the unilateral nature of the pain and the stabbing or throbbing characteristics of the pain. In addition, a patient with cluster headache may also complain of nausea, photophobia, or phonophobia during the attack. In contrast, however, patients with cluster headache tend to move about during at attack. A cluster headache is accompanied by ipsilateral symptoms of cranial parasympathetic activation including lacrimation, rhinorrhea or nasal congestion, and ptosis. T e headache in cluster headache is explosive in onset and associated with intense pain. During a cluster attack, the headaches can occur as infrequently as every other day to several times daily. T e duration of pain is variable, between 15 and 180 minutes. Cluster headache falls within a category of trigeminal autonomic cephalgias, along with paroxysmal hemicranias, short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headaches with cranial autonomic symptoms (SUNA). It can be differentiated from these

www.ketabpezeshki.com (021) 66485457 - 66485438

based on historical factors. In paroxysmal hemicrania, the attacks are more frequent, occurring between 1 and 20 times per day, and last 2–30 minutes. Males and females are equally affected. In contrast to cluster headache, indomethacin provides very effective prophylactic treatment. SUNCT and SUNA are rare disorders that are easily distinguished from cluster headache. A patient with one of these disorders will have 3–200 episodes of unilateral pain daily, but the duration is less than 5 minutes. Migraine headache is a unilateral throbbing headache associated with phonophobia, photophobia, and nausea and vomiting. It is more common in women than men and is not associated with the symptoms of tearing or nasal congestion. Tension headache is the most common cause of headache and does not typically cause debilitating pain. T e pain of a tension headache is described as band-like.

24. T e answer is C.
(Chap. 35) Significant memory loss affects about 10% of all individuals greater than 70 years of age, and in more than half, the cause is Alzheimer disease (AD). AD is the leading cause of dementia and typically presents as slowly progressive memory loss that develops over many years. Early in the disease, the memory loss often goes unrecognized or is attributed to the effects of aging. Memory deficits are typically not noticeable to the patient or spouse until the deficits fall to 1.5 standard deviations below normal on standardized memory tests. When this occurs, the term mild cognitive impairment (MCI) is applied. Among those diagnosed with MCI, about 50% progress to AD over 4 years. Many neurologists have begun to replace MCI with the term "early symptomatic AD." As the cognitive disease progresses, patients will lose their ability to maintain their higher order daily activities such as driving, shopping, housekeeping, and maintaining finances. Most patients are aware of the loss of these abilities in early stages of the disease. In middle stages of the disease, the patient loses the ability to work and is easily lost and confused. Language is increasingly impaired in both comprehension and fluency. Motor apraxia also becomes noticeable. In advanced stages of the disease, patients may remain ambulatory but often wander aimlessly. T ere is a loss of judgment and reasoning. T e patient may have delusions and may not recognize caregivers. T e pathologic hallmark of AD is the presence of neuritic plaques containing amyloid beta and neurofibrillary tangles (option C) containing hyperphosphorylated tau filament. T e earliest and most severe degeneration is seen in the medial temporal lobe, lateral temporal cortex, and nuclear basalis of Meynert. Amyloid deposition in cerebral blood vessels (option A) can be seen in AD but is not the pathologic hallmark of AD. It is also seen in a condition called cerebral amyloid angiopathy, which predisposes individuals to cerebral hemorrhage. Frontotemporal lobar degeneration spectrum disorders are a heterogeneous group of disorders including Pick disease, progressive supranuclear palsy, and corticobasal syndrome that share a common gross pathologic hallmark of focal atrophy of the frontal, insular, and/or temporal cortex (option B) with a concomitant loss of serotonergic innervation in many patients. Lewy bodies are intracytoplasmic inclusions that stain positive with periodic acid–Schiff (PAS) and ubiquitin (option D) that are found throughout specific brainstem nuclei, substantia nigra, amygdala, cingulate gyrus, and neocortex. Lewy bodies are seen in dementia syndromes with parkinsonian features.

25. T e answer is E.
(Chap. 35) MCI refers to a condition of impaired memory that is 1.5 standard deviations below normal on standardized memory tests. Over 4 years, about 50% of individuals with MCI will progress to AD. However, no treatment currently has been demonstrated to slow the decline in memory or delay the progression to AD. Donepezil, rivastigmine, and galantamine are anticholinesterase inhibitors that are FDA approved for use in patients diagnosed with AD. Memantine is also approved for use in moderate to severe AD and blocks N-methyl-D-aspartate (NMDA)–glutamate receptors. T ese medications have modest effects on caregiver ratings of patient functioning and slight decrease in rate of decline in cognitive test scores over periods of up to 3 years. However, these medications have significant side effects including nausea, diarrhea, altered sleep with vivid dreams, and muscle cramps. Interventions that have been attempted and failed to show benefit have included hormone replacement therapy in postmenopausal women and gingko biloba. Many potential therapies are being investigated to ascertain benefit including vaccination against amyloid beta and statin use in early AD. Despite its popularity in the media, "brain training" has not been shown to slow decline in cognitive function.

26. T e answer is C.
(Chap. 35) Frontotemporal dementia (FTD) refers to a group of clinical syndromes that demonstrate frontotemporal lobe degeneration (FTLD) on pathologic examination. FTD typically presents in the fifth to seventh decades of life and is

www.ketabpezeshki.com (021) 66485457 - 66485438

nearly as predominant as Alzheimer disease in this age group. T ree distinct clinical syndromes are described: behavioral variant FTD, semantic primary progressive aphasia, and nonfluent/agrammatic primary progressive aphasia. T ese syndromes have clinical and MRI findings that allow the clinician to determine the primary diagnosis, although patients may evolve to have prominent features of another syndrome. T is patient has behavioral variant FTD, the most common of the FTD syndromes. Individuals with behavioral variant FTD demonstrate social and emotional dysfunction with a variety of symptoms including apathy, disinhibition, compulsivity, loss of empathy, and overeating. In addition, there are typically deficits in executive control. Upper motor neuron disease is often seen as well. T e MRI shows atrophy of anterior cingulate and frontoinsular areas. In the semantic primary progressive aphasia variant of FTD, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, and the MRI shows prominent atrophy in the temporopolar area that is greater on the left. T e nonfluent/agrammatic primary progressive aphasia variant of FTD demonstrates profound inability to produce words and motor speech impairment. T e MRI shows dominant frontal opercular and dorsal insula degeneration.

27. T e answer is A.

(Chap. 36) Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease, affecting approximately 1 million individuals in the United States. PD affects men and women equally, with a typical age of symptom onset around age 60. T e frequency of PD increases with age but can present as early as the third decade of life. Most cases of PD occur sporadically, although genetic factors play a role in some individuals. T ese individuals are more likely to present at a younger age. T ere is no single gene found to be associated with PD. T e most likely genes to be altered in PD patients include α-synuclein, PINK1/Parkin, and LRRK2, but many others have been identified. Other epidemiologic risk factors for PD include exposure to pesticides, rural living, and drinking well water. Cigarette smoking and caffeine are associated with reduced risk of PD. Pathologically, the characteristic finding in PD is degeneration of the dopaminergic neurons in the substantia nigra pars compacta. Lewy bodies, which are intracytoplasmic inclusions containing primarily α-synuclein, may also be seen.

28. T e answer is E.

(Chap. 36) T is patient exhibits classic features of PD, a diagnosis made based on clinical presentation. Historically, PD could be diagnosed if the patient had two out of three of the following: bradykinesia, tremor, and rigidity. However, given the significant overlap of these symptoms with atypical or secondary Parkinson syndrome, the diagnosis of PD was incorrect in about 24% of cases. More recently, it has been determined that a more predictive trio of features is rest tremor, asymmetry, and positive response to levodopa. Imaging of the brain may show reduced uptake of striatal dopaminergic markers in the posterior putamen with sparing of the caudate nucleus on positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging. However, imaging is not required for a diagnosis of PD and is typically only performed under research settings or if there are features that would cause one to suspect an atypical Parkinson syndrome. T is patient does not have features that would lead one to suspect atypical parkinsonism **(Table 28)**. He also has no medications or other clinical conditions that would lead to secondary parkinsonism. T e most common causes of secondary parkinsonism include stroke, tumor, infection, exposure to toxins such as carbon monoxide, and particularly medications. T e medications most likely to cause secondary parkinsonism are neuroleptic agents, including metoclopramide and chlorpromazine. Treatment of PD is typically with either levodopa-carbidopa or a dopamine agonist. Levodopa has a long history of use in PD dating to the 1960s. Levodopa is administered in combination with carbidopa to prevent peripheral conversion to dopamine and thus prevent side effects, especially nausea and vomiting. In Europe, levodopa is combined with benserazide to prevent this conversion. Levodopa is the most effective symptomatic treatment of PD. It improves motor features, quality of life, and life span as well as improving productive years of life with increased independence and employability. However, the majority of patients treated with levodopa develop motor complications with "on/off" periods, referring to fluctuations in motor responsiveness to the drug. In addition, patients may develop involuntary movements. Further, the duration of benefit of levodopa subsides over time to where it approaches the short half-life of the drug. Nondopaminergic features, including falling, freezing, and autonomic dysfunction, are also not treated with levodopa. Many providers now prefer dopamine agonists as first-line therapy.

www.ketabpezeshki.com (021) 66485457 - 66485438

TABLE 28

FEATURES SUGGESTING AN ATYPICAL OR SECONDARY CAUSE OF PARKINSONISM

SYMPTOMS/SIGNS	ALTERNATIVE DIAGNOSIS TO CONSIDER
History	
Early speech and gait impairment (lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired downgaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Exam	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired downgaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple system atrophy–cerebellar type; MSA-p, multiple system atrophy–Parkinson type; PD, Parkinson disease; PSP, progressive supranuclear palsy.

These drugs include pramipexole, ropinirole, and rotigotine as non–ergot derivatives. Although these agents do not show comparable efficacy to levodopa, they are associated with fewer motor complications. It should be noted that even with use of the dopamine agonists, eventual treatment with levodopa is required in most patients. Selegiline is a monoamine oxidase inhibitor (MAOI). Although MAOIs can be used as monotherapy in early disease, there is a risk of serotonin syndrome when used with selective serotonin reuptake inhibitor (SSRI) agents such as fluoxetine. The risk is low overall, but because this patient is untreated, there are other better options for his care.

29. The answer is C.
(Chap. 36) Deep brain stimulation (DBS) is the most common surgical therapy performed for PD. In this surgery, an electrode is placed into a target area, typically the subthalamic nucleus or globus pallidus pars interna. The electrode is connected to a stimulator usually placed in the chest wall. The precise mechanism by which DBS works is not known, but it is thought to act by disrupting the abnormal signal associated with PD and motor symptoms. Once in place, DBS can be adjusted on many variables, including voltage, frequency, and pulse duration. The primary indication for DBS is severe tremor or levodopa-induced motor complications that cannot be controlled with medications. It does not improve features that fail to respond to levodopa, including falling, freezing, and dementia.

30. The answer is F.
(Chap. 39) Amyotrophic lateral sclerosis (ALS) is a common motor neuron disease with an incidence of 1–3 per 100,000 population and prevalence of 3–5 per 100,000 population. ALS is responsible for about 1 in 1000 deaths in North America and Western Europe. This is progressive disease has no treatment and leads to disability and death due to respiratory failure within 3–5 years after diagnosis. The pathologic hallmark of ALS is loss or death of both upper and lower motor neurons. The upper motor neuron loss can be demonstrated by degeneration of the corticospinal tracts typically originating in layer five of the motor cortex and descending downward via the pyramidal tract to synapse with the lower motor neurons both directly and indirectly via interneurons. The lower motor neuron disease is manifested by death of anterior horn cells in the spinal cord and brainstem, which can lead to bulbar symptoms. Clinically, this leads to the classic findings of both upper and lower motor neuron disease in ALS. The most common presenting symptom in ALS is asymmetric weakness of insidious onset, which is most prominent in the lower extremities. Muscle wasting and atrophy may be prominent. A detailed history can elicit cramping with volitional movements, such as stretching, that is most common in the early morning hours. Fasciculations may be identified. When the muscles of the hands are involved, extensor weakness is more common than flexor weakness. Bulbar symptoms include difficulty with chewing, swallowing, and movements of the face and tongue. Upper motor neuron symptoms may lead to spasticity with increased deep tendon reflexes. However, even in late stages of the disease, sensory and

www.ketabpezeshki.com (021) 66485457 - 66485438

cognitive functions are preserved. At present, the treatment for ALS is largely supportive. Riluzole has been approved for treatment of ALS as it may confer a modest increase in survival, although its true benefits are not clearly known. Its mechanism of action may be to reduce excitotoxicity by decreasing glutamate release. Supportive therapy may include use of cough assist devices, invasive or noninvasive ventilatory support, and gastrostomy feeding in addition to a variety of orthopedic assistive devices.

31. T e answer is B.
(Chap. 41) T e patient is presenting with parkinsonism with symptoms of orthostatic hypotension and constipation indicating concomitant autonomic dysfunction. Because the patient exhibits no dementia and has no tremor, the most likely diagnosis would be multiple system atrophy (MSA). T is rare disorder has a prevalence of about 2–5 per 100,000 and is commonly grouped within a category of disorders of atypical parkinsonism that includes progressive supranuclear palsy, corticobasal ganglionic degeneration, and frontotemporal dementia. MSA is typically diagnosed in the sixth decade of life and is slightly more common in men. MSA is characterized by degeneration of the substantia nigra pars compacta, striatum, cerebellum, and inferior olivary nuclei. Glial cytoplasmic inclusions that stain positive for α-synuclein are also a defining feature. T e diagnosis of MSA should be suspected in individuals presenting with parkinsonian symptoms in combination with prominent cerebellar and/or autonomic complaints. In most patients, either cerebellar or parkinsonian symptoms predominate, leading to a subclassification as MSA-c or MSA-p, respectively. Autonomic symptoms occur in all patients. T e most frequent autonomic symptoms include prominent orthostatic hypotension, severe constipation, neurogenic bladder, impotence in men, rapid eye movement (REM) behavior disorder, and laryngeal stridor. Diagnosis is made by clinical features. Treatment with dopaminergic agents is typically ineffective. Management is primarily symptomatic and focused on managing the concomitant autonomic features. Orthostatic hypotension often requires fludrocortisone. If that approach fails, other agents including midodrine, ephedrine, pseudoephedrine, or phenylephrine may be used. Conservative treatment of the gastrointestinal and urinary symptoms include frequent small meals, stool softeners, bulking agents, and intermittent bladder catheterization. T e median time to death after diagnosis is 10 years. Risk factors for decreased survival include female gender, urinary dysfunction, older age at onset, and parkinsonian variant of the disease.

32. T e answer is A.
(Chap. 42) Trigeminal neuralgia is a relatively common disorder with an annual incidence of 4–8 cases per 100,000 population. It is more common in women and typically presents in middle-aged or elderly individuals. It presents as sharp, and sometimes excruciating, paroxysms of pain in the lips, gums, cheek, or chin. T e pain typically lasts from just a few seconds to no more than a few minutes. T e painful sensations recur frequently in clusters and can occur day or night. Episodes of pain can last for several weeks at a time. Pain can occur spontaneously, but is often elicited by light touch or movements of the affected areas, including chewing, speaking, or smiling. On physical examination, there are no objective signs of sensory or motor loss. Trigeminal neuralgia is caused by ectopic generation of action potentials by pain-sensitive afferent fibers in the fifth cranial nerve. Compression of the trigeminal nerve root by a blood vessel is believed to be the most common cause of trigeminal neuralgia. Demyelination near the entry of the fifth nerve root has also been implicated. Diagnosis of trigeminal neuralgia is made based on clinical features, and laboratory or radiologic examination is not required. T ere is no role for electromyography (EMG) or nerve conduction studies in the evaluation of the disease. T e initial treatment is typically with carbamazepine, which has been demonstrated to be effective in 50%–75% of cases. T e initial dose is 100 mg in two to three divided doses daily. T e medication is titrated upward to achieve pain relief. Most patients require a dose of 200 mg qid or greater, although doses >1200 mg daily confer no added benefit. For patients who do not tolerate carbamazepine, other antiseizure medications have been used to control the symptoms. T ese include oxcarbazepine, lamotrigine, and Dilantin. In cases that are refractory to medical therapy, microvascular surgical decompression can be considered and has a >70% success rate in relieving pain. Gamma knife radiosurgery may also be used. Radiofrequency thermal rhizotomy is used less frequently. Despite an initial success rate of >95%, up to one-third of individuals will have recurrence of symptoms, and the procedure is associated with an increased risk of complications including facial numbness and jaw weakness. T e differential diagnosis of trigeminal neuralgia includes temporal arteritis, migraine or cluster headaches, and multiple sclerosis. Temporal

www.ketabpezeshki.com (021) 66485457 - 66485438

arteritis may present with superficial facial pain. One typically also has symptoms including jaw claudication, diffuse myalgias, and potential visual symptoms. Testing of erythrocyte sedimentation rate and performance of temporal artery biopsy are appropriate if this diagnosis is suspected. Migraine and cluster headaches present with a deeper sensation of pain. Although the pain is often throbbing in nature, it lacks the stabbing quality of trigeminal neuralgia. Multiple sclerosis can present with trigeminal neuralgia, but most patients have other symptoms of the disease as well, including weakness or visual symptoms. Multiple sclerosis may be more likely if a patient presents with bilateral trigeminal neuralgia or at a young age, and an MRI would be appropriate at that time.

33. T e answer is F.

(Chap. 43) T is patient presents with spinal cord compression, which represents an urgent need for treatment. Spinal cord compression can occur with any tumor but is most common with tumors of the breast, lung, prostate, and kidney and lymphoma and myeloma. T e thoracic spinal column is the most commonly affected area for most tumors. However, metastases from prostate or ovarian cancer invade locally into the spinal column. T us, they more commonly affect the sacral and lumbar vertebrae. Pain is typically the initial symptom of vertebral metastases. T e pain can be dull and aching or sharp and radiating. T e pain is usually worsened by movement, cough, and sneezing and at night. When cord compression occurs, the patient will develop weakness, sensory abnormalities, and bowel or bladder dysfunction. When spinal cord compression is suspected, imaging should be obtained promptly. Diagnosis typically is made with MRI, which also allows one to differentiate between metastasis, epidural abscess, epidural hemorrhage, or other lesions. On T1-weighted MRI, the vertebral metastases will appear hypodense relative to normal bone marrow. With gadolinium administration, the MRI may pseudonormalize as uptake of the contrast causes the lesions to appear at the same density as the bone marrow. Plain radiographs of the spine and radionuclide bone scans will not identify 10%–20% of metastatic lesions. Management of cord compression should include glucocorticoids, local radiotherapy, and treatment of the underlying malignancy. Glucocorticoids decrease cord edema, and dexamethasone is the most commonly used medication. Up to 40 mg daily of dexamethasone is frequently used. Prompt treatment with radiotherapy to the area of cord compression is essential to decrease morbidity associated with the finding. A good response to therapy is expected for individuals who are ambulatory at the time of presentation. If motor deficits persist for longer than 12 hours, however, these will not improve. Treatment would be expected to prevent new weakness. Finally, specific therapy for the underlying tumor type is important. Surgical decompression of cord compression is generally not a preferred therapy. If there is only a single metastasis to the spine, it can sometimes be considered as a therapy. Otherwise, surgical therapy is typically limited to individuals who fail to respond to the maximum-tolerated dose of radiotherapy.

34. T e answer is C.

(Chap. 43) Sarcoidosis is an important cause of acute or subacute myelopathy. It most often presents with slowly progressive weakness or a relapsing-remitting course. T e patient affected with sarcoid myelopathy typically has concomitant sensory loss with weakness. A distinct cord level may be demonstrated. T e MRI often shows diffuse edema of the spinal cord with gadolinium enhancement in active lesions. Nodular enhancement of the adjacent surface of the spinal cord is frequently seen, and the disease may affect many levels of the spinal cord. A lumbar puncture shows a lymphocyte-predominant cell count with mildly elevated CSF protein. Because sarcoidosis is often a multisystem disease, examination for evidence of disease outside of the spinal cord should be performed, including a chest radiograph, slit-lamp eye examination, serum calcium levels, and electrocardiogram. If there is evidence of abnormalities in other body systems, then definitive diagnosis can be made with a biopsy demonstrating noncaseating granulomas on pathologic examination. Patients are treated initially with high-dose glucocorticoids to decrease swelling and stimulate regression of the granulomatous lesions. Many patients will also require alternative immunosuppression including azathioprine, mycophenolate mofetil, or infliximab. Presence of caseating granulomas typically signifies an infectious process, most commonly tuberculosis or fungal infection. Atypical lymphocytes with clonality on flow cytometry are found in various types of lymphoma. A biopsy with small round cells that often resemble lymphocytes and that demonstrate scant cytoplasm, indistinct nucleoli, and mitotic figures is typical of small-cell lung carcinoma. Nonspecific chronic inflammation is nondiagnostic, and further workup would be required.

www.ketabpezeshki.com (021) 66485457 - 66485438

35. The answer is D.
(Chap. 43) Syringomyelia is a development disorder of the spinal cord that results in enlargement of the central cavity of the spinal cord. More than half of all cases are associated with a concomitant Chiari I malformation of the brainstem with protrusion of the cerebellar tonsils through the foramen magnum and into the cervical spinal canal. Although controversial, one theory for the pathogenesis of syringomyelia is impaired CSF flow with secondary enlargement of the central spinal cord, and the common coexistence with Chiari malformations may provide support for this theory. Symptoms of syringomyelia develop gradually, often beginning in late adolescence or early adulthood. The symptoms progress irregularly and may even arrest for a prolonged period. The presentation of syringomyelia includes both sensory loss and muscle wasting and weakness. The sensory disturbance is dissociative, with loss of pain and temperature sensation but preservation of vibration and touch. Patients may present with injuries or burns that occur when the patient is unaware of a painful sensation in the affected limb. The distribution of sensory loss is classically described as cape-like, affecting the nape of the neck, shoulders, upper arms, and hands. Patients are areflexic in the upper limbs. Symptoms may be asymmetric. As the cavity enlarges, it can further lead to spasticity and weakness in the lower extremities as well. There are no definitive treatment options for the disease. If a Chiari malformation is also present, surgical decompression may be required. Surgeons have attempted direct decompression of the spinal canal with varied results.

36 and 37. The answers are C and D, respectively.
(Chap. 45) This patient presents with visual disturbance and weakness affecting the lower extremities with a past history of prior visual disturbance. This suggests a diagnosis of multiple sclerosis (MS), an autoimmune demyelinating disorder of the central nervous system. This disease affects about 350,000 individuals in the United States and has a variable clinical course, with some individuals experiencing limited symptoms and others becoming very incapacitated due to the disease. MS is three times more common in women, with a typical age of onset between 20 and 40 years of age. MS is more common in white individuals that those of African or Asian descent. In addition, geographic variations in disease prevalence have been demonstrated, with higher prevalence in the temperate zone areas of northern North America, northern Europe, and southern Australia and New Zealand. In contrast, the tropics have a prevalence that is 10 to 20 times less. Other well-established risk factors for development of MS include vitamin D deficiency, exposure to Epstein-Barr virus after early childhood, and cigarette smoking. Despite the fact that this is an autoimmune disorder, there has not been an association between MS and other autoimmune disorders. The clinical manifestations of MS are varied. The disease can present with an abrupt onset of symptoms or may develop gradually. The most common initial presenting symptoms include sensory loss, optic neuritis, weakness, paresthesias, and diplopia. Weakness of the limbs may be asymmetric and manifest as loss of strength, speed, dexterity, or endurance. Symptoms are upper neuron in origin and have associated spasticity, hyperreflexia, and Babinski sign most commonly. However, if there is a spinal cord lesion, lower motor neuron signs and loss of reflexes may also be seen. The spasticity that is present may lead to spontaneous or movement-induced muscle spasms and affects up to 30% of patients with MS. Optic neuritis presents with blurred vision, dimness, or decreased color perception in the central visual fields. Visual symptoms typically only affect one eye. Periorbital pain often precedes or accompanies visual loss. Funduscopic examination may be normal or show optic disc swelling. Other common symptoms that occur with MS include bladder dysfunction, ataxia, constipation, chronic pain, fatigue, and depression. A diagnosis of MS can be difficult to confirm in some individuals. There is no definitive test for MS. The diagnostic criteria require two or more episodes of symptoms and two or more signs of dysfunction in noncontiguous white matter tracts. MRI characteristically shows multiple hyperintense T2-weighted lesions that can be present in the brain, brainstem, and spinal cord. More than 90% of lesions seen on MRI, however, are asymptomatic. Approximately one-third of lesions that appear hyperintense on T2-weighted images will be hypointense on T1-weighted images. These "black holes" may be a marker of irreversible demyelination and axonal loss. Evoked potentials are no longer commonly used in MS and are most useful in studying pathways that are not exhibiting clinical symptoms. Evoked potentials are not specific to MS, although a marked delay in latency of transmission suggests demyelination. The CSF may show an increased number of mononuclear cells, although CSF protein is typically normal. Oligoclonal bands help to assess the intrathecal production of immunoglobulin (Ig) G. The presence of two or more discrete oligoclonal bands in the CSF that are not present in serum is found in more than 75% of

www.ketabpezeshki.com (021) 66485457 - 66485438

MS patients. If a patient has a pleocytosis of >75 cells/μL, presence of polymorphonuclear cells, or protein concentration >100 mg/dL, an alternative diagnosis should be sought.

38. The answer is D.

(Chap. 45) Over the past two decades, 10 disease-modifying agents for the treatment of MS have been approved. Due to these multiple options, it is preferred that a patient with MS be referred to a treatment center with experience in the disease. The disease-modifying drugs approved for MS include interferon-β-1a, interferon-β-1b, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, mitoxantrone, and alemtuzumab. Given this patient's poor functional status, her disease should be treated as moderate disease. Generally, in those with moderate disease, the preferred agents are dimethyl fumarate, fingolimod, teriflunomide, and natalizumab, with interferon-β-1a and -1b treatment being reserved for individuals with milder disease. However, natalizumab is not recommended in this patient due to the presence of antibody to JC virus. About half of the population is antibody positive for JC virus, indicating past exposure typically with an asymptomatic infection. JC virus is implicated in the development of progressive multifocal leukoencephalopathy. This is life-threatening condition has occurred in 0.3% of all patients treated with natalizumab and in about 0.6% of patients who are positive for JC virus antibody. The risk is lower in the first year of treatment and increases thereafter. Thus, natalizumab should not be used in this patient unless she has failed alternative therapies or if the disease course has been particularly aggressive. If natalizumab is ultimately chosen for a patient who is JC virus antibody–positive, it should not be used for any longer than 1 year. In patients who are JC virus antibody–negative, it is recommended to follow the patient for development of antibody approximately every 6 months.

39. The answer is C.

(Chap. 53) When evaluating a patient with peripheral neuropathy, the clinician should consider the history and physical examination carefully to determine the location of the lesion, which will then further identify the cause and appropriate treatment. However, in as many as 50% of patients presenting with peripheral neuropathy, no cause is ever found, and these patients generally have a predominant sensory polyneuropathy. Seven key questions in the history and physical examination can assist with the identification of the site of the lesion and the cause **(Table 39)**. The first determination the clinician should make is which systems are involved—sensory, motor, autonomic, or some combination of these. An isolated motor neuropathy without sensory involvement should lead to diagnostic possibilities that include myopathy, motor neuropathy, or disorder of the neuromuscular junction. Autonomic symptoms can accompany a diabetic neuropathy and can also be seen in amyloid polyneuropathy. Another important determination is the distribution of the weakness (proximal vs. distal, symmetric vs. asymmetric). A third determination is the nature of the sensory involvement. Small-fiber neuropathy often has a burning or stabbing quality along with temperature loss, whereas a large-fiber sensory neuropathy will show loss of vibratory sense and proprioception. One should consider whether upper motor neuron symptoms are also present, which occurs with vitamin B_{12} deficiency most commonly, but also occurs with other causes of combined system degeneration

TABLE 39

APPROACH TO NEUROPATHIC DISORDERS: SEVEN KEY QUESTIONS

1. **What systems are involved?**
   - Motor, sensory, autonomic, or combinations
2. **What is the distribution of weakness?**
   - Only distal vs. proximal and distal
   - Focal/asymmetric vs. symmetric
3. **What is the nature of the sensory involvement?**
   - Temperature loss or burning or stabbing pain (e.g., small fiber)
   - Vibratory or proprioceptive loss (e.g., large fiber)
4. **Is there evidence of upper motor neuron involvement?**
   - Without sensory loss
   - With sensory loss
5. **What is the temporal evolution?**
   - Acute (days to 4 weeks)
   - Subacute (4–8 weeks)
   - Chronic (>8 weeks)
   - Monophasic, progressive, or relapsing-remitting
6. **Is there evidence for a hereditary neuropathy?**
   - Family history of neuropathy
   - Lack of sensory symptoms despite sensory signs
7. **Are there any associated medical conditions?**
   - Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy)
   - Medications, including over-the-counter drugs that may cause a toxic neuropathy
   - Preceding events, drugs, toxins

www.ketabpezeshki.com (021) 66485457 - 66485438

such as human immunodeficiency virus (HIV) and copper deficiency. T e temporal evolution of symptoms further provides the clinician with clues as to the cause of the disease. Most neuropathies have an insidious onset over weeks to months. Acute development of symptoms points to causes such as Guillain-Barré syndrome vasculitis or Lyme disease. Asking about symptoms in other family members will help to establish whether a hereditary neuropathy is present. Finally, it is important to obtain a full medical history to assess whether any associated conditions could be contributing to the neuropathy. Once a full history and physical examination is completed, a clinician will often order EMG and nerve conduction studies to complete the workup. Autonomic studies may also be helpful in selected patients.

40. T e answer is A.
(Chap. 53) Charcot-Marie-Tooth (CMT) syndrome is the most common type of hereditary neuropathy. CMT is comprised of several similar but genetically distinct conditions with different associated mutations. CMT1 is the most common syndrome and is an inherited demyelinating sensorimotor neuropathy. CMT1 most often affects patients in the first to third decades of life with distal leg weakness (ie, foot drop). T ere are several subtypes of CMT1, most of which are inherited in an autosomal dominant fashion. However, the penetrance is variable, and some affected family members may remain asymptomatic even late in life. T e most common genetic defect in CMT1 (CMT1A) is a 1.5-megabase duplication in the gene for peripheral myelin production (PMP-22) on chromosome 17. T is results in a patient having three copies of the gene rather than two. Although patients generally do not complain of sensory symptoms, these can be elicited often on physical examination. Muscle stretch reflexes are unobtainable or reduced throughout, and muscles below the knee are often atrophied, which makes legs appear to have so-called inverted champagne bottle appearance. T ere are no medical therapies for CMT, but patients are generally referred for physical and occupational therapy. Bracing and other orthotic devices are frequently used. Hereditary neuralgic amyotrophy is an autosomal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus that often begins in childhood. Hereditary sensory and autonomic neuropathy is a rare group of hereditary neuropathies in which sensory and autonomic dysfunction predominates over muscle weakness. T is would not fit the clinical pattern described here. Guillain-Barré syndrome generally presents acutely with rapid development of ascending paralysis. T e prolonged symptom period and distribution described here are not typical for Guillain-Barré syndrome. Fabry disease is an X-linked disorder in which men are more commonly affected then women. Patients have angiokeratomas, which are reddish-purple lesions usually found around the umbilicus, scrotum, and inguinal region. Burning pain in the hands and feet often is found in late childhood or early adult life. Patients also have premature atherosclerosis from the underlying mutation in the α-galactosidase gene with accumulation of ceramide in nerves and blood vessels.

41. T e answer is E.
(Chap. 53) One of the most common side effects of isoniazid treatment is peripheral neuropathy. T e elderly, malnourished patients, and "slow acetylators" are at increased risk for developing the neuropathy. Isoniazid inhibits pyridoxal phosphokinase, resulting in pyridoxine (vitamin B_6) deficiency and the neuropathy. Prophylactic administration of pyridoxine can prevent the neuropathy from developing. Symptoms are generally dysesthesias and sensory ataxia. Impaired large-fiber sensory modalities are found on examination. Cobalamin (vitamin B_{12}) is not reduced in this condition and unaffected by isoniazid. Neurontin and pregabalin may alleviate symptoms but will not reverse the neuropathy. T ere is no indication that hypothyroidism is present.

42. T e answer is C.
(Chap. 53) Diabetes mellitus is the most common cause of peripheral neuropathy in developed countries and is associated with several different types of polyneuropathy including distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradicular neuropathies, cranial neuropathies, and other mononeuropathies. Risk factors for development of neuropathy include long-standing and poorly controlled diabetes and the presence of retinopathy or nephropathy. T e patient here appears to have diabetic distal symmetric sensory and sensorimotor polyneuropathy (DSPN), which is the most common form of diabetic neuropathy. DSPN presents with sensory loss beginning in the toes that gradually progresses over time up the legs and into the fingers and arms. Symptoms also may include tingling, burning, and deep aching pains. Nerve biopsy, although rarely indicated, often shows axonal degeneration, endothelial hyperplasia, and occasionally perivascular inflammation. Tight glucose control prevents development of disease but does not reverse established disease.

www.ketabpezeshki.com (021) 66485457 - 66485438

Diabetic autonomic neuropathy is often seen in combination with DSPN and manifests by abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, postural hypotension, gastrointestinal abnormalities including gastroparesis, and genitourinary dysfunction.

43 and 44. T e answers are B and B, respectively.
(Chap. 54) Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy that can be severe and life-threatening if not immediately recognized and treated. Each year, there are about 5000–6000 cases in the United States, with an incidence of about 1–4 cases per 100,000 population annually. Men are slightly more commonly affected than women, and GBS is more commonly diagnosed in adulthood. T e typical presentation is a rapid ascending paralysis that may be first noticed as weak or "rubbery" legs. T e weakness can evolve over hours to a few days, with the legs being more affected than the arms. Tingling dysesthesias are also frequently present, although sensory neuropathy is always present. Facial paresis occurs in about 50% of patients, and other lower cranial nerves may also be affected. Pain is a frequent complaint, with pain in the neck, shoulders, back, and diffusely over the spine. In addition, vague sensation of deep aching pain in the weakened muscles may be present. Up to 30% of patients will require mechanical ventilation due to weakness of the respiratory muscles. Moreover, bulbar involvement increases the risk of aspiration and subsequent pneumonia. Deep tendon reflexes are decreased or disappear entirely within the first few days of onset. Cutaneous sensory deficits are usually only mild if present at all. Bladder dysfunction only rarely occurs and is transient. Persistent or severe bladder dysfunction should stimulate a workup for other causes. Autonomic symptoms are common. Blood pressure may be quite labile with marked postural changes. Cardiac dysrhythmias may also occur and require continuous monitoring. Typically within 4 weeks of onset or sooner, there is a plateau in symptoms with no further progression. Diagnosis of GBS relies upon a high degree of clinical suspicion because there is no one test that is diagnostic for the disorder. Typical CSF findings include a high CSF protein without pleocytosis. T e presence of a high CSF white blood cell count should prompt a search for an alternative diagnosis. Early in the disease process, electrodiagnostic testing may be normal or only show mild findings of demyelination. Approximately 70% of GBS cases occur within 1–3 weeks of an antecedent infectious illness. Most commonly, the illness is respiratory or gastrointestinal in nature. About 20%–30% of all cases in North America, Europe, and Australia are preceded by infection or reinfection with Campylobacter jejuni. A similar proportion of individuals will have had an infection with a human herpes virus, most often cytomegalovirus or Epstein-Barr virus. Less frequently, HIV, hepatitis E, or Mycoplasma pneumoniae may be implicated. Recent immunizations are a rare cause of GBS, with a risk of <1 per million. When a case of GBS is suspected, clinical vigilance and prompt treatment are required. Admission to intensive care is often required to monitor for development of respiratory failure or cardiac arrhythmias. If treatment is delayed longer than 2 weeks after initial symptoms or during the plateau stage, it may not be effective. Either high-dose IV immunoglobulin (IVIg) or plasmapheresis should be initiated as soon as possible. IVIg is given as a daily infusion for 5 days. Plasmapheresis should be performed four to five times over the first week. Functionally significant recovery may begin to be evident after the first week but may take several weeks. Lack of noticeable improvement following either IVIg or plasmapheresis is not an indication to switch to the alternative therapy as they are equally effective in treatment. Glucocorticoids have not been shown to be effective in GBS and should not be used. Approximately 85% of patients with GBS achieve full functional recovery after several months to a year. However, some physical examination findings such as areflexia may persist. T e mortality rate is <5%, and death is most often due to respiratory complications. Although macrolides have activity against Campylobacter species, most cases of diarrhea resolve spontaneously, and treatment has no effect on the course of GBS. Pyridostigmine may increase strength in patients with myasthenia gravis but will have no effect on strength in patients with GBS.

45. T e answer is A.
(Chap. 55) Myasthenia gravis (MG) is a relatively common neuromuscular disorder that is caused by antibody-mediated autoimmune destruction of acetylcholine receptors at the neuromuscular junction. MG has a prevalence of about 2–7 in 10,000 individuals and affects women more commonly than men at a ratio of 3:2. T e age of presentation in women is generally in the 20s to 30s, whereas men more commonly present in their 50s and 60s. T e key features of MG are weakness and fatigability of muscles. T e weakness increases with repeated use and is typically more prominent late in the day. T e distribution of muscle weakness often follows a typical pattern, with cranial muscles being affected

www.ketabpezeshki.com (021) 66485457 - 66485438

early in the course of disease. Common clinical features include diplopia, ptosis, inability to smile fully, weakness with chewing, dysarthria, and dysphagia. Aspiration of liquids may also occur. In the majority of patients, the weakness becomes generalized, affecting proximal muscles greater than distal muscles. Deep tendon reflexes are preserved, and the disease may be asymmetric. T e diagnosis is suspected after the appearance of the characteristic symptoms and signs. T e diagnosis should be confirmed with further testing because treatment may involve surgery and the prolonged use of immunosuppressive agents. T e most sensitive test for the diagnosis of MG is the presence of antibodies to the acetylcholine receptor (AChR). T ese antibodies are present in about 85% of patients with MG. T e presence of AChR antibodies in a patient with typical signs and symptoms is diagnostic. If AChR antibodies are negative, additional testing for muscle-specific kinase (MuSK) antibodies will be positive in another 40% of individuals. However, if the disease is limited to the ocular muscles alone, both of these tests are likely to be negative. Use of repetitive nerve stimulation characteristically shows decrements of >10%–15% in action potential amplitude with successive electric shocks delivered at two to three per second. Patients should be tested with repetitive stimulation in a proximal muscle group or in muscles that have been demonstrated to be weakened in the disease. Edrophonium is an acetylcholinesterase inhibitor that allows acetylcholine to interact repeatedly with the limited number of AChRs, producing improvement in the strength of myasthenic muscles. An objective end point must be chosen when performing the edrophonium test to determine if there is an improvement in muscle strength after administration. At this time, edrophonium is only used in individuals with suspected MG with negative antibody testing as well as negative electrodiagnostic testing. False-positive tests may occur in patients with other neurologic diseases, such as amyotrophic lateral sclerosis. Antibodies to voltage-gated calcium channels are found in patients with Lambert-Eaton syndrome, another neuromuscular disorder associated with complaints of weakness. In this disorder, however, individuals develop improved responses with repetitive nerve stimulation. Clinically, Lambert-Eaton syndrome can also be distinguished from MG because Lambert-Eaton syndrome typically has prominent autonomic changes as well as depressed deep tendon reflexes.

46. T e answer is E.

(Chap. 55) T e treatment of MG may include a variety of modalities including anticholinesterase medications, immunosuppression, IVIg or plasmapheresis, or surgical intervention. Initial treatment of symptoms with anticholinesterase medications such as pyridostigmine yields partial improvement in most patients. However, few patients achieve complete relief with this class of medications alone. In addition, dose-limiting side effects such as diarrhea, abdominal cramping, and excessive salivation are frequent. T ymectomy should be considered in all patients with MG. When considering thymectomy, there are two separate issues to be considered. If the patient has evidence of thymoma, thymectomy is necessary because local spread may occur. However, presence of a thymic shadow on CT scan is not indicative of thymoma and is common in young adulthood. In individuals without evidence of thymoma, thymectomy should still be considered an important therapeutic option. Even in the absence of tumor, up to 85% of individuals will experience improvement in disease after thymectomy, with ~35% achieving drug-free remission. Current literature suggests that individuals who undergo thymectomy are 1.7 times more likely to improve and 2 times more likely to achieve remission than those who do not undergo thymectomy. It is now consensus that individuals between the ages of puberty and 55 with generalized MG should be referred for thymectomy if surgically appropriate candidates. In the absence of thymectomy, addition of immunosuppressants in the form of glucocorticoids or other steroid-sparing agents will yield further benefits and often control the disease. Prednisone at a dose of 15–25 mg daily is the initial choice in most patients and should be increased for residual symptoms. Other immunomodulatory agents with proven effectiveness in MG include mycophenolate mofetil, azathioprine, cyclosporine, and tacrolimus. In addition, rituximab may be considered in refractory cases. In acute presentations with myasthenic crisis, IVIg or plasmapheresis is used concomitantly with immunosuppressants. Anticholinesterase drugs are typically withheld during a myasthenic crisis because overdosage of these drugs can worsen weakness.

47. T e answer is B.

(Chap. 55) Except for lumbar puncture, all of the options listed are indicated at this time. T ymic abnormalities are present in 75% of patients with MG. A CT or MRI of the mediastinum may show enlargement or neoplastic changes in the thymus

www.ketabpezeshki.com (021) 66485457 - 66485438

and is recommended upon diagnosis. Hyperthyroidism occurs in 3%–8% of patients with MG and may aggravate weakness. Testing for rheumatoid factor and antinuclear antibodies should also be obtained because of the association of MG with other autoimmune diseases. Due to side effects of immunosuppressive therapy, a thorough evaluation should be undertaken to rule out latent or chronic infections such as tuberculosis. Measurements of ventilatory function are valuable as a baseline because of the frequency and seriousness of respiratory impairment in patients with MG, and they can be used as an objective measure of response to therapy.

48. T e answer is E.
(Chap. 56) All classes of lipid-lowering agents have been implicated in muscle toxicity including fibrates, HMG-CoA reductase inhibitors, niacin, and ezetimibe. Myalgia, malaise, and muscle tenderness are the most common manifestations, and muscle pain may be exacerbated by exercise. Proximal weakness may be found on examination. In severe cases, rhabdomyolysis and myoglobinuria may occur, although most cases are more mild. Concomitant use of statins with fibrates and cyclosporine are more likely to cause adverse muscle reactions. Elevated serum creatine kinase (CK) is often identified, and muscle weakness is evidenced by myopathic EMG studies and myonecrosis on muscle biopsy. Severe myalgias, muscle weakness, significant elevations in CK (>3 × upper limit of normal), and myoglobinuria are indications for stopping. After cessation, improvement generally occurs in up to several weeks.

49. T e answer is E.
(Chap. 56) A number of endocrinologic conditions are associated with myopathy. Both hypo- and hyperthyroidism are associated with proximal muscle weakness. Hypothyroidism is associated with an elevated CK frequently, even with minimal clinical evidence of muscle disease. T yrotoxic patients may have fasciculations in addition to proximal myopathy, but in contrast to hypothyroid patients, CK is not generally elevated. Hyperparathyroidism is associated with muscle weakness, generally proximal. Muscle wasting and brisk reflexes are also generally present. Serum CK levels may be normal or slightly elevated. Serum calcium and phosphate levels show no correlation with clinical weakness. Hypoparathyroid patients also often have myopathy due to hypocalcemia. Patients with acromegaly usually have mild proximal weakness without atrophy. T e duration of acromegaly, not the serum growth hormone levels, correlates with the degree of myopathy. Diabetes mellitus is a rare cause of myopathy, generally due to ischemic infarction of muscle, and not a primary myopathy. Finally, vitamin D deficiency is associated with muscle weakness, as are glucocorticoid excess states (e.g., Cushing disease).

50. T e answer is D.
(Chap. 56) T ere are two recognized clinical forms of myotonic dystrophy, both of which are characterized by autosomal dominant inheritance. Myotonic dystrophy type 1 (DM1) is the most common form and the most likely disorder in this patient. Characteristic clinical features of this disorder include a "hatchet-faced" appearance, due to wasting of the facial muscles, and weakness of the neck muscles. In contrast to the muscular dystrophies (Becker and Duchenne), distal limb muscle weakness is more common in DM1. Palatal, pharyngeal, and tongue involvement are also common and produce the dysarthric voice that is frequently heard. T e failure of relaxation after a forced hand grip is characteristic of myotonia. Myotonia can also be elicited by percussion of the thenar eminence. In most individuals, myotonia is present by age 5, but clinical symptoms of weakness that lead to diagnosis may not be present until adulthood. Cardiac conduction abnormalities and heart failure are also common in myotonic dystrophy. Diagnosis can often be made by clinical features alone in an individual with classic symptoms and a positive family history. An EMG would confirm myotonia. Genetic testing for DM1 would show a characteristic trinucleotide repeat on chromosome 19. Genetic anticipation occurs with an increasing number of repeats and worsening clinical disease over successive generations. Myotonic dystrophy type 2 (DM2) causes proximal muscle weakness primarily and is also known by the name proximal myotonic myopathy. Other features of the disease overlap with DM1. Acid maltase deficiency (glucosidase deficiency, or Pompe disease) has three recognized forms, only one of which has onset in adulthood. In the adult-onset form, respiratory muscle weakness is prominent and often is the presenting symptom. As stated previously, Becker and Duchenne muscular dystrophies present with primarily proximal muscle weakness and are X-linked recessive disorders. Becker muscular dystrophy presents at a later age than Duchenne muscular dystrophy and has a more prolonged course. Otherwise, features are similar. Nemaline myopathy is a heterogeneous disorder marked by the

www.ketabpezeshki.com (021) 66485457 - 66485438

threadlike appearance of muscle fibers on biopsy. Nemaline myopathy usually presents in childhood and has a striking facial appearance similar to myotonic dystrophy with a long, narrow face. T is disease is inherited in an autosomal dominant fashion.

51. T e answer is E.
(Chap. 59) Chronic fatigue syndrome (CFS) is a disorder characterized by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Besides intense fatigue, most patients with CFS report concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and abdominal cramps. Criteria for the diagnosis of CFS have been developed by the U.S. Centers for Disease Control and Prevention **(Table 51)**. CFS is seen worldwide, with adult prevalence rates varying between 0.2% and 0.4%. In the United States, the prevalence is higher among women (~75% of cases), members of minority groups (African and Native Americans), and individuals with lower levels of education and occupational status. T e mean age of onset is between 29 and 35 years. Many patients probably go undiagnosed and/or do not seek help. T ere are numerous hypotheses about the etiology of CFS; there is no definitively identified cause. Physical inactivity and trauma in childhood tend to increase the risk of CFS in adults. Neuroendocrine dysfunction may be associated with childhood trauma, reflecting a biological correlate of vulnerability. Psychiatric illness and physical hyperactivity in adulthood raise the risk of CFS in later life. Twin studies suggest a familial predisposition to CFS, but no causative genes have been identified. Physical or psychological stress may elicit the onset of CFS. Most patients report an infection (usually a flulike illness or infectious mononucleosis) as the trigger of their fatigue. Relatively high percentages of CFS cases occur after Q fever and Lyme disease.

TABLE 5 1

DIAGNOSTIC CRITERIA FOR CHRONIC FATIGUE SYNDROME
Characteristic Persistent or Relapsing Unexplained Chronic Fatigue
Fatigue lasts for at least 6 months
Fatigue is of new or def nite onset
Fatigue is not the result of an organic disease or of continuing exertion
Fatigue is not alleviated by rest
Fatigue results in a substantial reduction in previous occupational, educational, social, and personal activities
Four or more of the following symptoms are concurrently present for 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep, or malaise after exertion
Exclusion Criteria
Medical condition explaining fatigue
Major depressive disorder (psychotic features) or bipolar disorder
Schizophrenia, dementia, or delusional disorder
Anorexia nervosa, bulimia nervosa
Alcohol or substance abuse
Severe obesity (body mass index >40)

52. T e answer is B.
(Chap. 59) Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have been found to be the only beneficial interventions in CFS. Some patient groups argue against these approaches because of the implication that CFS is a purely mental disorder. CBT is a psychotherapeutic approach directed at changing unhealthy disease-perpetuating patterns of thoughts and behaviors. It includes educating the patient about the etiologic model, setting goals, restoring fixed bedtimes and wake-up times, challenging and changing fatigue and activity-related concerns, reducing a focus on symptoms, spreading activities evenly throughout the day, gradually increasing physical activity, planning a return to work, and resuming other activities. T e intervention, which typically consists of 12–14 sessions spread over 6 months, helps CFS patients gain control over their symptoms. GET targets deconditioning and exercise intolerance and usually involves a home exercise program that continues for 3–5 months. Walking or cycling is systematically increased, with set goals for maximal heart rates. CBT and GET appear to improve fatigue primarily by changing the patient's perception of the fatigue and also by reducing the focus on symptoms. In general, CBT studies tend to yield better improvement rates than GET trials. Not all patients benefit from CBT or GET. Predictors of poor outcome are medical (including psychiatric) comorbidities, current disability claims, and severe pain. CBT offered in an early stage of the illness reduces the burden of CFS for the patient as well as for society in terms of decreased medical and disability-related costs. Full recovery from untreated CFS is rare: the median

www.ketabpezeshki.com (021) 66485457 - 66485438

annual recovery rate is 5% (range, 0%–31%), and the median improvement rate is 39% (range, 8%–63%). Patients with an underlying psychiatric disorder and those who continue to attribute their symptoms to an undiagnosed medical condition have poorer outcomes. T e other listed therapies have been tried in patients with CFS with no proven lasting benefit.

53. T e answer is A.
(Chap. 61) Generalized anxiety disorder (GAD) has a lifetime prevalence of about 5%–6% and presents with persistent, excessive, and/or unrealistic worry occurring on most days that persists for at least 6 months. T e worry typically pervades most aspects of life and is to a degree that it is uncontrollable and causes impairment in social, work, or interpersonal functioning. Associated physical symptoms include tension, restlessness, impaired concentration, insomnia, autonomic arousal, and feeling of being "on edge." Typical onset of symptoms is before the age of 20, although patients may not seek treatment for many years. A history of childhood fears may be present. More than 80% of patients with GAD have a concomitant mood disorder such as major depression or dysthymia or social phobia, but panic attacks (e.g., 10–30 minute episodes including palpitations, shortness of breath, and feelings of impending doom) generally do not occur. Comorbid substance abuse, most often with alcohol or sedative/hypnotics, is also common, perhaps as an attempt to self-treat anxiety. Treatment of GAD is most effective when psychotherapy is combined with medications, although complete relief of symptoms is rare. Initial intervention with benzodiazepines is often required for a period of 4–6 weeks. Other medications that are FDA-approved for the treatment of GAD are escitalopram, paroxetine, and venlafaxine, although other SSRIs have been demonstrated in clinical trials to be effective as well, typically at doses comparable to the effective dose for major depression. Buspirone is another anxiolytic agent that is nonsedating, does not produce tolerance or dependence, and has no abuse potential. However, it generally has mild effects and takes several weeks to produce results. It has demonstrated best results in individuals with dementia or head injury who develop agitation and/or anxiety. Anticonvulsants with GABAergic properties such as gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex also may have efficacy against anxiety.

54. T e answer is C.
(Chap. 61) T ere are an estimated 300,000 episodes of acute schizophrenia in the United States annually. T is disorder has a high degree of morbidity, with many individuals failing to achieve their premorbid level of functioning after an episode of acute schizophrenia. Symptoms of schizophrenia are heterogeneous with perturbations in language, thinking, perception, social activity, affect, and volition. T e most typical age of onset is late adolescence and young adulthood. Onset is insidious as individuals progressively experience social withdrawal and perceptual distortion and often progress to experience frank delusions and hallucinations. As individuals age, the positive symptoms of delusions and hallucinations tend to recede, and the negative symptoms of anhedonia, decreased emotional expression, and loss of function become more predominant. In a first episode, antipsychotic agents are effective about 70% of the time. Symptoms may improve within hours or days of dosing, but full remission often takes 6–8 weeks. If medications are discontinued, relapse will occur in 60% of patients within 6 months. T e long-term prognosis of most individuals with schizophrenia is somewhat grim. Prognosis of schizophrenia depends not on symptom severity at initial diagnosis but on the response to antipsychotic medication. A permanent remission rarely occurs. About 10% of schizophrenic patients commit suicide.

55. T e answer is D.
(Chap. 61) T is patient is experiencing her first episode of a panic attack and does not meet criteria for panic disorder. In this situation, no specific treatment is required. T e patient should be reassured that she does not have any evidence of a serious medical disorder in a manner that is empathetic and supportive. Panic disorder is a frequently occurring mental disorder with a lifetime prevalence of about 2%–3%. Panic attacks begin abruptly, most commonly without an immediate precipitating cause, and peak in severity over 10 minutes. T e first episode of panic attack is most often outside the home. T e symptoms usually subside spontaneously over the course of an hour. Panic attacks are often accompanied by intense fear and a variety of physical symptoms, including palpitations, dizziness, sweating, shortness of breath, chest pain, and a feeling of impending doom or death. Gastrointestinal distress, paresthesias, and syncope may occur. Panic disorder could be diagnosed if the patient developed recurrent attacks lasting at least 1 month or exhibited excessive worry or change in behavior related to these attacks. If the patient subsequently develops panic disorder, a variety of treatment options can be pursued. T e goals of therapy for panic attacks are to decrease the frequency of attacks and severity of

www.ketabpezeshki.com (021) 66485457 - 66485438

symptoms during the attack. Antidepressant medications are the cornerstone of therapy, with SSRIs being the most frequently used class of medication. T e dose of medication for panic disorder is typically lower than the antidepressant dose. For fluoxetine, this would be 5–10 mg daily. Because these medications take 2–6 weeks to become effective, they are often combined with benzodiazepines early in the course of treatment to alleviate anticipatory anxiety and provide immediate relief of panic symptoms. Alprazolam and clonazepam are common agents used for panic disorder, although alprazolam may have more associated dependence with need for escalating doses of medications. In combination with pharmacologic therapy, psychotherapy and education are also useful for the treatment of panic disorder. T e therapy often includes breathing techniques, cognitive behavioral therapy, and even homework assignments.

56. T e answer is A.
(Chap. 61) T ere are an increasing number of antidepressant medications available in a variety of classes. SSRIs are the most commonly used antidepressant drugs. T is class of medications includes fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. T ese medications are taken once daily and have side effects including sexual dysfunction, headache, and insomnia. Tricyclic antidepressants were commonly used in past decades for treatment of depression. However, overdoses can be lethal, and anticholinergic side effects including dry mouth, constipation, and urinary retention can limit the dose. Medications in the tricyclic class of antidepressants include amitriptyline, nortriptyline, imipramine, desipramine, doxepin, and clomipramine. Mixed norepinephrine/serotonin reuptake inhibitors and receptor blockers are a newer class of medications. T ese medications are increasing in use because they are quite effective and do not have the same frequency of sexual dysfunction. Medications in this class includes venlafaxine, desvenlafaxine, duloxetine, and mirtazapine. Monoamine oxidase inhibitors were once a common antidepressant class of medication, but these medications are now only rarely used because of a wide range of drug and food interactions that can lead to hypertensive crises. Examples of medication in this class include phenelzine, tranylcypromine, and isocarboxazid. A final class of antidepressants, called simply mixed-action, includes trazodone, bupropion, and nefazodone.

57. T e answer is E.
(Chap. 61) Posttraumatic stress disorder (PTSD) was only added as a discrete disorder in 1980. T e diagnostic criteria for PTSD are long and require that an individual experiences an event where there was an actual or perceived threat of death or serious injury and that the individual's reaction included intense fear or helplessness. Following the event, the individual continues to reexperience the event and avoids stimuli associated with the trauma. In association with this, there is also often a generalized withdrawal and decrease in responsiveness. At the same time, the patient exhibits an increase in arousal that is often exhibited by insomnia, irritability, hypervigilance, and difficulty concentrating. Treatment of PTSD is almost always multifactorial, including both pharmacotherapy and psychotherapy. It is not uncommon for an individual with PTSD to develop dependence on drugs or alcohol as an attempt to control the symptoms, and any substance abuse issues need to be treated simultaneously as well. T is patient's treatment would include avoidance of alcohol, and intensive substance abuse treatment as needed. Treatment with antidepressant medications can decrease anxiety and avoidance behaviors. Trazodone is often given at night for its sedating properties. Psychotherapeutic strategies include cognitive behavioral therapy to overcome avoidance behaviors.

58. T e answer is B.
(Chap. 61) Fifteen percent of the population will experience at least one episode of major depression over the course of a lifetime, and most episodes of major depression are treated by primary care practitioners. Treatment can be with any of a number of medications across a variety of classes. Despite the popularity of newer antidepressants, there is no evidence that these medications are more efficacious than older drugs like tricyclic antidepressants. Indeed, 60%–70% of patients will respond to any drug chosen if given in a sufficient dose for 6–8 weeks. However, up to 40% of patients treated at primary care offices discontinue treatment if there has not been a response within 1 month. Once a patient has been on treatment for ~2 months, the response should be evaluated and if there has been an insufficient response, a dose increase should be considered. In this patient, a dose increase yielded control of depressive symptoms at 4 months. Once control of symptoms has been achieved, the drug should be continued for an additional 6–9 months

www.ketabpezeshki.com (021) 66485457 - 66485438

to prevent relapse. If a patient experiences any additional episodes of major depression, he will likely require indefinite maintenance treatment because it is recommended that anyone with more than two episodes of major depression continue treatment indefinitely.

59. T e answer is F.
(Chap. 63) About 20% of all patients have an alcohol use disorder, even in af uent locales. Patients should be screened for an alcohol use disorder by asking specific questions regarding alcohol consumption, although many patients may minimize their alcohol use. T e patient in the scenario presented reports daily alcohol consumption and some symptoms of an alcohol use disorder, including blackouts from drinking and frequent hangovers while working. Laboratory tests may be helpful in this situation as they can be elevated in individuals who regularly consume six or more drinks daily. T e two tests with the greatest sensitivity and specificity (≥60%) are γ-glutamyl transferase (GGT) >35 U/L and carbohydrate-deficient transferrin (CDT). Using both of these tests combined is more likely to be accurate than using either test alone. Other blood tests that may be useful include high-normal MCV >91 μm^3 and serum uric acid >7 mg/dL. Elevations in AST or ALT are neither sensitive nor specific.

60. T e answer is A.
(Chap. 63) Alcohol is primarily absorbed through the proximal small intestine, but small amounts can also be absorbed in the mouth, esophagus, stomach, and large intestines. Several factors can increase the rate of absorption. One factor that increases absorption is rapid gastric emptying, which can be induced by concurrent consumption of carbonated beverages. Another factor that increases absorption from the gut to the blood is the ingestion of alcohol in the absence of other calorie sources such as proteins, fat, or carbohydrates. A final factor that can increase absorption is drinking of alcohol that is diluted to a modest concentration (~20% or less). At high alcohol concentrations, absorption is decreased, although high blood levels may be achieved because the amount of alcohol ingested is high.

61. T e answer is C.
(Chap. 63) Alcohol has effects on many neurotransmitters in the brain. T e predominant effect of alcohol lies in its ability to cause release of γ-aminobutyric acid (GABA), and it acts primarily at the $GABA_A$ receptors. GABA is the primary inhibitory neurotransmitter in the brain and is associated with the sedative effects of alcohol. Many other drugs affect the GABA system including benzodiazepines, nonbenzodiazepine sleep aids such as zolpidem, anticonvulsants, and muscle relaxants. T e euphoric effects of alcohol consumption are related to increases in dopamine, which is common to all pleasurable activities. T e effects on dopamine are thought to be important in alcohol craving and relapse. In addition, alcohol alters opioid receptors and can lead to a release of β-endorphins during acute ingestion. In addition to these effects, alcohol also inhibits postsynaptic NMDA excitatory glutamate receptors. Glutamate is the primary excitatory neurotransmitter of the brain, and its inhibition further contributes to the sedative effects of alcohol. Additional important effects on neurotransmitters include increased serotonin activity and decreased nicotinic acetylcholine receptors.

62. T e answer is D.
(Chap. 63) T e acute effects of any drug depend on many factors including amount consumed and absorbed, presence of other drugs, and past experience with the drug. In an individual who is naïve to alcohol, levels as low as 0.02 g/dL can lead to a decrease in inhibitions and a slight feeling of intoxication. In the United States, "legal" intoxication occurs at a blood alcohol level of 0.08 g/dL in most states. At this level, decreases in cognitive and motor abilities are seen. Once an alcohol level of 0.20 g/dL is achieved, an individual is obviously impaired with slurred speech, poor judgment, and impaired coordination. Light coma and depression of respiratory rate, blood pressure, and pulse occur at levels around 0.30 g/dL, and death is likely to occur at levels of 0.40 g/dL. However, in individuals who drink heavily, tolerance begins to develop to alcohol. After a period of 1–2 weeks of daily alcohol consumption, liver metabolism of alcohol increases by as much as 30%, but disappears quite quickly with abstinence. Cellular or pharmacodynamic tolerance also occurs and refers to the neurochemical changes that allow an individual to maintain more normal physiologic function despite the presence of alcohol.

63. T e answer is C.
(Chap. 63) In the most recent fifth edition of Diagnostic and Statistical Manual of Mental Disorders, the term alcohol use disorder replaced the two terms used

www.ketabpezeshki.com (021) 66485457 - 66485438

to describe problem areas with alcohol use: alcohol abuse and alcohol dependence. Under the new terminology, alcohol use disorder is defined as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period, and this disorder combines many of the criteria of dependence and abuse into a single diagnosis. T e diagnosis of alcohol use disorder is further characterized as mild, moderate, or severe based on how many criteria a person fulfills. Examples of these criteria include failure to fulfill obligations, drinking in hazardous situations, tolerance, withdrawal, craving, and inability to control drinking behaviors. T e lifetime risk of an alcohol use disorder in most Western countries is about 10%–15% in men and 5%–8% in women. T ere may be higher rates in Ireland, France, and Scandinavian countries. Native cultures appear to be especially susceptible to problems with alcohol use. T is has been seen in Native Americans, Maoris, and the aboriginal tribes of Australia. About 60% of the risk for alcohol use disorders is attributed to genetic influences. Children of alcoholics do have a higher risk of an alcohol use disorder; however, this risk is about 4 times higher, not 10 times higher. T is risk is conferred even when the children are adopted early and raised by nonalcoholics. Identical twins also exhibit a higher risk of concurrent alcoholism when compared to fraternal twins. T e genetic factors that appear to be most strongly linked to alcohol use disorders include genes that are linked to impulsivity, schizophrenia, and bipolar disorder. In addition, genes that affect alcohol metabolism or sensitivity to alcohol also contribute to the genetics of alcoholism. A mutation in aldehyde dehydrogenase that is more common in individuals of Asian descent results in intense flushing when alcohol is consumed and confers a decreased risk of alcohol dependence. Conversely, genetic variants that lead to a low sensitivity to alcohol increase the risk of a subsequent alcohol use disorder, as higher doses of alcohol are required to achieve the same effects. It is estimated that 20% of all patients have at least mild alcohol use disorder. T e age at first drink is similar between alcoholics and nonalcoholics. However, alcoholics report a slightly earlier onset of regular drinking and drunkenness. In most individuals with alcoholism, the course of the disease is one of remissions and relapse, but most individuals do require treatment to be able to sustain abstinence. T e chance of spontaneous remission is about 20%. If drinking continues without remission, the lifespan will decrease by about 10 years, with leading causes of death including heart disease, cancer, suicide, and accidents.

64. T e answer is B.

(Chap. 63) Individuals with alcohol dependence are susceptible to alcohol withdrawal when alcohol intake is stopped abruptly. T e individual in this case scenario is likely alcohol dependent given his large amount of alcohol intake on a daily basis. Symptoms of alcohol withdrawal can range from mild tremulousness to hallucinations, seizures, or development of delirium tremens. Other clinical features of alcohol withdrawal include anxiety, insomnia, and autonomic nervous system overactivity manifested as tachycardia, tachypnea, elevated blood pressure, and fever. T is patient exhibits symptoms of the more severe delirium tremens, with mental confusion, agitation, and fluctuating levels of consciousness. Although minor symptoms of alcohol withdrawal may begin as soon as 5–10 hours after cessation of alcohol intake, the symptoms do not peak for 48–72 hours, putting this patient in the appropriate time frame for alcohol withdrawal. T e best approach to the alcohol-dependent patient who abruptly stops all alcohol intake is a prophylactic approach, and the patient should be screened early for symptoms of alcohol withdrawal. Tools such as the Revised Clinical Institute for Withdrawal Assessment for Alcohol (CIWA-Ar) may help clinicians and nurses screen for early development of symptoms and allow intervention before symptoms escalate. In this setting, most experts recommend use of oral long-acting benzodiazepines such as chlordiazepoxide or diazepam beginning on the first day. However, in this case, the patient received no such treatment and is now experiencing severe alcohol withdrawal and delirium tremens. IV medications that have a rapid onset of action and can be titrated for more aggressive symptom management are often employed in this setting. T us, use of IV lorazepam or diazepam is preferred in this patient. Following an initial bolus, repeated doses can be used in short intervals until the patient is calm but arousable. In some instances, a continuous infusion may be required, although bolus dosing is preferred. In the most severe cases, propofol or barbiturates may be required, although the patient would most likely need to be intubated for airway protection with use of these medications. T e other options listed are not appropriate for initial management of this patient. IV fluids and thiamine had been administered since hospital admission. Administration of glucose-containing fluids without thiamine in the alcohol-dependent patient can precipitate Wernicke encephalopathy, which would present with ophthalmoparesis, ataxia, and encephalopathy. Given the patient's fever, an infectious etiology can be considered, and it would be appropriate to

www.ketabpezeshki.com (021) 66485457 - 66485438

perform blood cultures in this patient. However, given the clear symptoms of alcohol withdrawal and lack of necrotizing pancreatitis on abdominal CT, empiric treatment with antibiotics is not required. Likewise, without focal neurologic findings, a head CT would be a low-yield diagnostic procedure that would be difficult to perform in the patient's current agitated condition and would only delay appropriate therapy. Finally, restraints are best avoided if the patient's safety can be ensured through appropriate use of benzodiazepines because restraints are only likely to make the patient's agitation worse and may lead to iatrogenic harm. Haloperidol may have some sedative effect on the patient but could lead to torsades de pointes arrhythmia because this patient is at risk for electrolyte deficiencies from his alcoholism and pancreatitis.

65. T e answer is D.
(Chap. 63) In individuals recovering from alcoholism, several medications may have a modest benefit in increasing abstinence rates. T e two medications with the best risk-benefit ratio are acamprosate and naltrexone. Acamprosate inhibits NMDA receptors, decreasing symptoms of prolonged alcohol withdrawal. Naltrexone is an opioid antagonist that can be administered orally or as a monthly injection. It is thought to act by decreasing activity in the dopamine-rich ventral tegmental area of the brainstem and subsequently decreasing the pleasurable feelings associated with alcohol consumption. T ere is some research to suggest that the use of these medications in combination may be more effective than either one alone. Disulfiram is an aldehyde dehydrogenase inhibitor that has been used for many years in the treatment of alcoholism. However, it is no longer a commonly used drug due to its many side effects and risks associated with treatment. T e primary mechanism by which it acts is to create negative effects of vomiting and autonomic nervous system hyperactivity when alcohol is consumed concurrently with use of the medication. Because it inhibits an enzyme that is part of the normal metabolism of alcohol, it allows the buildup of acetaldehyde, which creates these unpleasant symptoms. As a result of the autonomic side effects, it is contraindicated in individuals with hypertension, a history of stroke, heart disease, or diabetes mellitus.

66. T e answer is B.
(Chap. 66) Although declining in prevalence, cigarette smoking and use of other nicotine-containing products remain a significant contributor to premature death in the United States and account for about one out of every five deaths in the United States, for a total of 400,000 deaths annually. Approximately 40% of cigarette smokers will die prematurely due to the habit unless they are able to quit. T e primary causes of premature death related to cigarette smoking are cardiovascular diseases, including both myocardial infarction and stroke; chronic obstructive pulmonary disease (COPD); and myriad cancers including lung, oral, esophageal, urogenital, and pancreatic. Cigarette smoking promotes both large- and small-vessel vascular disease. Approximately 90% of peripheral vascular disease in the nondiabetic population can be attributed to cigarette smoking. In addition, 50% of aortic aneurysms, 20%–30% of coronary artery diseases, and 10% of ischemic and hemorrhagic strokes are caused by cigarette smoking. Moreover, if additional cardiac risk factors are present, the incremental risk added by cigarette smoking is multiplicative. As noted, cigarette smoking increases the risk of many different cancers, not just those of the respiratory tract. T e digestive tract appears to be particularly susceptible to the effects of cigarette smoking because cigarette smoking has been linked to esophageal, stomach, pancreatic, liver, and colorectal cancer. Urogenital cancers are also increased in cigarette smokers, with increases in both kidney and bladder cancer. In women, cervical cancer is also increased among smokers. Interestingly, however, uterine cancer may be decreased among postmenopausal woman who smoke. Cigarette smoking is responsible for 90% of COPD. Cigarette smoking induces chronic inflammation in the small airways, although most smokers do not develop symptomatic respiratory disease. Chronic inflammation, narrowing of the small airways, and destruction of the alveoli lead to symptoms of COPD and emphysema in 15%–25% of smokers. In any given year, more than half of smokers would like to quit smoking. However, only 6% quit for 6 months, and less than 3% remain abstinent at 3 years. Most individuals have to make multiple attempts to quit before being successful, and they are more likely to be successful if advised to quit by a physician. Other triggers for smoking cessation include an acute illness, the cost of cigarettes, media campaigns, and workplace smoking restrictions.

67. T e answer is E.
(Chap. 66) Smoking cessation is more likely to be successful when an individual is advised to quit by a physician and has a supervised smoking cessation plan. At every medical visit, all patients should be asked whether they smoke, how much they smoke, and whether they are interested in quitting. Even patients who state that they are not interested in

www.ketabpezeshki.com (021) 66485457 - 66485438

quitting should receive a clear message from their provider that smoking is an important health hazard and be offered assistance with quitting in the future. For those interested in quitting, negotiating a quit date is an important step in the process, and close follow-up with office contact near the quit date is an important part of the process. In addition, sometimes a more intensive counseling approach may be necessary. Current recommendations are to offer pharmacologic therapy with either nicotine replacement therapy (NRT) or varenicline. A variety of NRTs are available, including transdermal patches, nasal inhalers, oral inhalers, gum, or lozenges, with success rates of 1.5–2.7 times greater than no intervention. Varenicline is an oral partial agonist of the nicotinic acetylcholine receptor that has a published success rate of 2.7 times greater than no intervention. T ere has been some concern regarding use of varenicline in individuals with severe psychiatric illness, including suicidal ideation, but this individual does not meet this level of concern. With planned close follow-up, varenicline should be considered an available option for this patient.

68. T e answer is D.
(Chap. 66) Varenicline is a partial agonist of the nicotinic acetylcholine receptor and has been demonstrated to be more effective than placebo in promoting smoking cessation. Severe psychiatric symptoms including suicidal ideation have been reported, prompting a warning by the FDA. In addition, closer therapeutic supervision has been recommended, but at this time, the true frequency of these responses remains unclear. A recent publication retrospectively reviewed the use of varenicline in over 69,000 individuals in Sweden. When compared to the general population, there was no increased risk of suicide or psychosis in individuals prescribed varenicline even though these individuals were twice as likely to have had a prior psychiatric diagnosis (T omas KH et al. BMJ 347:f5704, 2013). However, the FDA is currently continuing its surveillance of the drug until more data are available. Alternative agents such as bupropion in combination with nicotine replacement therapy should be considered.

69. T e answer is B.
(Chap. 66) Smokers regulate their blood levels of nicotine by adjusting the frequency and intensity of their tobacco use. Smokers can compensate for the lower levels of nicotine in low-yield cigarettes by smoking more cigarettes or by adjusting their smoking technique with a deeper inhalation and breathhold. T erefore, smoking low-yield cigarettes is not a reasonable alternative to smoking cessation. Moreover, there is no difference in the harmful physical effects of smoking or in the potential for drug interactions. Finally, although not definitively proven, there is some thought that the rise in adenocarcinoma of the lung over the past 50 years is associated with introduction of the low-tar cigarette and the resultant change in smoking behavior associated with this introduction.

www.ketabpezeshki.com (021) 66485457 - 66485438

INDEX

Bold page number indicates the start of the main discussion of the topic; page numbers with "f" and "t" refer to figures and tables, respectively.

AAG. See Autoimmune autonomic ganglionopathy
Abciximab, 81
Abdominal aortic aneurysm, 117
Abducens nerve
  examination of, 6
  palsy of, 242
  paresis of, 240
A-beta (Aß) fibers, 88
Abetalipoproteinemia, 440
Abscess, 533
  brain. See Brain abscess
  epidural. See Epidural abscess
  hematogenous, 559
Absence seizures, 299
Abstract thought, assessment of, 6
Abulia, 171, 343f
Acalculia, 196
Acamprosate, in alcoholism management, 806, 861, 885
Acanthamoeba infections, chronic meningitis in, 571t
Acephalgic migraine, 380
Acephalic migraine, 324
Acetaminophen
  adverse effects of, 93
  for back pain, 119
  for migraine, 382t, 384
  for pain, 93, 94t
  for spinal stenosis, 113
Acetaminophen-aspirin-caffeine, for migraine, 382t
Acetazolamide
  for acute angle-closure glaucoma, 229
  for episodic ataxia, 441
  for hypokalemic periodic paralysis, 724
  for pseudotumor cerebri, 233
  for raised cerebrospinal fluid pressure headache, 105
Acetylcholine
  anatomic and clinical aspects of, 282t, 469
  deficiency of, in delirium, 165–166
  structure of, 282t
Acetylcholine receptor, in myasthenia gravis, 691–692, 857, 878
Acetylcholinesterase test, in myasthenia gravis, 693–694
Achromatopsia, 200, 224
Acid maltase deficiency, 858, 879
Acidophil stem cell, 620t
Acoustic neuroma. See Vestibular schwannoma
Acoustic reflex, 272
Acoustic reflex decay, 272
Acromegaly, **626**
  cardiovascular system affected by, 626
  clinical presentation of, 626–627, 627f
  colonic polyp risks, 627
  dopamine agonists for, 629
  etiology of, 626, 626t
  familial, 622
  growth hormone receptor antagonists for, 629
  laboratory investigations of, 627
  medical treatment of, 618
  radiation therapy for, 629
  respiratory system affected by, 627–628
  screening tests for, 617t
  somatostatin analogues for, 627–628
  transsphenoidal surgery for, 628
  treatment of, 627–629, 628f
Acrylamide, 670t
ACTH. See Adrenocorticotropic hormone
Actinomycosis, chronic meningitis in, 570t
Acupuncture, for back pain, 119–120
Acute angle-closure glaucoma, 229, 236
Acute disseminated encephalomyelitis (ADEM), **531**–532
  clinical features of, 532
  diagnosis of, 532
  etiology of, 531
  neuroimaging of, 53f
  pathophysiology of, 531
  treatment of, 532
Acute inflammatory demyelinating polyneuropathy (AIDP), 682, 682t, 684t
Acute motor axonal neuropathy (AMAN), 682t, 684t
Acute motor sensory axonal neuropathy (AMSAN), 682t
Acute necrotizing intensive care myopathy, 371
Acute necrotizing myopathy, paraneoplastic, 614
Acute pharyngeal cervicobrachial neuropathy (APCBN), 684t
Acute quadriparesis, 148
Acute transverse myelitis
  neuroimaging of, 52f
  weakness in, 147
Acyclovir
  for Bell's palsy, 486
  for ocular herpes simplex virus infections, 228
  for viral encephalitis, 553–554
  for viral meningitis, 547
A-delta (Aδ) fibers, 88–89
ADEM. See Acute disseminated encephalomyelitis
Adenomas
  macroadenomas, 616, 624–625, 627
  microadenomas, 624–625, 629, 631
  pituitary. See Pituitary adenomas
  thyroid-stimulating hormone-secreting, 618, 633–634
Adenovirus infections, 227
Adhesive arachnoiditis, lumbar, 115
Adie's syndrome, 223
Adipsic hypernatremia, 642f
Adolescents, seizures in, 304t
Adrenal insufficiency
  delirium in, 168
  fatigue in, 141
  muscle weakness in, 726
Adrenocorticotropic hormone (ACTH), **637**
Adrenocorticotropin hormone-secreting adenomas, 618, 629–632. See also Cushing's syndrome
Adrenoleukodystrophy, 68f, 657–658, 658t
Adrenomyeloneuropathy, 503, 657–658
Adult Tay-Sachs disease, 454t, 457
Advanced sleep-wake phase disorder (ASWPD), 218

www.ketabpezeshki.com (021) 66485457 - 66485438

AEDs. See Antiepileptic drugs (AEDs)
Aerophobia, 552
Aflibercept, for macular degeneration, 237
Aging
  olfactory function and, 258, 258f, 263
  sleep patterns and, 205–206, 206f
Agnosia
  apperceptive, 200
  associative, 200
  object, 200, 345
Agoraphobia, 139, 766
Agrammatic-variant primary progressive aphasia, 196
Agrammatism, 194, 196
Agraphesthesia, 154
Agraphia, 192
AIDP. See Acute inflammatory demyelinating polyneuropathy (AIDP)
AIDS, 577, 578t, 589. See also HIV infection
AIDS dementia complex (HIV-associated dementia), 585–587, 587f
AIP gene, 622
Air-conduction threshold, 271
Akathisia, 431, 777, 786
Akinetic mutism, 171
AL amyloidosis, 659–660
Albendazole, for cysticercosis, 562
Alcohol, **798**. See also Alcohol use
  absorption of, 798, 860, 883
  abuse of. See Alcohol abuse or dependence (alcoholism)
  blood levels of, in absence of tolerance, 799, 799t
  death caused by, 861, 883
  inhibitory neurons affected by, 283
  metabolism of, 798, 799f
  myopathy caused by, 728t
  neurotransmitters affected by, 860, 882
  pharmacology of, 798–799, 799f
  tolerance of, 799–800
  withdrawal from, 850, 865, 884
Alcohol abuse or dependence (alcoholism), **802**
  acute intoxication, 160, 861, 883
  chronic, dementia caused by, 404
  definition of, 802
  genetic factors in, 803, 861, 884
  lifetime risk for, 802
  myopathy in, 729, 802
  natural history of, 803
  neural circuitry of, 763
  neuropathy in, 476
  ocular involvement in, 244
  olfactory/taste dysfunction in, 261
  psychiatric comorbidity with, 800–801
  questions regarding, 860, 883
  treatment of, 804–806
    acute intoxication, 804
    alcohol withdrawal in. See Alcohol withdrawal syndrome
    AUDIT in, 804, 804t
    identification of alcoholic in, 803–804, 804t
    interventions, 804–805
    rehabilitation, 805–806
    relapse prevention, 805, 861, 885
Alcohol dehydrogenase (ADH), 798
Alcoholic myopathy, 802
Alcoholic neuropathy, 476
Alcohol-induced psychotic disorders, 801
Alcohol ketoacidosis, 798
Alcohol use
  behavioral effects of, 799t, 799–800
  nutritional impact of, 798–799
  in pregnancy, 802
  questions regarding, 860–861, 883–884
  systemic effects of, 798–799
Alcohol use disorder, 860–861, 883–884
Alcohol Use Disorder Screening Test (AUDIT), 804, 804t
Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) module, 793, 794t
Alcohol withdrawal syndrome, 164, 168, 805, 850, 865, 884
Aldehyde dehydrogenase (ALDH), 798
Alemtuzumab, 527
Alexia, 192, 193t, 195
Alien hand (limb) syndrome, 195, 402
Allergic hypersensitivity, 21
Allergies, to intravenous iodinated contrast, 17, 17t
Allodynia, 89, 92, 150, 478
Allostasis, 208
Almotriptan, for migraine, 382t–383t
α_2-adrenergic agonists
  for acute angle-closure glaucoma, 229
  for opiate detoxification, 811
α-adrenergic antagonists, adverse effects of, 131
α-lipoic acid, for olfactory dysfunction, 262
α motor neurons, 147f
Alport's syndrome, hearing loss in, 268, 270t
Alprazolam
  for generalized anxiety disorder, 770t
  for panic disorder, 767
  pharmacology of, 770t
ALS. See Amyotrophic lateral sclerosis (ALS)
ALS/parkinsonian/dementia complex of Guam, 407
Alternative splicing, 279
Aluminum toxicity, 406
Alvimopan, 96
Alzheimer's disease (AD), **392**
  amyloid deposition in, 853, 869
  aphasia in, 194, 196
  Bálint's syndrome in, 199
  clinical features of, 186t, 392–393
  cost of care for, 392
  diagnosis of, 188f
  differential diagnosis of, 183t, 188f, 393–394
  early onset, 395–396
  epidemiology of, 394
  frontal lobe syndromes in, 202
  genetic factors in, 290–291, 395f, 395–396
  Lewy body variant of, 403
  memory loss in, 201, 853, 869
  mild cognitive impairment progression to, 869
  molecular basis of, 184t
  neurotransmitter systems in, 281
  olfactory dysfunction in, 255, 259, 263
  pathology of, 394, 395f
  presenilins in, 395–396
  prions in, 293
  risk factors for, 394
  treatment of, 396–398
  trisomy 21 and, 395
Amacrine cells, of retina, 221
Amantadine
  for fatigue in multiple sclerosis, 530
  for Parkinson's disease, 418, 421
  for selective serotonin reuptake inhibitors-related sexual dysfunction, 777
Amaurosis fugax, 230–231, 344
Amblyopia, 240
Amenorrhea, 623
American trypanosomiasis. See Chagas' disease
Aminoglutethimide, for Cushing's syndrome, 632
Aminoglycosides, 267
4-Amino pyridine, for weakness in multiple sclerosis, 529
Amiodarone, adverse effects of
  myopathy, 728t, 729
  neuropathy, 668t, 671
  optic neuropathy, 232
Amitriptyline
  adverse effects of, 263, 385t, 768t
  for chronic daily headache, 103
  for depression, 768t
  dosage of, 768t
  for migraine prevention, 385t, 868
  for olfactory dysfunction, 263
  for pain, 94t, 529
  for posttraumatic headache, 105
  for tension-type headache, 386
Ammonium chloride, 817
Amnesia, **200**
  anterograde, 200
  caring for patient with, 203
  clinical examination in, 200–201
  etiology of, 201
  af er head injury, 505
  psychogenic, dementia caused by, 407
  retrograde, 200
  transient global, 201, 406
  video library, 204
Amnestic state, 200
Amoxapine, for depression, 768t, 777
AMPA receptor antibodies, 611
Amphetamine(s)
  action of, 283
  myopathy caused by, 728t
Amphotericin B
  for Cryptococcus infections, 556
  for Histoplasma infections, 556
Ampicillin, for meningitis, 539t, 541
Amygdalohippocampectomy, for epilepsy, 318
Amyloid angiopathy, 187–188, 394
Amyloidosis
  AL, 659–660
  autonomic dysfunction in, 476
  neuropathy in, 476, 659

www.ketabpezeshki.com (021) 66485457 - 66485438

ocular involvement in, 223
pathophysiology of, 476
Amyloid polyneuropathy, familial, 658t, 659
Amyloid precursor protein (APP), 394, 395f
Amyotrophic lateral sclerosis (ALS), **449**
clinical features of, 450–451
"definite," criteria for, 451
diagnosis of, 123, 451, 451f
differential diagnosis of, 450t, 452, 455
epidemiology of, 452
familial, 291, 452, 453t
pathogenesis of, 456
pathology of, 449–450
questions regarding, 871–872
websites for, 458
Amyotrophic lateral sclerosis (ALS)/parkinsonian/dementia complex of Guam, 407
Amyotrophy, **449**
definition of, 449
diabetic, 660, 727
Analgesia (sensory abnormality), 150
Analgesics
for lumbar puncture, 81–82
medication-overuse headache and, 103
Anaplasma spp. infections, 540
Andersen-Tawil syndrome, 723t, 725
Anemia
delirium in, 169
fatigue caused by, 142
Anesthesia (sensory abnormality), 150
Aneurysm
abdominal aortic, 117
cerebral, 15f
mycotic, circle of Willis, 372
repair of, 374f
saccular, 371–372
Angelman's syndrome, imprinting in, 279
Angiitis, chronic meningitis in, 573t
Angina pectoris, in orthostatic hypotension, 131
Angiography
cerebral, in stroke, 352–353
complications, 26
computed tomography, 13–14, 15f
in neurologic disease, 26
spinal, 26
Angioma, cavernous, 360
Angiopathy
amyloid, 187–188
cerebral amyloid, 398
Angiostrongylus spp. infections, chronic meningitis in, 571t
Angle-closure glaucoma, 229, 236
Anisocoria, 223
Ankylosing spondylitis
back pain in, 114
diagnosis of, 114
neck pain in, 123
ocular involvement in, 229
pathogenesis of, 114
treatment of, 114
Anomia, 191, 200
color, 195, 224
finger, 196
Anorexia nervosa, 782
Anosognosia, 199, 323, 392
Anterior cerebral artery
lesion in territory of, 147, 194
occlusion of, 342–343, 343f
Anterior chamber, 245
Anterior choroidal artery occlusion, 343, 344f
Anterior dens dislocation, 58f
Anterior horn cell disorders, weakness in, 145, 147, 149
Anterior ischemic optic neuropathy, 231f, 231–232
Anterior pituitary tumor syndromes
acromegaly. See Acromegaly
Cushing's syndrome. See Cushing's syndrome
galactorrhea, 623
hyperprolactinemia, 622t, 622–623
pituitary adenomas. See Pituitary adenomas
pituitary tumors. See Pituitary tumors
prolactinoma. See Prolactinoma
sellar masses. See Sellar masses
Anterior spinal artery syndrome, 492
Anterocollis, 425
Anterolateral system, 151
Anti-AChR antibody, 607t
Anti-AMPA receptor antibodies, 607t
Anti-amphiphysin, 607t
Antiarrhythmics, for pain, 95t, 98
Antibacterial drugs, for bacterial meningitis, 539t, 541t, 541–542
Antibodies, in neurologic paraneoplastic syndromes, 607t
Anticardiolipin antibodies, 230, 230f
Anticholinergics, 139t, 165–166
Anticoagulant(s)
embolism risk reductions using, 339
guidelines for use, 80
heparin, 81
intracerebral hemorrhage caused by, 356
for ischemic stroke, 328
in stroke prevention, 338–339
for suppurative thrombophlebitis, 567
Anticonvulsants, for generalized anxiety disorder, 770
Anti-CV2/CRMP5 antibody, 607t, 609
Antidepressants. See also specific drugs
adverse effects of, 385t, 768t–769t
cataplexy treated with, 213
chronic fatigue treated with, 143, 860, 882
depression treated with, 768t, 776–778, 777f
dosage of, 768t
heterocyclic, for insomnia, 216
for insomnia, 216
for migraine prevention, 385t
pain treated with, 94t, 97–98, 98t, 529
questions regarding, 860, 882
for smoking cessation, 825
Antidiuresis, 637
Antiepileptic drugs (AEDs). See also specific drugs
adverse effects of, 313t–316t, 321–322
breast-feeding and, 322
discontinuation of, 318, 850, 866
drug interactions of, 313t–316t, 321–322
for focal seizures, 312, 317
initiation of, 312
mechanisms of action of, 307
monitoring of, 317–318
oral contraceptives and, 322
for pain, 95t, 98
pharmacology of, 313t–316t
questions regarding, 850, 866
for refractory epilepsy, 318
selection of, 312, 312t
Anti-GABA antibodies, 607t
Anti-GAD antibody, 607t
Antigliadin antibodies, 435, 441
Anti-glutamic acid decarboxylase, 435
Anti–glycolipid antibodies, in immune neuropathies, 683–684, 684f
Antihistamines
for insomnia, 216
for vertigo, 139
Anti-Hu antibody, 253, 607t, 609–610
Anti-Hu paraneoplastic neuropathy, 690
Anti-Jo-1, 733
Anti-Ma proteins, 607t, 610, 610f
Antineuronal antibodies, 607t
Anti-NMDA receptor antibodies, 607t, 608f
Antinuclear antibody (ANA) test, 143
Antinucleosides, 669t
Antiplatelet agents
guidelines for use, 80
for ischemic stroke, 327–328
in stroke/TIA prevention, 337–338
Antipsychotics
action of, 784–785
for acute alcohol intoxication, 804
adverse effects of, 431, 786
in Alzheimer's disease, 397
for schizophrenia, 784–786, 785t
side effects of, 785t
Anti-Ri antibody, 607t, 612
Antithrombin deficiency, 230
Antithrombotic drugs
chronic use in cardiac conditions, 331t
for ischemic stroke, 327–328
Anti-Tr antibody, 607t, 612
Anti-VGCC antibodies, 607t
Anti-Yo antibody, 607t, 612
Anton's syndrome, 345
Anxiety, syncope versus, 132
Anxiety disorders
generalized anxiety disorder, 767–770, 770t, 859, 881
insomnia caused by, 214
panic disorder, 766–768
phobic disorders, 770–771
stress disorders, 771–773, 772t
vertigo in, 139
Aortic aneurysm, abdominal, 117
APC gene, 593t
Aphasia, **191**
anomic, 193t, 194
Broca's, 193t, 193–194
caring for patient with, 203
conduction, 193t, 194
fluent transcortical, 193t, 194
global, 193t, 194
isolation, 193t, 194
jargon, 192

www.ketabpezeshki.com (021) 66485457 - 66485438

Aphasia, (Cont.):
nonfluent transcortical, 193t, 194
primary progressive, 196–197, 204, 399
subcortical, 196
video library, 204
Wernicke's, 192–193, 193t
Aphemia, 195
Apnea testing, 179
ApoE gene, 396
Apomorphine
adverse effects of, 417
for Parkinson's disease, 417, 419t
Aponeurotic ptosis, 240
Apoptosis
mitochondria in, 290
in neurologic disease, 289–290, 362
APP (amyloid precursor protein), 394, 395f
Apperceptive agnosias, 200
APP gene, 292
Apraxia, 144, **195**
buccofacial, 195
construction, 199
dressing, 199
gait, 159
ideational, 195
ideomotor, 195
limb, 195
limb-kinetic, 195
ocular, 243
oculomotor, 199
of speech, 195
sympathetic, 195
Aprepitant, 104
Aprosodia, 196
Aß protein, 184t, 188, 395f
Aquaporin 2, 637–638
Aquaporins, 531
Arachnoiditis, lumbar, 115
Argyll Robertson pupil, 223
Aripiprazole, for schizophrenia, 785t, 786
Armodafinil, for shif -work disorder, 220
Arousal level, in coma, 175
Arsenic exposure/poisoning
clinical features of, 406
neuropathies in, 671t, 673
optic neuropathy in, 232
Arterial spin labeling (ASL), 24
Arterial thoracic outlet syndrome, 123
Arteriovenous fistula
dural, 360
weakness in, 147
Arteriovenous malformation (AVM)
cerebral, 359
dural, 239
spinal cord, 500f
Arteritis, stroke caused by, 334
Artery of Percheron, occlusion of, 345
Artery-to-artery embolic stroke, 330–332
Arthritis
autoimmune inflammatory, 116
back pain in, 114
Arthrogryposis, 712
Artificial saliva, 262
Artificial tears, 227
Asenapine
for schizophrenia, 785t
side effects of, 785t
Aseptic meningitis, 585
Ashkenazi Jewish population
dystonia in, 424
hearing loss in, 268
Asimultanagnosia, 346
ASL. See Arterial spin labeling (ASL)
Asparaginase, 605t
Aspergillosis
central nervous system, 35f–36f
invasive sinonasal, 36f–37f
Aspergillus infections, 571t
Aspirin
adverse effects of, 93
as antithrombotic in cardiac conditions, 331t
for ischemic stroke, 327–328
in lumbar puncture patients, 81
for pain, 93, 94t
for stroke/TIA prevention, 336–338, 851, 867
Association cortex, 191, 192f
Associative agnosias, 200
Associative prosopagnosia, 200
Astasia-abasia, 160
Astereognosis, 154
Asterixis, 160, 175
Asthenia, 702
Astigmatism, 222
Astrocytoma
high-grade, 594–595, 595f
intramedullary, 495, 495f
low-grade, 594, 594f
pilocytic, 66f
ASWPD. See Advanced sleep-wake phase disorder (ASWPD)
Ataxia, 435
with antigliadin antibodies, 435, 441
approach to the patient, 435–436
autosomal dominant, 436–439, 443t–447t
autosomal recessive, 439–442, 446t–448t. See also Ataxia telangiectasia; Friedreich's ataxia
cerebellar, 159, 160t
clinical manifestations of, 161
differential diagnosis of, 435
early-onset, 447t
etiology of, 436t
with muscle coenzyme Q10 deficiency, 448t
types of, 445t, 447t–448t
chemotherapy-induced, 605t
chronic symmetric, 435–436
episodic, 280t, 436, 439, 446t–447t
focal, 436
Friedreich's, 291, 439–442, 440f, 446t
gait, 435–436
global features of, 442
ion channel defects causing, 280t
mitochondrial, 441
in multiple sclerosis, 517, 529
neoplastic, 609
ocular/optic, 199, 243
with oculomotor apraxia, 447t
paraneoplastic disorders in, 441
sensory, 151, 159–160, 160t
signs and symptoms of, 435
spinocerebellar. See Spinocerebellar ataxia (SCA)
subacute development of, 435
symmetric, 435–436
treatment of, 441
with vitamin E deficiency, 440–441, 446t
Ataxia telangiectasia, 441, 447t
Ataxic hemiparesis, 333
Atherosclerosis
carotid. See Carotid atherosclerosis
cigarette smoking and, 822
intracranial, 332, 340
risk factors for, 336–337, 851, 867
Athetosis, 423t
Athlete(s), concussion in, 510
Atlastin gene, 454t, 458
ATM gene, 441
Atomoxetine and yohimbine, 480
Atonic seizures, 300
Atopic conjunctivitis, 227
Atorvastatin, 851, 858
Atrial fibrillation
chronic use of antithrombotics in, 331t
stroke and, 329, 332t
Atrophy
dentatorubropallidoluysian, 436, 439, 445t
muscle, 704
spinal muscle, 449, 453t, 457
Atropine, 223
Attentional deficit, 202
Attention assessment, 166
Atypical parkinsonism, 410t, 411–412, 412t, 870t
Audiogram, 271
Audiometry, 271–272
AUDIT (Alcohol Use Disorder Screening Test), 804, 804t
AUDIT-C (Alcohol Use Disorders Identification Test-Consumption) module, 793, 794t
Auditory brainstem responses, 267, 272
Auditory cortex, 192f
Auditory nerve, 264
Aura, 298
Autism spectrum disorders, **758**
epidemiology of, 758
genetic factors in, 758–760, 759t
gut microbiome and, 287
neurogenetics of, 758–760
pathogenesis of, 760
Autoantibodies
in inflammatory myopathies, 733
questions regarding, 850, 865
Autoimmune autonomic ganglionopathy (AAG), 476–477
Autoimmune inflammatory arthritis, 116
Automatisms, 298
Autonomic dysfunction, **470**
acute syndromes of, 478
in alcoholic neuropathy, 476
in amyloidosis, 476
approach to the patient, 472–474, 474t
autonomic testing in, 473–474, 474t
in botulism, 477
classification of, 469, 471t

www.ketabpezeshki.com (021) 66485457 - 66485438

clinical evaluation of, 469–472, 471t
clinical features of, 469–472
in CRPS, 478–479
in diabetes mellitus, 476
drug-related, 472, 473t
in Guillain-Barré syndrome, 476
heart rate variation with deep breathing in, 473, 474t
in inherited disorders, 477
in multiple system atrophy, 474–475, 475f
in neuromuscular junction disorders, 476–477
orthostatic blood pressure recordings in, 474
orthostatic hypotension and, 472, 472t
in Parkinson's disease, 420
in porphyrias, 476
in postural orthostatic tachycardia syndrome, 477
in primary hyperhidrosis, 477–478
in pure autonomic failure, 477
in reflex sympathetic dystrophy, 478–479
spinal cord lesions and, 475
sudomotor function in, 473–474, 474t
syndromes of, **474**
tilt table testing for syncope in, 474, 474t
treatment of, 479t, 479–480
Valsalva response in, 473, 474t
Autonomic dysreflexia, 475
Autonomic failure, pure, 477
Autonomic nervous system, 469, 470f, 470t
disorders of. See Autonomic dysfunction
testing of, 133–134
Autonomic neuropathy
diabetic, 660, 857, 876
paraneoplastic, 614
Autonomic storm, 478
Autophagy, 291
Autoregulation, 362
Autosomal dominant ataxias, 436–439, 443t–447t
Autosomal dominant nocturnal frontal lobe, 301t, 446t–448t
Autosomal dominant partial epilepsy with auditory features, 301t
Autosomal recessive ataxias, 439–442
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), 446t
AVM. See Arteriovenous malformation (AVM)
Avoidant/restrictive food intake disorder, 782
AVP. See Vasopressin
AVP-neurophysin II, 637, 643
Azathioprine
for inflammatory myopathies, 740
for multiple sclerosis, 529
for myasthenia gravis, 697
for neuromyelitis optica, 531
Azithromycin, for blepharitis, 227
AZT (zidovudine), 728, 728t

Babinski sign, 8, 145, 145t, 172–173, 849, 863
Back pain, **107**
approach to the patient, 108–111
in arthritis, 114
breakaway weakness in, 110
in cancer patient, 114
in cauda equina syndrome, 112–113
causes of, 112t
chronic, 119–120
in congenital anomalies of lumbar spine, 112t, 116–117
costs of, 107
in degenerative conditions, 112t, 113–114, 114f–115f
diagnosis of, 111
electromyography in, 110
idiopathic, 118
imaging in, 111
in infections/inflammation, 112t, 115
local, 108
lumbar disk disease, 111–113
in lumbar disk disease. See Intervertebral disk, herniation of
metabolic causes of, 112t, 116
with muscle spasm, 109
nerve conduction studies in, 111
patient education in, 119
physical examination in, 109–110, 110t
postural, 117–118
in psychiatric disease, 118
radicular, 108
referred, 108, 117
risk factors for structural cause, 109t
of spine origin, 108
in spondylolisthesis, 114
in sprains and strains, 116
trauma-related, 112t, 116
treatment of, 118–121
acute pain without radiculopathy, 119
chronic pain without radiculopathy, 119–120
pain with radiculopathy, 120–121
types of, 108–109
in vertebral fracture, 116
Baclofen
for dystonia, 425–426
for spasticity in neurologic disease, 504, 529
for stiff-person syndrome, 613
for tardive dyskinesia, 431
for trigeminal neuralgia, 483
Bacterial endocarditis. See Infective endocarditis
Bacterial meningitis. See Meningitis, bacterial
BAEPs (brainstem auditory evoked potentials), 74–75, 272
BAERs (brainstem auditory evoked responses), 272
Balamuthia
in chronic meningitis, 571t
in encephalitis, 551–552
Balance
anatomy and physiology of, 157–158
disorders of, 159–161. See also Fall(s)
standing, 157
Bálint's syndrome, 199, 243, 345
Baló's concentric sclerosis, 54f–55f
Baltic myoclonus, 446t
Bannwarth's syndrome, 570t
Barbiturates, for epilepsy, 317
Baroreceptors, 126, 127f
Basal cell nevus syndrome, 593t
Basal ganglia, 410f, 415f
Basal meningitis, 569
Basic fibroblast growth factor, 621
Basilar artery
ischemia in territory of, 243
occlusion of, 268, 346–350, 348f–351f
Basilar artery migraine, 380
Basilar skull fracture, 507
Basilar-type migraine, 380
Bassen-Kornzweig disease/syndrome, 237, 440
Bath salts, 817–818
Baylisascaris procyonis infections
chronic meningitis in, 572t
encephalitis in, 552
BCNU (carmustine), 605t
Beck Depression Inventory, 97
Becker disease, 725
Becker's muscular dystrophy, **710**–711
clinical features of, 707t, 711
genetic factors in, 707t
laboratory evaluation of, 710
questions regarding, 858, 880
treatment of, 711
Bed rest, for back pain, 119
Beevor's sign, 491
Behçet's syndrome
chronic meningitis in, 573t
neuroimaging of, 37f
ocular involvement in, 229
Bell's palsy, **484**
clinical features of, 485
differential diagnosis of, 485–486
incidence of, 484
laboratory evaluation of, 486, 486f
neuroimaging of, 51f
pathophysiology of, 485
taste disorders in, 260
treatment of, 486
Bell's phenomenon, 484
Benedikt's syndrome, 241
Benign familial neonatal convulsions, 301t
Benign forgetfulness of the elderly, 184
Benign hereditary chorea of childhood, 428
Benign paroxysmal positional vertigo, 136t, 137
Benign senile chorea, 428
Benserazide/levodopa, for Parkinson's disease, 414, 419t
Benznidazole, for Chagas' disease, 589
Benzodiazepine(s)
for acute alcohol intoxication, 804
adverse effects of, 167–168
for delirium, 170
dosage of, 770t
for generalized anxiety disorder, 769, 770t
for insomnia, 216
in opiate overdose management, 810
for vertigo, 139t
withdrawal from, 168, 769
Benzodiazepine receptor agonists
for coma, 179
for insomnia, 216

www.ketabpezeshki.com (021) 66485457 - 66485438

Benztropine
for extrapyramidal symptoms, 786
for Parkinson's disease, 418
Beriberi, 674. See also T iamine deficiency
ß-adrenergic antagonists (beta blockers)
for acute angle-closure glaucoma, 229
for glaucoma, 236
for phobic disorders, 771
for syncope, 130
ß-carotene, for macular degeneration, 236
Bethanechol
for bladder dysfunction in multiple sclerosis, 530
for selective serotonin reuptake inhibitor-related sexual dysfunction, 777
Bethlem myopathy, 704
Bevacizumab
adverse neurologic effects of, 605, 605t
for macular degeneration, 237
Bilateral simultaneous stimulation test, 154
Biliary disease, back pain in, 117
Binge eating, 782
Binge-eating disorder, 783
Binswanger's disease, 159, 398
Bipolar cell antibodies, 607t
Bipolar disorder, 778
clinical manifestations of, 778–779
diagnosis of, 779, 779t
differential diagnosis of, 779
etiology of, 779
pathophysiology of, 779
treatment of, 779–780, 780t
Bipolar II disorder, 778
Bitemporal hemianopia, 616
Bitter taste sensation, 257
Blackout, 800
Bladder dysfunction
in multiple sclerosis, 529
in neurologic disease, 504, 517
Blastomyces spp. infections, chronic meningitis in, 571t
Blepharitis, 227
Blepharoptosis, 239–240
Blepharospasm, 425
Blessed Dementia Rating Scale, 167
Blindness
color, 224
cortical, 226
in diabetic retinopathy, 237
legal, 222
transient, 230–232
Blind spot, 226
Blink reflexes, 79
Blood-oxygen-level-dependent contrast, 295
Blood pressure
changes during Valsalva maneuver, 473, 474t
during sleep, 209
Blot hemorrhages, 247
Bone-anchored hearing aid, 273
Bone-conduction threshold, 271
Bone disease, neck pain in, 123
Bone marrow transplantation, neuropathy as complication of, 666
Bone spicules, 237, 238f
BOR (branchio-oto-renal) syndrome, 270t
Bortezomib, 605, 605t, 667t
Botulinum toxin
for dystonia, 426
for hemifacial spasm, 487
for hyperhidrosis, 478
for Tourette's syndrome, 429
Botulism
autonomic dysfunction in, 477
clinical features of, 477, 695
diplopia in, 241
pathogenesis of, 695
treatment of, 695
Bound morphemes, 193
Bourneville's disease. See Tuberous sclerosis
Bovine spongiform encephalopathy, 460, 461t, 464
Brachial neuritis, 123–124
Brachial plexopathy, 57f–58f, 678–679
Brachial plexus
anatomy of, 678, 678f
injury to, neck pain in, 123–124
Bradyarrhythmia, syncope in, 132
Bradykinesia, 144
Bradykinin, 90f
Brain
alcohol effects on, 799
inferior aspect of, 344f
Brain abscess, **558**
approach to the patient, 533–534, 534f–535f
clinical features of, 560
definition of, 558
diagnosis of, 18f, 560f, 560–561
differential diagnosis of, 561
epidemiology of, 559
etiology of, 559
pathogenesis of, 559–560
prognosis of, 561–562
treatment of, 561
Brain biopsy
in dementia, 189
in viral encephalitis, 551
Brain death, criteria for, 178–179
Brain-derived neurotrophic factor, 761
Brain edema, 361
"Brainfreeze" headache, 391
Brain hemorrhage, 506f, 506–507
BRAIN initiative, 295–296
Brain injury. See also Head injury
caring for patient with, 203
post–cardiac bypass, 744f, 744–745
post–solid organ transplantation, 745
Brainstem accessory optic system, 221
Brainstem auditory evoked potentials (BAEPs), 74–75, 272
Brainstem auditory evoked responses (BAERs), 272
Brainstem disorders/lesions
clinical features of, 10t
glioma, 66f
questions regarding, 849, 863
sensory abnormalities in, 155
weakness in, 146
Brainstem ischemia, bilateral, 347
Brainstem reflexes examination, in coma, 175–177, 176f
Brain tumors, **591**
amnesia in, 201
approach to the patient, 591–592
clinical features of, 591t, 591–592
extrinsic "benign," **598**
craniopharyngioma. See Craniopharyngioma
meningioma. See Meningioma
pituitary adenomas. See Pituitary adenomas
schwannoma, 598, 599f
headache in, 100t, 101–102
hemorrhage into, 356
intrinsic malignant, **594**
astrocytoma. See Astrocytoma
ependymoma, 596
medulloblastoma, 597
oligodendroglioma, 596
pineal region tumors, 243, 597
primary lymphoma, 596–597, 597f
metastatic, 600t, **600**
diagnosis of, 600–601, 601f
epidural. See Spinal cord compression, neoplastic
leptomeningeal, 602f, 602–603
treatment of, 601–602
neuroimaging of, 592
primary, **592**
genetic syndromes associated with, 593t
pathogenesis of, 592–593, 593t, 594f
questions regarding, 850, 865
treatment of, 592
Branching enzyme deficiency (type IV glycogenosis), 719
Branchio-oto-renal (BOR) syndrome, 270t
Branch retinal vein occlusion, 231
Breast cancer
alcohol effects on, 801
metastatic
to central nervous system, 493, 494f, 600t
to eye, 238–239
paraneoplastic syndromes in, 607t
Breast-feeding, AEDs and, 322
Broca's aphasia, 193t, 193–194
Broca's area, 191, 197f
Bromocriptine, for prolactinoma, 625
Brown-Séquard syndrome, 146, 155, 492
Brucella spp. infections
chronic meningitis in, 570t
ocular involvement in, 229
Brudzinski's sign, 533
Brugada syndrome, 132
Bruns-Garland syndrome, 660
Bruxism, 217
Bulbospinal pathway, 146f
Bulimia nervosa, 261, 782–783
Buprenorphine
as maintenance drug, 811
for opiate detoxification, 811
in opiate overdose management, 811
for pain, 94t, 96
Bupropion
adverse effects of, 768t
for depression, 768t, 777

www.ketabpezeshki.com (021) 66485457 - 66485438

for selective serotonin reuptake inhibitor-related sexual dysfunction, 777
for smoking cessation, 825
Burning mouth syndrome (glossodynia), 260, 262
Buspirone
for generalized anxiety disorder, 770, 770t
for selective serotonin reuptake inhibitor-related sexual dysfunction, 777
Busulfan, 605t
Butorphanol
for migraine, 382t
other opioids and, 98
for pain, 94t, 96

Cabergoline, for prolactinoma, 625
Cachectic myopathy, 371
CACNA1A, 379
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), 44f–45f, 335, 398
CADNA1A gene, 439
Caffeine
action of, 208
for migraine, 382t–383t
CAG repeats, 437–438
Calcific emboli, 249
Calcinosis, dermatomyositis and, 741
Calcitonin gene-related peptide, 90, 281, 376, 868
Calcium channel disorders, 723t, 723–724
Calculation ability assessment, 6
Caloric irrigation, 177, 243
cAMP response element-binding protein, 761
Campylobacter spp. infections, Guillain-Barré syndrome and, 682, 683f, 877
Canadian C-spine rule, 121
Cancer
alcohol effects on, 801
chemotherapy for, 605, 605t, 667t
chronic meningitis in, 573t
cigarette smoking as risk factor for, 822, 822t
depression in, 774
fatigue related to, 142
inflammatory myopathies and, 732
neuropathies associated with, 665–666
recurrent, 680
Candesartan
adverse effects of, 385t
for chronic daily headache, 103
for migraine prevention, 385t
Candida spp. infections
candidiasis in newborn, 34f
chronic meningitis in, 571t
Candidiasis, in newborn, 34f
Cannabinoid(s), 815
Capgras' syndrome, 185, 393
Capillary telangiectasias, 360
Capsaicin, for neuropathy, 661t
Carbamazepine
adverse effects of
common, 483, 780t
hematologic, 317
liver dysfunction, 317, 661t
neurologic, 313t, 661t
rare, 780t
systemic, 313t
for bipolar disorder, 779, 780t
dosage of, 313t, 661t
drug interactions of, 313t
for epilepsy, 312, 313t
for focal seizures, 312
for neuromyotonia, 614
for neuropathy, 661t
for pain, 95t, 98, 529
pharmacology of, 312, 313t
for SUNCT/SUNA, 389
for trigeminal neuralgia, 483, 854, 872
Carbidopa/levodopa, for Parkinson's disease, 414, 419t
Carbon disulfide, 670t
Carbonic anhydrase inhibitors, for glaucoma, 236
Carbon monoxide poisoning
aphasia in, 194
complications of, 367
hypoxia in, 366
optic neuropathy in, 232
treatment of, 367
Carcinoid tumors, 614
Cardiac arrhythmias, syncope in, 132
Cardiac syncope, 129t, 132–134
Cardioembolic stroke, 328–330, 330t
Cardioinhibitory syncope, 128
Cardiomyopathy, syncope in, 132
Cardiopulmonary bypass, brain injury af er, 744f, 744–745
Cardiovascular disease
cigarette smoking as cause of, 822, 822t
depression in, 774
embolic stroke in, 328–330, 330t
syncope in, 132–134
Cardiovascular system
acromegaly manifestations of, 626
alcohol effects on, 801–802
in sleep, 209
Carmustine (BCNU), 605t
Carney complex, 621t
Carney's syndrome, 621t, 621–622
Carnitine palmitoyltransferase deficiency, 720
Carotid artery
occlusion of, 343–345, 344f
stenosis, 230, 332t
Carotid atherosclerosis
asymptomatic, surgical treatment of, 339–340
stroke caused by, 332
treatment of, 339
endovascular therapy in, 340
extracranial-to-intracranial bypass surgery in, 340
surgical, 339–340
Carotid cavernous fistula, 239
Carotid endarterectomy, 340, 851, 867
Carotid sinus massage, 133
Carotid stenosis, 851, 867
Carpal tunnel syndrome, 124
Caseating granulomas, 855, 873
Caspase, 290
Catamenial epilepsy, 321
Cataplexy, 133, 212–213
Cataract, 235
Catatonia, 172
Catecholaminergic polymorphic ventricular tachycardia, 132
Catechol-O-methyltransferase (COMT) inhibitors, for Parkinson's disease, 417, 419t
Cathinones, synthetic, 817–818
Cat-scratch disease, 229
Cauda equina syndrome
clinical features of, 112, 492
diagnosis of, 112
treatment of, 113
weakness in, 147
Causalgia, 93
Cavernomas, 65f
Cavernous angiomas, 360
Cavernous malformations, 20f
Cavernous sinus syndrome, 489, 489f
CBT. See Cognitive behavioral therapy (CBT)
Cefepime, 539t, 541–542
Cefotaxime, 539t, 541–542
Cef azidime, 539t
Cef riaxone, 539t, 541–542
Celecoxib, 93, 94t
Celiac disease (gluten-induced enteropathy), 662
Cellulitis, orbital, 239
Central cord syndrome, 492
Central core disease, 717
Central fever, 175
Central nervous system (CNS)
alcohol effects on, 800
aspergillosis of, 35f–36f
cancer of
dementia in, 405
lymphoma, 587, 596–597, 597f
primary and metastatic tumors, 591. See also specific tumors
approach to the patient, 591–592
clinical features of, 591t, 591–592
electrodiagnostic studies of, 71. See also Electrodiagnostic studies; specific technique
infections of
brain abscess. See Brain abscess
cranial epidural abscess, 565, 565f
dementia caused by, 405
empyema. See Subdural empyema
encephalitis. See Encephalitis
meningitis. See Meningitis
nonbacterial causes of, 562
sarcoidosis, 573t
treatment of, 534f–535f
paraneoplastic syndromes of, 606t
severe dysfunction of, 363–364
toxoplasmosis of, 588f
tuberculosis of, 28f–29f
vasculitis of, 45f–46f, 406
Central pontine myelinolysis, 368, 368f

www.ketabpezeshki.com (021) 66485457 - 66485438

Central retinal artery occlusion, 230f, 231
Central retinal vein occlusion, 231, 231f
Central sensitization, 89
Central sleep apnea, 212
Central transtentorial herniation, 172f, 173
Centronuclear (myotubular) myopathy, **718**
Cerebellar arteries, occlusion of, 346
Cerebellar ataxia, 159, 160t
  clinical manifestations of, 161
  differential diagnosis of, 435
  early-onset, 447t
  etiology of, 436t
  with muscle coenzyme Q10 deficiency, 448t
  types of, 445t, 447t–448t
Cerebellar degeneration/atrophy
  alcohol and, 800
  gait disorders in, 158t, 159
  paraneoplastic, 607t, 612
Cerebellar gait ataxia, 159, 160t
Cerebellar hemorrhages, 356
Cerebral amyloid angiopathy, 356, 398
Cerebral angiography, in stroke, 335f, 352–353
Cerebral arteries
  aneurysm of, 15f
  anterior. See Anterior cerebral artery
  middle. See Middle cerebral artery
  posterior. See Posterior cerebral artery
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), 44f–45f, 335, 398
Cerebral blood flow, autoregulation of, 362, 363f
Cerebral glioma, 23f
Cerebral hemispheres, 192f, 341f–343f
Cerebral ischemia, 323, 325f
Cerebral palsy, 158
Cerebral perfusion pressure, 362, 363f
Cerebral venous sinuses, 566f, 566–567
Cerebritis, 533, 559
Cerebrospinal fluid (CSF)
  leakage of, 104–105, 105f
  low volume, headache with, 104–105
  raised pressure. See Intracranial pressure, increased
Cerebrospinal fluid (CSF) analysis
  in bacterial meningitis, 537–538, 539t
  in chronic meningitis, 574–575
  in coma, 177
  in delirium, 170
  in multiple sclerosis, 519t, 521
  normal values, 84t, 85
  in viral encephalitis, 549–550
  in viral meningitis, 544
Cerebrotendinous xanthomatosis, 448t
Cerebrovascular disease, **323**. See also Stroke
  approach to the patient, 323–324, 324f
  definition of, 323
  dementia associated with, 398
  imaging studies of, 350–353
  incidence of, 323
  seizures caused by, 305
  types of, 323
Cerumen impaction, 270
Cervical angina syndrome, 123
Cervical collar, 124
Cervical dystonia, 425
Cervical radiculopathy, 122t
Cervical spine
  disk disease, 122, 122t
  lesions of, 491
  trauma to, 121–122
C2 facet fracture, 58f
C fibers, 88–89
CHADS2 score, 329, 331t
Chagas' disease, in HIV infection, 589
Chalazion, 227
Channelopathies
  muscular, 723t, 723–725, 724f
  neurologic, 280t, 280–281
Charcot-Marie-Tooth (CMT) disease, **653**
  CMT1, 654t, 655–656, 876
  CMT2, 654t, 655–656
  CMT3, 654t, 655–656
  CMT4, 655–656
  CMT1A, 279, 654t, 656
  CMTDI, 656
  CMT1X, 654t, 656–657
  connexin in, 283
  genetic factors in, 654t–655t
  questions regarding, 856, 876
Chemical restraints, 170
Chemotherapy, for brain metastases, 601
Cherry red spot at macula, 249, 250f
Chewing tobacco, 823
Cheyne-Stokes respiration, 177
Chiari malformation, 242
  headache in, 104
  syringomyelia associated with, 501, 501f, 874
Chiasmal tumor, 238
Chlamydia trachomatis infections, 228
Chloramphenicol, 232
Chlordiazepoxide, 770t
Chlorhexidine mouthwash, 262
Chloride channel disorders, 725
Chloroquine, adverse effects of
  myopathy, 728t, 729
  neuropathy, 668, 668t
  ocular, 237
Chlorpromazine
  for medication-overuse headache, 104
  for migraine, 382t
  for schizophrenia, 785t
  side effects of, 785t
Cholesteatoma, 265
Cholesterol emboli, 249
Cholinergics, for glaucoma, 236
Cholinesterase inhibitors
  for dementia, 397
    with Lewy bodies, 403
  for myasthenia gravis, 696–697
Chorda tympani nerve, 258, 258f
Chorea, 423t, **426**
  disorders associated with, 428
  paraneoplastic, 428, 607t
  Sydenham's, 428
Chorea-acanthocytosis, 428
Choriocarcinomas, 620
Choriomeningitis, lymphocytic, 572t
Chorioretinal mass lesions, 251, 251f
Chorioretinal scarring, from Toxoplasma retinitis, 252, 252f
Chorioretinopathy, central serous, 237
Choroidal artery occlusion, 343, 344f
Choroidal malignant melanoma, 251, 251f
Choroidal neovascularization, 247
CHRNA4 gene, 301t
Chronic cerebrospinal insufficiency, in multiple sclerosis, 529
Chronic fatigue syndrome, **752**
  antidepressants for, 143
  cognitive behavioral therapy for, 143, 754–755, 859, 880–881
  definition of, 752
  description of, 142
  diagnosis of, 752t, 753–754, 858–859, 880, 880t
  epidemiology of, 752
  etiology of, 752–753, 753t
  graded exercise therapy for, 143, 754–755
  pathophysiology of, 753
  prognosis of, 755
  questions regarding, 858–859, 880
  treatment of, 143, 754f, 754–755
Chronic inflammatory demyelinating polyneuropathy (CIDP), **687**
  clinical features of, 687
  diagnosis of, 687
  Guillain-Barré syndrome versus, 687
  pathogenesis of, 684t, 688
  treatment of, 688
Chronic kidney disease (CKD), 168, 168t, 173–174, 850, 864–865
Chronic liver disease, 663
Chronic liver failure, 141
Chronic obstructive pulmonary disease, 823, 885
Chronic progressive external ophthalmoplegia, 240
Chronic quadriparesis, 148
Chronic renal failure, 727
Chronic sensory ataxic neuropathy, 684t
Chronic subjective dizziness, 139
Chronic traumatic encephalopathy (CTE), 406, 510
Chronic wasting disease, 292, 460, 461t
Cidofovir
  for HIV-associated progressive multifocal leukoencephalopathy, 558
  for viral encephalitis, 553–554
CIDP. See Chronic inflammatory demyelinating polyneuropathy (CIDP)
Cigarette smoking
  assessment of, 824
  cancer risks associated with, 822, 822t
  cardiovascular diseases caused by, 822, 822t
  cessation of, 822, 824–825, 851, 861–862, 867, 886
  chronic obstructive pulmonary disease caused by, 823, 885
  deaths caused by, 821–822, 885
  in developing world, 821
  disease manifestations of, 821–823, 822t

www.ketabpezeshki.com (021) 66485457 - 66485438

environmental tobacco smoke, 823
nicotine-replacement therapy for, 825, 886
Parkinson's disease and, 853, 870
pharmacologic interactions, 823, 824t
in pregnancy, 823
prevalence of, 821
questions regarding, 861, 885–886
respiratory diseases caused by, 822t, 823
stroke risk and, 332t
wound healing affected by, 823
Cingulate cortex, 197
Ciprofloxacin, 232
Circadian rhythmicity, 208, 220
Circadian rhythm sleep disorders, 218–220
Cisplatin, adverse effects of
hearing loss, 267
neurologic, 605, 605t, 667t
Cisternography, computed tomography, 14
Citalopram, 768t
CKD. See Chronic kidney disease (CKD)
Clasp-knife phenomenon, 144
Claude's syndrome, 241, 345
Claudication, neurogenic, 113
Clinical Dementia Rating, 167
Clobazam
adverse effects of, 313t
for epilepsy, 313t
pharmacology of, 313t
Clomipramine
adverse effects of, 768t
for cataplexy, 213
for depression, 768t
for obsessive-compulsive disorder, 773
Clonazepam
adverse effects of, 313t
for ataxia/tremor, 529
for bipolar disorder, 780
for epilepsy, 313t
for generalized anxiety disorder, 770t
for myoclonus, 430
for panic disorder, 767
pharmacology of, 313t
for posthypoxic myoclonus, 367
for REM sleep behavior disorder, 218
for tardive dyskinesia, 431
for vertigo, 139t
Clonidine
adverse effects of, 385t
for migraine prevention, 385t
for opioid withdrawal syndrome, 104, 812
Clopidogrel
lumbar puncture and, 81
for stroke/TIA prevention, 336–338
Clorazepate, for generalized anxiety disorder, 770t
Clozapine
for Huntington's disease, 428
for schizophrenia, 785, 785t
side effects of, 785t
Cluster headache, 100t, 380f, 386–387, 388t, 852, 868–869
Cluster-tic, 483
CMDs (congenital muscular dystrophies), 707t, 712, 713t
CMS (congenital myasthenic syndromes), 694, 694t
CMT disease. See Charcot-Marie-Tooth (CMT) disease
CMV. See Cytomegalovirus (CMV) infections
CNS. See Central nervous system (CNS)
Cobalamin. See Vitamin B12
Cobblestone papillae, 227
Cocaine, **813**
abuse of, 811–812
action of, 283
acute and chronic intoxication, 814
adverse effects of, 814
autonomic, 478
myopathy, 728t, 729
intracerebral hemorrhage caused by, 356
overdose of, 811–812
reinforcing effects of, 813
systemic effects of, 814
Coccidioides spp. infections. See also Meningitis
meningitis in, 33f, 571t
ocular involvement in, 229
subacute meningitis in, 556
Coccidiomycosis meningitis, 33f
Cochlea, 264, 265f
Cochlear implant, 267, 273–274, 274f
Codeine, for pain, 94t
Cognistat, 187
Cognitive behavioral therapy (CBT)
for back pain, 119
for chronic fatigue syndrome, 143, 754–755, 859, 880–881
for insomnia, 215
for PTSD, 795
questions regarding, 859–860, 880–882
Cognitive dysfunction
alcohol and, 800
caring for patient with, 203
delirium and, 165
in multiple sclerosis, 517
Cognitive evoked potentials, 75
Cognitive function assessment, 166
Cognitive rehabilitation procedures, 203
Colchicine, adverse effects of
myopathy, 728t, 729
neuropathy, 669t, 671
Cold-stimulus headache, 391
Collier's sign, 243
Colloid cysts, 161, 599
Color anomia, 224
Color blindness, 224
Color vision assessments, 224
Coma, **171**
anatomy of, 172–174
approach to the patient
brainstem reflexes, 175–177, 176f
history, 174
level of arousal, 175
neurologic examination, 175
physical examination, 175
brain death determination in, 178–179
cerebral mass lesions and herniations as cause of, 172f, 172–173
definition of, 171
differential diagnosis of, 178, 178t
EEG in, 73
epileptic, 174
imaging in, 177
laboratory studies in, 177
metabolic disorders as cause of, 173–174
prognosis of, 179–180
respiratory patterns in, 177
sodium shif s as cause of, 174
toxic/drug-induced, 174
treatment of, 179
water balance shif s as cause of, 174
widespread cerebral damage as cause of, 174
Comatose patient, examination of, 181
Combination antiretroviral therapy (cART), 672
Common carotid artery occlusion, 345
Common cold, 259
Complement factor H, in macular degeneration, 236
Complex febrile seizures, 304
Complex partial status epilepticus, 406
Complex regional pain syndrome (CRPS), 93, 478–479
Comprehension assessment, 192
Comprehensive stroke centers, 328
Compression fracture, 58f
Computed tomography (CT)
in cerebral artery occlusion, 16f, 352f
in cerebral contusion, 506f
in coma, 177
in diffuse axonal injury, 506f
in epidural hematoma, 509f
in hearing loss, 272–273
in neurologic critical illness, 363–364
in neurologic disease, 13
complications of, 14–17, 17t
guidelines for, 14t
indications for, 14, 14t
premedication guidelines for patients with prior contrast allergy, 17t
technique, 13–14, 15f
in stroke, 350–352, 352f
in subarachnoid hemorrhage, 373–374, 374f, 849, 863
in subdural hematoma, 508f–509f
in viral encephalitis, 550
Computed tomography (CT) angiography, 13–14, 15f
Computed tomography (CT) cisternography, 14
Computed tomography (CT) myelography, 14, 24–25
COMT (catechol-O-methyltransferase) inhibitors, 417, 419t
Concussion, **508**
definition of, 505
mechanics of, 505–506
moderate/severe head injury versus, 791t. See also Head injury
sports-related, 510
in war veterans, 790–792, 791t, 795–796
Cones, 221, 224
Confabulation, 200
Confusion, 164
Confusion Assessment Method, 166
Congeners, 798

www.ketabpezeshki.com (021) 66485457 - 66485438

Congenital amaurosis. See Leber hereditary optic neuropathy (congenital amaurosis)
Congenital heart disease, brain abscess and, 559
Congenital motor nystagmus, 243
Congenital muscular dystrophies (CMDs), 707t, **712**, 713t
Congenital myasthenic syndromes (CMS), 694, 694t
Congenital myotonic dystrophy, 714
Congenital sensory nystagmus, 243
Congenital vascular malformations, 359–360
Conjugate eye movement, 176
Conjunctivitis, 227
Connexin(s), 283
Connexin 26, 268
Conn's syndrome, 726
Consciousness, 5
Constipation
  in multiple sclerosis, 517
  opioid-induced, 96
  treatment of, 96
Contactin-associated protein-like 2 antibodies, 611
Contact lenses, 228
Contraception, 322
Contracture, 704
Contrast agents
  adverse effects of
    allergies, 17, 17t, 21
    nephrogenic systemic fibrosis, 21
    nephropathy, 15
  precautionary measures for, 17t
Contusion, cerebral, 506f, 506–507
Conus medullaris syndrome, 491–492
Convergence-projection hypothesis, of referred pain, 91f
Convulsion, 508
Coordination assessment, 9
Copper deficiency, 675
C9ORF72 gene, 399
Corneal abrasions, 226–227
Corneal blink reflex, 176f
Corneal light reflex, 224
Coronary artery bypass graf ing, 745
Cortical laminar necrosis, 367f
Cortical venous thrombosis, 147
Corticobasal degeneration, 159, 195, 259, 402, 411–412
Corticobasal syndrome, 399
Corticospinal pathway, 146f
Corticosteroids. See Glucocorticoid(s)
Corticotrope, 620, 620t, 633
Corticotropin-releasing factor, 761
Cortisol excess, 629
Cotton-wool spots, 230f, 233f, 248–249, 249f
Cough Assist Device, for ALS, 456
Cover test, 224, 240
Cowden's syndrome, 593t
COX inhibitors. See Cyclooxygenase (COX) inhibitors
Coxsackievirus, in meningitis, 543
Cramps, muscle, 704
Cranial epidural abscess
  clinical features of, 565
  definition of, 565, 565f
  diagnosis of, 565
  etiology of, 565
  pathophysiology of, 565
  prognosis of, 565
  treatment of, 565
Cranial nerve(s)
  examination of, 6–7
  injuries to, 507–508
  palsies of, 488–489, 489f
  syndromes involving, 487–488, 488t
Craniopharyngioma
  clinical features of, 599
  ocular signs in, 226
  treatment of, 599
Craniopharyngiomas, 619
Creutzfeldt-Jakob disease, **292**
  clinical course of, 465
  clinical features of, 186t, 459, 465
  dementia caused by, 403
  diagnosis of, 465, 466f
  differential diagnosis of, 465–466
  af er dura matter graf s, 464
  familial, 461t
  af er human growth hormone therapy, 464
  iatrogenic, 460, 461t, 463–464
  laboratory evaluation of, 466, 466f
  molecular basis of, 184t
  myoclonus in, 465
  neuropathology of, 464–465
  af er pituitary gonadotropin therapy, 464
  prevention of, 467
  as prion disease, 459
  prions associated with, 467–468
  sporadic, 461t
  treatment of, 467
  variant, 461t, 464
Cricopharyngeal myotomy, 715
Critical illness myopathy, 371
Critical illness polyneuropathy, 370, 663
Critically ill patient
  neurologic disorders in, 362t
    approach to the patient, 363–366
      diagnostic studies, 363–364
      elevated ICP treatment, 364–365, 365t
      ICP monitoring, 364, 364f
      secondary brain insults, 365–366
    central pontine myelinolysis, 368, 368f
    delirium, 170, 367–368
    hypoxic-ischemic encephalopathy, 366–367, 367f
    metabolic encephalopathies, 367–368
    myopathy, 371
    neuromuscular transmission disorders, 370–371
    neuropathy, 370, 663
    pathophysiology of
      brain edema, 361
      cerebral perfusion and autoregulation, 362, 363f
      cerebrospinal fluid and intracranial pressure, 362–363, 363f
      ischemic cascade and cellular injury, 361–362
    peripheral nervous system, 362t, 370–371
    respiratory evaluation in, 370
    sepsis-associated encephalopathy, 368
    status epilepticus, 364, 367
    Wernicke's disease, 369, 369f
CROS hearing aid, 273
Crossed straight-leg raising sign, 110
Crow-Fukase syndrome (POEMS syndrome), 613
CRPS (complex regional pain syndrome), 93, 478–479
Cryptococcus spp. infections
  chronic meningitis in, 571t
  in HIV infection, 585
  subacute meningitis in, 555–556
Cryptogenic sensory and sensorimotor polyneuropathy (CSPN), 675–676
Crystal deposition, in retina, 250
CSF. See Cerebrospinal fluid (CSF)
CSTB gene, 301t
CT. See Computed tomography (CT)
Cushing's syndrome
  clinical features of, 629–630, 630t
  clinical presentation of, 629–630
  diagnosis of, 629–630
  differential diagnosis of, 631t
  etiology of, 629
  hypercortisolism in, 630
  inferior petrosal venous sampling for, 630
  laboratory investigations for, 630
  prevalence of, 629
  screening tests for, 617t
  transsphenoidal resection for, 631
  treatment of, 631f, 631–632
Cutaneous reflexes, 8, 144
Cyanide poisoning, 367
Cyclobenzaprine
  for back pain, 119
  for spasticity in multiple sclerosis, 529
Cyclooxygenase (COX) inhibitors
  adverse effects of, 93
  opioid combinations, 96
  for pain, 93
Cyclopentolate hydrochloride, for red or painful eye, 227
Cyclophosphamide
  for cerebellar degeneration, 612
  for inflammatory myopathies, 741
  for multiple sclerosis, 529
  for myasthenia gravis, 697–698
Cyclosporine
  for inflammatory myopathies, 741
  for myasthenia gravis, 697–698
Cyclothymic disorder, 778
Cyproheptadine, for Cushing's syndrome, 469, 632
Cystatin B, 301t
Cysticercosis
  chronic meningitis in, 571t
  clinical features of, 562
  diagnosis of, 562
  etiology of, 562
  ocular involvement in, 229, 243
  treatment of, 562
Cytarabine, 605t, 667t

www.ketabpezeshki.com (021) 66485457 - 66485438

Cytokines, in fatigue, 143
Cytomegalovirus (CMV) infections
  myelopathy and polyradiculopathy in, 589–590
  neuropathy in, 665
Cytotoxic edema, 361

Dabigatran, 338–339
Dacarbazine (DTIC), 605t
Dacryocystitis, 227
Dalfampridine, 529
Dantrolene, 504, 529
Dapsone, 669t
Daytime sleepiness
  disorders associated with, 210
  evaluation of, 210–211, 211t
  excessive, 141
  insufficient sleep as cause of, 211
  multiple sleep latency test for, 210
DDAVP, 635f. See also Desmopressin (DDAVP)
ddC (zalcitabine), 672
Debranching enzyme deficiency (type III glycogenosis), 719
Decerebrate rigidity, 175
Decorticate rigidity, 175
Decubitus ulcers, 504
Deep brain stimulation (DBS)
  description of, 295
  for dystonia, 426
  for Parkinson's disease, 418, 421, 854, 871
Dehydration, delirium in, 167, 169
Déjerine-Roussy syndrome, 155, 355
Delayed puberty, anosmia in, 261
Delayed sleep-wake phase disorder (DSWPD), **218**
Delirium, **164**
  approach to the patient, 166–170, 169t
  clinical features of, 164
  in critically ill patient, 170, 367–368
  dementia and, 165
  diagnosis of, 169t, 169–170
  drug-induced, 165–166, 168t
  in elderly, 165
  epidemiology of, 165
  etiology of, 167–169, 168t
  history in, 166–167
  hyperactive, 164
  hypoactive, 164
  pathogenesis of, 165–166
  physical examination in, 167
  postoperative/ICU, 164
  prevention of, 170
  reversibility of, 164
  risk factors for, 164–165
  screening tools for, 166–167
  treatment of, 170
Delirium Detection Score, 166
Delirium Rating Scale, 166
Delirium tremens, 164, 805
Demecarium bromide, 224
Demeclocycline, 646
Dementia, **182**. See also specific types
  in alcoholism, 404
  ALS/parkinsonian/dementia complex of Guam and, 407
  aphasia in, 196
  approach to the patient, 184, 185t
  caring for patient with, 203
  central nervous system infections and, 405
  central nervous system neoplasms and, 405
  clinical features of, 186t
  cognitive examination in, 187
  in corticobasal degeneration, 402
  in Creutzfeldt-Jakob disease, 403
  definition of, 182
  delirium and, 165–166
  differential diagnosis of, 183t
  etiology of, 183t, 183–184
  frontotemporal. See Frontotemporal dementia (FTD)
  functional anatomy of, 182–183
  head trauma–related, 406
  HIV-associated, 585–587, 587f
  in Huntington's disease, 404
  in isolated vasculitis of central nervous system, 406
  in Korsakoff's syndrome, 405
  laboratory tests in, 185t, 187–189
  memory loss in, 204
  metal exposure and, 406
  molecular basis of, 184t
  multi-infarct, 398
  neurologic examination in, 185t, 186–187
  in nicotinic acid deficiency, 405
  in normal-pressure hydrocephalus, 404
  in Parkinson's disease, 403, 420
  patient history in, 184–186, 185t
  physical examination in, 185t, 186–187
  in Pick's disease, 400, 402f
  prevalence of, 182
  in prion diseases, 403–404
  in progressive supranuclear palsy, 400
  in psychiatric diseases, 407
  in seizure disorders, 405
  semantic, 200
  sleep affected by, 215
  transient global amnesia and, 406
  treatment of, 189–190
  types of, 184, 184t
  vascular, 182, 188f, 398
  in vitamin B1 deficiency, 405
  in vitamin B12 deficiency, 405
Dementia pugilistica, 406, 510, 790
Dementia with Lewy bodies, **403**
  clinical features of, 165, 184–185, 186t, 403
  molecular basis of, 184t
  neuropathology of, 403
  olfactory dysfunction in, 259
  orthostatic hypotension in, 131
  Parkinson's disease dementia versus, 420
  treatment of, 403
Dentatorubropallidoluysian atrophy, 436, 439, 445t
DEPDC5 gene, 301t
Dependence
  alcohol. See Alcohol abuse or dependence (alcoholism)
  substance. See Substance use disorders
Depression/depressive disorders, **774**
  agitated, 778
  chemosensory alterations in, 261
  clinical manifestations of, 775–776
  diagnosis of, 775t
  dizziness in, 139
  drug-related, 774
  in epilepsy, 320
  etiology of, 776
  headache and, 101
  insomnia caused by, 214
  major depression, 775, 775t, 777f, 860, 882–883
  medical illness–related, 774
  in multiple sclerosis, 517, 530
  neural circuitry of, 762f
  neuroinflammation, 764
  pain and, 97
  in Parkinson's disease, 420
  pathophysiology of, 776
  treatment of
    algorithm for, 777f
    antidepressants, 768t–769t, 776–778
    in cerebral function disorders, 203
  unipolar, 776
  in war veterans, 795
Dermatomes, 154f
Dermatomyositis, **730**
  calcinosis in, 741
  clinical features of, 149, 730–731, 731t
  diagnosis of, 737–739, 738t, 739f
  differential diagnosis of, 735–737
  drug-induced, 737
  immunopathogenesis of, 733f
  malignancies associated with, 732
  pathogenesis of, 733–734
  prognosis of, 741
  treatment of, 739–741
Dermatomyositis sine myositis, 731
Dermoid cysts, 599
Desipramine
  adverse effects of, 768t
  for depression, 768t
  dosage of, 768t
  for pain, 95t, 97, 99, 529
Desmopressin (DDAVP)
  for diabetes insipidus, 640–641
  fluid intake affected by, 641f
  for orthostatic hypotension, 131
Desvenlafaxine, for depression, 768t
Detrusor dyssynergia, 529
Detrusor hyperreflexia, 529
Devic's syndrome, 530
Dexamethasone
  for bacterial meningitis, 542–543
  for brain abscess, 561
  for cerebral edema, 674–675
  for increased intracranial pressure, 365t
  for spinal cord compression, 855, 873
Dextroamphetamine, for narcolepsy, 213
Diabetes insipidus (DI)
  characteristics of, 637
  clinical pearls for, 647
  definition of, 635
  desmopressin for, 640–641
  differential diagnosis of, 639–640, 640f
  dipsogenic, 638, 638t, 640
  etiology of, 637–639, 638t

www.ketabpezeshki.com (021) 66485457 - 66485438

Diabetes insipidus (DI) (Cont.):
gestational, 638t, 639
nephrogenic, 638–641
partial, 640
pathophysiology of, 639
pituitary, 637, 638t, 639
psychogenic, 638, 638t
vasopressin measurements to differentiate types of, 640, 640f
Diabetes mellitus (DM)
autonomic dysfunction in, 476
depression in, 774
myopathy in, 727
neuropathy in. See Diabetic neuropathy
ocular involvement in
abducens nerve palsy, 242
cataracts, 235
epiretinal membrane, 238
mydriasis, 223
myopia, 222
oculomotor nerve palsy, 241
optic neuropathy, 231
retinal hemorrhage, 229
retinal vein occlusion, 231
tonic pupil, 223
vitreous degeneration, 234
questions regarding, 857, 876–877
stroke risk in, 332t
taste disorders in, 260
type 2, in schizophrenia, 786
Diabetic amyotrophy, 660, 727
Diabetic autonomic neuropathy, 660
Diabetic neuropathy
autonomic, 660
distal symmetric sensory and sensorimotor polyneuropathy, 660
mononeuropathy, 661
pathophysiology of, 92
polyneuropathy, 660
radiculoplexus neuropathy, 660
treatment of, 97, 661t
Diabetic radiculoplexus neuropathy, 660
Diabetic retinopathy, 237, 237f
Dialectical behavior therapy, 783
Diazepam
in cocaine abuse management, 811
dosage of, 770t
for generalized anxiety disorder, 770t
for spasticity in multiple sclerosis, 529
for stiff-person syndrome, 613
for vertigo, 139t
Dichloralphenazone, for migraine, 382t, 384
Dichromat, 224
Diclofenac, for pain, 93
Diclofenac K, for migraine, 382t
Diffuse axonal injury, 506–507
Diffuse white matter disease, 187, 188f, 398
Diffusion-perfusion mismatch, 353f
Diffusion tensor imaging (DTI), 24
Diffusion tractography, in cerebral glioma, 23f
Diffusion-weighted imaging (DWI), 23
Digitalis, 232
Digit span tests, 167, 202
Dihydroergotamine
for medication-overuse headache, 104
for migraine, 382t–383t
nasal spray, 382t, 383
parenteral administration of, 383
for primary exercise headache, 390
Dilantin, 872
Diltiazem, for sexual activity-related primary headache, 390
Dimenhydrinate. for vertigo, 139t
Dimethyl fumarate, for multiple sclerosis, 526, 856, 875
Dim-light melatonin onset, 218
Dipeptidyl-peptidase-like protein-6 antibodies, 611
Diphtheria, neuropathy in, 664
Diplopia, 239–241, 517
Dipsogenic diabetes insipidus, 638, 638t, 640
Dipyridamole, for stroke/TIA prevention, 337–338
Direct ophthalmoscope, 246, 247t
Direct thrombin inhibitors, 81
Disequilibrium, 161. See also Balance
Diskectomy with fusion, cervical, 124
Diskography, 25, 120
Disputed thoracic outlet syndrome, 123
Distal myopathies, 715, 716t
Distal sensory polyneuropathy (DSPN), 590
Disulfiram
adverse effects of, 232, 669t
in alcoholism management, 806, 861, 885
Ditans, 376
Diuretics
hearing loss and, 267
for Ménière's disease, 267
for vertigo, 139t
Dix-Hallpike maneuver, 136
Dizziness, **135**
approach to the patient, 135–136
history in, 135–136
physical examination in, 136
psychosomatic, 139
in vascular disorders, 135
vestibular causes, 135
DJ-1, 291
DM. See Diabetes mellitus (DM)
Docetaxel, 667t
"Doll's eyes," 176
Domoic acid intoxication, 306
Domperidone, for nausea, 104
Donepezil
for Alzheimer's disease, 189, 263, 397, 853, 869
for Parkinson's disease dementia, 420
Dopamine
anatomic and clinical aspects of, 282t
midbrain neurons, 763
in migraine, 378, 868
structure of, 282t
Dopamine agonists
adverse effects of, 417
for hyperprolactinemia, 623
for Parkinson's disease, 416–417, 419t, 422f
for prolactinoma, 625
for restless legs syndrome, 216
side effects of, 625
Dopamine receptor antagonists, for migraine, 378, 382t, 384
Dopa-responsive dystonia, 412, 424
Dorsal midbrain syndrome (Parinaud's syndrome), 243
Dorsal root ganglia, 88, 89f, 90
Dorsal root ganglionopathy, 613
Dosulepin, for migraine prevention, 385t
Dot hemorrhages, 247, 247f
Doublecortin gene, 302t
Downbeat nystagmus, 244, 253
Down syndrome, 259, 395
Doxepin
adverse effects of, 768t
for depression, 768t
dosage of, 768t
for pain, 94t
Driving ability/privileges, epilepsy effects on, 321
Dronabinol, 816
Drop attacks, 161
Drowsiness, 171
Drp1, 291
Drug(s)
of abuse
initial actions of, 764t
neurotransmission affected by, 763
autonomic function effects of, 472, 473t
fatigue caused by, 141
hyperprolactinemia caused by, 623
insomnia caused by, 214
Drusen, 233–234
in hard exudates, 248
in macular degeneration, 236, 236f
optic disc, 233–234, 234f
Dry beriberi, 674
Dry eye (keratoconjunctivitis sicca), 228
DSM-5, 765
DSPN. See Distal sensory polyneuropathy (DSPN)
DSPN (diabetic distal symmetric sensory and sensorimotor polyneuropathy), 660
DSWPD. See Delayed sleep-wake phase disorder (DSWPD)
DTIC (dacarbazine), 605t
DTI (diffusion tensor imaging), 24
Dual task walking, 158
Duchenne's muscular dystrophy, **706**
clinical features of, 706, 707t
genetic factors in, 707t
incidence of, 706
laboratory evaluation of, 706–708
pathogenesis of, 708, 710, 710f
questions regarding, 858, 880
Duloxetine, 860, 882
adverse effects of, 661t, 768t
for depression, 768t
dosage of, 768t
for neuropathy, 661t
for pain, 95t, 98–99
Dural arteriovenous fistulas, 360
Dural sinus thrombosis, 340
Dural vascular malformations, 360, 500f
Dura matter graf s, Creutzfeldt-Jakob disease af er, 464
Dynamic visual acuity, 136
Dysalbuminemic hyperthyroxinemia syndromes, 633

www.ketabpezeshki.com (021) 66485457 - 66485438

Dysarthria, 191, 333
Dysdiadochokinesis, 849, 863
Dysembryoplastic neuroepithelial tumors, 599
Dysesthesia, 150, 154
Dysgerminomas, 620
Dysgeusia, 260
Dysgraphia, 196
Dyskinesia
  diphasic, levodopa-related, 415
  paroxysmal, 431–432
  tardive, 159, 430, 786
Dysphagia, 487–488, 488t
Dysphonia, 487–488, 488t
Dysplasia, fibromuscular, 334
Dyspnea, in orthostatic hypotension, 131
Dysproteinemia, 230
Dysreflexia, autonomic, 475
Dysthymic disorder, 774
Dystonia, 158, 423t, **424**
  cervical, 425
  clinical features of, 424
  dopa responsive, 424
  drug-induced, 431
  focal, 425
  idiopathic torsion, 424
  limb, 425
  Oppenheim's, 424
  oromandibular, 425
  pathophysiology of, 425
  primary, 424
  secondary, 425
  Segawa variant, 424
  spasmodic, 425
  treatment of, 425–426
Dystonia plus syndromes, 425
Dystonic storm, 426
α-Dystroglycan, 708
Dystrophin, 708, 710, 710f, 712f
DYT1 gene, 424–426

Ear, 264, 265f
Ear canal atresia, 273
Eating disorders, 781–783
EBV infections. See Epstein-Barr virus (EBV) infections
Echolalia, 193t, 194
Echo-planar magnetic resonance imaging, 22–24
Echovirus infections, chronic meningitis in, 572t
Ecstasy (MDMA), 168, 168t, 817
Ectropion, 227
ED. See Erectile dysfunction (ED)
Edema
  brain, 361
  cytotoxic, 361
  optic disc, 233, 233f, 251, 251f
  vasogenic, 361
Edinger-Westphal nuclei, 221
Edrophonium, 857, 878
EDSS (Expanded Disability Status Score), 523t
EEG. See Electroencephalography (EEG)
Ehrlichia chaffeensis, 540
Elderly. See also Aging
  benign forgetfulness of, 184
  cerumen impaction in, 270
  delirium in, 165
  falls in, 157, 161. See also Fall(s)
  hearing loss in, 267
  olfactory dysfunction in, 258, 258f, 263
  seizures in, 304t
Electrocochleography, 272
Electroconvulsive therapy, for depression, 778
Electrodiagnostic studies, 71
  electroencephalography. See Electroencephalography (EEG)
  electrophysiologic studies. See Electrophysiologic studies
  evoked potentials. See Evoked potentials
  magnetoencephalography, 74, 309
  in myasthenia gravis, 693
  in myopathies, 705
  nerve conduction studies. See Nerve conduction studies
  in peripheral neuropathy, 650–652, 652t
Electroencephalography (EEG), 71, 72f
  in brain death, 179
  in coma, 73, 177
  continuous monitoring, 74
  in delirium, 165
  in epilepsy, 71–73
  in neurologic critical illness, 364
  in seizures, 71–73, 73f, 298–300, 309, 865
  in vasovagal syncope, 128f
  video, 865
Electrolyte disturbances
  delirium in, 168, 168t
  neurologic complications of, 746–747
  weakness in, 149t
Electromyography (EMG)
  in back pain, 110
  in peripheral neuropathy, 650–652, 652t
  principles of, 76f, 76–77
  single-fiber, 79
Electrophysiologic studies, **76**
  blink reflexes, 79
  clinical utility of, 75
  F-wave studies, 78
  H-reflex studies, 78
  muscle response to repetitive nerve stimulation, 78–79
  in seizures, 309
Eletriptan, for migraine, 382t–383t
Emboli, retinal, 249, 253
Embolic stroke
  artery-to-artery, 330–332
  prevention of, 338–339
Embryonal carcinomas, 620
Emery-Dreifuss muscular dystrophy, **711**
  clinical features of, 707t, 711
  genetic factors in, 707t, 711–712
  laboratory evaluation of, 712, 712f
  treatment of, 711
Emetine, 232
EMG. See Electromyography (EMG)
Emmetropia, 222
Encephalitis, 611
  amnesia in, 201
  AMPA receptor antibodies, 611
  approach to the patient, 533–534, 534f–535f
  brainstem, 606t, 609
  chronic, **556**
  progressive multifocal leukoencephalopathy. See Progressive multifocal leukoencephalopathy (PML)
  progressive rubella panencephalitis, 558
  subacute sclerosing panencephalitis, 558
contactin-associated protein-like 2 antibodies, 611
cortical, 609
definition of, 533
delirium in, 168
dipeptidyl-peptidase-like protein-6 antibodies, 611
focal, 609–610
GABAA receptor antibodies, 611
τ-aminobutyric acid type B receptor antibodies, 611
glycine receptor antibodies, 611
leucine-rich glioma-inactivated 1 antibodies, 611
limbic, 27f–28f, 405
NMDA receptor, 610, 610f6–611f
paraneoplastic, 405
viral, **548**
  approach to the patient, 533–534, 534f–535f
  clinical features of, 548
  definition of, 548
  diagnosis of, 550f
  brain biopsy in, 551
  cerebrospinal fluid analysis in, 549–550
  computed tomography for, 550
  MRI in, 550–551
  serologic studies and antigen detection in, 550
  differential diagnosis of, 551–553
  enteroviral, 545–546
  etiology of, 543t, 548–549
  herpes simplex virus
  differential diagnosis of, 540
  memory loss in, 201
  MRI in, 19f
  sequelae of, 554–555
  treatment of, 553–554
  West Nile virus, 551, 551t, 552, 554
Encephalomyelitis
  acute disseminated. See Acute disseminated encephalomyelitis (ADEM)
  definition of, 609
  experimental allergic, 285, 286f
  paraneoplastic, 607t, 609–610
  postinfectious, 531
Encephalopathy, 164. See also Delirium
  chemotherapy-induced, 605t
  chronic traumatic, 406, 510
  feline spongiform, 461t
  Hashimoto's, 56f, 465–466
  hepatic
  coma in, 179
  delirium in, 168t
  neuroimaging of, 69f
  HIV, 584–587, 587f
  hypertensive, 168t, 356

www.ketabpezeshki.com (021) 66485457 - 66485438

کتاب پزشکی

66485457 - 66485438

www.ketabpezeshki.com

Encephalopathy, (Cont.):
hypoxic-ischemic, 323, 366–367, 367f
metabolic, 194, 202, 367–368
sepsis-associated, 368
Endarterectomy, carotid, 340, 851, 867
Endocrine myopathies, 725
Endolymphatic hydrops, 137. See also Ménière's disease
Endolymphatic sac decompression, 267
Endometrial cancer, 117
Endometriosis, 117
Endophthalmitis, 229
Endovascular procedures
for carotid atherosclerosis, 340
for ischemic stroke, 326–327
Enophthalmos, 238
Enoxaparin, 81
Entacapone, for Parkinson's disease, 417, 419t
Enteric autonomic nervous system, 287
Enteroviruses, in meningitis, 545–546
Entrapment neuropathy, 747
Entropion, 227
Enuresis, sleep, 217
Environmental factors, in neuropathy, 670t, 672–673
Environmental tobacco smoke, 823
Enzymes, in myopathy, 705
Eosinophilia-myalgia syndrome (EMS), 729, 731
Ependymoma, 67f, 596
Epidermoid cyst, 599
Epidural abscess
cranial, 565, 565f
spinal, 113, 495–496, 496f
Epidural hematoma
clinical features of, 508–509
neuroimaging in, 59f, 509f
spinal, 496
treatment of, 509
Epidural metastases, 603f, 603–604
Epidural spinal hemorrhage, 357
Epigenetics, 279
Epilepsia partialis continua, 298, 609
Epilepsy, **297**. See also Seizure(s)
adverse effects of, 320
autonomic, 133
catamenial, 321
coma in, 174
definition of, 297
electroencephalography findings in, 71–73
employment and, 321
etiology of, 303–305
age-related, 304t, 304–305
drug-related, 305, 305t
genetic, 301t–302t, 306–307
incidence of, 297
interictal behavior, 320–321
ion channel defects causing, 280t, 281
loss of driving privileges in, 321
mortality of, 321
pregnancy and, 321–322
prevalence of, 297
psychiatric disorders associated with, 320
psychosocial issues in, 321
refractory, 318
taste disorders in, 260
treatment of, **311**
antiepileptic drugs, 312–318, 313t–316t
avoidance of precipitating factors in, 311–312
surgical, 318–319
underlying conditions–related, 311
in women, 321–322
Epilepsy syndromes, 297, 300
genetic, 301t–302t
juvenile myoclonic epilepsy, 300, 302
Lennox-Gastaut syndrome, 302
mesial temporal lobe epilepsy, 302, 302t, 303f
Epileptic spasms, 300
Epileptiform activity, 71, 309
Epileptiform spikes, 298
Epileptogenesis, 303, 306
Epiretinal membrane, 237–238
Episcleritis, 228–229
Episodic ataxia, 280t, 436, 439, 446t–447t
Epithelial growth factor receptor signaling, 621
Epley maneuver, 137, 138f
EPM2A gene, 301t
Epstein-Barr virus (EBV) infections
meningitis, 546
neuropathy in, 665
Eptifibatide, 81
Epworth Sleepiness Scale, 210
ERBB4, 763
Erectile dysfunction (ED), 470
Ergotamine
for migraine, 382t–383t, 383
for primary exercise headache, 390
for sexual activity-related primary headache, 390
Erythrocyte sedimentation rate
in fatigue evaluations, 143
in temporal arteritis, 102
Erythropoietin therapy, for orthostatic hypotension, 131, 479
Escitalopram, for depression, 189, 397, 768t
Esophageal cancer, 801
Esophagus, 801
Essential tremor, 423
Estrogen
for Alzheimer's disease prevention, 397
for migraine, 383t
Eszopiclone, 216, 260
Ethacrynic acid, 267
Ethambutol
adverse effects of, 232, 669t
for tuberculous meningitis, 556
Ethanol. See Alcohol
Ethchlorvynol, 232
Ethosuximide, 313t, 317
Ethylene glycol poisoning
delirium in, 168t
optic neuropathy in, 232
Ethylene oxide, 670t
Etomidate, for Cushing's syndrome, 632
Etoposide, 667t
Eustachian tube
dysfunction of, 265
obstruction of, 272
Euvolemic hyponatremia, 643–644, 645t, 646
Evoked potentials, 74–75
cognitive, 75
motor, 75
in multiple sclerosis, 519t, 521
somatosensory, 75
Excitotoxicity, 289–290
Executive functions, 201
Exercise
for back pain, 119
in Parkinson's disease, 421
for prevention of falls, 162
for spinal stenosis, 113
Exertional headache, primary, 100t
Exophthalmos, 238
Exotic ungulate encephalopathy, 461t
Expanded Disability Status Score (EDSS), 523t
Experimental allergic neuritis, 682
Extensor plantar response, 8
External pressure headache, 391
Extinction (sensory phenomenon), 154, 198
Extracranial-to-intracranial bypass surgery, 340
Extramedullary syndromes, 493
Eye(s). See also Ocular disorders
alignment of, 224
anatomy of, 245–246, 245f–246f
dry (keratoconjunctivitis sicca), 228
melanoma of, 238, 238f
movements of, 221
in coma, 176f, 176–177
in dizziness evaluation, 136
video library, 253–254
painful or red, 226–229
physiology of, 221
tumors of, 238
Eye fields, frontal, 197, 197f
Eyelid disorders, 227, 239–240
Ezetimibe, 858
Ezogabine
adverse effects of, 313t
for epilepsy, 313t
pharmacology of, 313t

Fabry's disease, 657, 658t, 856, 876
Face recognition, 199–200
Facet joint, 107
Facet joint hypertrophy, 114
Facial hemiatrophy, 487
Facial myokymia, 487, 518
Facial nerve
anatomy of, 258f, 485f
examination of, 7
injury to, 268
in taste sensation, 258
Facial numbness, 481
Facial pain, 481
Facial weakness, **484**
anatomic considerations in, 484, 485f
facial hemiatrophy, 487
facial myokymia, 487
hemifacial spasm, 487
in multiple sclerosis, 517
Facioscapulohumeral muscular dystrophy, 702f, 707t, 714–715
Factitious illness
characteristics of, 781
visual loss, 235

www.ketabpezeshki.com (021) 66485457 - 66485438

Factor Xa inhibitors, 81, 338
Fall(s), 161
collapsing, 161
drop attacks, 161
in elderly, 157, 161
epidemiology of, 157, 161
gait freezing and, 162
mechanical, 161
prevention of, 162
recurrent, 161
reducing injury risk in, 162
risk factors for, 162, 162t
sensory deficits and, 162
slipping and tripping, 161
toppling, 162
weakness and frailty and, 162
Famciclovir, for viral meningitis, 547
Familial acromegaly, 622
Familial amyloid polyneuropathy, 658t, 659
Familial amyotrophic lateral sclerosis, 452, 453t
Familial Creutzfeldt-Jakob disease, 461t
Familial dementia with amyloid angiopathy and spastic ataxia, 445t
Familial focal epilepsy with variable foci, 301t
Familial hemiplegic migraine, 378–379
Familial spastic paraplegia, 458, 502–503
Fasciculations, 145, 145t
Fatal familial insomnia, 215, 292, 460, 461t
Fatigability, 140
Fatigable weakness, 143
Fatigue, **140**
in adrenal insufficiency, 141
anemia as cause of, 142
approach to the patient, 142–143
cancer-related, 142
cardiovascular causes of, 141
chronic kidney disease as cause of, 141
chronic liver failure as cause of, 141
definition of, 140, 702
differential diagnosis of, 140–142
drugs as cause of, 141
endocrine disorders versus, 141
epidemiology of, 140
episodic, 141
global considerations for, 140
hematologic causes of, 142
in hypercalcemia, 141
in hyperglycemia, 141
in hypoglycemia, 141
in hypothyroidism, 141
increased fatigability, 144
infections as cause of, 141
laboratory testing for, 143
malignancy and, 141–142
malnutrition as cause of, 141
in multiple sclerosis, 141, 517, 530
muscle weakness versus, 140
myasthenic, 692
in neurodegenerative diseases, 141
neurologic disease versus, 140–141
neurologic examination for, 143
obesity as cause of, 141
physical examination of, 142–143
in pregnancy, 142
prognosis for, 143
proinflammatory cytokines in, 143
psychiatric disease versus, 140
psychostimulants for, 143
pulmonary causes of, 141
rheumatologic disorders as cause of, 142
risk management programs for, 220
sleep disorders versus, 141
sleepiness versus, 210
systemic inflammatory disorders as cause of, 142
treatment of, 143
Fazio-Londe syndrome, 457
Feeding disorders, 781–783
Felbamate, 313t
Feline spongiform encephalopathy (FSE), 461t
Femoral neuropathy, 677
Fenoprofen, for pain, 94t
Fentanyl
for pain, 94t, 96
transdermal, 96, 98
Fetal alcohol spectrum disorder, 802
Fetal alcohol syndrome, 802
Fetal nigral dopamine cells, 419
Fetal posterior cerebral artery, 344
Fever
central, 175
in coma, 175
quadriplegic, 504
Fibric acid derivatives, 728t
Fibrillation potential, 145
Fibromuscular dysplasia, 334
Fibromyalgia, 142, 703
Fibrovascular proliferation, 250
Fila, 255
Finger anomia, 196
Fingolimod
action of, 526
for multiple sclerosis, 524t, 526, 856, 875
Fisher's syndrome, 242, 253
Fistula, dural arteriovenous, 360
Flaccidity, 144
Flavor enhancers, 262
Floaters, 234
Fluconazole, 556
Fludarabine, 605, 605t
Fludrocortisone
for orthostatic hypotension, 131, 420, 480
for syncope, 130
for syndrome of inappropriate antidiuretic hormone, 646
Fluid-attenuated inversion recovery (FLAIR), 18
in brain tumors, 592, 594f
in Creutzfeldt-Jakob disease, 466f
in diffuse white matter disease, 188f
in Huntington's disease, 427f
in limbic encephalitis, 609f
in multiple sclerosis, 520f
in seizures, 310
in viral encephalitis, 540, 550f, 550–551, 551t
Flumazenil, 811
Flunarizine
adverse effects of, 385t
for chronic daily headache, 103
for migraine prevention, 385t, 868
Flunitrazepam, 819
Fluoride, for otosclerosis, 266
5-Fluorouracil (5-FU), 605t
Fluoxetine, 860, 882
adverse effects of, 768t
for depression, 768t, 777
dosage of, 768t
for obsessive-compulsive disorder, 773
for pain, 98
for panic disorder, 767
Fluphenazine, 785t
Flurazepam, 770t
Fluvoxamine
for depression, 768t
for obsessive-compulsive disorder, 773
Focal ataxia, 436
Focal ischemia, 323
Focal seizures. See Seizure(s), focal
Folate deficiency, 233
Folinic acid, for megaloblastic anemia prophylaxis, 562
Follicle-stimulating hormone (FSH), 632
Footdrop, 748
Footdrop splints, 456
Foramen magnum syndrome, 493
Foraminal herniation, 173
Forearm exercise test, 705–706
Foreign body, in eye, 226
Fortification spectra, 3, 234
Foscarnet, for viral encephalitis, 553–554
Fosphenytoin, 850, 866
Foster Kennedy syndrome, 261
Fourth ventricle ependymoma, 67f
Fovea, 221
Foveation, 221
Foville's syndrome, 242
Fragile X mental retardation protein, 760
Fragile X pre-mutation, 159
Fragile X tremor/ataxia syndrome, 447t
Frataxin gene, 440
Freezing episodes, in Parkinson's disease, 421
Frenzel eyeglasses, 136
Friedreich's ataxia, 291, 439–442, 440f, 446t
Frontal abulic syndrome, 201–202
Frontal bone fractures, 507
Frontal disinhibition syndrome, 201–202
Frontal eye field, 243
Frontal gait disorder, 159, 160t
Frontal lobe syndrome, 201
Frontal network syndrome, 203
Frontotemporal degenerations, 195
Frontotemporal dementia (FTD), **291**, 398
behavioral variant, 202, 399, 870
clinical features of, 184, 186t, 202, 398–399
functional anatomy of, 182
genetic factors in, 278–279, 291, 399–400
imaging in, 399f, 400
molecular basis of, 184t
olfactory dysfunction in, 259
questions regarding, 853, 870
Frontotemporal dementia (FTD) syndromes, 401f
Frontotemporal lobar degeneration (FTLD), 400, 402f, 870

www.ketabpezeshki.com (021) 66485457 - 66485438

Frovatriptan, for migraine, 382t–383t
FSE. See Feline spongiform encephalopathy (FSE)
FSH. See Follicle-stimulating hormone (FSH)
FTD. See Frontotemporal dementia (FTD)
Fukitin-related protein deficiency, 712, 713t
Fukuyama congenital muscular dystrophy, 712, 713t
Functional Status (FS) Score, 523t
Fundus
  anatomy of, 245–246, 245f–246f
  examination of, 229
  pigmented lesions of, 252, 252t, 252f
Fungal infections, chronic meningitis in, 571t
Furosemide, 267
FUS gene, 184t, 291, 400
FUS/TLS gene, 452, 453t
F-wave studies, 78

GABA. See τ-aminobutyric acid (GABA)
Gabapentin
  adverse effects of, 313t, 661t
  for chronic daily headache, 105
  for cluster headache prevention, 388t
  for epilepsy, 313t
  for neuropathy, 661t
  for pain, 98–99, 529
  pharmacology of, 313t
  for posttraumatic headache, 105
  for SUNCT/SUNA, 389
Gadolinium contrast, 20–21, 850, 864–865. See also Contrast agents
Gag reflex, 7
Gait
  anatomy and physiology of, 157–158
  examination of, 9–10
Gait apraxia, 159
Gait ataxia, 435–436
Gait cycle, 157
Gait disorders, 158t, **158**
  approach to the patient, 160–161
  cautious gait, 158
  cerebellar gait ataxia, 159, 160t
  freezing gait, 159, 162. See also Parkinson's disease (PD)
  frontal, 159, 160t
  in neuromuscular disease, 160
  in Parkinson's disease, 421
  psychogenic, 160
  sensory ataxia, 159–160, 160t
  slowly progressive, 160–161
  spastic, 158
  spastic-ataxic, 158
  stiff-legged, 158–159
  in toxic and metabolic disorders, 160
  video library, 163
Galactorrhea, 623
Galactosemia, ocular involvement in, 235
Galantamine, for Alzheimer's disease, 189, 397, 869
Gallium nitrate, 605t
τ-Aminobutyric acid (GABA)
  alcohol effects on, 799, 860, 883
  anatomic and clinical aspects of, 282t
  structure of, 282t
τ-Hydroxybutyric acid (GHB) abuse, 168, 168t, 819–820
Gamma knife surgery, for trigeminal neuralgia, 483, 872
Gamma motor neurons, 147f
Ganciclovir, for viral encephalitis, 553–554
Gangliocytomas, 620
Gangliogliomas, 596
Ganglion cells, of retina, 221
Ganglionopathy, dorsal root, 613
Gangrenous calcification, 727
Gap junctions, 283
Gardner's syndrome, brain tumors and, 593t
Gaze disorders
  horizontal, 243, 244f
  in multiple sclerosis, 517
  supranuclear, 243
  vertical gaze, 243
Gaze-evoked nystagmus, 244
Gaze stabilization reflex, 221
GBA gene, 414
GBS. See Guillain-Barré syndrome (GBS)
Gegenhalten, 144
Gemfibrozil, 858
Generalized anxiety disorder, **767**
  anticonvulsants for, 770
  clinical manifestations of, 767
  diagnosis of, 771t
  etiology of, 767
  pathophysiology of, 767
  questions regarding, 859, 881
  treatment of, 767–770, 881
Generalized convulsive status epilepticus, 319, 850, 866
Generalized epilepsy with febrile seizures, 301t
Generalized tonic-clonic seizures, 850, 865–866
Generalized tonic-clonic status epilepticus, 320
Gene therapy, for Parkinson's disease, 419–420
Genome-wide association studies, 278
Gentamicin
  intratympanic, for Ménière's disease, 267
  for meningitis, 539t, 542
Gepants, 376
German measles (rubella), congenital, 558
Germ cell tumors, 620
Germinomas, 620
Gerstmann's syndrome, 196
Gerstmann-Strassler-Scheinker (GSS) disease, 292, 460, 461t, 464–465
Gestational diabetes insipidus, 638t, 639
GHB. See τ-Hydroxybutyric acid (GHB)
Ghrelin, 782
Giant cell arteritis
  clinical features of, 102
  erythrocyte sedimentation rate in, 102
  headache in, 102
  ocular involvement in, 230–231, 231f, 242
  questions regarding, 873
  stroke caused by, 334
Gigantism, 627f
Gingivitis, taste disorders in, 260
Gingko biloba, 397, 853, 869
Glasgow Coma Scale, 179, 511, 511t
Glatiramer acetate
  adverse effects of, 525
  for multiple sclerosis, 524t, 525
Glaucoma, **235–236**, 236f
  acute angle-closure, 229, 236
  headache in, 102
  low-tension, 236
  treatment of, 236
  visual field assessment in, 226
Glial-derived neurotrophic factor (GDNF), 420
Glioblastoma(s), 593–595, 595f, 850
Glioma
  brainstem, 66f
  cerebral, 23f
  hypothalamic, 620
  ocular signs in, 226
  optic, 620
Gliomatosis cerebri, 168t, 595
Gliosarcoma, 596
Glossodynia, 260, 262
Glossopharyngeal nerve
  anatomy of, 258f
  examination of, 7
  in taste sensation, 258
Glossopharyngeal neuralgia, 487, 488t, 518
Glucocorticoids
  adverse effects of
    cataracts, 235
    myopathy, 728, 728t, 740
  for allergic conjunctivitis, 227
  for anterior ischemic optic neuropathy, 231
  for brain abscess, 561
  for chronic inflammatory demyelinating polyneuropathy, 688
  for cluster headache, 388
  epidural
    for back pain, 119–120
    for neck pain, 124
  for episcleritis, 229
  for inflammatory myopathies, 739–740
  intranasal, for sinusitis, 262
  for multiple sclerosis, 522, 524
  for muscular dystrophy, 711
  for myasthenia gravis, 697
  for neck pain, 124
  for neuromyelitis optica, 531
  for optic neuritis, 232
  for orbital pseudotumor, 239
  for scleritis, 229
  for spinal cord compression, 855, 873
  systemic
    for Ménière's disease, 267
    for sinusitis, 259
  topical
    for herpes simplex keratitis, 228
    for uveitis, 228
Glue sniffer's neuropathy, 672
Glutamate
  anatomic and clinical aspects of, 282t
  as neurotransmitter, 90
  questions regarding, 883
  structure of, 282t
Glutamic acid decarboxylase 1, 763
Glycine, 282t

www.ketabpezeshki.com (021) 66485457 - 66485438

Glycine receptor, 607t
Glycogen storage diseases, **718**
with exercise intolerance, 719–720
with skeletal myopathy/progressive weakness, 718–719
type II (acid maltase deficiency), 718–719
type III (debranching enzyme deficiency), 719
type IV (branching enzyme deficiency), 719
type VII (phosphofructokinase deficiency), 719
type V (myophosphorylase deficiency), 719
Glycolysis abnormalities, 719
Glycoprotein IIb/IIIa inhibitors, 81
Glycopyrrolate, 478
GM2-gangliosidosis, 453t
Gnathostoma spinigerum/gnathostomiasis, chronic meningitis in, 571t
Gold therapy, 671t
Gonadotrope, 620, 620t
Gonadotropin-producing pituitary adenomas, 632–633
Gonadotropin-releasing hormone-producing tumors, 620
Go-no-go test, 202
Gorlin's syndrome (nevoid basal cell carcinoma syndrome), 593t
Gottron's sign, 731
Gowers' sign, 700, 703f
G protein–coupled receptors (GPCRs), in taste sensation, 257
Graded exercise therapy, for chronic fatigue syndrome, 143, 754–755
Gradenigo's syndrome, 242, 566
Granisetron, for nausea and vomiting, 104
Granule cells, 255
Granulomatosis with polyangiitis (Wegener's)
chronic meningitis in, 574t
ocular disease in, 228
Graphesthesia, 154
Graves' disease, 254
Graves' ophthalmopathy, 238–239, 727
Greater petrosal nerve, 258
GRN gene, 399–400
Growth hormone (GH)
acromegaly and, 626–628
Creutzfeldt-Jakob disease af er treatment with, 464
hypersecretion of, 626
opioid effects on, 809
Growth hormone (GH) receptor antagonists, 629
Growth hormone (GH)-secreting adenomas, 627, 629
Guanfacine, for Tourette's syndrome, 429
Guillain-Barré syndrome (GBS), **681**
antecedent events, 682
autonomic dysfunction in, 476
chronic inflammatory demyelinating polyneuropathy versus, 687
clinical features of, 681–682, 682t
cranial nerve palsies in, 488–489
diagnosis of, 685, 686t
facial nerve disorders in, 487
immunopathogenesis of, 682–685, 683f
incidence of, 877
laboratory evaluation of, 685
neuroimaging of, 70f
pathophysiology of, 685
prevalence of, 681
prognosis of, 687
questions regarding, 856–857, 876–877
recovery from, 687
subtypes of, 681–682, 682t
treatment of, 685–687, 857, 877
weakness in, 147, 149

Haemophilus inf uenzae infections, 535–536. See also Meningitis
Hallervorden-Spatz disease, 412
Hallucinations
alcohol and, 801
chemosensory, 261
in Parkinson's disease, 420
Hallucinosis, peduncular, 345
Haloperidol
for acute alcohol intoxication, 804
for delirium, 367
side effects of, 785t
Hamartin, 600
Hamartomas, hypothalamic, 620
HAND. See HIV-associated neurocognitive disorders
Hand, mechanic's, 731
Hand-Schüller-Christian disease, 619
Hansen's disease. See Leprosy
Hard exudates, 248, 248t
Hashimoto's encephalopathy, 56f, 465–466
Hashish, 815
Haw River syndrome, 439
HBP. See Human Brain Project (HBP)
Headache, **100**
acute, new-onset, 101, 101t, 372
anatomy and physiology of, 100–101
with autonomic symptoms, 101
in brain abscess, 560
"brainfreeze," 391
in brain tumor, 100t, 102
chronic daily, **103**
classification of, 103, 103t
diagnosis of, 103
from medication overuse, 103–104
classification of, 103t, 377t
clinical evaluation of, 101
cluster, 100t, 380f, 386–387, 388t, 852, 868–869
cold-stimulus, 391
depression and, 101
external pressure, 391
in glaucoma, 102
in head injury, 100t, 105
hemicrania continua, 103, 103t, 389
hypnic, 391
in intracranial hemorrhage, 102
medication-overuse, **103–104**, 384
in meningitis, 101–102
migraine. See Migraine
new daily persistent, **104**
clinical features of, 104
description of, 391
diagnosis of, 104t
low cerebrospinal fluid volume headache, 104–105, 105f
posttraumatic, 105
raised cerebrospinal fluid pressure headache, 105
nummular, 391
in papilledema, 233
paroxysmal hemicrania, 103t, 388
phonophobia associated with, 387, 391
photophobia associated with, 387, 391
post–lumbar puncture, 83–84, 84t
primary
description of, 100, 100t, 102, 389–390
sexual activity-related, 390
primary care and, 106
primary cough, 389
primary exercise, 390
primary exertional, 100t
primary stabbing, 100t, 391
primary thunderclap, 390–391
questions regarding, 849, 852, 863–864, 868
secondary, 100, 100t, 101
in subarachnoid hemorrhage, 100t, 101, 372
SUNCT/SUNA, 103, 103t, 386, 387t, 388–389, 852, 869
symptoms of serious underlying disorder, 101t
tension-type, 100t, 377t, 386, 852, 869
triggers for, 852, 868–869
Headache diary, 379
Head drop, 730
Head impulse test, 136
Head injury, **505**. See also specific types
amnesia in, 201
aphasia in, 193
autonomic storm following, 478
brain hemorrhage in, 506f, 506–507
clinical syndromes of, 510
concussion in. See Concussion
contusion in, 506f, 506–507
convulsions af er, 508
cranial nerve injuries, 507–508
diffuse axonal injury in, 506f, 506–507
emergency care of, 505
grading of, 511t, 511–512
headache in, 100t, 105
of intermediate severity, 510–511
intracerebral hemorrhage caused by, 356
minor injury, 510
olfactory dysfunction in, 259
postconcussion syndrome, 512
prevalence of, 505
prognosis of, 511–512
recurrent, dementia caused by, 406
seizures and, 303–305, 508
severe injury, 511
skull fractures in, 507
types of, 505
in war veterans, 790–792, 791t, 795–796
Head tilt test, 242
Head-up tilt test, 474t
Hearing, 264
Hearing aid, 267, 273

www.ketabpezeshki.com (021) 66485457 - 66485438

Hearing loss, **264**
approach to the patient, 266f, 270–271
audiologic assessment of, 271–272
conductive, 265–266
drug-induced, 267
evoked responses in, 272
genetic causes of, 268–270, 269t–270t
imaging studies in, 272–273
ion channel defects causing, 280t
mixed, 268
noise-induced, 270, 275
prevention of, 275
sensorineural, 266–268
treatment of, 273–274
Heart failure (HF), 168t, 169
Heart rate
response to deep breathing, 473, 474t
during sleep, 209
Heat sensitivity, in multiple sclerosis, 517
Hematogenous abscesses, 559
Hematoma
epidural. See Epidural hematoma
spinal, 496
subdural. See Subdural hematoma
Hematomyelia, 496
Hemianopia, 225f
bitemporal, 226
homonymous, 225f, 226
Hemiatrophy, facial, 487
Hemiballismus, 428–429
Hemicrania continua, 103, 103t, 389
Hemifacial spasm, 484, 487, 518
Hemilaminectomy, in lumbar disk disease, 121
Hemiparesis, **146**–147
acute or episodic, 146
cerebral artery occlusion and, 16f
chronic, 147
subacute, 146–147
Hemiplegic migraine, 70f
Hemispatial neglect, 197f, 197–199, 198f
Hemorrhage
brain, traumatic, 506f, 506–507
cerebellar, 356
epidural spinal, 357
intracranial. See Intracranial hemorrhage
pontine, 254
retinal, 230f, 247–248, 247f–248f
subarachnoid. See Subarachnoid hemorrhage
subconjunctival, 227
thalamic, 355
Heparin, 81
Heparin-induced thrombocytopenia (HIT), 81
Hepatic encephalopathy
coma in, 179
delirium in, 168t
neuroimaging of, 69f
Hepatitis, neuropathy in, 665
Hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNs), 335
Hereditary myopathies, **706**, 707t. See also Muscular dystrophy
Hereditary neuropathies
approach to, 650, 650t
Charcot-Marie-Tooth disease. See Charcot-Marie-Tooth (CMT) disease
Fabry disease, 657
Fabry's disease, 658t
familial amyloid polyneuropathy, 658t, 659
hereditary neuralgic amyotrophy, 655t, 657
hereditary neuropathy with liability to pressure palsies, 654t, 657
porphyria, 658t, 659
Tangier disease, 658t, 658–659
Hereditary sensory and autonomic neuropathy (HSAN)
autonomic dysfunction in, 477
clinical features of, 657
genetic factors in, 477, 655t
orthostatic hypotension in, 131
questions regarding, 856, 876
Herniation, cerebral, 172f, 172–173
HERNS (hereditary endotheliopathy, retinopathy, nephropathy, and stroke), 335
Heroin
adverse effects of, 224, 728t, 729
systems effects of, 809
Herpes simplex virus (HSV) infections
encephalitis
magnetic resonance imaging of, 550f
memory loss in, 201
meningitis versus, 540
MRI in, 19f
keratitis, 228
meningitis, 546, 572t
uveitis, 228
Herpes zoster
clinical features of
glossopharyngeal neuropathy, 487
neck pain, 123
neuropathy, 665
ocular, 228
postherpetic neuralgia, 665
pathogenesis of, 92
Herpes zoster ophthalmicus, 228
Hertel exophthalmometer, 238
Heterocyclic antidepressants, for insomnia, 216
Heterotropia, 224
Hexacarbons, neuropathies caused by, 670t, 672
High-voltage electrical injury, 499
Hip pain, 110
Histamine, pain and, 90f
Histiocytosis, 42f
Histiocytosis X, 619
Histoplasma spp. infections
chronic meningitis in, 571t
ocular involvement in, 229
subacute meningitis in, 556
Histoplasmosis, pons, 32f
HIT. See Heparin-induced thrombocytopenia (HIT)
HIV
genome of, 582–583
replication cycle of, 579–582, 581f
structure of, 578–579, 579f
HIV-2, 578
HIV-associated neurocognitive disorders, 584, 586t
HIV infection
classification of, 577, 578t
course of, 583f
depression in, 775
hearing loss in, 267
neurologic manifestations of, 577t, 584–585
Chagas' disease, 589
chronic meningitis, 572t, 576
cognitive impairment, 584–585
cryptococcosis, 585
HIV-associated dementia, 585–587, 587f
meningitis, 547, 585
myelopathy, 589
myopathy, 590
neuropathy, 664
pathogenesis of, 584
peripheral neuropathy, 590
progressive multifocal leukoencephalopathy, 557, 588–589
seizures, 587, 587t
stroke, 587
toxoplasmosis, 587–588, 588f
olfactory dysfunction in, 259
orthostatic hypotension in, 131
pathophysiology of, 583
spinal cord disease in, 589
weakness in, 147
HMG-CoA reductase inhibitors, 728t
H1N1 influenza A vaccine, 212
HNPP (hereditary neuropathy with liability to pressure palsies), 654t, 657
Hodgkin's disease, paraneoplastic syndromes in, 612
Hollenhorst plaque, 230, 230f, 249
Homeless, mental health problems in, 787
Homer-Wright rosettes, 597
Homonymous hemianopia, 616
Hordeolum, 227
Horizontal cells, of retina, 221
Hormone(s), alcohol effects on, 802
Horner's syndrome
in cervical cord lesions, 491
ocular manifestations of, 223, 238, 240
"Hot cross buns sign," 475, 475f
H-reflex studies, 78
HSAN. See Hereditary sensory and autonomic neuropathy (HSAN)
HSV infections. See Herpes simplex virus (HSV) infections
Human Brain Project (HBP), 295–296
Human leukocyte antigens (HLAs), 212
Human T-cell lymphotropic virus-I (HTLV-I) infections, myelopathy and, 500–501
Humoral autoimmunity, in multiple sclerosis, 515
Hunt-Hess scale, for subarachnoid hemorrhage, 372, 373t
huntingtin gene, 427–428
Huntington's disease, **426**

www.ketabpezeshki.com (021) 66485457 - 66485438

clinical features of, 426
dementia in, 182, 404
etiology of, 427
frontal lobe syndrome in, 202
functional anatomy of, 182
gait disorders in, 159
neuroimaging in, 50f, 427f
neuropathology of, 291, 427
ocular involvement in, 243
olfactory dysfunction in, 259
parkinsonism in, 412
prevalence of, 426
treatment of, 427–428
Huntington's disease–like 1, 428
Huntington's disease–like 2, 428
Hutchinson's sign, 228
Hybrid cochlear implant, 273–274, 274f
Hydrocephalus
balance disorders in, 160
coma in, 178
fourth ventricle ependymoma as cause of, 67f
gait disorders in, 158t, 159
normal-pressure, dementia caused by, 188f, 404
obstructive, ocular involvement in, 243
af er subarachnoid hemorrhage, 373
weakness in, 147
Hydromorphone, for pain, 94t
Hydrophobia, in rabies, 552
Hydroxychloroquine, adverse effects of
myopathy, 728t, 729
neuropathy, 668, 668t
ocular, 237
5-Hydroxytryptamine, 376
Hypalgesia, 150
Hyperaldosteronism, weakness in, 726
Hyperalgesia, 89, 150
Hypercalcemia
fatigue caused by, 141
neurologic consultation for, 747
Hypercarbia, delirium in, 168, 168t
Hypercoagulable state, stroke caused by, 334
Hypercortisolism, 630
Hypereosinophilic syndrome, 662
Hyperesthesia, 150
Hyperglycemia
fatigue in, 141
myopia in, 222
Hyperhidrosis, primary, 477–478
Hyperkalemia, neurologic consultation for, 747
Hyperkalemic periodic paralysis (HyperKPP), 280t, 723t, 724–725
Hyperkinetic movement disorders, 422, 423t, 431
Hyperkyphosis, 110
Hyperlipidemia, 332t
Hyperlordosis, 110
Hypermagnesemia, neurologic consultation for, 747
Hypernatremia
adipsic, 642f
hypodipsic, 641–643
neurologic consultation for, 746
Hyperopia, 222
Hyperosmolality, neurologic consultation for, 746
Hyperparathyroidism
delirium in, 168t
muscle weakness in, 726
myopathy in, 858, 879
Hyperpathia, 92, 150–151, 478
Hyperperfusion states
diagnosis of, 743, 743f
etiology of, 742, 743t
neurologic consultation for, 742–744
treatment of, 744
Hyperprolactinemia, 622t, 622–623
Hypersensitivity reactions, chronic meningitis caused by, 573t
Hypertension
atherosclerosis risks, 336
intracranial, 404
optic neuropathy in, 231
retinopathy in, 230–231, 231f
stroke risk in, 332t
supine, 131
Hypertensive encephalopathy, 168t, 356
Hypertensive intracerebral hemorrhage, 355
Hyperthermia, delirium in, 168t
Hyperthyroidism
delirium in, 168, 168t
muscle involvement in, 726
myopathy in, 858
Hypertonic saline
for increased intracranial pressure, 365t
for syndrome of inappropriate antidiuretic hormone, 646–647
Hypertrophic cardiomyopathy, syncope in, 132
Hyperviscosity states, 248
Hypervolemic hyponatremia, 643–644, 645t, 647
Hypesthesia, 150
Hypnic headache, 391
Hypocalcemia, 747
Hypoceruloplasminemia with ataxia and dysarthria, 448t
Hypocupric myelopathy, 502
Hypodipsic hypernatremia, 641–643
Hypoesthesia, 150
Hypoglossal nerve, 7
Hypoglycemia
Bálint's syndrome in, 199
fatigue in, 141
syncope and, 133
Hypokalemia, neurologic consultation for, 746–747
Hypokalemic periodic paralysis (HypoKPP), 280t, 723–724, 724f
Hypomagnesemia, neurologic consultation for, 747
Hypomania, 214
Hyponatremia
euvolemic, 643–644, 645t, 646
hypervolemic, 643–644, 645t, 647
hypovolemic, 643–644, 645t, 647
inappropriate antidiuresis as cause of, 643–647
infectious diseases as cause of, 647
neurologic consultation for, 746
af er subarachnoid hemorrhage, 373
Hypoparathyroidism, muscle weakness in, 726
Hypopyon, 228
Hyposmia, 262
Hypotension, in coma, 175
Hypothalamic masses
craniopharyngiomas, 619
gangliocytomas, 620
germ cell tumors, 620
gliomas, 620
hamartomas, 620
meningiomas, 619
Rathke's cysts, 619
sella chordomas, 619
treatment of, 617–618
types of, 619–620
Hypothalamic-pituitary-adrenal axis, 760
Hypothalamus
masses of. See Hypothalamic masses
in sleep onset, 206
Hypothermia
coma and, 175
delirium in, 168t
for hypoxic-ischemic encephalopathy, 367
Hypothyroidism
depression in, 774
fatigue in, 141
gait ataxia caused by, 435–436
muscle disorders in, 726
myopathy in, 858, 879
neuropathy in, 661
Hypovolemic hyponatremia, 643–644, 645t, 647
Hypoxemia, delirium in, 168, 168t
Hypoxic-ischemic encephalopathy, 323, 366–367, 367f

Iatrogenic Creutzfeldt-Jakob disease, 460, 461t
Iatrogenic polydipsia, 638
IBD. See Inflammatory bowel disease (IBD)
IBPN (immune-mediated brachial plexus neuropathy), 678
Ibuprofen
for migraine, 382t
for pain, 94t
ICAM-1 (intercellular adhesion molecule-1), 584
ICP. See Intracranial pressure (ICP)
Ideational apraxia, 195
Idebenone, 441
Ideomotor apraxia, 195
Idiopathic torsion dystonia, 424
Ifosfamide, 605, 605t
IKBKAP gene, 477
Ileus, postoperative, 96
Iloperidone, 785t
Imipramine
adverse effects of, 768t
for depression, 768t
dosage of, 768t
for pain, 94t
Immune-mediated brachial plexus neuropathy (IBPN), 678
Immune myelopathies, 497–499
Immune neuropathies, 684f

www.ketabpezeshki.com (021) 66485457 - 66485438

Immunocompromised patient, primary central nervous system lymphoma in, 596–597
Immunodeficiency viruses, 578
Immunomodulators
  for inflammatory myopathies, 741
  for myasthenia gravis, 878
Immunosuppressive therapy
  chronic meningitis associated with, 576
  for myasthenia gravis, 697
Implicit memory, 200
Impotence, cocaine and, 811
Imprinting, 279
Inclusion body myositis, **730**
  clinical features of, 730, 731t, 731–732
  diagnosis of, 737–739, 738t, 740f
  differential diagnosis of, 735–737
  drug-induced, 737
  genetic factors in, 732
  muscle damage in, 734, 735f
  nonimmune factors in, 734
  prognosis of, 741
  treatment of, 739–741
  viral infections and, 734–735
Incus, 264
Indomethacin
  for pain, 94t
  for paroxysmal hemicrania, 388
  for primary cough headache, 389
  for primary exercise headache, 390
  for primary stabbing headache, 391
  for sexual activity-related primary headache, 390
Induced pluripotent stem cells (iPSCs), 288
Infantile-onset spinocerebellar ataxia, 448t
Infants, seizures in, 304t
Infections
  Acanthamoeba, 571t
  adenovirus, 227
  Anaplasma spp., 540
  Angiostrongylus spp., 571t
  Aspergillus, 571t
  Baylisascaris procyonis, 552, 572t
  Blastomyces spp., 571t
  Brucella spp., 229, 570t
  Campylobacter spp., 682
  central nervous system. See Central nervous system (CNS), infections of
  Chlamydia trachomatis, 228
  Cryptococcus spp., 555–556, 571t, 585
  cytomegalovirus
    myelopathy and polyradiculopathy in, 589–590
    neuropathy in, 665
  echovirus, 572t
  Epstein-Barr virus (EBV), 546, 665
  fatigue caused by, 141
  fungal, 571t
  Haemophilus influenzae, 535–536
  HIV. See HIV infection
  Listeria monocytogenes, 535–536, 541t, 542. See also Meningitis
  Naegleria, 551
  Neisseria meningitidis, 535
  Nocardia spp., 570t
  parameningeal, 570t
  respiratory tract
    mastoiditis, 242, 559
    olfactory disorders in, 259
  Toxoplasma gondii. See Toxoplasma gondii infection
  urinary tract
    delirium in, 168, 168t
    in multiple sclerosis, 530
  Xylohypha, 571t
Infective endocarditis
  retinal hemorrhage in, 229
  valvular vegetations caused by, 330
Inferior petrosal venous sampling, 630
Inferior pontine syndrome, lateral/medial, 348f
Inflammation, nociceptor-induced, 89
Inflammatory bowel disease (IBD)
  neuropathy in, 663
  ocular involvement in, 229
Inflammatory mediators, in sensitization, 89
Inflammatory myelopathies, 497–499
Inflammatory myopathies
  autoantibodies in, 733
  clinical features of, 730–732, 731t
  diagnosis of, 737–739, 738t, 739f–740f
  differential diagnosis of, 735–737
  drug-induced, 737
  immunogenetics in, 733
  immunopathologic mechanisms in, 733–734, 735f
  malignancies associated with, 732
  overlap syndrome, 732
  pathogenesis of, 733–735
  prevalence of, 730
  prognosis of, 741
  treatment of, 739–741
  viral infections associated with, 734–735
Influenza
  description of, 259
  vaccine for, Guillain-Barré syndrome and, 682
Insomnia
  acute, 214
  antihistamines for, 216
  benzodiazepine receptor agonists for, 216
  causes of, 214
  chronic, 214
  cognitive behavioral therapy for, 215
  in dementia patients, 215
  drugs for, 207f, 208
  drugs of abuse as cause of, 214
  evaluation of, 209–210, 213–215
  fatal familial, 215, 292, 460, 461t
  inadequate sleep hygiene as cause of, 214–215, 215t
  medical conditions as cause of, 214–215
  medications as cause of, 214
  medications for, 215–216
  neurologic disorders as cause of, 215
  psychiatric conditions as cause of, 214
  psychophysiologic factors associated with, 214
  rebound, 214
  stress as cause of, 208
  treatment of, 207f, 208, 215–216
Insufficient sleep, 211
Insulin growth factor-1, 626–627, 629
Integrase, 581
Intercellular adhesion molecule 1 (ICAM-1), 584
Interferon-ß1a (IFN-ß1a), 524t, 525, 856, 875
Interferon-ß1b (IFN-ß1b), 524t, 525
Interferon-ß (IFN-ß), 524t, 525
Interictal behavior, 320–321
Internal carotid artery
  dissection of, 332
  occlusion of, 343f, 343–344, 344f
Internuclear ophthalmoplegia, 243, 244f, 253
Interventional neuroradiology, 26
Intervertebral disk
  anatomy of, 107, 108f
  herniation of
    diagnosis of, 111–112
    imaging in, 112, 113f
    nerve compression in, 109f
    pain mechanism in, 111–112, 112t
    physical examination in, 110t, 111–112
    weakness in, 147
  replacement, 120
Intracerebral hemorrhage
  aphasia in, 193
  hypertensive, 355
Intracranial atherosclerosis, 340
Intracranial hemorrhage, **353**
  anticoagulant therapy and, 356
  brain tumor and, 356
  in cerebral amyloid angiopathy, 356
  clinical outcomes of, 358t
  in cocaine users, 356
  diagnosis of, 353
  etiology of, 323, 354t, 356–357
  headache in, 102
  head injury and, 356
  hypertensive encephalopathy and, 356–357
  intraparenchymal, 355f, 356–357
  laboratory/imaging evaluation of, 357
  lobar, 356
  prevention of, 358–359
  primary intraventricular, 357
  prognosis of, 358t
  treatment of, 354, 357–358
Intracranial hypertension, 404, 851–852, 867
Intracranial meningitis, 568–569
Intracranial pressure (ICP)
  increased
    in bacterial meningitis, 538, 543
    headache with, 105
    in intracranial hemorrhage, 358
    monitoring of, 364, 364f
    ocular manifestations of, 233, 233f, 242
    pathophysiology of, 363, 363f
    signs of, 365
    treatment of, 364–365, 365t
  low, ocular manifestations of, 242
Intramedullary syndromes, 493
Intraocular pressure, increased, 229, 235–236
Intraparenchymal hemorrhage, hypertensive, 355f, 356–357
Intrasellar tumors, 616

www.ketabpezeshki.com (021) 66485457 - 66485438

Intravenous immunoglobulin (IVIg)
for chronic inflammatory demyelinating polyneuropathy, 688
for dermatomyositis, 741
for GBS, 686–687, 857, 877
for multiple sclerosis, 529
for myasthenia gravis, 697–698, 878
for stiff-person syndrome, 613
Intravenous iodinated contrast
allergies to, 17, 17t
description of, 14
Invasive sinonasal aspergillosis, 36f–37f
Ion channel disorders, 280t, 280–281
Ionotropic receptors, 281
Ipr4, 693
iPSCs. See Induced pluripotent stem cells (iPSCs)
Iridectomy, laser, 229
Iridocyclitis, 229
Iritis, 229
Iron, brain accumulation of, 433
Isaacs' syndrome, 614, 704
Ischemia
bilateral brainstem, 347
cerebral, 323, 325f
Ischemic cascade, 361–362
Ischemic penumbra, 324
Ischemic stroke, **324**
etiology of, 328, 330t
artery-to-artery embolic, 330–332
cardioembolic, 328–330, 329f
pathophysiology of, 324–325, 325f, 329f
treatment of, **325**
anticoagulants in, 328
antiplatelet agents in, 327–328
approach to, 324f, 325
endovascular techniques in, 326–327
intravenous thrombolysis in, 326, 327t
medical support in, 325–326
neuroprotective agents in, 328
rehabilitation in, 328
rtPA in, 326, 327t, 851, 866
stroke centers in, 328
Ishihara color plates, 224
Isocarboxazid, for depression, 768t
Isoflurane anesthesia, 850
Isometheptene, for migraine, 382t, 384
Isoniazid
adverse effects of
neuropathy, 669t, 672
optic neuropathy, 232
questions regarding, 857, 876
for tuberculous meningitis, 556
Isoprinosine, for subacute sclerosing panencephalitis, 558
IVIg. See Intravenous immunoglobulin (IVIg)

JC virus infection, in HIV infection, 557, 588–589
Jefferson fracture, 59f
Jerk nystagmus, 244
Jervell and Lange-Nielsen syndrome, 268, 270t, 280t
Jet lag disorder, **220**
Joints, position testing of, 152t, 153
Joubert's syndrome, 448t
Juvenile myotonic epilepsy, 300, 302

Kallmann's syndrome, 261
Kayser-Fleischer ring, in Wilson disease, 433
KCNQ2 gene, 301t
Kearns-Sayre syndrome, 446t
clinical features of, 721
diagnosis of, 721
genetic factors in, 721
mitochondrial DNA mutation in, 721
ocular manifestations of, 237, 240
treatment of, 721
Kennedy's disease, 457
Keratic precipitates, 229
Keratitis, 228
Keratoconjunctivitis, 228
Keratoconjunctivitis sicca, 228
Keratoconus, 240
Kernig's sign, 533
Kernohan-Woltman sign, 173
Ketamine
abuse of, 168, 168t, 820
antidepressant effects of, 761
Ketoconazole, for Cushing's syndrome, 632
Ketorolac
for conjunctivitis, 227
for pain, 93, 94t
Kjer's dominant optic atrophy, 226
Korsakoff's psychosis, 369
Korsakoff's syndrome, 405, 800
Krabbe's disease, 68f
Kugelberg-Welander disease, 457
Kuru, 292, 460, 461t
Kussmaul respiration, 177

Labyrinthectomy, for Ménière's disease, 268
Labyrinthine infarction, 267
Lacosamide, 314t
Lacrimal system, obstruction of, 228
Lacrimation, with headache, 101
Lactic acidosis, 850, 864–865
Lactobacillus rhamnosus, 287
Lactotrope, 620, 620t
Lacunar infarction, 43f–44f, 332
Lacunar syndromes, 333
LaFora's disease, 301t
Laforin, 301t
Laing's distal myopathy, 716t, 717
Lambert-Eaton myasthenic syndrome (LEMS)
cranial nerve palsy in, 242, 695
diagnosis of, 695
in lung cancer, 609
muscle response to repetitive nerve stimulation in, 79
myasthenia gravis versus, 878
paraneoplastic, 609
reflex responses in, 145
treatment of, 695
weakness in, 149t
Laminectomy, for neck pain, 124
Lamotrigine, 865
adverse effects of, 314t, 317, 780t
dosage of, 314t, 780t
for epilepsy, 314t
for focal seizures, 312
for generalized seizures, 317
pharmacology of, 314t
for SUNCT/SUNA, 389
for trigeminal neuralgia, 483, 872
Lancinations, 150
Language
assessment of, 5, 191–192
perisylvian network for, 191
Lanreotide, for acromegaly, 628
Laser iridectomy, 229
Laser therapy, for neck pain, 124
LASIK, 222
Lateral femoral cutaneous neuropathy, 676–677, 748f
Lateral geniculate body, 221, 226
Lateral medullary syndrome, 346, 347f
Lateral sclerosis, 449, 503
Latex agglutination assay, 539
LCM (lymphocytic choriomeningitis), 547, 572t
Lead poisoning
clinical features of, 406
neuropathy in, 670t, 672
optic neuropathy in, 232
treatment of, 405
Leber hereditary optic neuropathy (congenital amaurosis)
clinical features of, 232
genetic factors in, 232
treatment of, 237
visual fields in, 226
Leflunomide, 669t
Leigh's disease, 68f
LEMS. See Lambert-Eaton myasthenic syndrome (LEMS)
Lennox-Gastaut syndrome, 302
Lenticulostriate arteries, 341
Lentiviruses, 578
Leprosy
complications of, 229
neuropathy in, 663–664
ocular involvement in, 229
Leptomeningeal metastases, 602f, 602–603
Leptospira/leptospirosis, 570t
Leucine-rich glioma-inactivated 1 antibodies, 611
Leukemia, ocular invasion by, 238
Leukoaraiosis, 335
Leukodystrophy(ies), 407
Leukoencephalopathy
reversible posterior, 357
af er whole-brain radiation therapy, 604
Leukotrienes, pain and, 89
Levetiracetam, 314t
Levodopa
action of, 414–416
adverse effects of, 414–416, 416f, 421
for dystonia, 424–425
for Parkinson's disease, 414–421, 416f, 419t, 421, 422f, 854, 871
Levomilnacipran
adverse effects of, 768t
for depression, 768t
dosage of, 768t
Levorphanol, for pain, 94t, 98

www.ketabpezeshki.com (021) 66485457 - 66485438

Lewis-Sumner syndrome, 687
Lewy bodies, 413
Lewy body variant of Alzheimer's disease, 403
LGI1 gene, 301t
LGMD. See Limb-girdle muscular dystrophy (LGMD)
LH. See Luteinizing hormone (LH)
Lhermitte's sign/symptom, 3, 121, 155, 517–518, 849, 863
Lidocaine, for neuropathy, 99, 661t
Lidoderm patch, 661t
Li-Fraumeni syndrome, brain tumors and, 593t
Ligament
  traumatic injury to, 60f
  uterosacral, 117
Light-headedness, 135
Limb(s)
  alien, 195, 402
  apraxia, 195
  dystonias of, 425
Limb-girdle muscular dystrophy (LGMD)
  autosomal dominant, 707t
  autosomal recessive, 709t–710t
  classification of, 711
Limbic encephalitis
  clinical features of, 405, 609
  neuroimaging of, 27f–28f, 609f
  pathogenesis of, 607t
Limbic network, for memory, 200–201
Limulus amebocyte lysate assay, 539–540
LINGO1 gene, 423
Lingual nerve, 258
Lipid(s)
  defects in metabolism of, 720
  as energy source, 720
Lipid-lowering agents, 858, 879
Lip reading, 274
Lissencephaly, classic, 302t
Listeria monocytogenes infections, 535–536, 541t, 542. See also Meningitis
Lithium
  adverse effects of
    common, 779, 780t
    nystagmus, 244
    rare, 780t
  for bipolar disorder, 779–780, 780t
  for cluster headache prevention, 388t
  dosage of, 780, 780t
  toxic neuropathy caused by, 670t
Liver, alcohol effects on, 801
Liver disease/failure
  delirium in, 168, 168t
  neuropathy in, 663
Lobar hemorrhage, 356
Locked-in state, 172, 348
Locked-in syndrome, 254
Locus ceruleus, 761f
Logopenic-variant primary progressive aphasia, 196
Long QT syndrome, 132
Loop diuretics, 267
Lorazepam
  for acute alcohol intoxication, 804
  for bipolar disorder, 780
  for generalized anxiety disorder, 770t
Lordotic posture, 702, 703f
Lower motor neuron diseases, 453t–454t, 457, 871. See also Amyotrophic lateral sclerosis (ALS)
Lower motor neuron (neuropathic) weakness, 145, 145t
Lower motor neuron pathways, 147f
Low-molecular-weight heparin, 81
Low-tar cigarettes, 824
Loxapine, 785t
LRRK2 gene, 410, 412–414
LSD (lysergic acid diethylamide), 818
Lumbar disk disease, 111–113
Lumbar fusion, 120
Lumbar plexus, 679f
Lumbar puncture, 80
  analgesia for, 81–82
  bleeding af er, 80
  in coma, 177
  in delirium evaluations, 170
  in dementia evaluations, 188
  headache following, 83–84, 84t, 105
  imaging and laboratory studies prior to, 80
  needles for, 84, 84f
  in neurologic critical illness, 364
  normal values, 84t, 85
  patient positioning for, 82, 82f
  technique, 82–83
Lumbar spinal stenosis, 113, 114f
Lumbosacral plexopathy, 679–680, 680t
Lumbosacral plexus, 679f
Lumbosacral radiculopathy, 110t
Lung cancer
  metastatic, 238, 600t, 601f
  small cell, 609–610, 690
Lupus erythematosus
  delirium in, 168t
  ocular involvement in, 228, 230
Lurasidone
  for schizophrenia, 785t
  side effects of, 785t
Luteinizing hormone (LH), 632
Lyme borreliosis (Lyme disease)
  chronic meningitis in, 570t
  neuropathy in, 664
  ocular involvement in, 229
Lymphocytic choriomeningitis (LCM), 547, 572t
Lymphocytic meningitis, 573t
Lymphoid malignancies
  central nervous system, primary, 596–597, 597f
  metastatic, 238
  neuropathy in, 666
  paraneoplastic syndromes in, 613
  weakness in, 147
Lysergic acid diethylamide (LSD), 818

Machado-Joseph disease, 436, 438–439, 442, 443t, 457
Macroadenomas, 616, 624–625, 627
Macula
  cherry red spot at, 249, 250f
  description of, 221, 224, 246
  ganglion cells of, 226
Macular degeneration, 236f, 236–237
  dry (nonexudative), 236
  treatment of, 237
  wet (exudative), 236
Macular hole, 238
Magnesium supplements, for migraine, 262
Magnetic resonance angiography (MRA)
  in neurologic disease, 22
  phase-contrast, 22
  TOF imaging, 22
Magnetic resonance imaging
  in Friedreich's ataxia, 440f
  in pituitary adenoma, 616f
  in SCA1, 437f
  in sellar masses, 616f, 616–617
Magnetic resonance imaging (MRI), 17
  in acute disseminated encephalomyelitis, 53f
  in acute transverse myelitis, 52f
  in adrenoleukodystrophy, 68f
  in Alzheimer's disease, 188f
  in amyotrophic lateral sclerosis, 451f
  in anterior dens dislocation, 58f
  in arteriovenous malformation in spine, 500f
  in aspergillosis, 34f, 36f–37f
  in astrocytoma, 595f
  in Baló's concentric sclerosis, 54f–55f
  in Behçet's syndrome, 37f
  in Bell's palsy, 51f, 486f
  in brachial plexopathy, 57f–58f
  in brain abscess, 560f, 560–561
  in brain metastases, 601f
  in brainstem glioma, 66f
  in brain tumors, 592, 595f, 597f
  in candidiasis in newborn, 34f
  in cavernomas, 65f
  in central nervous system aspergillosis, 34f
  in central nervous system tuberculosis, 28f–29f
  in central nervous system vasculitis, 45f–46f
  in central pontine myelinolysis, 368, 368f
  in cerebral abscess, 18f
  in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), 44f–45f
  in C2 facet fracture, 58f
  complications of, 21–22
  in compression fracture, 58f
  contraindications to, 22, 22t
  contrast agents, 20–21
  in Creutzfeldt-Jakob disease, 466f
  in demyelinating disease, 62f
  in diffuse white matter disease, 188f
  in epidural hematoma, 59f
  in epidural metastases, 603f
  in epidural spinal compression, 494f
  in facet fracture, 58f
  in fourth ventricle ependymoma causing hydrocephalus, 67f
  in frontotemporal dementia, 399f
  functional, 24, 197f, 294–295
  in glioblastoma, 595f
  guidelines for, 14t
  in Guillain-Barré syndrome, 70f

www.ketabpezeshki.com (021) 66485457 - 66485438

in Hashimoto's encephalopathy, 56f
in hearing loss, 273
in histiocytosis, 42f
in histoplasmosis, 32f
in Huntington's disease, 50f, 427f
in hypoxic-ischemic encephalopathy, 367f
in intramedullary astrocytoma, 495f
in invasive sinonasal aspergillosis, 36f–37f
in Jefferson fracture, 59f
in Krabbe's disease, 68f
in lacunar infarction, 43f–44f
in Leigh's disease, 68f
in leptomeningeal metastases, 602f
in ligament injury af er trauma, 60f
in limbic encephalitis, 27f–28f
in low cerebrospinal fluid volume headache, 105f
in meningioma, 598f
in meningitis, 540
in mesial temporal lobe epilepsy, 303f
in middle cerebral artery stenosis, 43f
in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome, 67f
in moyamoya disease, 69f
in multiple sclerosis, 519t, 519–521, 520f
in multiple system atrophy, 49f, 475f
in neurocutaneous melanosis, 64f
in neurofibromatosis type 1, 62f
in neurofibromatosis type 2, 63f
in neurosarcoid, 37f–42f
in neurosyphilis, 29f–31f
in odontoid fracture, 60f
in paraneoplastic encephalitis, 610f
in pathologic fracture, 60f
perfusion, 24
in pilocytic astrocytoma, 66f
in primary central nervous system lymphoma, 574f, 596, 597f
in progressive multifocal leukoencephalopathy, 557
questions regarding, 849, 864
relaxation times, 18t
in retropharyngeal sof tissue mass, 59f
in sacral insufficiency fracture, 60f
in seizures, 310
in sickle cell disease, 69f
in spinal cord infarction, 52f
in spinal epidural abscess, 496f
in stroke, 351–352, 353f
in Sturge-Weber syndrome, 65f
in subdural empyema, 564, 564f
in subdural hematoma, 61f
in superior sagittal sinus thrombosis, 46f–49f
in syringomyelia associated with Chiari malformations, 501f
T1 and T2 relaxation times, 17–19, 18t
in teardrop fracture, 61f
technique, 17–21, 18t, 18f–20f
in thoracic meningioma, 495f
in tuberous sclerosis, 63f
in vasculitis, 45f–46f
in vestibular schwannoma, 599f
in viral encephalitis, 19f, 550–551, 551t
in von Hippel-Lindau disease, 64f
in Wernicke's disease, 369f
in X-linked adrenoleukodystrophy, 68f
Magnetic resonance neurography, 24
Magnetoencephalography (MEG), 74, 309
Major depression, 775, 775t, 777f, 860, 882–883
Malignant hyperthermia, 717
Malignant melanoma, choroidal, 251, 251f
Malingering, 235, 261, 781
Malleus, 264
Malnutrition, 141
Mammosomatotrope, 620, 620t
Mania
insomnia caused by, 214
mixed, 778
Mannitol, for increased intracranial pressure, 365t
MAO-B inhibitors. See Monoamine oxidase type B (MAO-B) inhibitors
MAOIs. See Monoamine oxidase inhibitors (MAOIs)
Maprotiline, 777
MAPT gene, 399–400
Marburg's variant, multiple sclerosis, 530
Marchiafava-Bignami disease, 404
Marcus Gunn pupil, 223, 223f
Marijuana, 815
dependence on, 816
physical effects of, 816
THC in, 283, 815
therapeutic applications, 816–817
tolerance to, 816
Marijuana use/abuse, 815
acute and chronic intoxication, 815–816
adverse effects of, 816
prevalence of, 815
withdrawal signs, 816
Marinesco-Sjögren syndrome, 446t
Markesbery-Griggs distal myopathy, 716t, 717
Mastoiditis, 242, 559
Maudsley family-based therapy, for anorexia nervosa, 782
MBP (myelin basic protein), 284f
McArdle disease (myophosphorylase deficiency), 719
McCune-Albright syndrome, 622
MCI (mild cognitive impairment), 184
McLeod syndrome, 428
MCTD (mixed connective tissue disease), 662
MDCT (multidetector computed tomography), 13–14
MDMA (ecstasy), 168, 168t, 817
MDPV, 817–818
Measles (rubeola), 531, 558
Mechanical ptosis, 240
Mechanical ventilation, in coma, 179
Mechanic's hands, 731
Mechlorethamine (nitrogen mustard), 605t
Meckel's cave, 37f
Meclizine, for vertigo, 139t
Medial medullary syndrome, 346, 347f
Median neuropathy, 676
Medication-overuse headache, 103–104, 384
Medulloblastoma, 593, 597
MEG (magnetoencephalography), 74, 309
Meibomian gland carcinoma, 227
Meibomitis, 227
Melanoma
of eye, 238, 238f
metastatic to central nervous system, 600t
retinopathy in, 607t, 614
Melanopsin, 221
MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome
characteristics of, 446t
clinical features of, 722
hearing loss in, 270
mitochondrial DNA mutation in, 722
neuroimaging of, 67f
Melatonin
for cluster headache prevention, 388t
for sleep, 209, 219
Melkersson-Rosenthal syndrome, 486
Melodic intonation therapy, 193
Memantine, for Alzheimer's disease, 190, 397, 853, 869
Memory
assessment of, 5, 200–201, 295
implicit, 200
limbic network for, 200–201
loss of, in Alzheimer's disease, 201, 853, 869
retentive, 202
working, 202
MEN 1. See Multiple endocrine neoplasia type 1 (MEN 1)
MEN 4. See Multiple endocrine neoplasia type 4 (MEN 4)
Ménière's disease
clinical features of, 137, 267
diagnosis of, 137, 272
dizziness in, 135
epidemiology of, 267
hearing loss in, 267, 270, 272
nystagmus in, 244
pathophysiology of, 137, 267
treatment of, 137–138, 267
vertigo in, 267
MENIN, 621
Meningeal biopsy, in chronic meningitis, 575
Meningioma
clinical features of, 598
imaging in, 273, 598, 598f
ocular signs in, 226
parasagittal, 147
pathophysiology of, 598
in sellar region, 619
thoracic, 494, 495f
treatment of, 598
Meningitis
approach to the patient, 533–534, 534f–535f
aseptic, 585
bacterial, **535**
cerebrospinal fluid abnormalities in, 539t
chronic, 570t
clinical features of, 538
definition of, 535
diagnosis of, 538–540, 539t

www.ketabpezeshki.com (021) 66485457 - 66485438

Meningitis (Cont.):
differential diagnosis of, 540
epidemiology of, 535
etiology of, 535–536
gram-negative, 541t, 542
H. influenzae, 535–536
incidence of, 535–536
increased ICP in, 543
L. monocytogenes, 535–536, 541t, 542
M. tuberculosis, 555
meningococcal, 535–536, 541t, 541–542
mortality data, 543
pathophysiology of, 536–538, 537f
pneumococcal, 535, 541t, 542
prognosis of, 543
staphylococcal, 536, 541t, 542
treatment of
adjunctive therapy in, 542–543
algorithm for, 534f–535f
antimicrobial therapy based on pathogen, 541t, 541–542
dexamethasone, 542–543
empirical antimicrobial therapy, 539t, 541
ICP-related, 543
basal, 569
chronic, **568**
approach to the patient, 569, 572
cerebrospinal fluid analysis in, 574–575
clinical features of, 568t, 568–569
epidemiology of, 569
in HIV infection, 576
imaging in, 574, 574f
in immunosuppressed patients, 576
infectious causes of, 569, 570t–572t
laboratory studies in, 575
meningeal biopsy in, 575
noninfectious causes of, 573t–574t
pathophysiology of, 568–569
systemic manifestations of, 569
treatment of, 575
Coccidioides, 571t
Cryptococcus, 555–556, 571t, 585
delirium in, 168, 168t
fungal, 555–556
headache in, 101–102
hearing loss in, 267
intracranial, 568–569
Mollaret's, 573t
in neurosyphilis, 556
spinal, 569
subacute, **555**–556
viral, **543**
arborvirus, 546
clinical features of, 543
differential diagnosis of, 545
EBV, 546
enteroviral, 545–546
epidemiology of, 544
etiology of, 543t, 543–547
herpes simplex virus, 546, 572t
in HIV infection, 547, 585
laboratory evaluation of, 544–545
lymphocytic choriomeningitis, 547
in mumps infection, 547
polymerase chain reaction amplification of viral nucleic acid in, 544
prevention of, 547–548
prognosis of, 547
treatment of, 547–548
VZV, 546
weakness in, 147
Menstrual disorders, 117
Mental disorders
anorexia nervosa, 782
avoidant/restrictive food intake disorder, 782
binge-eating disorder, 783
bulimia nervosa, 782–783
DSM-5, 765
eating disorders, 781–783
feeding disorders, 781–783
generalized anxiety disorder, 767–770, 770t
global considerations, 765–766
insomnia caused by, 214
Munchausen's syndrome, 781
overview of, 765
panic disorder, 766–768
phobic disorders, 770–771
pica, 781
prevalence of, 765
rumination disorder, 781–782
somatic symptom disorder, 780–781
stress disorders, 771–773, 772t
vertigo in, 139
Mental status assessment, 5–6
Meperidine
myopathy caused by, 728t
for pain, 94t
Meralgia paresthetica, 676–677
Mercury exposure/poisoning
clinical features of, 406
neuropathy caused by, 670t, 672
Meropenem, for meningitis, 539t, 541
Merosin deficiency, 712, 713t
MERRF (myoclonic epilepsy and ragged red fiber) syndrome
characteristics of, 446t
clinical features of, 722
diagnosis of, 722
hearing loss in, 270
mitochondrial DNA mutation in, 722
Mesial temporal lobe epilepsy, 302, 302t, 303f
Metabolic disease, coma caused by, 173–174
Metabolic encephalopathy, 194, 202, 367–368
Metabolic myopathies, **725**
Metabotropic receptors, 281
Metachromatic leukodystrophy (MLD), 407
Metamorphopsia, 236–237
Metastatic disease
to brain. See Brain tumors, metastatic
to eye, 238
pituitary, 619–620
questions regarding, 849, 863
to spine, 114
epidural, 603f, 603–604
leptomeningeal, 602f, 602–603
Methadone, 809
as maintenance drug, 811
for opiate detoxification, 811
for pain, 94t, 98
Methamphetamine
abuse of, 817
intracerebral hemorrhage caused by, 356
Methanol poisoning, 232
Methocarbamol, for back pain, 119
Methotrexate
adverse effects of, 605t
for inflammatory myopathies, 740–741
for multiple sclerosis, 529
for primary central nervous system lymphoma, 597
Methylnaltrexone, 96
Methylphenidate
for fatigue in multiple sclerosis, 530
for narcolepsy, 213
Methylprednisolone
for multiple sclerosis, 524, 529
for optic neuritis, 232
for vertigo, 139t
Methysergide
adverse effects of, 385t
for cluster headache, 388, 388t
for migraine headache prevention, 384, 852, 868
for migraine prevention, 385t
for primary exercise headache, 390
Metoclopramide, for migraine, 382t, 384
Metoprolol
adverse effects of, 385t
for migraine prevention, 385t
Metronidazole
adverse effects of, 668t
for meningitis, 539t, 541
Metyrapone, for Cushing's syndrome, 632
Mexiletine
adverse effects of, 661t
for neuropathy, 661t
for pain, 99, 529
Meyer's loop, 226
Microadenomas, 624–625, 629, 631
Microaneurysms, retinal, 248, 248t
Microbiota, 286–287
Microsomal triglyceride transfer protein, 440
Microvascular decompression
for SUNCT/SUNA, 389
for trigeminal neuralgia, 483
Midbrain syndrome, lateral/medial, 351f
Middle cerebral artery
lesion in territory of, 193–194
occlusion of, 16f, 329, 341–342, 342f, 352f
stenosis of, 43f
Middle cerebral artery stroke, 194
Midodrine, for orthostatic hypotension, 131, 480
Midpontine syndrome, lateral/medial, 349f
Mifepristone, for Cushing's syndrome, 632
Migraine, 100t, **376**
acephalgic, 380
acephalic, 324
autonomic symptoms in, 101
basilar artery, 380
basilar-type, 380
brainstem pathways involved in, 378f
classification of, 377t
clinical features of, 379–380

www.ketabpezeshki.com (021) 66485457 - 66485438

definition of, 376
diagnosis of, 379–380, 380t, 868
dopamine's role in, 378, 868
familial hemiplegic, 378–379
headache diary for, 379
hemiplegic, 70f
5-hydroxytryptamine in, 376
ion channel defects causing, 280t
memory loss in, 201
ocular manifestations of, 234–235
pathogenesis of, 92, 376, 378–379
patient education about, 380
positron emission tomography of, 379f
prevention of, 384, 385t, 852, 868
questions regarding, 852, 868
retinal, 230
sensory sensitivity associated with, 376
symptoms associated with, 378t
taste disorders in, 260
treatment of, 380–385
acute attack therapies, 381, 382t–383t
dopamine receptor antagonists, 382t, 384
5-HT1 agonists, 382t
5-HT/d1B/1D/D receptor agonists, 381, 383
lifestyle changes, 380
nonpharmacologic, 380–381
nonsteroidal anti-inflammatory drugs, 381, 382t
opioids, 384
preventive, 384, 385t
triggers of, 376, 868
vascular theory of, 868
vertigo in, 135, 137
Migraine Disability Assessment Score (MIDAS), 380, 381f
Mild cognitive impairment (MCI), 184, 189f, 869
Millard-Gubler syndrome, 242
Miller Fisher syndrome, 681–682, 682t, 684t, 686t
Minimally conscious state, 171
Mini-Mental Status Examination (MMSE)
in delirium evaluation, 167
in dementia, 187
in neurologic examination, 5–6
Miosis, 224
Mirror neuron systems, 295
Mirtazapine, 557, 768t, 778
Misonidazole, 668t
Mitochondria
in apoptosis, 285f, 290
dysfunction, in neurodegenerative disease, 291
Mitochondrial ataxias, 441
Mitochondrial DNA diseases, 722
Mitochondrial DNA skeletal muscle–central nervous system syndromes, 722
Mitochondrial myopathies, **720**
drug-induced, 728–729
genetic factors in, 720
pathogenesis of, 720–721
progressive external ophthalmoplegia syndromes, 240, 721–722. See also Kearns-Sayre syndrome
pure myopathy syndromes, 722
skeletal muscle-central nervous system syndromes
MELAS syndrome. See MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome
MERRF syndrome. See MERRF (myoclonic epilepsy and ragged red fiber) syndrome
video library of, 253
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome. See MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome
Mitofuscin 1, 291
Mitofuscin 2, 291
Mitotane, for Cushing's syndrome, 632
Mitoxantrone
action of, 527
adverse effects of, 527
for multiple sclerosis, 524t, 527
Mitral cells, 255
Mitral valve prolapse, 331t
Mixed connective tissue disease (MCTD), 662
Mixed mania, 778
Mixed sleep apnea, 212
Miyoshi's myopathy, 716t, 717
MLD (metachromatic leukodystrophy), 407
MMSE. See Mini-Mental Status Examination (MMSE)
MOC. See Montreal Cognitive Assessment (MOC)
Modafinil
for fatigue in multiple sclerosis, 530
for shif -work disorder, 220
Modified Epley maneuver, 137, 138f
Moffett's position, 262
MOG (myelin oligodendrocyte glycoprotein), 284f
Molecular mimicry, 286
Molindone, 785t
Mollaret's meningitis, 573t
Molly (MDMA), 817
Monoamine oxidase inhibitors (MAOIs)
adverse effects of, 768t, 778
for depression, 778
drug interactions of, 778
for panic disorder, 767
for Parkinson's disease, 871
questions regarding, 860, 882
Monoamine oxidase type B (MAO-B) inhibitors
action of, 417
adverse effects of, 417
for Parkinson's disease, 417, 419t, 421, 422f
Monoclonal antibodies
anti-CD3, 232
anti-CD20, 530–531
anti-CD52, 530
Monoclonal gammopathy of undetermined significance (MGUS), **666**, 689
Monocyte chemotactic protein-1, 764
Mononeuropathy
diabetic, 661
multiple, HIV-related, 665
Monoparesis, 148–149
Monosodium glutamate, 262–263
Montreal Cognitive Assessment (MOC), 187
Mood disorders, **773**. See also specific disorders
bipolar disorder. See Bipolar disorder
in the homeless, 787
personality disorders, 783
schizophrenia. See Schizophrenia
Mood stabilizers, 780t
Morphine
adverse effects of, 224
for pain, 94t, 96
sustained-release, 94t, 98
Morvan's syndrome, 614
Motor apraxia, 869
Motor cortex, 191, 192f
Motor evoked potentials, 75
Motor examination, 7–8
Motor neuron disorders
differential diagnosis of, 450t
etiology of, 450t
genetic, 453t–455t
lower, 453t–454t, 457
sporadic, 451t
upper, 453t–455t, 457–458
Motor neuropathy
multifocal, **688**
subacute, paraneoplastic, 612
Motor tic, 429
Movement disorders
drug-induced, **430**
acute, 430
subacute, 430
tardive syndromes, 430–431
Huntington's disease. See Huntington's disease
hyperkinetic, 422, 423t. See also specific disorders
Parkinson's disease. See Parkinson's disease (PD)
psychogenic, 433
tics, 423t, 429
Tourette's syndrome. See Tourette's syndrome
Moyamoya disease, 69f, 335, 357
MPTP, 412
MRA. See Magnetic resonance angiography (MRA)
MRF (myelin gene regulatory factor), 284
MRI. See Magnetic resonance imaging (MRI)
MS. See Multiple sclerosis (MS)
MSA. See Multiple system atrophy (MSA)
Multidetector computed tomography (MDCT), 13–14
Multifocal motor neuropathy, 684t, **688**
with conduction block, 452, 457
Multi-infarct dementia, 398
Multiple endocrine neoplasia type 1 (MEN 1), 593t, 621, 621t
Multiple endocrine neoplasia type 4 (MEN 4), 621t

www.ketabpezeshki.com (021) 66485457 - 66485438

Multiple hamartoma syndrome (Cowden syndrome), 445t, 593t
Multiple myeloma
  neuropathy in, 666, 688–689
  paraneoplastic syndromes in, 613
Multiple sclerosis (MS), **513**
  acute, 530
  acute myelitis in, 498
  anatomy of, 513
  Baló's concentric sclerosis, 54f–55f
  chronic cerebrospinal insufficiency in, 529
  chronic myelopathy in, 502
  clinical features of, 516t, 516–518
  clinical variants of, 530
  course of, 518, 518f
  demyelinating disease, 62f
  diagnosis of, 123, 518–519, 519t
    cerebrospinal fluid analysis in, 521
    evoked potentials in, 521
    neuroimaging in, 519–521, 520f
  differential diagnosis of, 521t, 521–522
  epidemiology of, 514–515, 874
  fatigue in, 140–141
  frontal lobe syndrome in, 202
  gait disorders in, 158
  genetic factors in, 279, 515t, 515–516
  hearing loss in, 268
  immunology of, 515
  Marburg's variant, 530
  myelitis in, 498
  neurodegeneration in, 516
  ocular involvement in, 229, 232, 243–244
  olfactory dysfunction in, 259
  paroxysmal symptoms of, 518, 530
  pathogenesis of, 284f, 513–514, 514f
  physiology of, 513–514, 514f
  pregnancy and, 522
  primary progressive, 518, 518f, 528f, 529
  prognosis of, 522
  progressive/relapsing, 518, 518f
  questions regarding, 856, 874–875
  relapsing/remitting, 518, 518f, 528f, 856, 875
  risk factors for, 514, 515t, 874
  scoring systems for, 522, 523t
  secondary progressive, 518, 518f, 528f, 528–529
  taste disorders in, 260
  treatment of
    acute attacks, 522, 524
    changing of, 527–528, 528f
    dietary therapies in, 529
    disease-modifying therapies in, 524t, 524–528, 528f
    experimental therapies in, 529
    fingolimod in, 526
    glatiramer acetate in, 525
    glucocorticoids in, 522, 524
    INF-ß in, 525
    initial demyelinating episodes, 522, 524
    initiation of, 527–528, 528f
    mitoxantrone hydrochloride in, 527
    natalizumab in, 525–526
    off-label options in, 529
    questions regarding, 858, 878
    symptomatic therapy in, 529–530
  trigeminal neuralgia and, 873
  triggers of, 515–516
  types of, 518, 518f
  video library, 253
  weakness in, 147, 149t
Multiple sleep latency test (MSLT)
  for daytime sleepiness, 210
  for narcolepsy, 213
Multiple system atrophy (MSA)
  autonomic dysfunction in, 474–475, 475f
  clinical features of, 474–475
  gait disorders in, 159
  neuroimaging in, 49f, 475f
  olfactory dysfunction in, 259
  orthostatic hypotension in, 131
  parkinsonism in, 411, 412t
  questions regarding, 854, 872
  treatment of, 475
Mumps, meningitis in, 547, 572t
Munchausen's syndrome, 781
Mu receptors, 808, 808t, 808f
Muscle(s)
  atrophy of, 704
  calcium channel disorders of, **723**–724
  contracture of, 704
  electrophysiologic studies of. See Electromyography (EMG)
  enlargement of, 704
  fatigability of, 140
  response to repetitive nerve stimulation, 78–79
  sodium channel disorders of, **724**–725
Muscle biopsy
  in dermatomyositis, 738t, 739f
  in inclusion body myositis, 738t, 740f
  in myopathy, 706
  in polymyositis, 738t, 739f
Muscle bulk, 144
Muscle contracture, 704
Muscle cramps, 704
Muscle disorders
  energy metabolism disorders, **718**. See also Glycogen storage diseases
  membrane excitability disorders, 723t, **723**
  muscle fiber disorders. See Myopathies
  muscular dystrophy. See Muscular dystrophy
Muscle-eye-brain disease, 712, 713t
Muscle pain
  drugs causing, 703, 703t
  in myopathy, 703–704
  weakness caused by, 737
Muscle relaxants, for back pain, 119
Muscle-specific tyrosine kinase (MuSK), in myasthenia gravis, 693, 857, 878
Muscle spindle, 147f
Muscle stiffness, 704
Muscle stretch (tendon) reflexes, 8, 144, 145t, 147f
Muscle tone, 144, 145t
Muscle weakness
  acute, differential diagnosis of, 736
  diagnostic evaluation of, 700–702, 701f–702f, 702t
  fatigue versus, 140
  in parathyroid disorders, 726
  subacute or chronic progressive, differential diagnosis of, 735–736
Muscular dystrophy, **700**
  Becker's. See Becker's muscular dystrophy
  congenital, 707t, 712, 713t
  cramps in, 704
  distal myopathies, **715**, 716t
  Duchenne's. See Duchenne's muscular dystrophy
  Emery-Dreifuss. See Emery-Dreifuss muscular dystrophy
  facioscapulohumeral, 707t, **714**–715
  gait disorders in, 160
  hereditary myopathies, 707t
  laboratory evaluation of, 701f, 705
    DNA analysis, 705
    electrodiagnostic studies, 705
    forearm exercise test, 705–706
    muscle biopsy, 706
    serum enzymes, 705
  limb-girdle, 711
    autosomal dominant, 708t
    autosomal recessive, 709t–710t
  muscle pain in, 703t, 703–704
  muscle weakness in, 700–702, 701f–702f, 702t, 703f
  myotonic. See Myotonic dystrophy
  oculopharyngeal, 240, 707t, 715
  progressive, 707t
  proteins associated with, 708, 710, 710f, 712f
  stiffness in, 704
MuSK (muscle-specific tyrosine kinase), in myasthenia gravis, 693
Mutism, 191, 195
Myalgia. See Muscle pain
Myasthenia gravis, **691**
  ACh test in, 693–694
  antibodies to AChR or MuSK, 693
  clinical features of, 692, 878
  conditions associated with, 695–696
  diagnosis of, 693t, 693–695, 694t, 696t
  differential diagnosis of, 694–695
  diplopia in, 241
  disorders associated with, 696t
  drugs affecting, 699
  drugs to avoid in, 699, 699t
  electrodiagnostic studies in, 693
  laboratory testing for, 858, 879
  Lambert-Eaton myasthenic syndrome versus, 878
  muscle response to repetitive nerve stimulation in, 78–79
  nystagmus in, 244
  ocular, 692
  pathophysiology of, 691f, 691–692
  prevalence of, 878
  ptosis in, 240
  questions regarding, 857–858, 877–878
  reflex responses in, 145
  treatment of, **696**
    algorithm for, 696f
    azathioprine, 697–698
    cyclosporine, 697–698
    glucocorticoids, 697

www.ketabpezeshki.com (021) 66485457 - 66485438

immunosuppression, 697
IVIg, 698–699
mycophenolate mofetil, 697–698
patient assessment in, 699, 699f
plasmapheresis, 698–699
pyridostigmine, 696–697
tacrolimus, 697–698
thymectomy, 697
video library, 253
weakness in, 145, 149, 149t
Myasthenic crisis, 698–699
Myasthenic fatigue, 692
Mycobacterium spp. infections, 570t. See also Meningitis
Mycophenolate mofetil
for inflammatory myopathies, 741
for myasthenia gravis, 697–698
for neuromyelitis optica, 531
Mycotic aneurysm, 372
Mydriasis, 223
Myelin basic protein (MBP), 284f
Myelin defects, in neurologic disease, 283–285, 284f, 286f
Myelin gene regulatory factor (MRF), 284
Myelin oligodendrocyte glycoprotein (MOG), 284f
Myelin sheath, 284f
Myelitis, 497–499
acute infectious, 499
acute transverse
neuroimaging of, 52f
weakness in, 147
neuromyelitis optica, 498, 530–531
paraneoplastic syndromes, 609, 612
postinfectious, 499
Myelography, 24–25
Myeloma
multiple. See Multiple myeloma
sclerotic, 613
Myelopathy
acute transverse, 497t
chemotherapy-induced, 605t
chronic, **499**
adrenomyeloneuropathy, 503
familial spastic paraplegia, 458, 502–503
hypocupric, 502
in multiple sclerosis, 502
primary lateral sclerosis, 457–458, 503
spondylitic, 499–500
syringomyelia, 123, 501f, 501–502
in tabes dorsalis, 502
tethered cord syndrome, 117, 503
toxic causes of, 503
in vascular malformations of cord and dura, 500, 500f
in vitamin B12 deficiency, 502
compressive. See Spinal cord compression
gait disorders in, 158t
HIV-associated, 589
immune, 497–498
inflammatory, 497–499
noncompressive, **496**
compressive myelopathy versus, 493
evaluation of, 497t
spinal cord infarction, 497
paraneoplastic, 612
Myoadenylate deaminase deficiency, 720
Myoclonic dystonia, 424
Myoclonic epilepsy, juvenile, 300, 302
Myoclonic epilepsy and ragged red fiber syndrome. See MERRF
Myoclonic seizures, 300
Myoclonus, 423t, **429**–430
clinical features of, 429–430
in Creutzfeldt-Jakob disease, 465
posthypoxic, 367
treatment of, 430
Myofascial pain syndrome, 97
Myofasciitis, 736
Myofibrillar myopathies, 716t, 717
Myogenic ptosis, 240
Myokymia, 487, 704
Myopathies
alcoholic, 729, 802
autoimmune, 729
centronuclear (myotubular), **718**
in critical/systemic illness, 371, 727
distal, **715**, 716t
drug-induced, **727**–728, 728t, 737
drugs of abuse and, 728t, 729
endocrine, **725**, 858, 879
gait disorders in, 160
glucocorticoid-related, 728, 728t, 739–740
hereditary, **706**, 707t. See also Muscular dystrophy
HIV-related, 590
inflammatory. See Inflammatory myopathies
laboratory evaluation of, 701f, 705
DNA analysis, 705
electrodiagnostic studies, 705
forearm exercise test, 705–706
muscle biopsy, 706
serum enzymes, 705
metabolic, **725**
mitochondrial. See Mitochondrial myopathies
muscle enlargement and atrophy in, 704
muscle pain in, 703t, 703–704
muscle weakness in, 145–146, 149, 700–702, 701f–702f, 702t
nemaline, **718**
paraneoplastic, 614
proximal myotonic, 704
sarcotubular, 717
Myophosphorylase deficiency (type V glycogenosis), 719
Myopia, 222
Myositis, necrotizing autoimmune, 736–737
Myotonia
conditions associated with, 704
definition of, 704
ion channel defects causing, 280t
nondystrophic, 723t
potassium-aggravated, 724
Myotonia congenita, 280t, 704
Myotonic disorders, 705t
Myotonic dystrophy, 713
clinical features of, 707t, 713–714
congenital, 714
laboratory features of, 714
ocular involvement in, 235, 240
questions regarding, 858, 879–880
treatment of, 714
type 1, 879
Myotubular myopathy, **718**
Myxoma, syncope in, 132

Naegleria infection, in encephalitis, 551
Nafcillin, for meningitis, 539t, 542
Naloxone
as opiate antagonist, 95
for opioid overdose, 811
Naltrexone
in alcoholism management, 806, 861, 885
for opioid antagonism, 811–812
Naming deficit, 191
Naproxen
for migraine, 382t
for pain, 94t
Naratriptan, for migraine, 382t–383t
Narcolepsy, **212**
cataplexy in, 212–213
characteristics of, 212
diagnosis of, 212–213
multiple sleep latency test for, 213
olfactory dysfunction in, 259–260
pathophysiology of, 212
polysomnographic recordings of, 212, 213f
REM sleep in, 212
sleepiness associated with, 212
treatment of, 213
video of, 212
Nasal congestion, with headache, 101
Natalizumab
adverse effects of, 525–526
for multiple sclerosis, 524t, 525–526, 856, 875
Neck pain, **121**
in ankylosing spondylitis, 123
in brachial plexus injury, 123–124
in cancer, 123
in carpal tunnel syndrome, 124
in cervical disk disease, 122, 122t
in cervical spine trauma, 121
in cervical spondylosis, 122
in herpes zoster, 123
in orthostatic hypotension, 131
in peripheral nerve disorders, 123
physical examination in, 122t
in rheumatoid arthritis, 123
in thoracic outlet syndrome, 123
treatment of, 124
Neck weakness, 488, 488t
Necrotizing arteritis, 334
Necrotizing autoimmune myositis, 736–737
Necrotizing fasciitis, 737
Neglect (sensory phenomenon), 154, 197–199
caring for patient with, 203
hemispatial, 197f, 197–199, 198f
Neisseria meningitidis infections, 535. See also Meningitis
Nemaline myopathy, **718**, 858, 880
Neonate(s)
candidiasis in, 34f
seizures in, 304t, 865t

www.ketabpezeshki.com (021) 66485457 - 66485438

Neovascularization, 249, 249f
Nephrogenic diabetes insipidus, 638–641
Nephrogenic systemic fibrosis, 21, 864
Nephrogenic systemic sclerosis, 850
Nephrolithiasis, 117
Nephropathy, contrast-induced, 15
Nerve biopsy, in peripheral neuropathy, 653
Nerve conduction studies
  in back pain, 111
  in peripheral neuropathy, 650, 652, 652t
  principles of, 77f, 77–78
Nerve growth factor, 89
Neural foraminal narrowing with radiculopathy, 113–114, 115f
Neuralgia(s)
  glossopharyngeal, 487, 488t
  trigeminal. See Trigeminal neuralgia
Neural network, large-scale, 191
Neurasthenia, 695
Neuritic plaque, in Alzheimer's disease, 188, 395f
Neuroacanthocytosis, 428
Neuroblastoma, paraneoplastic syndromes in, 612
Neurocutaneous syndromes, 599, **599**
Neurocysticercosis. See Cysticercosis
Neurodegeneration
  in multiple sclerosis, 516
  protein aggregation and, 290–292
Neurodegenerative diseases, 292–294
Neurofibromatosis type 1 (NF1)
  brain tumors and, 593t
  clinical features of, 599–600
  genetic factors in, 599
  neuroimaging of, 62f
  skin manifestations of, 600
Neurofibromatosis type 2 (NF2)
  brain tumors and, 593t
  clinical features of, 600
  genetic factors in, 600
  hearing loss in, 268
  neuroimaging of, 63f
  ocular involvement in, 235
Neurofibromin, 599
Neurogenetics, **278**–280
Neurogenic ptosis, 240
Neurohypophysis
  anatomy of, 635
  diabetes insipidus of. See Diabetes insipidus
  hormones produced by, 635–637
Neuroimaging, 13. See also specific disorders
  atlas of, 27–70
  CT. See Computed tomography (CT)
  echo-planar MR imaging, 22–24
  interventional neuroradiology, 26
  magnetic resonance neurography, 24
  MRA. See Magnetic resonance angiography (MRA)
  MRI. See Magnetic resonance imaging (MRI)
  myelography, 24–25
  PET. See Positron emission tomography (PET)
  spine interventions, 25–26
Neuroinflammation, 764
Neuroleptic malignant syndrome (NMS)
  clinical features of, 431, 478
  treatment of, 431
Neuroleptics. See also Antipsychotics
  adverse effects of, 430
  for dystonia, 426
  for Tourette's syndrome, 429
Neurologic disease, **278**. See also specific diseases
  angiography in, 26
  apoptosis in, 289–290
  approach to the patient. See Neurologic examination/consultation
  cell death in, 289–290
  channelopathies, 280t, 280–281
  in critically ill patient. See Critically ill patient, neurologic disorders in
  depression in, 774
  gene transcription disorders, 283
  genome-wide association studies of, 278–280
  imaging studies. See Neuroimaging
  ion channel disorders, 280t, 280–281
  localization of, 10, 10t
  mechanisms of, 278
  microbiota and, 286–287
  myelin disorders, 283–285, 284f, 286f
  neurotransmitter/neurotransmitter receptor disorders, 281–283, 282t
  neurotrophic factors in, 287, 287t
  prevalence of, 2, 2t
  protein aggregation in, 290–292
  signaling pathway defects, 283
  stem cell therapy for, 287–289
Neurologic examination/consultation, 4–5, 11–12
  in back pain, 110
  af er cardiac bypass, 744f, 744–745
  in central nervous system dysfunction, 742–744, 743t, 744f
  in coma, 175–177
  coordination examination, 9
  cranial nerve examination, 6–7
  in delirium, 166–167
  in dizziness and vertigo, 136
  in electrolyte disturbances, 746–747
  gait examination, 9–10
  in headache, 101
  imaging studies. See Neuroimaging
  localization of findings in nervous system, 10, 10t
  mental status examination, 5–6
  motor examination, 7–8
  neurologic history in, 3–4
  neurologic method in, 2–3
  in olfactory/taste dysfunction, 261
  in peripheral nervous system dysfunction, 747–749
  sensory examination, 9
  af er solid organ transplantation, 745
  video library, 11–12
Neuromuscular blocking agents, 370–371, 728t
Neuromuscular disease, gait disorders in, 160
Neuromuscular jitter, 79
Neuromuscular junction disorders, **691**
  autonomic dysfunction in, 476–477
  clinical features of, 10t
  questions regarding, 849, 863
  reflex responses in, 145
  weakness in, 149, 149t
Neuromuscular junction weakness, 145
Neuromyelitis optica, 498, 530t, 530–531
Neuromyotonia, 614, 704
Neuronal nitric oxide synthase (nNOS), 708
Neuropathic (lower motor neuron) weakness, 145, 145t
Neuropathic pain, 92–93, 98–99
Neuropathies. See also specific neuropathies
  alcoholic, 476
  anti-Hu paraneoplastic, 690
  approach to, 650t
  autonomic, 660
  as bone marrow transplantation complication, 666
  chemotherapy-related, 605, 605t
  diabetic. See Diabetic neuropathy
  diphtheritic, 664
  entrapment, 747
  femoral, 677
  gastric surgery–related, 675
  hereditary. See Hereditary neuropathies
  in hypothyroidism, 661
  immune, 684f
  lateral femoral cutaneous, 676–677, 748f, 749
  median, 676
  with monoclonal gammopathy, **688**–689
  multifocal motor, **688**
  obstetric, 749
  optic. See Optic neuropathy
  paraneoplastic syndromes, 613–614
  peripheral. See Peripheral neuropathy
  peroneal, 677, 748f, 748–749
  proximal femoral, 748f, 749
  radial, 676, 747, 748f
  in rheumatoid arthritis, 662
  sciatic, 677
  sensory, 661
  sensory deficits in, 154–155
  in systemic sclerosis, 662
  trigeminal, **483**–484, 484t
  tumor infiltration as cause of, 666
  ulnar, 676, 747–748, 748f
  uremic, 663
  vasculitic, 689–690
Neuropathy, ataxia, retinitis pigmentosa (NARP), 446t
Neuropeptides, 281
Neuroprotective agents
  for ischemic stroke, 328
  for Parkinson's disease, 418
Neurosarcoid, 37f–42f
Neurostimulation therapy
  for cluster headache, 388
  for SUNCT/SUNA, 103
Neurosyphilis
  clinical features of, 159
  neuroimaging of, 29f–31f
  viral meningitis versus, 545
Neurotransmitter(s)
  clinical aspects, 281, 282t

www.ketabpezeshki.com (021) 66485457 - 66485438

functions, 281
inotropic, 281
metabotropic, 281
Neurotransmitter receptors, 281, 282t
Neurotrophic factors, in neurologic disease, 287, 287t
Neurovegetative symptoms, 763
Newborn
candidiasis in, 34f
seizures in, 304t
New daily persistent headache, 104
clinical features of, 104
description of, 391
diagnosis of, 104t
low cerebrospinal fluid volume headache, 104–105, 105f
posttraumatic, 105
raised cerebrospinal fluid pressure headache, 105
NF1. See Neurofibromatosis type 1 (NF1)
NF2. See Neurofibromatosis type 2 (NF2)
NF1 gene, 593t, 599–600
NF2 gene, 600
Niacin, 728t, 858
Nicotinamide adenine dinucleotide dehydrogenase (NADH) deficiency, 232
Nicotine, 283
addiction to, 821–825
cessation of use, 822, 824–825
description of, 821
Nicotine-replacement therapy, 825, 862, 886
Nicotinic acid
deficiency of. See Pellagra
description of, 728t
Niemann-Pick disease, 448t
Nifurtimox, for Chagas' disease, 589
Nimodipine
adverse effects of, 385t
for migraine prevention, 385t
af er subarachnoid hemorrhage, 375
Nitrates, 131
Nitrofurantoin, 669t
NMDA receptors, 289–290, 608f
antibodies to. See Anti-NMDA receptor antibodies
encephalitis, 610, 611f
questions regarding, 860, 882
Nocardia spp. infections, chronic meningitis in, 570t
Nocebo effect, 91
Nociceptor(s)
inflammation induced by, 89
primary afferent, 88, 89f–90f
Noise-induced hearing loss, 270, 275, 275t
Nonaka's distal myopathy, 716t, 717
Noncompressive myelopathies, **493**, 496
Nondepolarizing neuromuscular blocking agents, 728t
Non-24-h sleep-wake rhythm disorder (N24SWRD), 218–219
Nonsteroidal anti-inflammatory drugs (NSAIDs)
adverse effects of, 93
for Alzheimer's disease, 397
for back pain, 119
for episcleritis and scleritis, 229
in lumbar puncture patients, 81
for migraine, 382t
for neck pain, 124
for pain, 93, 94t
for spinal stenosis, 113
topical, for conjunctivitis, 227
Norepinephrine, 282t, 469
Normal-pressure hydrocephalus, 188f, 404
Normeperidine, 95
Norrie's disease, 270t
Nortriptyline, 860, 882
adverse effects of, 768t
for chronic daily headache, 103
for depression, 768t
dosage of, 768t
for migraine prevention, 385t, 868
for pain, 95t, 97, 99, 529
Notch-3, 335
Nothnagel's syndrome, 241
NREM sleep, 205–207, 206f, 209
NSAIDs. See Nonsteroidal anti-inflammatory drugs (NSAIDs)
N24SWRD. See Non-24-h sleep-wake rhythm disorder (N24SWRD)
Nuchal rigidity, 533
Nucleus of the solitary tract (NTS), 258
Null cell, 620, 620t
Numbness, 150. See also Sensation
Nummular headache, 391
Nutritional diseases, neuropathies in, 673–675
Nutritional support/therapy, for multiple sclerosis, 529
Nystagmus, 136, 136t, 243–244, 253

Obesity, 141
Object recognition, 199–200
Obsessive-compulsive disorder (OCD), **773**
Obstetric neuropathies, 749
Obstructive sleep apnea, 141, 212
Occipital lobe stroke, 235
Occipital nerve stimulation, for SUNCT/SUNA, 103, 389
Occipitotemporal network, 199–200
Occupational illness, 275
Octreotide
for acromegaly, 628–629
for postprandial orthostatic hypotension, 480
Ocular alignment, 224
"Ocular bobbing," 176
"Ocular dipping," 176
Ocular disorders, **226**. See also Visual loss
corneal abrasions, 226–227
in myasthenia gravis, 692
painful or red eye, 226–229
video library, 253–254
Ocular flutter, 244, 253
Ocular lubricants, 228
Oculocephalic reflexes, 176
Oculomotor nerve
description of, 6
palsy of, 223, 240–241
paresis of, 223
Oculopharyngeal dystrophy, 240, 707t, 715
Odontoid fracture, 60f
Off-pump coronary artery bypass graf ing, 745
Olanzapine
for acute alcohol intoxication, 804
for schizophrenia, 785, 785t
side effects of, 785t
Olfactory bulb, 255, 256f
Olfactory disorders, **258**–260
diseases and conditions associated with, 259t, 259–260
epidemiology of, 258, 258f
etiology of, 259, 259t
evaluation of, 261
taste disorders and, 260
treatment of, 261–263
Olfactory nerve, 6
Olfactory pathways, 256f
Olfactory system, 255–256, 256f
Olig 2 gene, 284
Oligodendroglioma, 596
Oligomers, 291, 394
Olivopontocerebellar degeneration, 237, 243
Onabotulinum toxin type A, for migraine prevention, 385t
Onchocerca volvulus/onchocerciasis, 229
Oncocytoma, 620, 620t
Ondansetron
for ataxia/tremor in multiple sclerosis, 529
for nausea, 104
One-and-a-half syndrome, 243
Opa1, 291
Ophthalmopathy, Graves', 238–239, 726
Ophthalmoplegia
internuclear, 243, 244f
neuromuscular causes of, 700, 702t
Ophthalmoscope
direct, 246, 247t
panoptic, 246, 247t
Ophthalmoscopy, **245**–246, 245f–246f
Opioid(s)
action of, 95, 283
administration of
intrathecal, 96
intravenous, 95
patient-controlled, 95–96
spinal, 96
adverse effects of, 807
delirium, 168t
management of, 96
respiratory depression, 95
for back pain, 119
COX inhibitor combinations, 96
endogenous, 92
guidelines for receiving, 99t
locus ceruleus action of, 761f
for migraine, 382t, 384
most commonly abused, 807
neurobiology of, 807–809, 808t
overdosage/poisoning with, 810–812
for pain, 94t, 95–96, 98
pharmacology of, 809–810
systems effects of, 809
withdrawal from, 810–811
Opioid abuse/dependence, 807
diagnosis of, 807

www.ketabpezeshki.com (021) 66485457 - 66485438

Opioid abuse/dependence, (Cont.):
prevention of, 812
treatment of, 810t, **811**
agonist medications in, 811
antagonist medications in, 811–812
medication-free, 812
residential program in, 812
withdrawal management in, 811–812
Opioid receptors, 95, 808, 808t
Oppenheim's dystonia, 424
Opsoclonus, 244, 253, 612
Opsoclonus-myoclonus syndrome, paraneoplastic, 612
Optic atrophy, 232, 233f, 261
Optic chiasm, 221
Optic cup, 235, 236f
Optic disc
anatomy of, 246, 246f
drusen, 226, 233–234, 234f
edema, 233, 233f, 251, 251f
neovascularization of, 249f
pathologic findings of, 246
swelling of, 251, 251f
Optic glioma, 620
Optic nerve, 221
disorders of, visual field defects in, 226
examination of, 6
Optic neuritis, **223**, 232
color desaturation in, 224
in multiple sclerosis, 232, 517
paraneoplastic, 614
retrobulbar, 223, 232, 233f
visual field defects in, 226
Optic neuropathy
anterior ischemic, 231f, 231–232
compressive, 226
drug-induced, 232
Leber, 226, 232
nutritional, 226
posterior ischemic, 232
toxic, 226, 232–233
Optokinetic reflex, 221
Oral cancer, 801
Oral contraceptives, 322
Orbit, 238
Orexin, 206, 212, 260
Organic Brain Syndrome Scale, 166
Organ of Corti, 264, 265f
Organophosphates, 670t
Oromandibular dystonia, 425
Orthostatic hypotension, 872
approach to the patient, 472–474
in autonomic dysfunction, 472, 472t
causes of, 129t, 472t
clinical features of, 131, 472t
dizziness in, 135
falls and, 162
neurogenic, 131
nonneurogenic, 472t
in Parkinson's disease, 420
pathophysiology of, 126, 130f, 130–131
postprandial, 480
prevalence of, 472t
treatment of, 131, 479t, 479–480
Orthostatic intolerance, 470, 472t
Oscillopsia, 135, 137, 244
Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), 360
Osmoregulatory system, 635
Osteoarthritis
back pain in, 114
neck pain in, 122
Osteogenesis imperfecta, 265
Osteomyelitis, vertebral, 115
Osteoporosis
back pain in, 116
treatment of, 116
vertebral fracture in, 116
Osteosclerosis, 116
Otitis media
brain abscess associated with, 559
hearing loss in, 265
Otoacoustic emissions, 267, 272
Otoconia, 137
Otosclerosis, 265, 270
Otoscopy, 265
Ovarian cancer, paraneoplastic syndromes in, 612
Ovarian teratoma, 608f, 612
Overlap syndrome, in inflammatory myopathy, 732
Oxazepam, 770t
Oxcarbazepine
adverse effects of, 314t, 780t
for bipolar disorder, 779, 780t
for epilepsy, 314t
for focal seizures, 312
for pain, 95t
pharmacology of, 314t
for trigeminal neuralgia, 483, 872
Oxidative phosphorylation, 720
Oxybutynin, for detrusor spasticity, 504, 529
Oxycodone, for pain, 94t
Oxytocin
description of, 637
functions of, 635
structure of, 635f

Paclitaxel, 667t
Paget's disease of bone, back pain in, 116
Pain
acute, treatment of, **93**
chronic, **96**–97
treatment of, 97
anticonvulsants and antiarrhythmics for, 98
antidepressants for, 97–98, 98t
opioids for, 98
depression and, 97
modulation in different situations/individuals, 91–92
in multiple sclerosis, 529
neuropathic, **92**–93, 98–99
pathophysiology of, 88
ascending pathways, 90–91, 91f
central mechanisms, 90f, 90–91
pain sensory system, 88–91
peripheral mechanisms, 89f–90f
perception of, 100
psychological variables, 91–92
sympathetically maintained, 93
testing sense of, 152, 152t
Palatal tremor, 254
Palinopsia, 345
Paliperidone, 785t
Pallister-Hall syndrome, 620
Pancoast tumor, 123
Pancreas, alcohol effects on, 801
Pancreatic disease, back pain in, 117
Pancuronium, 370
Panencephalitis
progressive rubella, 558
subacute sclerosing, 558
Panic attacks, 214, 859, 881–882
Panic disorder, **766**
clinical manifestations of, 766
diagnosis of, 766
etiology of, 766–767
pathophysiology of, 766–767
treatment of, 767
Panoptic ophthalmoscope, 246, 247t
Pantothenate kinase (PANK)-associated neurodegeneration, 412
Panuveitis, 229
Papilledema, 233, 233f, 251, 251f, 261
Paralysis, **144**
periodic. See Periodic paralysis
Todd's, 298
tongue, 488
Parameningeal infection, 570t
Paramyotonia congenita, 280t, 704, 723t, 725
Paraneoplastic sensory neuronopathy/ganglionopathy (PEM/SN), 665–666
Paraneoplastic syndromes
in ataxia, 441
ion channel defects causing, 280t
limbic encephalitis, 405
neurologic, 606t, **606**
acute necrotizing myopathy, 614
approach to the patient, 608–609
central nervous system and dorsal root ganglia, 608–609
cerebellar degeneration, 612
incidence of, 606
nerve and muscle, 609
opsoclonus-myoclonus syndrome, 612
pathogenesis of, 606, 607t, 608, 608f
peripheral neuropathies, 613–614
sensory neuronopathy, 613
in spinal cord disease/injury, 612
stiff-person syndrome, 612–613
visual, 607t, 614
video library of, 253
Paraparesis, 147
Paraphasia, 191
Paraplegia(s), spastic familial, 458, 502–503
Paraplegin gene, 458
Parasomnias, **209**, 217–218
Parathyroid disease, muscle weakness in, 726
Paratonia, 144
Parcopa, for Parkinson's disease, 419t
Paresis, 144
Paresthesia, 150
Parietal cortex, posterior, 197, 197f
Parietal lesions, 243, 849
Parietofrontal network, 197, 197f
Parinaud's syndrome, 223, 243, 597

www.ketabpezeshki.com (021) 66485457 - 66485438

parkin gene, 410, 413–414
Parkinsonian dementia syndromes, **403**
Parkinsonism
  atypical, 410t, 411–412, 412t, 870t
  disorders associated with, 432–433
  drug-induced, 431
  gait disorders in, 158t, 159
  lower body, 159
  questions regarding, 854, 872
  secondary, 410t, 411–412, 412t
Parkinsonism-dementia complex of Guam, 259
Parkinson's disease dementia (PDD), 403, 420
Parkinson's disease (PD), **408**
  autonomic disturbances in, 420
  clinical features of, 408, 409t
  delirium in, 167
  dementia in, 403, 420
  depression in, 420
  differential diagnosis of, 408–412, 410f, 410t, 411f, 412t
  etiology of, 412–414, 413f
  falls in, 162
  familial, 291
  frontal lobe syndrome in, 202
  gait disorders in, 159
  genetic factors in, 291, 412t–413t, 413–414, 870
  glial-derived neurotrophic factor for, 420
  hallmark features of, 408
  nondopaminergic features of, 420–421
  nonmotor features of, 420–421
  ocular involvement in, 243
  olfactory dysfunction in, 255, 259
  orthostatic hypotension in, 131
  pathogenesis of, 412–414, 413f
  pathophysiology of, 414, 415f
  prevalence of, 408
  progressive supranuclear palsy versus, 401–402
  psychoses in, 420
  questions regarding, 853–854, 870–871
  REM sleep behavior disorder in, 421
  sleep disorders in, 215, 421
  treatment of, **414**–422
    amantadine, 418
    benztropine, 418
    COMT inhibitors, 417, 419t
    current methods, 421, 422f
    deep brain stimulation, 418, 421, 854, 871
    dopamine agonists, 416–417, 419t, 421
    levodopa, 414–421, 416f, 419t, 421, 854, 871
    MAO-B inhibitors, 417, 419t, 421
    neuroprotective agents, 418
    nonmotor and nondopaminergic features, 420–421
    nonpharmacologic, 421
    questions regarding, 853–854, 871
    surgical, 418–419
    trihexyphenidyl, 418
  tremor in, 422
  trophic factors for, 419–420
Paroxetine, 767, 768t
Paroxysmal autonomic hyperreflexia, 504
Paroxysmal dyskinesias, 431–432
Paroxysmal hemicrania, 101, 103t, 387t, 388–389, 852
Paroxysmal nonkinesigenic dyskinesia (PNKD), 432
Parsonage-Turner syndrome, 678
Pars planitis, 229
Partially treated suppurative meningitis, 570t
Parvocellular neurons, 638
Pasireotide, for Cushing's syndrome, 631–632
Patent foramen ovale, 331t
Pathologic fracture, 60f
Patient-controlled analgesia, 95–96
Patient Health Questionnaire-2, in war veterans, 793, 794t
PD. See Parkinson's disease (PD)
PDD (Parkinson's disease dementia), **403**, 420
Peak-dose dyskinesia, 415
Peduncular hallucinosis, 345
Pegvisomant, for acromegaly, 629
Pellagra
  clinical features of, 405
  global considerations, 674–675
  treatment of, 675
Pendred's syndrome, 268, 270t
D-Penicillamine, adverse effects of
  myopathy, 728t
  optic neuropathy, 232
Penicillin G
  for meningitis, 539t, 541
  for subacute meningitis, 556
Pentobarbital, 850
Penumbra, 361
PER2, 218
Perfusion magnetic resonance imaging, 24
Perfusion techniques, in stroke, 353
Periglomerular cells, 255
Perilymphatic fistula, 268
Perimeter, computer-driven, 225, 225f
Periodic hypothermia syndrome, 619
Periodic lateralizing leptiform discharges (PLEDs), 74
Periodic limb movement disorder (PLMD), 216–217
Periodic paralysis
  clinical features of, 723t
  hyperkalemic, 724–725
  hypokalemic, 723–724, 724f
  ion channel defects causing, 280t
Peripheral nerve(s)
  components, 89f
  cutaneous fields of, 153f
  pain mechanisms, 88–90
  questions regarding, 849, 863
Peripheral neuropathy, **648**. See also specific disorders
  alcohol and, 800
  approach to, **648**, 649f, 650t, 875t
    distribution of weakness, 648–649
    hereditary neuropathy, 650
    medical conditions, 650
    pattern recognition, 650, 651t
    sensory involvement, 649–650
    systems involved, 648
    temporal evolution, 650
    upper motor neuron involvement, 650
  axonal, 667t
  CSPN, 675–676
  demyelinating, 667t
  drug-induced, 605t, 666–673, 667t–671t
  electrodiagnostic studies in, 650–652, 652t
  EMG in, 650–652, 652t
  gait disorders in, 160
  hereditary. See Hereditary neuropathies
  HIV-related, 590
  laboratory evaluation of, 652t, 652–653
  malignancy-related, 665–666
  nerve biopsies in, 653
  nerve conduction studies in, 650, 652, 652t
  nutritional, 673–675
  painful sensory, 661t
  paraneoplastic, 613–614
  questions regarding, 856, 875–876
  skin biopsies in, 653
  toxic causes of, 666–673, 668t–671t
  weakness in, 147, 648–649
Peripheral sensitization, 89
Peripheral vascular disease, 822
Perisylvian network, **191**
Periventricular white matter disease, 335
Permeability transition pore, 285f, 290
Peroneal neuropathy, 677, 748f, 748–749
Perphenazine
  for schizophrenia, 785t
  side effects of, 785t
PERRLA, 222
Persistent vegetative state, 171
Personality disorders, 783
PET. See Positron emission tomography (PET)
Petrous bone fractures, 507
PGC-1α, 292
p53 gene, 593t
Phakomatosis(es), **599**
Phencyclidine (PCP)
  abuse/overdose of, 818–819
  actions of, 818
  adverse effects of, 168t
  myopathy caused by, 728t
Phenelzine, 860, 882
  adverse effects of, 768t
  for depression, 768t
  for migraine prevention, 868
  for posttraumatic headache, 105
Phenobarbital, 314t
Phenothiazines, adverse effects of
  ocular, 237
  orthostatic hypotension, 131
Phenytoin
  adverse effects of, 317
    hepatotoxicity, 661t
    long-term, 317
    neurologic, 315t, 661t, 670t
    systemic, 315t
  dosage of, 315t
  drug interactions of, 315t
  for epilepsy, 315t
  for neuromyotonia, 614

www.ketabpezeshki.com (021) 66485457 - 66485438

Phenytoin (Cont.):
for neuropathy, 661t
for pain, 95t, 98, 529
pharmacology of, 315t
for trigeminal neuralgia, 483
Phobic disorders, **770**
Phobic postural vertigo, 139
Phonemic paraphasia, 191
Phonophobia, 387, 391
Phosphofructokinase deficiency (type VII glycogenosis), 719
Photophobia, 387, 391
Photoreceptors, 221
Photorefractive keratectomy (PRK), 222
Physical restraints, in delirium, 165, 170
Physical therapy
for back pain, 119
for vertigo, 139t
Physostigmine, 179
Pica, 781
Pick bodies, 400
Pick's disease, 201, 400, 402f
Pigmented lesions, of fundus, 252, 252t, 252f
Pilizaeus-Merzbacher disease, 458
Pilocarpine
for acute angle-closure glaucoma, 229
adverse effects of, 224
in diagnosis of tonic pupil, 223
Pilocystic astrocytoma, 66f
Pineal region tumors, 243, 597–598
Pinguecula, 227
PINK1, 291, 413–414
Piracetam, for myoclonus, 430
Pituitary adenomas, **598**
classification of, 598–599, 620t
epidemiology of, 620
familial, 621t
genetic syndromes associated with, 621t, 621–622
gonadotropin-producing, 632–633
magnetic resonance imaging of, 616f
nonfunctioning, 599, 632–633
ocular signs in, 226, 238
pathogenesis of, 620–621
prolactin-secreting, 622
screening tests for, 616, 617t
transsphenoidal surgery for, 633
treatment of, 599, 617
Pituitary apoplexy, 238
Pituitary diabetes insipidus, 637, 638t, 639
Pituitary disorders, 727
Pituitary metastases, 619–620
Pituitary tumors and masses
adenomas. See Pituitary adenoma
evaluation of, 616–618
features of, 616t
genetic syndromes associated with, 621t, 621–622
histologic evaluation of, 617
hypothalamic, 619–620
laboratory investigations for, 616–617
local effects of, 615–616
magnetic resonance imaging of, 616f, 616–617
medical therapy for, 618
ophthalmologic evaluation of, 616
pituitary adenoma, 616f
radiation therapy for, 618
suprasellar extension of, 615
transsphenoidal surgery for, 617–618, 618f
treatment of, 617–618
Pizotifen, for migraine prevention, 385t
Placebo effect, 91, 92f
Plaque, neuritic, 188, 395f
Plaques jaunes, 506
Plasmapheresis
for Guillain-Barré syndrome, 686
for myasthenia gravis, 698–699
Platelet aggregability, 220
Platelet antiaggregation agents, 337
Platelet emboli, 249
PLEDs. See Periodic lateralizing leptiform discharges (PLEDs)
Pleiotropy, 760
Pleomorphic xanthoastrocytomas, 596
Plexopathy
brachial, 57f–58f, 678–679
evaluation and treatment of, 680
lumbosacral, 679–680, 680t
perioperative, 679
radiation-induced, 680
Plurihormonal adenomas, 622
PML (progressive multifocal leukoencephalopathy), 556–558
Pneumonia
delirium in, 168, 168t
olfactory dysfunction and, 259
PNKD (paroxysmal nonkinesigenic dyskinesia), 432
Podophyllin, adverse effects of, 669t
POEMS syndrome (Crow-Fukase syndrome), 613
Poliovirus infection, weakness in, 147
Polyarteritis nodosa
neuropathy in, 689
ocular involvement in, 228
Polydipsia
iatrogenic, 638
primary, 638, 638t
Polydrug abuse, 820
Polymyalgia rheumatica, 231, 703
Polymyositis, **730**
clinical features of, 149, 730–731, 731t
diagnosis of, 737–739, 738t
differential diagnosis of, 735–737
drug-induced, 737
muscle damage in, 734, 735f
prognosis of, 741
treatment of, 739–741
viral infections and, 734–735
Polymyxin-bacitracin, for conjunctivitis, 227
Polyneuropathy
acute inflammatory demyelinating, 682, 682t
acute toxic, 149
critical illness, 663
cryptogenic sensory and sensorimotor, 675–676
distal sensory, 590
distal symmetric, HIV-related, 664
familial amyloid, 658t, 659
large-fiber, 155
sensory deficits in, 155
small-fiber, 155
weakness in, 149
Polyradiculopathy, in HIV infection, 665
Polysomnography
definition, 205
in sleep disorder evaluation, 210
Polyuria, 637, 639
Pompe disease (acid maltase deficiency; type II glycogenosis), 718–719, 858, 879
Pons
histoplasmosis of, 32f
inferior of, 348f
mid, 349f
superior, 350f
Pontine hemorrhage, 254
Porphyria(s)
autonomic dysfunction in, 476
clinical features of, 659
neuropathy in, 658t, 659
Positron emission tomography (PET)
in cluster headache, 380f
in migraine, 379f
in mild cognitive impairment, 189f
in neurologic disease, 24
in Parkinson's disease, 410, 411f
in stroke, 353
Postconcussion syndrome, 512
Posterior cerebral artery
fetal, 344
lesion in territory of, 195, 200–201
occlusion of, 226, 344f, 345
Posterior column-medial lemniscal pathway, 151f, 152
Posterior cortical atrophy syndrome, 199
Posterior fossa brain tumor, 102
Posterior reversible encephalopathy syndrome (PRES), 335, 743
Postictal state, 174
Postinfectious myelitis, 499
Postpartum galactorrhea, 623
Postprandial orthostatic hypotension, 480
Posttraumatic stress disorder (PTSD)
biological correlates of, 790
clinical features of, 790
definition of, 789
diagnosis of, 772t
etiology of, 772
pathophysiology of, 772
questions regarding, 860, 882
treatment of, 773
in war veterans, 789–790, 795–796
Postural control, 157, 160–161
Postural orthostatic tachycardia syndrome, 104, 477
Potassium channel disorders, **725**
Pott's disease, 115
Prader-Willi syndrome, 279
Pragmatics, 196
Pramipexole
adverse effects of, 417
for Parkinson's disease, 416–417, 419t, 871
for restless legs syndrome, 216, 432
Praziquantel, for cysticercosis, 562

www.ketabpezeshki.com (021) 66485457 - 66485438

Prednisone
adverse effects of, 728, 740
for Bell's palsy, 486
for cluster headache, 388, 388t
for Duchenne's muscular dystrophy, 710
for Graves' ophthalmopathy, 239
for myasthenia gravis, 697, 878
for sinusitis with hyposmia, 262
Prefrontal cortex, 201
Prefrontal network, 201–202
Pregabalin
adverse effects of, 661t
for neuropathy, 661t
for pain, 98–99, 529
Pregnancy
alcohol use in, 802
bromocriptine use during, 625–626
cigarette smoking during, 823
epilepsy in, 321–322
fatigue during, 142
hyperprolactinemia caused by, 622
in multiple sclerosis, 522
prolactinomas in, 625–626
retinal artery occlusion in, 230
taste function alterations during, 261
Presbycusis, 267, 267f, 273
Presbyopia, 222
Presbyosmia, 258
Presenilin, in Alzheimer's disease, 395–396
Pressure ulcers, 504
Presynaptic rundown, 692
Presyncope, 125
Primary afferent(s), 88, 89f
Primary afferent nociceptors, 88, 89f–90f
Primary Care Evaluation of Mental Disorders (PRIME-MD), 765
Primary Care PTSD Screen, 793, 794t
Primary cough headache, **389**
Primary exercise headache, **390**
Primary intraventricular hemorrhage, 357
Primary lateral sclerosis, 457–458, 503
Primary olfactory cortex, 255–256, 256f
Primary polydipsia, 638t, 638–640
Primary progressive aphasia, 196–197, 204, 399
Primary stabbing headache, 100t, **391**
Primary taste cortex (PTC), 258
Primary thunderclap headache, 390–391
Primidone
adverse effects of, 315t
for essential tremor, 424
for myoclonus, 430
pharmacology of, 315t
Primitive reflexes, 8–9
Prion(s)
decontamination of, 467
definition of, 459
neurodegenerative diseases and, 292–294
strains of, 461–462, 462t
terminology related to, 460t
transmissibility of, 460
Prion disease(s), 445t, **459**. See also Creutzfeldt-Jakob disease
clinical features of, 465
dementia caused by, 403–404
diagnosis of, 465
differential diagnosis of, 465–466
epidemiology of, 460, 461t
human PRNP gene polymorphisms in, 463
infectious, 463, 466f
inherited, 463
laboratory evaluation of, 466, 466f
neuropathology of, 464–465
pathogenesis of, 460–463, 461f, 462t
prevention of, 467
prion strains in, 461–462, 462t
species barrier in, 462–463
spectrum of, 460
sporadic, 463
treatment of, 467
types of, 460, 461t
Prion proteins, 459, 459f
PRK. See Photorefractive keratectomy (PRK)
PRKARIA, 622
PRNP gene, 460t, 463
Procarbazine, 605t
Prochlorperazine, for migraine, 382t
Progranulin, in FTD, 399–400
Progressive external ophthalmoplegia, 721–722
differential diagnosis of, 695
hearing loss in, 270
video library of, 253
Progressive multifocal leukoencephalopathy (PML), 436, 556–558, 588–589
Progressive muscular atrophy, 449
Progressive muscular dystrophies, 707t
Progressive myoclonus epilepsy, 301t
Progressive polyradiculopathy, HIV-related, 665
Progressive rubella panencephalitis, 558
Progressive supranuclear palsy
balance disorders in, 162
clinical features of, 401
falls in, 162
gait disorders in, 159
parkinsonism in, 411
Parkinson's disease versus, 401–402
pathology of, 401, 412t
Proinflammatory cytokines, in fatigue, 143
Prolactin, **616**
Prolactinoma, **624**
clinical presentation of, 624
diagnosis of, 624
etiology of, 624
in pregnancy, 625–626
prevalence of, 624
screening tests for, 617t
surgical treatment of, 625
treatment of, 618, 624f, 624–626
Promethazine. for vertigo, 139t
Promitochondrial agents, for Huntington's disease, 428
PROMM (proximal myotonic myopathy), 704
Pronator drif , 7, 849, 863
Pro-opiomelanocortin, 619
Propofol, 850
Propranolol
adverse effects of, 385t
for ataxia/tremor in multiple sclerosis, 529
for essential tremor, 424
for migraine prevention, 385t, 868
for phobic disorders, 771
Proprioception, 151
Proprioceptive sensory loss, 144
Proptosis, 238–239
Prosody, 196
Prosopagnosia, 199–200, 224
Prostaglandin analogues
for acute angle-closure glaucoma, 229
for glaucoma, 236
Prostaglandins, 89, 90f
Prostate cancer
back pain in, 117
central nervous system metastases in, 600t
paraneoplastic syndromes in, 614
Prostatitis, back pain in, 117
Prosthetic heart valve, antithrombotic prophylaxis for, 331t
Protein(s)
aggregation of, in neurologic disease, 290–292
muscular dystrophy–associated, 708, 710f, 712f
prion, 459, 459f
Protein C deficiency, 230
Protein S deficiency, 230
Protriptyline, for cataplexy, 213
Proximal femoral neuropathy, 748f, 749
Proximal myotonic myopathy (PROMM), 704
PrP amyloid, 460t
PS-1, 395–396
PS-2, 395–396
Pseudoathetosis, 151
Pseudobulbar palsy, 145
Pseudodementia, 407, 776
Pseudoephedrine, for orthostatic hypotension, 131
Pseudohypocalcemia, 864
Pseudopapilledema, 233
Pseudotumor, orbital, 239
Pseudotumor cerebri, 105, 233
Psoriasis, ocular involvement in, 229
Psychiatric/psychological disorders. See also specific disorders
back pain in, 118
biology of, 758
dementia caused by, 407
gait disorders in, 160
in homeless, 787
neural circuitry involved in, 762f, 762–764
neuroinflammation, 764
signal transduction in, 760–761
syncope in, 133–134
in war veterans. See War veterans, neuropsychiatric illnesses in
Psychogenic amnesia, 407
Psychogenic diabetes insipidus, 638, 638t
Psychogenic movement disorders, 433
Psychogenic seizures, 311, 850, 865
Psychophysiologic vertigo, 139
Psychosis
acute, 819
in epilepsy, 320
in Parkinson's disease, 420

www.ketabpezeshki.com (021) 66485457 - 66485438

Psychostimulants, for fatigue, 143
Psychotherapy
  for depression, 776
  for generalized anxiety disorder, 767
  for panic disorder, 767
  for phobic disorders, 771
  for stress disorders, 773
P1 syndromes, 343f–344f, 345
P2 syndromes, 343f–344f, 345
PTEN gene mutations, 593t
Pterygium, 227, 240
Ptosis, 239–240, 253, 700, 702t
PTSD. See Posttraumatic stress disorder (PTSD)
PTTG, 621
"Puff of smoke" lesion, 335
Pulmonary embolism (PE), af er subarachnoid hemorrhage, 375
"Punch drunk" syndrome, 406
Pupil(s), 222–224
  Argyll Robertson, 223
  in coma, 175–176
  inequality in size of, 223
  Marcus Gunn, 223, 223f
  tonic, 223
Pupillary defect, afferent, 223
Pure alexia without agraphia, 193t, 195
Pure autonomic failure
  autonomic dysfunction in, 477
  orthostatic hypotension in, 131
Pure motor hemiparesis, 333
Pure myopathy syndromes, **722**–723
Pure sensory stroke, 333
Pure tone audiometry, 271
Pure word deafness, 193t, 194–195
Purtscher's-like retinopathy, 249
Pyramidal (corticospinal) system, 146f
Pyrazinamide, for tuberculous meningitis, 556
Pyridostigmine
  for myasthenia gravis, 696–697, 858, 878
  for orthostatic hypotension, 131, 480
Pyridoxine (vitamin B6)
  deficiency of, 674
  toxicity of, 669t, 671–672
  for tuberculous meningitis, 556
Pyrimethamine, for toxoplasmosis, 562

Quadrantanopsia, 225f
Quadriparesis, 147–148
Quadriplegic fever, 504
Quantitative sudomotor axon reflex test, 473–474, 474t
Quetiapine
  for bipolar disorder, 780
  for dementia, 397
  for psychosis in Huntington's disease, 428
  for schizophrenia, 785t, 786
  side effects of, 785t
Quinine, 267

Rabies, 552
Radial neuropathy, 676, 747, 748f
Radiation therapy
  for acromegaly, 629
  adverse effects of
    cataract, 235
    neurologic, 604–605
    plexopathy, 680
  for metastatic brain tumors, 601
  sellar masses treated with, 618
  side effects of, 618
  stereotactic, 618
Radiculopathy, 107, 677, 677t
Radiofrequency denervation, 120
Radiofrequency thermal rhizotomy, for trigeminal neuralgia, 483, 872
Ragged-red fibers, 240
Ramsay Hunt syndrome, 137, 485
Ranibizumab, for macular degeneration, 237
Rasagiline, for Parkinson's disease, 417–418, 419t
RAS (reticular activating system), 172
Rathke's cysts, 619
Reactivation American trypanosomiasis, 589
Reactive arthritis (Reiter's syndrome), 229
Reading assessment, 192
Rebound insomnia, 214
Recombinant tissue plasminogen activator, 851, 866–867
Recoverin, 607t
Referred pain, 90
  to back, 108, 117
  convergence-projection hypothesis of, 91f
Reflex(es), testing of, 8–9. See also specific ref exes
Reflex sympathetic dystrophy, 93, 478–479
Reflex syncope, 125
Refractive state, 222
Refsum's disease, 237, 447t, 658, 658t
Rehabilitation
  of alcoholics, 805–806
  in ischemic stroke management, 328
  in opiate abusers, 812
  of spinal cord disorders, 503–504
Relapsing polychondritis, 228
Relative afferent pupil defect, 223, 223f
Relaxation rate, 17
REM sleep
  description of, 205–207, 206f
  in narcolepsy, 212
REM sleep behavior disorder, 185, 207, 217–218, 259–260, 421
Repetition, assessment of, 192
Resistance strength training, 162
Respiratory function, during sleep, 209
Respiratory tract infections
  mastoiditis, 242, 559
  olfactory disorders in, 259
Restless legs syndrome (RLS), **216**, 432
Restrictive food intake disorder, 782
Reticular activating system (RAS), 172
Reticulospinal pathway, 146f
Retina, 221
  age-related changes, 246
  cotton-wool spots, 230f, 233f, 248–249, 249f
  crystal deposition in, 250
  detached/detachment, 226, 234, 234f, 250–251
  emboli of, 249, 253
  hard exudates of, 248, 248t
  infarction of, 230
  lesions of, 226
  microaneurysms of, 248, 248t
  neovascularization of, 249, 249f
  ophthalmoscopy of, 246
  peripheral, 246
  vascular sheathing of, 250, 250f
Retinal artery embolism, 249
Retinal artery occlusion, 230, 230f
Retinal hemorrhages, 230f, 247–248, 247f–248f
Retinal pigment epithelium, 245
Retinal vein occlusion, 231, 231f
Retinitis, Toxoplasma, 252, 252f
Retinitis pigmentosa, 237, 238f
Retinoids, for olfactory dysfunction, 262
Retinopathy
  cancer-associated (paraneoplastic), 614
  hypertensive, 230–231, 231f
Retrobulbar tumor, 238
Retrocollis, 425
Retroperitoneal hemorrhage, 117
Retropharyngeal sof tissue mass, 59f
Retroviruses, myopathies associated with, 500–501, 734
Rett's syndrome, 283
Reverse straight-leg raising sign, 110
Reverse transcriptase enzyme, HIV, 579
Reversible cerebral vasoconstriction syndrome (RCVS), 335
Reversible posterior leukoencephalopathy (RPLE), 357, 743
Rhegmatogenous retinal detachment, 250–251
Rheumatic fever, prophylaxis for cardiac complications of, 331t
Rheumatoid arthritis
  juvenile, 229
  neck pain in, 123
  neuropathy in, 662
  ocular involvement in, 228
Ribavirin, for viral encephalitis, 554
Riboflavin, 262
Rifampin
  prophylactic, 541
  for tuberculous meningitis, 556
Right-lef confusion, 196
Rigidity, 144
Riley-Day syndrome, 477
Riluzole
  for ALS, 456
  for ataxia, 441
Rinne test, 271
Risperidone
  for psychosis in Huntington's disease, 428
  for schizophrenia, 785, 785t
  side effects of, 785t
Rituximab
  for cerebellar degeneration, 612
  for inflammatory myopathies, 741
  for myasthenia gravis, 698
Rivaroxaban, 81
Rivastigmine
  for Alzheimer's disease, 189, 397, 869
  for Parkinson's disease dementia, 420
Rizatriptan, for migraine, 382t–383t
Rocky Mountain spotted fever (RMSF), 540

www.ketabpezeshki.com (021) 66485457 - 66485438

Rods, 221
Romberg maneuver, 9
Romberg sign, 138, 151, 161, 435, 849, 863
Ropinirole
  adverse effects of, 417
  for Parkinson's disease, 416, 419t
  for restless legs syndrome, 216, 432
Rosenbaum card, 222, 222f
Roth's spots, 229, 230f, 247, 249
Rotigotine
  adverse effects of, 417
  for Parkinson's disease, 416–417, 419t, 854, 871
rtPA, 326, 851, 866
Rubella, 558
Rubeola, 558
Rubrospinal pathway, 146f
Rufinamide, 315t
Rumination disorder, 781–782

Saccades, 224
Saccadomania, 244
Saccular aneurysm, 371–372
Sacral insufficiency fracture, 60f
Sacral pain, 117
Sagging brain syndrome, 404
Sagittal sinus thrombosis, Bálint's syndrome in, 199
Salicylates, 267
Saliva, artificial, 262
Salt therapy, for syncope, 130
Salty taste sensation, 257
Salvia divinorum, 819
Salvinorin A, 819
Sandhoff's disease, 453t
Sandostatin-LAR, for acromegaly, 628
Sarcoidosis
  neurologic features of
    chronic meningitis, 573t
    myelopathy, 498
    peripheral neuropathy, 662
  ocular involvement in, 228–229
  questions regarding, 873
  weakness in, 147
Sarcotubular myopathy, 717
SCA. See Spinocerebellar ataxia (SCA)
Schirmer strip, 228
Schistosomiasis, myelitis in, 499
Schizoaffective disorder, 784
Schizophrenia, **783**
  brain volume loss in, 763
  catatonia, 784
  CATIE study of, 786
  chemosensory alterations in, 261
  clinical manifestations of, 783–784
  diabetes mellitus type 2 in, 786
  differential diagnosis of, 784
  epidemiology of, 784
  functional imaging studies of, 763
  neuroimaging findings in, 763
  pathophysiology of, 784
  questions regarding, 859, 881
  treatment of, 784–786, 785t
Schizophreniform disorder, 784
Schwannoma, 274, 598, 599f. See also Vestibular schwannoma
Schwannomatosis, familial, 593t
Sciatica, 120–121
Sciatic neuropathy, 677
Scleritis, 228
Scleroderma. See Systemic sclerosis (scleroderma)
SCN1A gene, 301t
Scoliosis, 110, 117
Scopolamine
  ocular effects, 224
  for vertigo, 139t
Scotoma, 225, 225f, 226, 234–235
Scrapie, 461t
Seasonal affective disorder, 776
Secondary brain insults, 361
Secondary taste cortex, 258
Second impact syndrome, 510
Segawa variant dystonia, 424
Seizure(s), **297**. See also Epilepsy
  absence, 299
  approach to the patient, 307, 308f
  atonic, 300
  in brain abscess, 560
  in brain tumor, 592
  causes of, 865t
  chemotherapy-induced, 605t
  classification of, 297t, 298
  coma in, 174
  complex febrile, 304
  definition of, 297
  delirium and, 168t, 169, 405
  differential diagnosis of, 310t, 310–311
  EEG studies in, 309
  electrographic, 71–73, 73f
  electrophysiologic studies in, 309
  etiology of, 303–305, 304t–305t
  focal, **298**
    AEDs for, 312, 317
    with dyscognitive features, 298
    evolution to generalized seizures, 299
    without dyscognitive features, 298
  focal sensory, 156
  generalized, **299**
    absence, 299
    AEDs for, 317
    atonic, 300
    evolution from focal seizures, 299
    myoclonic, 300
    questions regarding, 850, 865
    tonic-clonic, 299–300, 850, 865–866
  af er head injury, 508
  history and examination in, 307, 309
  in HIV infection, 587, 587t
  laboratory evaluation of, 309
  magnetoencephalography in, 309
  mechanisms of, 305–307
    epileptogenesis in, 306
    initiation phase, 305–306
    propagation phase, 305–306
  in meningitis, 538
  in neonates, 865t
  neuroimaging in, 309–310
  psychogenic, 311, 850, 865
  questions regarding, 850, 865
  recurrent, 850
  sodium shif s as cause of, 174
  syncope versus, 132–133, 310t, 310–311
  temporal lobe, 201
  treatment of, **311**
    avoidance of precipitating factors in, 311–312
    underlying conditions–related, 311
  unclassifiable, 300
  water balance shif s as cause of, 174
Selective serotonin reuptake inhibitors (SSRIs)
  adverse effects of, 768t, 777
    serotonin syndrome, 777
    sexual dysfunction, 777
  for depression, 189, 397, 768t, 777, 777f
  drug interactions of, 769t
  for neuropathic pain, 98
  for panic disorder, 767
  pharmacology of, 777
  for PTSD, 795
  questions regarding, 860, 882
  for vertigo, 139, 139t
Selegiline
  for depression, 768t
  for Parkinson's disease, 417–418, 419t, 854, 871
Sella chordomas, 619
Sellar masses
  evaluation of, 616–618
  features of, 616t
  histologic evaluation of, 617
  hypothalamic, 619–620
  laboratory investigations for, 616–617
  local effects of, 615–616
  magnetic resonance imaging of, 616f, 616–617
  ophthalmologic evaluation of, 616
  pituitary adenoma, 616f
  radiation therapy for, 618
  suprasellar extension of, 615
  transsphenoidal surgery for, 617–618, 618f
  treatment of, 617–618
Semantic dementia, 200
Semantic paraphasia, 191
Semantic-variant primary progressive aphasia, 196
Sensation
  abnormalities of, **150**
    in brainstem lesions, 155
    in cortical lesions, 156
    falls and, 162
    focal seizures, 156
    localization of, 153f, 154
    in nerve and root lesions, 153f, 154–155
    in spinal cord lesions, 155
    in thalamic lesions, 155
  anatomy of, 151f, 151–152
  examination of, 152t, **152**
    cortical, 154
    primary, 152–153
    quantitative sensory, 153
  positive and negative phenomena, 150
  terminology in, 150–151
Sensorimotor neuropathy, paraneoplastic, 613
Sensory area, primary, 191

www.ketabpezeshki.com (021) 66485457 - 66485438

Sensory ataxia, 151, 159–160, 160t
Sensory ataxic neuropathy and ophthalmoparesis (SANDO), 446t
Sensory balance training, 162
Sensory dissociation, 155
Sensory examination, 9
Sensory neuronopathy, 155
Sensory neuropathy
  autoimmune subacute, 161
  HIV-related, 665
  painful, 661
  paraneoplastic, 613
Sentinel bleeds, in subarachnoid hemorrhage, 372
Sepsis/septic shock
  delirium in, 168t, 168–169
  encephalopathy in, 368
Septic cavernous sinus thrombosis, 566
Septic thrombosis, of superior sagittal sinus, 566
Serotonin
  anatomic and clinical aspects of, 282t
  pain and, 90f
  structure of, 282t
Serotonin agonists, 382t
Serotonin antagonists, 104
Serotonin norepinephrine reuptake inhibitors, for PTSD, 795
Serotonin syndrome, 431, 777
Serous retinal detachment, 250
Sertraline
  adverse effects of, 768t
  for depression, 768t
  dosage of, 768t
  for obsessive-compulsive disorder, 773
  for panic disorder, 767
Setting sun sign, 243
Sexual activity, primary headache associated, 390
Sexual dysfunction
  alcohol and, 802
  cocaine and, 811
  in multiple sclerosis, 517, 530
Shawl sign, 731
Shif -work disorder, **219**–220
Shingles. See Herpes zoster
Shortened Fatigue Questionnaire, 754, 754f
Shoulder pain, 123–124
SIAD. See Syndrome of inappropriate antidiuresis (SIAD)
Sialadenitis, 260
Sickle cell anemia
  ocular involvement in, 234
  stroke caused by, 334
Sickle cell disease, 69f
Signal transduction pathway defects, 283
Silent nociceptors, 89
Simultanagnosia, 198f, 199, 243
Simultaneous bilateral stimulation test, 198
Single-fiber electromyography, 79
Single-photon emission computed tomography (SPECT), in Parkinson's disease, 410
Sinusitis
  brain abscess and, 559
  olfactory dysfunction in, 259, 262
  subdural empyema and, 563–564
Sinus thrombosis
  cavernous, 566
  superior sagittal, 46f–49f, 566
  transverse, 566
Sjögren syndrome, 155
  neuropathy in, 661–662
  ocular involvement in, 228
Skew deviation, 243
Skin biopsy, 653
Skull fractures, 507
Sleep, **205**
  adenosine promotion of, 208
  age-related changes in, 205–206, 206f
  behavioral changes in, 209
  circadian rhythmicity in, 208
  endocrine function affected by, 209
  homeostatic mechanisms in, 208
  insufficient, 211
  melatonin and, 209
  neuroanatomy of, 206–207, 207f
  neurochemistry of, 206
  NREM, 205–207, 206f, 209
  organization of, 205–206
  physiologic systems affected by, 209
  physiology of, 205–209
  polysomnography of, 209
  REM, 205–207, 206f, 209
  states and stages of, 205, 209
  systemic effects of, 209
Sleep apnea syndromes, **212**
Sleep bruxism, 217
Sleep disorders, 209–210
  advanced sleep-wake phase disorder, 218
  approach to the patient, 209–210
  circadian rhythm, **218**–220
  daytime sleepiness, 141, 210–211, 211t
  delayed sleep-wake phase disorder, 218
  fatigue versus, 141
  insomnia. See Insomnia
  insufficient sleep, 211
  jet lag disorder, 220
  narcolepsy. See Narcolepsy
  non-24-h sleep-wake rhythm disorder, 218–219
  parasomnias, 209, 217–218
  in Parkinson's disease, 421
  periodic limb movement disorder, **216**–217
  REM sleep behavior disorder, 217–218
  restless legs syndrome, **216**
  shif -work disorder, **219**–220
  sleep apnea syndromes, 212
  sleep bruxism, 217
  sleep enuresis, 217
  sleep terrors, 217
  sleepwalking, 217
  in war veterans, 795
Sleep enuresis, 217
Sleep hygiene, 214–215, 215t
Sleepiness, daytime
  disorders associated with, 210
  evaluation of, 210–211, 211t
  excessive, 141
  insufficient sleep as cause of, 211
  multiple sleep latency test for, 210
  narcolepsy as cause of, 212
Sleep log, 211
Sleep terrors, 217
Sleep-wake cycle, 207f, 208
Sleepwalking, 217
Slipping clutch syndrome, 159
Slit-lamp examination, 224, 228–229
Small-vessel stroke, 330t, **332**
  clinical features of, 333–334
  definition of, 332
  pathophysiology of, 332–333, 333f
SMA (spinal muscle atrophy), 449, 453t, 457
Smoking. See Cigarette smoking
Snellen chart, 222, 222f
Social jet lag, 220
SOD1, 452
Sodium channel disorders, **724**–725
Sodium dodecyl sulfate, 295
Sodium oxybate, for cataplexy, 213
Sodium valproate, 868
Solid organ transplantation, brain injury af er, 745
Solitary tract nucleus, 258
Somatic symptom disorder, 780–781
Somatosensory cortex, 91, 91f, 192f
Somatosensory deficits, 161
Somatosensory evoked potentials (SSEPs), 75
Somatosensory pathways, 151f
Somatostatin analogues
  for acromegaly, 627–628
  side effects of, 629
Somatotrope, 620, 620t, 633
Somnambulism, 217
Sour taste sensation, 257
Spasmodic dystonia, 425
Spasms
  hemifacial, 484, 487
  in multiple sclerosis, 516, 529
  muscle, 704
Spasticity, 144, 158, 504
Spastic paraplegia, familial, 158, 458, 502–503
Spastin gene, 454t, 458
Spatial orientation, 197f, 197–199
Speech
  apraxia of, 195
  assessment of, 5
  spontaneous, 192
Speech audiometry, 271
Speech reception threshold, 271
Sphincter dyssynergia, 529
Sphingosine-1-phosphate receptor antagonists, 530
Spina bifida occulta, 117
Spinal accessory nerve, 7
Spinal angiography, 26
Spinal cord
  disorders of. See Spinal cord disease/injury
  infarction of, 52f, 147
  pain mechanisms of, 90–91, 91f
  questions regarding, 849, 863
  transverse section through, 492f
  vascular malformations of, 500, 500f
Spinal cord compression
  in hematomyelia, 496
  neoplastic

www.ketabpezeshki.com (021) 66485457 - 66485438

clinical features of, 493–494
diagnosis of, 494, 494f
intradural mass lesions, 494, 494f
pathogenesis of, 493–494
in primary intramedullary tumors, 495, 495f
treatment of, 494
questions regarding, 854–855, 873
in spinal epidural abscess, 115, 495–496, 496f
in spinal epidural hematoma, 496
treatment of, 854–855, 873
Spinal cord disease/injury, **490**
acute, 493
anatomy related to, 490–491, 491t, 492f
approach to the patient, 490t, 490–493
autonomic dysfunction in, 475
bladder dysfunction in, 504
cervical cord, 121, 491
chronic myelopathies, 499
adrenomyeloneuropathy, 503
familial spastic paraplegia, 458, 502–503
hypocupric, 502
in multiple sclerosis, 502
primary lateral sclerosis, 457–458, 503
retrovirus-associated, 500–501
spondylitic myelopathy, 499–500
syringomyelia, 123, 501f, 501–502
in tabes dorsalis, 502
tethered cord syndrome, 117, 503
toxic causes of, 503
in vascular malformations of cord and dura, 500, 500f
in vitamin B12 deficiency, 502
compressive vs. noncompressive myelopathy, 493
extramedullary syndromes, 493
high-voltage electrical injury as cause of, 499
in HIV infection, 589
intramedullary syndromes, 493
level of lesion in, 10t, 491
lumbar cord, 491
meningitis, 569. See also Meningitis
noncompressive myelopathies, 496
evaluation of, 497t
spinal cord infarction, 497
paraneoplastic syndromes and, 612
patterns of, 492–493
rehabilitation of, 503–504
sacral cord/conus medullaris, 491–492
sensory abnormalities in, 155
subacute, 493
thoracic cord, 491
Spinal epidural abscess, 115, 495–496, 496f
Spinal epidural hematoma, 496
Spinal fusion, 120
Spinal muscle atrophy (SMA), 449, 453t, 457
Spinal stenosis
acquired, 113
back pain in, 113–114
congenital, 113
lumbar, 113–114, 114f
treatment of, 113–114
Spine
anatomy of, 107, 108f
lumbar, 116–117
pain sensitive structures in, 107
Spinobulbar muscular atrophy, 454t, 457
Spinocerebellar ataxia (SCA)
classification of, 443t–445t
genetic factors in, 280t
infantile-onset, 448t
with neuropathy, 448t
SCA1, 436–438, 437f, 443t
SCA2, 436–438, 443t
SCA3, 436, 438–439, 442, 443t
SCA4, 443t
SCA5, 443t
SCA6, 280t, 436, 439, 443t
SCA7, 436, 439, 444t
SCA8, 439, 444t
SCA10, 444t
SCA11, 444t
SCA12, 444t
SCA13, 444t
SCA14, 444t
SCA15, 444t
SCA16, 444t
SCA17, 436, 444t
SCA18, 444t
SCA19, 444t
SCA20, 444t
SCA21, 444t
SCA22, 444t
SCA23, 445t
SCA25, 445t
SCA26, 445t
SCA27, 445t
SCA28, 445t
SCA30, 445t
SCA31, 445t
SCA32, 445t
SCA35, 445t
SCA36, 445t
sideroblastic anemia and, 448t
types of, 436
Spinothalamic tract, 90, 91f, 151, 151f
Spondylitic myelopathy, 499–500
Spondylolisthesis, 114
Spondylolysis, vertebral, 116–117
Spondylosis
back pain in, 114
cervical, 122–123, 158
Spontaneous speech, 192
Sporadic Creutzfeldt-Jakob disease, 461t
Sporadic fatal insomnia, 461t
Sporothrix infections, chronic meningitis in, 571t
Sprain, low back, 116
Spurling's sign, 122
SSEPs (somatosensory evoked potentials), 75
SSPE (subacute sclerosing panencephalitis), 558
SSRIs. See Selective serotonin reuptake inhibitors (SSRIs)
St. Vitus' dance, 428
Stabbing headache, primary, 100t, **391**
"Stalk section" phenomenon, 616
Stapedectomy, 266, 273
Stapes, 264, 265f
Staphylococcus aureus infections. See Meningitis, bacterial
Statins
adverse effects of, 727–728, 728t
for Alzheimer's disease, 397
for stroke prevention, 336–337, 851, 867
Status epilepticus, **319**
complex partial, 406
in critically ill patient, 364, 367
definition of, 319
delirium in, 168t, 169
generalized convulsive, 319, 850, 866
generalized tonic-clonic, 320
nonconvulsive, 319
questions regarding, 850, 866
Stem cell(s), in neurologic disease, 287–289
Stem cell therapy
for Huntington's disease, 288
for Parkinson's disease, 288, 419
sources of cells for, 288
Stereognosis, 154
Stereopsis, 224
Stereotactic radiotherapy, 618
Steroidogenic inhibitors, 632
Stiff-person syndrome
clinical features of, 704
gait disorders in, 158–159
paraneoplastic, 607t, 612–613
pathogenesis of, 704
Stokes-Adams attack, 132
Stomach, alcohol effects on, 801
Strabismus, 240
Straight-leg raising sign, 110, 110t
Strain, low back, 116
Strength testing, 7–8
Streptococcal infections
meningitis. See Meningitis
S. pneumoniae, 535
Streptomycin, 232
Stress, 208, 771, 772t
Stroke, **324**–325. See also Cerebrovascular disease; Stroke syndromes
aphasia in, 194
in CADASIL, 335
cardioembolic, 328–330, 330t
clinical features of, 323
definition of, 323
delirium in, 168t, 169
drugs and, 335
embolic, artery-to-artery, 330–332
etiology of, 324f, 329f, 330t
fibromuscular dysplasia and, 334
gait disorders in, 158
hearing loss in, 270
hypercoagulable disorders and, 334
imaging studies in, 350–353
cerebral angiography, 335f, 352–353
computed tomography, 350–352, 352f
MRI, 351–352, 353f
PET, 353
ultrasound, 353
intracranial hemorrhage in. See Intracranial hemorrhage
ischemic. See Ischemic stroke
leukoaraiosis and, 335
in Moyamoya disease, 335

www.ketabpezeshki.com (021) 66485457 - 66485438

Stroke, (Cont.):
necrotizing arteritis and, 334
noncardiogenic, prevention of, 339
ocular manifestations of, 224, 235, 244
prevention of, 336–339, 851, 867
primary central nervous system vasculitis and, 334–335, 335f
reversible posterior leukoencephalopathy and, 357
with right hemiplegia but preserved language, 352f
risk factors for, 332t
small-vessel, 330t, 332–334, 333f
taste disorders in, 260
temporal arteritis and, 334
af er TIA, 336, 336t
treatment of, 324f, 325
venous sinus thrombosis and, 334
Stroke centers
comprehensive, 328
in ischemic stroke management, 328
Stroke syndromes, **340**–341
within anterior circulation, 341
anterior cerebral artery, 342–343, 343f
anterior choroidal artery, 343, 344f
common carotid artery, 345
internal carotid artery, 343f, 343–344, 344f
middle cerebral artery, 341–342, 342f
within posterior circulation, 345
basilar artery, 346–350, 348f–351f
posterior cerebral artery, 343f–344f, 345
P1 syndrome, 345
P2 syndrome, 345
vertebral artery, 346, 347f
Structural heart disease, 132
Stupor, 171
Sturge-Weber syndrome, 65f
Sty (hordeolum), 227
Subacute combined degeneration, 502
Subacute necrotizing encephalomyelopathy (Leigh's disease), 68f
Subacute quadriparesis, 148
Subacute sclerosing panencephalitis (SSPE), 558
Subarachnoid hemorrhage
clinical features of, 372
in critically ill patient, 371
delayed neurologic deficits af er, 372–373
DVT prophylaxis af er, 375
etiology of, 371–372
fundus examination in, 175
grading of, 372, 373t
headache in, 100t, 101, 372
hyponatremia in, 373
imaging in, 373–374, 374f
laboratory evaluation of, 373–374
pathophysiology of, 372
questions regarding, 849, 863–864
saccular aneurysms in, 371–372
treatment of, 374–375
Subclavian artery occlusion, 346
Subconjunctival hemorrhage, 227
Subdural empyema, **563**. See also Epidural abscess
approach to the patient, 533–534, 534f–535f
clinical features of, 563
definition of, 563, 563f
diagnosis of, 564, 564f
differential diagnosis of, 564
epidemiology of, 563
etiology of, 563
pathophysiology of, 563
prognosis of, 564
treatment of, 564
Subdural hematoma
acute, 508f, 508–509
chronic, 509f, 509–510
neuroimaging in, 61f, 173f, 509f
weakness in, 147
Subhyaloid hemorrhages, 247
Subretinal hemorrhages, 247
Substance P, pain and, 89–90, 90f
Substance use disorders. See also specific drugs
delirium in, 168, 168t
neuropathology of, 283
Sudden respiratory arrest, 346
Sudomotor function, in autonomic dysfunction, 473–474, 474t
Sulfacetamide, for conjunctivitis, 227
Sulfadiazine, for central nervous system toxoplasmosis, 562
Sulfonamides, 232
Sumatriptan
for cluster headache, 387
for migraine, 382t–383t
nasal spray, 382t, 383
parenteral administration of, 383
SUNCT/SUNA, 103, 386, 387t, 388–389, 852, 869
Sundowning, 166, 170
Superior pontine syndrome, lateral/medial, 350f
Superior sagittal sinus thrombosis
clinical features of, 566
neuroimaging of, 46f–49f
Supine hypertension, 131
Suppurative thrombophlebitis, intracranial. See Venous thromboembolism (VTE), suppurative intracranial
Suprachiasmatic nucleus, 208, 221
Suprascapular neuropathy, 123
Suramin, 605t, 667t
Surgery, for brain metastases, 601
Swinging flashlight test, 223, 223f
Sydenham's chorea, 428
Sympathetic apraxia, 195
Sympathetic postganglionic neuron, 89f
Symptomatic carotid stenosis, 339
Symptom-Driven Diagnostic System for Primary Care (SDDS-PC), 765
Syncope, **125**
approach to the patient, 132–134
in arrhythmias, 129t, 132
cardioinhibitory, 128
in cardiovascular disease, 129t, 132–134
definition of, 125
ECG in, 133–134
epidemiology of, 125
falls in neurologic disease versus, 133
high-risk features of, 126t
hypoglycemia and, 133
natural history of, 125
neurally mediated
causes of, 129t
classification of, 127–128, 130
clinical features of, 130
pathophysiology of, 126
treatment of, 130
in orthostatic hypotension. See Orthostatic hypotension
pathophysiology of, 126
in psychiatric disorders, 133–134
seizure versus, 132–133, 310t, 310–311
tilt table testing for, 474
treatment of, 130
vasopressor, 128
vasovagal, 127, 128f, 129t
Syndrome of inappropriate antidiuresis (SIAD), 642f, 644
Syndrome of inappropriate antidiuretic hormone (SIADH)
characteristics of, 643
definition of, 643
differential diagnosis of, 645t, 645–646
etiology of, 643–644, 644t
hypertonic saline for, 646–647
pathophysiology of, 644–645
self-limiting nature of, 644
treatment of, 646–647
vaptans for, 646, 646f
Synkinesis, 484
Syntax, 192
Synthetic cathinones, 817–818
α-Synuclein, 413, 870
Syphilis, secondary
neurologic manifestations of
chronic meningitis, 570t
subacute meningitis, 555–556
ocular involvement in, 229
Syringomyelia
Chiari malformation and, 501, 501f
clinical features of, 501
diagnosis of, 123
questions regarding, 855, 874
treatment of, 502
Systemic lupus erythematosus (SLE), 428, 498, 573t, 662
Systemic sclerosis (scleroderma)
facial hemiatrophy in, 487
neuropathy in, 662
Systems neuroscience, 294–295

Tabes dorsalis, 502
Tachyarrhythmias, syncope in, 95
Tachycardia-bradycardia syndrome, 132
Tacrine, for Alzheimer's disease, 397
Tacrolimus, for myasthenia gravis, 698–699
Takayasu's arteritis, 334
Talc embolism, 249
Tamoxifen, 605t
Tangier disease (ABCA1 deficiency), 658t, 658–659

www.ketabpezeshki.com (021) 66485457 - 66485438

Tardive dyskinesia, 159, 430–431, 786
Tardive syndromes, 430–431
Target of rapamycin complex 1 (TORC1), 760, 761
Taste buds, 256–257, 257f, 260
Taste disorders
  diseases and conditions associated with, 260
  drug-related, 260
  etiology of, 260
  evaluation of, 261
  olfactory dysfunction and, 260
  treatment of, 261–263
Taste pore, 257
Taste system, 256–258
Tau protein, 184t, 188
Taxanes, 667t
Tay-Sachs disease, adult, 454t, 457
TCAs. See Tricyclic antidepressants (TCAs)
T cell(s), autoreactive, 515
TDP-43 gene, 184t, 291
Teardrop fracture, 61f
Telangiectasia(s), capillary, 360
Telmisartan, for stroke/TIC prevention, 338
Temazepam
  for generalized anxiety disorder, 770t
  for insomnia, 216
Temperature sense, testing of, 152t, 152–153
Temporal arteritis. See Giant cell arteritis
Temporal bone
  computed tomography of, 272
  fracture of, 268
Temporal lobectomy, for refractory epilepsy, 318
Tension-type headache, 100t, 377t, 386, 852, 869
Teratoma
  description of, 620
  ovarian, 608f, 612
Terazosin, for urinary dyssynergia, 490, 504
Terbinafine, 260
Teriflunomide, for multiple sclerosis, 526–527, 856, 875
Terminally ill patient, delirium in, 168t, 169
Terminal restlessness, 169
Terson's syndrome, 248
Tethered cord syndrome, 117, 503
Tetrabenazine
  adverse effects of, 431
  for dystonia, 426
  for tardive dyskinesia, 431
Tetracyclines, for meibomitis, 227
Tetrahydrocannabinol (THC), 815
T alamic Déjerine-Roussy syndrome, 345
T alamus
  hemorrhage of, 355
  lesions of, sensory disturbances in, 155
  in olfaction, 255
T alidomide, 605, 669t, 671
T allium poisoning, 232, 671t, 672–673
THAP1 gene, 424
T ermoregulation, 209
T iamine deficiency
  delirium in, 168
  dementia in, 405
  neuropathies in, 674
  optic neuropathy in, 233
  Wernicke's disease, 369, 369f
T ick-filament myopathy, 371
T ioridazine, 785t
T iotepa, 605t
T iothixene, 785t
T ird nerve palsy, 253
T ird window, inner ear, 265–266
T irst, 637, 639
T omsen disease, 725
T oracic outlet, 123
T oracic outlet syndrome, 123
T rombolytic therapy, for ischemic stroke, 326
T rombophlebitis. See Venous thromboembolism (VTE)
T rombosis
  dural sinus, 340
  superior sagittal sinus, 46f–49f, 566
  venous sinus, 334
T underclap headache, primary, **390**–391
T ymectomy, for myasthenia gravis, 697, 858, 878
T ymoma, paraneoplastic syndromes in, 614
T yroid-associated ophthalmopathy, 254
T yroid disorders, muscle disorders and, 726
T yroid-stimulating hormone (TSH)-secreting adenomas, 618, 633–634
T yrotrope, 620, 620t
T yrotropin, 809
TIA. See Transient ischemic attack (TIA)
Tiagabine
  for epilepsy, 315t
  for stiff-person syndrome, 613
Tibial muscular dystrophy (Udd's distal myopathy), 716t, 717
Tic(s), **429**
  definition of, 423t
  motor, 429
  in Tourette's syndrome, 429
  vocal, 429
Ticlopidine, 81, 337
Tilt table test, 133, 474, 474t
Time-of-flight (TOF) imaging, 22
Timolol, 868
Tingling, 150. See also Sensation
Tinnitus, 267–268, 274
Tinnitus masker, 274
Tissue plasminogen activator, recombinant, 851, 866–867
Tizanidine, for spasticity in neurologic disease, 504, 529
TME. See Transmissible mink encephalopathy (TME)
Tobacco. See also Cigarette smoking
  chewing, 823
  components of, 821
  environmental tobacco smoke, 823
  forms of, 823–824
  oral, 823
Todd's paralysis, 298
Tolcapone, for Parkinson's disease, 417, 419t
Tolfenamic acid, for migraine, 382t
Tolosa-Hunt syndrome, 239, 241–242, 489
Tone, 144, 145t
Tongue paralysis, 488
Tonic-clonic seizures. See also Seizure(s)
  characteristics of, 299–300
  questions regarding, 850, 865–866
  syncope versus, 310t, 311
Tonic pupil, 223
Topiramate
  adverse effects of, 315t, 317, 385t
  for chronic daily headache, 103, 105
  for cluster headache prevention, 388t
  for epilepsy, 315t
  for migraine prevention, 385t, 868
  pharmacology of, 315t
  for posttraumatic headache, 105
  for raised cerebrospinal fluid pressure headache, 105
  for SUNCT/SUNA, 389
"Top of the basilar" syndromes, 346
  Target of rapamycin complex 1 (TORC1), 760, 761
Torsades de pointes, 132
Torsin A, 424
Torticollis, 425
Touch localization test, 154
Touch sensation, testing of, 152t, 153
Tourette's syndrome, 429
  etiology of, 429
  pathophysiology of, 429
  prevalence of, 429
  treatment of, 429
Toxin-induced neuropathies, 671t, 672–673
Toxoplasma gondii infection
  cerebral/central nervous system, 562, 587–588, 588f
  chronic meningitis in, 571t
  ocular, 229
  treatment of, 562
  weakness in, 147
Toxoplasma retinitis, chorioretinal scarring caused by, 252, 252f
Trachoma, 228
Traction retinal detachment, 250
Tractography, diffusion, 23f
Tramadol
  adverse effects of, 661t
  for back pain, 119
  for neuropathy, 661t
  for pain, 94t
Transcranial Doppler ultrasound, 849, 864
Transcranial magnetic stimulation, for depression, 778
Transfalcial herniation, 172f, 173
Transgenic mouse models, 280
Transient global amnesia, 406
Transient ischemic attack (TIA), **336**
  definition of, 323
  prevention of, 336
    anticoagulants in, 338–339
    antiplatelet agents in, 337–338
  risk factors for, 336–337
  stroke following, 336, 336t
  treatment of, 324f
  visual symptoms of, 235
  weakness in, 149t
Transient monocular blindness, 230
Transmissible mink encephalopathy (TME), 292–293, 461t

www.ketabpezeshki.com (021) 66485457 - 66485438

Transsphenoidal surgery
for acromegaly, 628
for craniopharyngioma, 619
for Cushing's syndrome, 631
for macroadenomas, 633
for sellar masses, 617–618, 618f
for thyroid-stimulating hormone-secreting adenomas, 634
Transtentorial herniation, 172–173
Transverse sinus thrombosis, 566
Tranylcypromine, for depression, 768t
Trauma
back pain following, 112t, 116
cervical spine, 121–122
ligament injury af er, 60f
Traumatic brain injury (TBI). See Head injury
Trazodone
adverse effects of, 768t
for depression, 768t
for insomnia, 216
questions regarding, 860, 882
for stress disorders, 773
Treacher Collins syndrome, 270t
Tremor(s), **422**–423
clinical features of, 423
definition of, 423t
essential, 423
etiology of, 423
in Parkinson's disease, 423
pathophysiology of, 423
prevalence of, 423
treatment of, 423–424
in Wilson's disease, 433
Triazolam
for generalized anxiety disorder, 770t
for insomnia, 216
Trichinella/trichinellosis, chronic meningitis in, 572t
Trichromat, 224
Tricyclic antidepressants (TCAs)
adverse effects of, 98, 131, 661t, 768t
for back pain, 119
for cataplexy, 213
for chronic daily headache, 103, 105
contraindications to, 777
for depression, 768t, 776–777, 777f
for neuropathy, 661t
orthostatic hypotension caused by, 131
for pain, 94t, 97, 98t
pharmacology of, 777
for posttraumatic headache, 105
questions regarding, 860, 882
Trifluoperazine
for schizophrenia, 785t
side effects of, 785t
Trigeminal autonomic cephalalgias, **101**, 377t, 386, 387t
Trigeminal nerve
disorders of, 484t
examination of, 6–7
in facial pain or numbness, 481
sensory divisions of, 482f
Trigeminal neuralgia, **481**
clinical features of, 481–482
differential diagnosis of, 483, 873
incidence of, 482
laboratory evaluation of, 483
in multiple sclerosis, 518
pathophysiology of, 482–483
questions regarding, 872–873
treatment of, 98, 483, 872–873
Trigeminal neuropathy, **483**–484, 484t
Trigeminovascular system, 101
Trigger point injections, 119
Triggers
migraine, 376
multiple sclerosis, 515–516
Trihexyphenidyl
for dystonia, 425
for extrapyramidal symptoms, 786
for Parkinson's disease, 418
Trilostane, for Cushing's syndrome, 632
Trimethoprim-polymyxin, for conjunctivitis, 227
Trimethoprim-sulfamethoxazole (TMP-SMZ), for meningitis, 542
Triptans
description of, 376
for migraine, 382t–383t, 383
Trismus, 484
Trochlear nerve
description of, 6
palsy of, 241–242
Trophic factors, for Parkinson's disease, 419–420
True neurogenic thoracic outlet syndrome, 123
Trypanosoma spp. infections
chronic meningitis in, 571t. See also Meningitis
in HIV infection, 589
TSC1 gene, 593t, 600
TSC2 gene, 593t, 600
TSH. See T yroid-stimulating hormone (TSH)
TSH-secreting adenomas. See T yroid-stimulating hormone (TSH)-secreting adenomas
Tuberculosis (TB)
central nervous system, 28f–29f
extrapulmonary
meningitis, 570t
ocular manifestations, 229
spinal/skeletal, 495, 496f
Tuberous sclerosis
brain tumors and, 593t, 600
clinical features of, 600
neuroimaging of, 63f
pathogenesis of, 600
seizures in, 600
Tuf ed cells, 255
Tullio phenomenon, 266
Turcot's syndrome, 593t
Two-point discrimination test, 154
Tympanic membrane, 264, 265f
assessment of, 270
perforation of, 262, 273
Tympanogram, 272
Tympanometry, 265, 272
Tympanoplasty, 262, 273
Tympanostomy tubes, 273
Tyramine, MAOIs and, 417

Udd's distal myopathy (tibial muscular dystrophy), 716t, 717
Ulnar nerve, motor conduction studies of, 77f
Ulnar neuropathy, 676, 747–748, 748f
Ultrasonography
in neurologic disease, 14t
in stroke, 353
Umami, 257
Uncal transtentorial herniation, 172f, 172–173
Unfractionated heparin, 81
Unipolar depressive disorders, 776
University of Pennsylvania Smell Identification Test, 258f, 261
Unthoff's symptom, 517
Unverricht-Lundborg disease, 301t, 446t
Upbeat nystagmus, 244
Upper motor neuron diseases, 453t–455t, 457–458, 870
Upper motor neuron pathways, 146f
Upper motor neuron weakness, 145, 145t
Uremia, delirium in, 168t
Urinary tract infections (UTIs)
delirium in, 168, 168t
in multiple sclerosis, 530
Usher's syndrome, 268, 270t
Uterosacral ligament, disorders involving, 117
Uveitis, 228–229, 235
anterior, 228–229
intermediate, 229
paraneoplastic, 614
posterior, 229

Vagus nerve
anatomy of, 258f
diseases of, 487
examination of, 7
in taste sensation, 258
Vagus nerve stimulation
for depression, 778
for epilepsy, 319
Valacyclovir
for Bell's palsy, 486
for viral encephalitis, 553
for viral meningitis, 547
Valdecoxib, 94t
Valproate/valproic acid, 865
adverse effects of, 385t, 780t
bone marrow suppression, 317
common, 780t
hepatotoxicity, 317
neurologic, 316t
rare, 780t
systemic, 316t
teratogenic, 322
for bipolar disorder, 780, 780t
for chronic daily headache, 103, 105
dosage of, 316t, 780t
drug interactions of, 316t
for epilepsy, 316t, 317
for focal seizures, 317

www.ketabpezeshki.com (021) 66485457 - 66485438

for generalized seizures, 317
for migraine prevention, 385t
for myoclonus, 430
pharmacology of, 316t
for posthypoxic myoclonus, 367
for posttraumatic headache, 105
for stiff-person syndrome, 613
for tardive dyskinesia, 431
Valsalva response, in autonomic dysfunction, 474t
Valsalva maneuver, 473, 474t
Valvular vegetations, 330
Vancomycin, for meningitis, 539t, 541–542
Vaptans, for syndrome of inappropriate antidiuretic hormone, 646, 646f
Varenicline, for smoking cessation, 825, 862, 886
Varicella (chickenpox), 531
Varicella-zoster virus (VZV) infections
meningitis, 546
neuropathy in, 665
Vascular anomalies, 359–360
Vascular dementia, **182**, 186t, 187, 188f, 398
Vascular disease, 253
Vascular endothelial growth factor (VEGF) inhibitors, 237
Vascular sheathing, of retina, 250, 250f
Vasculitic neuropathy, **689**–690
Vasculitis
central nervous system
neuroimaging of, 45f–46f
stroke caused by, 334–335, 335f
isolated, dementia caused by, 406
of nerve and muscle, 613
paraneoplastic, 613
Vasogenic edema, 361
Vasopressin
actions of, 636–637
antidiuretic effect of, 636f
metabolism of, 637
plasma osmolarity and, 639f
synthesis and secretion of, 635f, 635–636
urine osmolarity and, 639f
urine volume regulation by, 636f
Vasopressin disorders
diabetes insipidus. See Diabetes insipidus
hypodipsic hypernatremia, 641–643
hyponatremia caused by inappropriate antidiuresis, 643–647
primary polydipsia, 638t, 638–640
Vasopressor syncope, 128
Vasospasm, af er subarachnoid hemorrhage, 373–375
Vasovagal syncope, 128f
Vegetative state, 171
Venlafaxine, 860, 882
adverse effects of, 385t, 661t, 768t
for cataplexy, 213
for depression, 768t, 778–779
dosage of, 768t
for migraine prevention, 385t
for neuropathy, 661t
for pain, 95t, 98–99, 529
for panic disorder, 767
pharmacology of, 779
Venous anomalies, 359–360
Venous sinus thrombosis, stroke caused by, 334
Venous thoracic outlet syndrome, 123
Venous thromboembolism (VTE)
with brain tumor, 592
suppurative intracranial
anatomy of, 566, 566f
clinical features of, 566
definition of, 566
diagnosis of, 566–567
pathophysiology of, 566
treatment of, 567
Ventral tegmental area, 762, 762f
Ventricular tachycardia, syncope in, 132
Ventriculostomy, for ICP and brain tissue monitoring, 364, 364f
Ventrolateral preoptic hypothalamus, 206, 208
VEPs (visual evoked potentials), 74
Verapamil, for cluster headache prevention, 388, 388t
Vertebrae, 107, 108f
Vertebral artery
dissection of, 332
occlusion of, 346
Vertebral fractures
in osteoporosis, 116
pain in, 116
Vertigo, **135**
acute prolonged, 137
approach to the patient, 135–136
benign paroxysmal positional, 136t, 137
central, 136t
evoked by loud sounds, 265
in Ménière's disease, 267
in migraine, 135, 137
in multiple sclerosis, 517
peripheral, 136t
psychosomatic, 139
treatment of, 139, 139t
in vestibular dysfunction, 136t, 137
Vestibular dysfunction
balance disorders in, 138, 161
clinical features of, 138
evaluation of, 137
vertigo in, 136t, 137
Vestibular-evoked myogenic potential test, 272
Vestibular function, bilateral loss of, 138–139
Vestibular nerve section, for Ménière's disease, 267
Vestibular neuritis, 137
Vestibular nystagmus, 244
Vestibular rehabilitation therapy, 139
Vestibular schwannoma
diagnosis of, 138, 272, 598, 599f
facial nerve involvement in, 486
hearing loss in, 138, 267, 270, 272
imaging in, 273, 598, 599f
Vestibulocochlear nerve, 7
Vestibuloocular reflex, 136
Vestibulospinal pathway, 146f
Vibration sense, 152t, 153
Video electroencephalography, 865
Vigabatrin, for stiff-person syndrome, 613
Vilazodone
adverse effects of, 768t
for depression, 768t
dosage of, 768t
Vinca alkaloids, 667t
Vincristine, 605, 605t
Violence assessment, 786–787
Viral encephalitis, **548**
approach to the patient, 533–534, 534f–535f
clinical features of, 548
definition of, 548
diagnosis of, 550f
brain biopsy in, 551
cerebrospinal fluid analysis in, 549–550
computed tomography for, 550
MRI in, 550–551
serologic studies and antigen detection in, 550
differential diagnosis of, 551–553
enteroviral, 545–546
etiology of, 543t, 548–549
herpes simplex virus
differential diagnosis of, 540
memory loss in, 201
MRI in, 19f
sequelae of, 554–555
treatment of, 553–554
West Nile virus, 551, 551t, 552, 554
Visual acuity, 136, 138, 222, 222f
Visual aura, 234
Visual blurring, in multiple sclerosis, 517
Visual cortex, 192f
Visual evoked potentials (VEPs), 74
Visual fields assessment, 224–226, 225f
Visual function assessments
color vision, 224
eye movements and alignment, 224
pupils, 222–224, 223f
refractive state, 222
stereopsis, 224
visual acuity, 222, 222f
visual fields, 224–226, 225f
Visual loss
chemotherapy-induced, 605t
chronic, 235–238
factitious, 235
transient or sudden, 230–235
Visual object agnosia, 200
Visual target cancellation test, 198
Visual vertigo, 139
Vitamin A
deficiency of, 228
for retinitis pigmentosa, 237
supplements, for olfactory dysfunction, 262
Vitamin B1. See T iamine
Vitamin B2. See Riboflavin
Vitamin B6. See Pyridoxine
Vitamin B12
deficiency of, 502
delirium caused by, 168
dementia caused by, 405
frontal lobe syndrome in, 202
gait disorders in, 159
neuropathies in, 502, 673
olfactory dysfunction in, 262
optic neuropathy in, 233

www.ketabpezeshki.com (021) 66485457 - 66485438

Vitamin B12 (Cont.):
orthostatic hypotension associated with, 131
sensory disturbances in, 154
malabsorption of, 262
questions regarding, 857, 876
Vitamin C, for macular degeneration, 236
Vitamin D deficiency, 727
Vitamin E
deficiency of
ataxia with, 440–441, 446t
neuropathies in, 674
for macular degeneration, 236
Vitreous degeneration, 234
Vitreous detachment, 234
Vitreous hemorrhage, 234
Vocal tic, 429
Vogt-Koyanagi-Harada syndrome, 229, 573t
von Hippel-Lindau disease
brain tumors in, 593t
characteristics of, 446t
neuroimaging in, 64f
von Recklinghausen's disease. See Neurofibromatosis type 1 (NF1)
Vortioxetine
adverse effects of, 768t
for depression, 768t
dosage of, 768t
V sign, 731
VTE. See Venous thromboembolism (VTE)
VZV infections. See Varicella-zoster virus (VZV) infections

Waardenburg's syndrome, 268, 270t
Wakefulness, 205
Wake-sleep systems, 207f, 208
Waldenström's macroglobulinemia, paraneoplastic syndromes in, 613
Walker-Warburg syndrome, 713, 713t
Wallenberg's syndrome, 346, 347f
Warfarin, 81
War veterans
concussion in, 790–792, 791t
neuropsychiatric illnesses in, 788
clinical features of, 788–789
epidemiology of, 788
evaluation of, 792–793, 793t–794t
stigma and barriers to care, 792
treatment of, 793–796
postwar symptoms in, 789
PTSD in, 789–790, 795–796
sleep disturbance in, 795
Weakness, **144**
approach to the patient, 148f, 700–702, 701f, 702t
definition of, 144
distal, 149
facial, 484, 517
falls and, 162
generalized (quadriparesis), 147, 149t
hemiparesis, 146–147
lower motor neuron (neuropathic), 145, 145t
monoparesis, 148–149
in multiple sclerosis, 516, 529
myopathic, 144, 145t, 145–146
neuromuscular junction, 145
paraparesis, 147
in peripheral neuropathy, 648–649
proximal, 149
in restricted distribution, 149
upper motor neuron, 145, 145t
Weber's syndrome, 241, 344f, 345
Weber test, 271
Wegener's syndrome. See Granulomatosis with polyangiitis (Wegener's)
Welander's distal myopathy, 716t, 717
Werdnig-Hoffmann disease, 290, 457
Wernicke-Korsakoff syndrome, 200
Wernicke's aphasia, 192–193, 193t
Wernicke's area, 191, 196, 197f
Wernicke's disease/encephalopathy
clinical features of, 243, 369, 405
in critically ill patient, 369, 369f
pathology of, 369
treatment of, 369, 405
video library of, 254
West Nile virus infections
encephalitis, 551, 551t, 554
meningoencephalitis, 546
weakness in, 147
Westphal variant, Huntington's disease, 426
Wet beriberi, 674
Whiplash injury, 121–122
Whipple's disease
chronic meningitis in, 570t
ocular involvement in, 229, 243
White matter disease
diffuse, 187, 188f, 398
periventricular, stroke caused by, 335
Wilson's disease
movement disorders in, 432–433
parkinsonism in, 412, 412t
prevalence of, 433
treatment of, 433
"Work hardening" regimens, 119
World Federation of Neurosurgical Societies scale, for subarachnoid hemorrhage, 373t
"Wrong-way" eyes, 176

Xanthoastrocytoma(s), pleomorphic, 596
Xenon techniques, in stroke, 353
X-linked adrenoleukodystrophy, 68f
X-linked disorders
color blindness, 224
mental retardation, 283
spinobulbar muscular atrophy, 454t, 457
Xylohypha infections, chronic meningitis in, 571t

Yin Yang 1 gene, 284
Yohimbine, for orthostatic hypotension, 131

Zalcitabine (ddC), 672
Zaleplon, for insomnia, 216
Zidovudine (AZT), 728, 728t
Zinc
for macular degeneration, 236
supplements
adverse effects of, 260
for olfactory dysfunction, 262
Ziprasidone
for schizophrenia, 785t, 786
side effects of, 785t
Zolmitriptan
for migraine, 382t–383t
nasal spray, 382t
Zolpidem, for insomnia, 216
Zonisamide, 316t

www.ketabpezeshki.com (021) 66485457 - 66485438