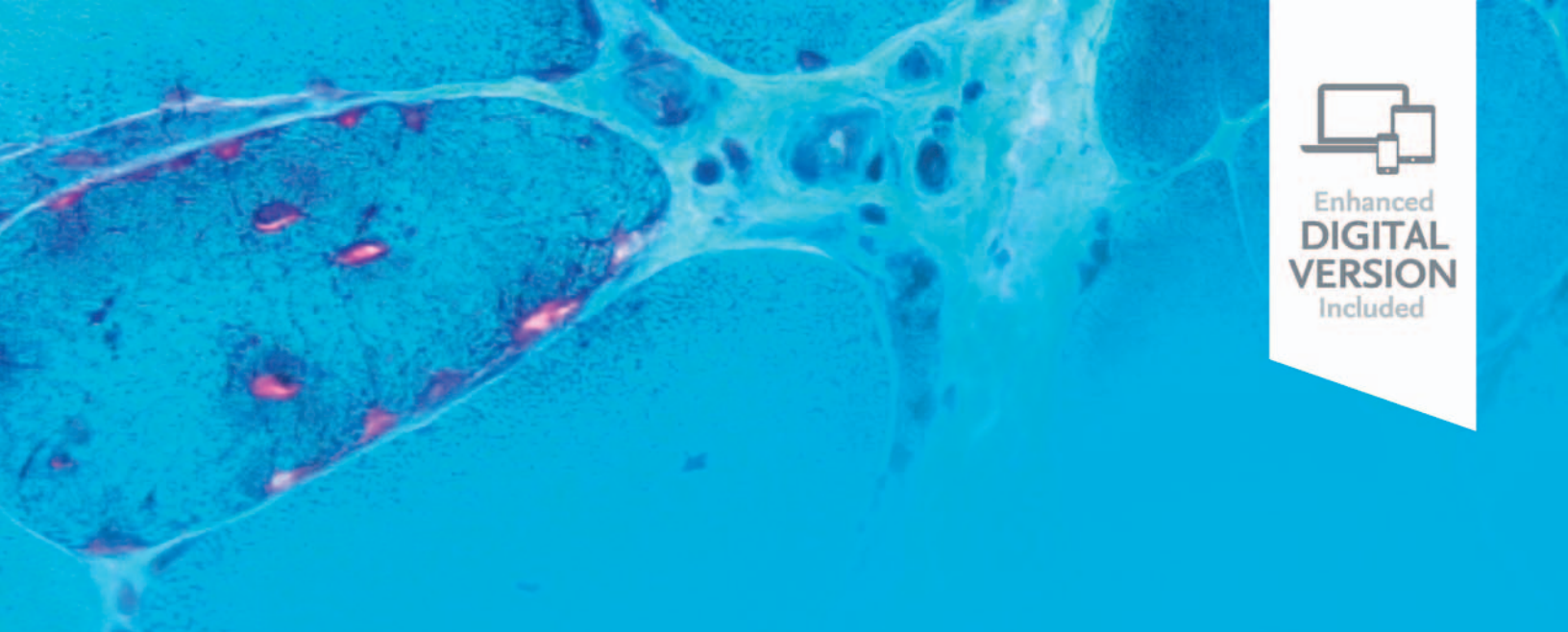


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TREATMENT AND MANAGEMENT

SECOND EDITION



Tulio E. Bertorini

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NEUROMUSCULAR DISORDERS

TREATMENT AND MANAGEMENT

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Second Edition

NEUROMUSCULAR DISORDERS

TREATMENT AND MANAGEMENT

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Cover image
Top: IBM - Rimmed vacuoles (left) and a ragged red fiber (right) seen in Inclusion Body Myositis stained with Gomri's Modified Trichrome (200x)

Bottom: Inflammatory - Inflammatory cells stained with hematoxylin and eosin (100x)

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To my wife, Emma, for her patience, support, and encouragement; my children, Tulio J. Paola and Francisco; my grandchildren, Nicolas, Rafael, and Gabriela; and the memory of my parents, Nico and Queta.

To the Peruvian American Medical Society (PAMS) for their dedication to the care of the indigent and improving medical education in Peru.

To the Ernesto Guevara class of the San Fernando Medical School in Lima on the golden anniversary of their graduation.

To my patients.

To all that died in the front lines fighting the COVID-19 pandemic.

Preface

There have been great advances in the diagnosis and evaluation of patients with segmental and generalized neuromuscular disorders since the first edition of this book. Tests applied to different types of the disorders are discussed in the introduction as well as specific chapters.

The management of these diseases have also improved significantly, particularly in cardiac and pulmonary care, and in the management of autonomic and peripheral neuropathies, and for this reason these chapters have been expanded. We have also expanded chapters in orthopedic surgery and rehabilitation with the use of robotics to manage patients with chronic weakness.

Immunotherapy has improved greatly with the use of new monoclonal antibodies, which increases the armamentarium of clinicians that take care of autoimmune disorders. The basic aspects of immunotherapy are covered in Chapter 7, but also are detailed chapters dedicated to autoimmune neuropathies and myopathies, and disorders of neuromuscular disorders of neuromuscular junction.

The most important development in neuromuscular disorders has been the discovery of pathogenic genes and improved testing in hereditary conditions, which has allowed us to diagnose patients even without muscle biopsies, and this has led to genetic therapies. We have included a new chapter that introduces the readers to these treatments, which are also discussed in detail in those chapters dedicated to hereditary myopathies and neuropathies.

Some topics are discussed in various chapters, causing some repetition, but the intent is that each reader could consult individual chapters independently.

These have been very difficult times, because of the COVID-19 pandemic, which affects more severely patients with weakening neuromuscular disorders. Medical care has also been complicated by this, and COVID-19 infections are associated with neuromuscular conditions that are discussed in different chapters.

The pandemic has also created difficulties in the completion of this book, and I am most grateful to the Elsevier personnel and the other collaborators that have helped overcome these difficulties. I am also very thankful that they dedicated their time and effort to the completion of this volume, which I believe will be very useful to those taking care of patients with neuromuscular disorders.

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We extend our sincere appreciation to Dr. Michael Cartwright and Dr. Francis Walker for providing great ultrasound figures.

Finally, we want to acknowledge the excellent and dedicated collaboration from the authors of the different chapters, and express gratitude to Wesley Neurology and UTHSC for their support, and to Kathleen Nahm and Nadhiya Sekar at Elsevier for editorial help.

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PART 1

GENERAL PRINCIPLES IN THE TREATMENT AND MANAGEMENT OF NEUROMUSCULAR DISORDERS

1 Introduction: Evaluation of Patients with Neuromuscular Disorders

Tulio E. Bertorini, MD

This book is dedicated to the treatment of neuromuscular disorders (NMDs), which include those that affect the anterior horn cells, nerve roots, plexi, peripheral nerves, neuromuscular junction, and muscles (Fig. 1.1) (Dubowitz, 1996); some also affect other areas of the nervous system, such as amyotrophic lateral sclerosis (ALS). These disorders may be caused by genetic defects or may be acquired, as the autoimmune diseases, may be secondary to general medical conditions or may arise as complications of surgery. To make therapeutic decisions about these disorders, clinicians should be able to recognize their clinical presentation and characteristics. This chapter provides a brief introduction to the evaluation of patients with NMDs.

MEDICAL HISTORY AND SYMPTOMS

The evaluation should include obtaining detailed medical and family histories as well as identifying possible complicating factors. In children, information should be obtained on the prenatal period and delivery, especially if the patient was a "floppy baby," and details of the patient's developmental milestones should be recorded (Brooke, 1999; Dubowitz, 1996).

Identifying general medical problems is important because some NMDs are associated with other conditions, such as endocrine and connective tissue diseases that might affect other organs. Medications also should be considered, because many are known to produce neurologic complications.

Muscle weakness is a common symptom, except in patients with sensory or autonomic neuropathy or in some radiculopathies and entrapment syndromes. The rate of progression varies, and in some conditions, such as Guillain-Barré syndrome (GBS), electrolyte imbalance, toxic neuropathy, and myopathy associated with rhabdomyolysis, it is rapid (Box 1.1). In disorders of neuromuscular transmission, such as myasthenia gravis (MG), weakness fluctuates during the day. In periodic paralysis, weakness is recurrent (Brooke, 1986), whereas in other disorders, such as muscular dystrophies, or in hereditary and some autoimmune neuropathies, it is subacute or chronic (Box 1.2) (Bertorini, 2002; Brooke, 1986).

The distribution of weakness also is important in diagnosis; for example, it is proximal in spinal muscular atrophies and most myopathies, except for some disorders in which it is more distal, for example, inclusion body myositis (IBM) and Miyoshi myopathy. In myopathies, weakness usually is symmetric, although asymmetry can be seen in some diseases like fascioscapulohumeral dystrophy and IBM. In polyneuropathies, this characteristically begins in the legs but may initially manifest more prominently in the upper extremities, as in multifocal neuropathy, and also in brachial plexopathies, and cervical spinal canal disorders as well as in ALS. This follows the territory of roots or nerves in radiculopathies, focal neuropathies, (Bertorini, 2002), mononeuritis multiplex, and entrapment neuropathies.

Dysphagia, diplopia, and ptosis also help to identify NMDs because they occur in some myopathies and also in disorders of neuromuscular transmission, such as MG. Symptoms of respiratory difficulty should be recognized and treated promptly because this can be the first manifestation of some disorders such as MG, GBS, ALS, and some myopathies, such as acid maltase deficiency, whereas in other disorders, it appears at later stages (Bertorini, 2002, 2008). During the evaluation, one should always inquire about sleep difficulties, as sleep apnea can be seen in some of these diseases.

Difficulty combing the hair and placing objects in high cabinets commonly occurs in patients with shoulder-girdle weakness, whereas difficulty writing and grasping objects indicates involvement of the forearm and hand muscles, as in ALS and IBM. Weakness of the hip extensors usually causes inability to rise from a low chair or a toilet seat, whereas difficulty ascending stairs indicates dysfunction of the hip flexors and quadriceps muscles. More severe weakness of the quadriceps muscles occurs in IBM, causing difficulty descending stairs (Brooke, 1986; Griggs, Mendell, & Miller, 1995). When the distal muscles are affected, foot drop may cause a steppage gait and difficulty negotiating curves or changing courses, as seen in polyneuropathies, distal dystrophies, and ALS.

Muscle stiffness, tightness, and spasms occur as a result of spasticity in disorders affecting the upper motor neuron, but these also occur in patients with motor unit hyperactivity, such as "stiff-person" and Isaac syndromes and the myotonias. Those with inflammatory myopathies, polymyalgia rheumatica, fasciitis, and hypothyroidism also complain of stiff limbs. Cramping at rest or during exercise is a prominent symptom of the cramp-fasciculation syndrome (Masland, 1992) and also some neuropathies. In metabolic myopathies, this usually occurs during or after exercise, or after fasting in some cases. Fatigue is common in disorders of neuromuscular transmission, such as Eaton-Lambert syndrome (ELS) and MG, but also in myopathies, even though weakness is the major symptom. In ELS, there may be temporary improvement after a brief exercise.

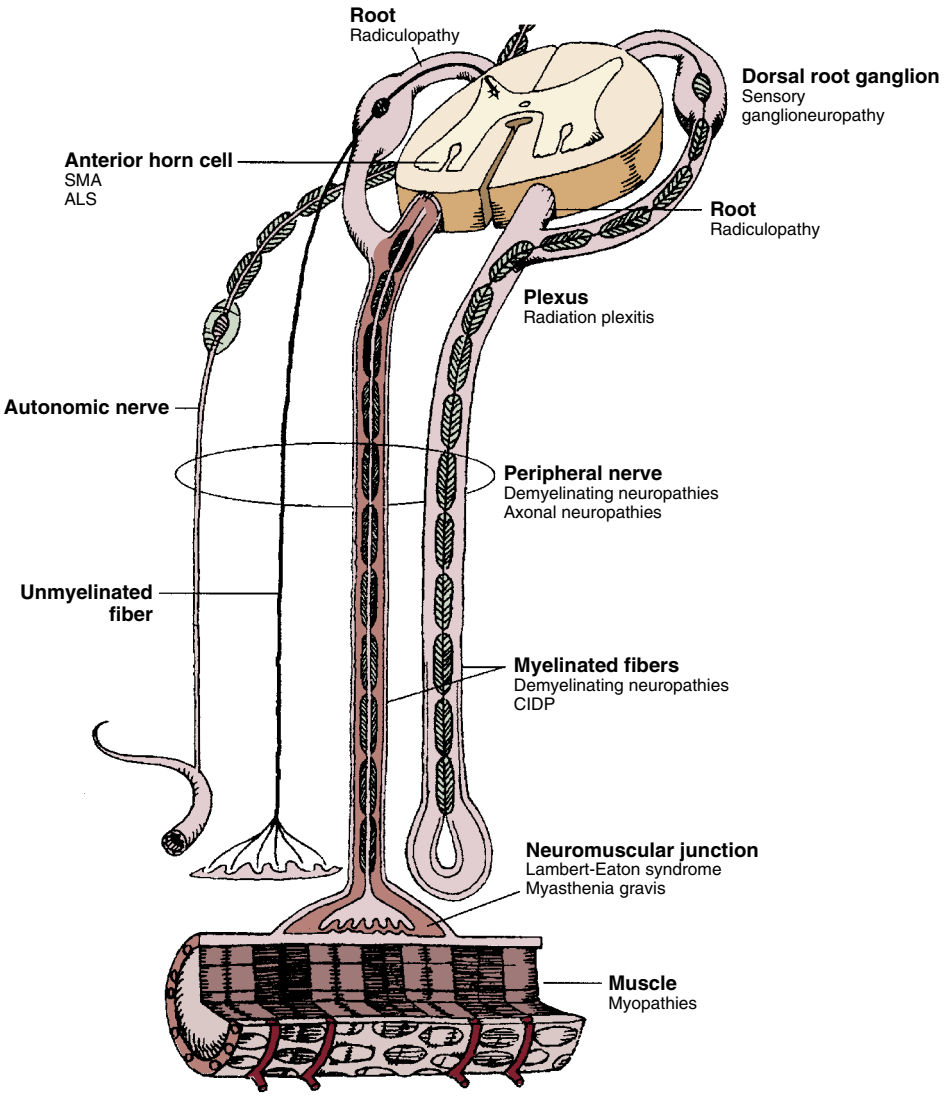


Fig. 1.1 Anatomic elements of the peripheral nervous system and related neurologic disorders. *ALS*, Amyotrophic lateral sclerosis; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *SMA*, spinal muscular atrophy. (Adapted from Bertorini, T. E. (2002). Overview and classification of neuromuscular disorders. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (pp. 1–13). Woburn, MA: Butterworth-Heinemann.)

Decreased sensation as well as paresthesias and neuropathic pain are symptoms of peripheral neuropathies (Ochoa, 1995). These symptoms are localized in the affected areas in those with radiculopathies, plexopathies, and entrapment neuropathies. Autonomic dysfunction can occur in some neuropathies and also in ELS, and the clinician should ask the patient for dysautonomic symptoms such as orthostatic hypotension and urinary and sexual dysfunction.

PHYSICAL EXAMINATION

A careful general physical examination is essential to arrive at a diagnosis, and the clinician should assess cardiac and lung function, examine the eyes for cataracts and retinal disease, and check for hearing loss and lipoma, which are often seen in mitochondrial disorders. Visceromegaly and skin changes are present in some patients with neuropathies, for example, those with POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, *s*kin changes) syndrome. Skin abnormalities can also be seen in connective tissue disorders, whereas patients with dermatomyositis have a characteristic rash, including the Gottron sign, carpenter fingers, and dilatation of the periungual capillaries (Fig 1.2) (also see figures of patients in Chapter 22) (Bertorini, 2002). High arches of the feet are seen in hereditary motor sensory neuropathy.

Clubbing of the fingers is seen in some chronic lung disorders, whereas Mees lines are seen in patients with arsenic and other poisoning (Fig 1.3).

Intellectual function should be assessed because it could be impaired, such as in some cases of ALS and in myotonic dystrophy. Examination of posture and gait is useful to determine if there is hyperextension of the knees, if there is evidence of a waddling gait in myopathies, and if there is a spastic or ataxic gait, or the steppage seen in peripheral neuropathy and some distal dystrophies should test tandem gait which is abnormal in cerebellar disease. Difficulty walking on tiptoes is seen in people with gastrocnemius and soleus weakness, whereas walking on heels cannot be done in persons with foot dorsiflexor weakness. Patients should be asked to get up and down from a stool to determine if there is thigh muscle weakness. The examiner should also notice difficulty arising from the chair or going upstairs, and if the patient has the characteristic Gower maneuver, when arising from the floor, due to proximal muscle weakness (Fig. 1.4), and

Box 1.1 Neuromuscular Disorders That May Present with Acute Generalized Weakness

Motor Neuron Diseases

Poliomyelitis, West Nile virus infection
Amyotrophic lateral sclerosis (rarely)

Neuropathies

Guillain-Barré syndrome and variants
Porphyria, particularly acute intermittent
Dinoflagellate toxins
Diphtheria
Arsenic poisoning and other acute toxic neuropathies
West Nile virus infection

Disorders of Neuromuscular Transmission

Botulism and other biologic toxins (black widow spider bites, snake bites)
Organophosphate poisoning
Eaton-Lambert myasthenic syndrome (rarely)
Hypermagnesemia
Myasthenia gravis

Myopathies

Rhabdomyolysis (from various causes, including metabolic, toxic, and infectious)
Polymyositis/dermatomyositis
Infectious myositis (e.g., trichinosis, toxoplasmosis)
Electrolyte imbalance (e.g., hypohyperkalemia, hypermagnesemia, hypocalcemia, hypercalcemia, hypophosphatemia)
Hyperthyroidism
Toxins
Intensive care myopathy (after immobilization with paralyzing agents and steroids in the intensive care unit)

Box 1.2 Examples of Conditions That Present with Progressive Subacute or Chronic Proximal Muscle Weakness

Progressive spinal muscular atrophy
Bulbospinal muscular atrophy (Kennedy disease)
Amyotrophic lateral sclerosis (sometimes)
Chronic inflammatory demyelinating neuropathy
Eaton-Lambert myasthenic syndrome
Myasthenia gravis
Endocrine diseases (e.g., hypothyroidism, Cushing disease, hyperparathyroidism)
Drugs (e.g., steroids, cholesterol-lowering agents, zidovudine, colchicine, chloroquine)
Toxins (e.g., alcoholic myopathy)
Electrolyte imbalance
Congenital myopathies (usually of earlier onset)
Muscular dystrophies
Polymyositis and dermatomyositis
Inclusion body myositis
Adult "nemaline" or "rod" myopathy
Mitochondrial myopathy
Juvenile and adult forms of acid maltase deficiency
Carnitine deficiency
Other metabolic myopathies

should observe if there is hyperlordosis with proximal atrophy in myopathies and distal atrophy in neuropathies and whether it is symmetric or focal (Figs. 1.5 and 1.6) or whether it affects the upper or lower extremities more prominently. The clinician should examine the patient for muscle hypertrophy, which is seen in some dystrophies and disorders of neuromuscular hyperactivity such as myotonia congenita (Fig. 1.7). Examination of muscle tone also is important to determine whether there is hypotonia, particularly in infants (Fig. 1.8 and Box 1.3), or spasticity and also to determine if there is limitation of passive joint movement like from muscle fibrosis that occurs in various myopathies (Fig. 1.9).

Examination of the eyelids and eye movements is helpful to diagnose acute paralysis in diabetic ophthalmoplegia and Miller-Fisher syndrome or chronic paralysis in mitochondrial myopathy and oculopharyngeal dystrophy (Fig. 1.10). Fluctuating ophthalmoplegia and ptosis are seen in MG (Fig. 1.11) (Barton & Fouladvand, 2000). Assessment of the pupils determines the presence of Horner syndrome (Fig. 1.12), whereas poorly reactive pupils may be seen in some neuropathies (Bertorini, 2002, 2008). The examiner should also assess the presence of eyelid myotonia in the myotonic disorders.

Prominent facial weakness occurs in GBS, but also in MG and some dystrophies (Fig. 1.13). A decreased or hyperactive gag reflex, as in ALS, not only might provide help in the diagnosis but also might determine the risk of aspiration. Tongue atrophy and fasciculations are characteristically seen in motor neuron diseases, whereas a typical forked tongue occurs in MG (Fig. 1.14). Examination of the neck muscles helps to identify neck extensor muscle weakness causing head drop (Fig. 1.15 and Box 1.4) (Narayanaswami & Bertorini, 2000). Rarely, patients with myasthenia can also have a "drop" jaw syndrome.

Manual muscle testing with proper grading helps to determine the distribution and degree of involvement and assess the progression of the disease, as well as diagnose and localize segmental neurologic disorders. For example, focal atrophy in ulnar innervated muscles is seen in ulnar neuropathy, and there is thenar atrophy in median neuropathy or both in C8 radiculopathy and lower plexus lesions. Moreover, dynamometry using different methods, particularly with handheld dynamometers, is used to monitor the progression of muscle weakness.

The examination should also include observation for fasciculations, which are more common in motor neuron disorders but also are seen in some neuropathies, such as multifocal motor neuropathy. Increased reflexes with the presence of the Babinski sign indicate involvement of the corticospinal tracts, as in ALS, whereas generalized hypo- or areflexia is seen in peripheral neuropathies, spinal muscular atrophy, and some neuromuscular transmission disorders, such as ELS and botulism. Distal reflexes are lost early in neuropathies and are preserved until the later stages in myopathies (Table 1.1). The examiner also should observe the patient for grip myotonia (Fig. 1.16) and percussion myotonia, myoedema, and slow relaxation of the ankle reflexes, as seen in hypothyroidism.

The sensory examination helps to assess the type and distribution of deficits to determine whether they are distal or symmetric or follow the dermatomes of nerve roots or individual nerves and whether they affect more severely the large myelinated axons (proprioceptive deficits), the unmyelinated axons (dysautonomia, pain, and temperature deficits),



Fig. 1.2 (A) Heliotrope rash in a child with dermatomyositis. (B) Diffuse erythematous facial rash in an adult with dermatomyositis. (Adapted from Bertorini, T. E. (2002). Overview and classification of neuromuscular disorders. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (pp. 1–13). Woburn, MA: Butterworth-Heinemann.) (C) Also see Gottron sign, erythema of the knuckles on dermatomyositis. (2D) Periungual capillary dilatation and carpenter finger in dermatomyositis.)

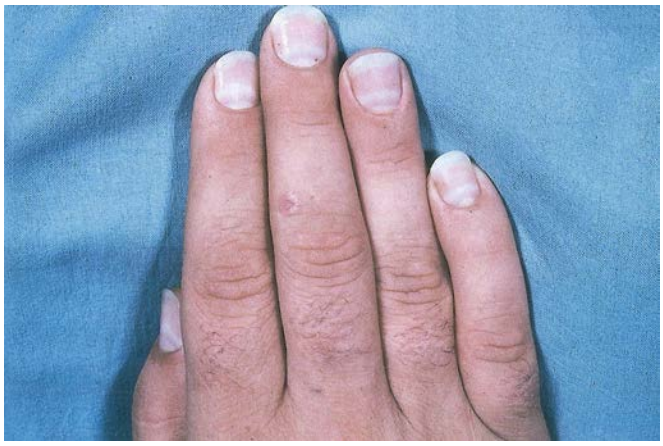


Fig. 1.3 White lines (Mees lines) noticed in the fingernails of a patient with arsenic poisoning. (Adapted from Bertorini, T. E. (2002). Overview and classification of neuromuscular disorders. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (pp. 1–13). Woburn, MA: Butterworth-Heinemann.)

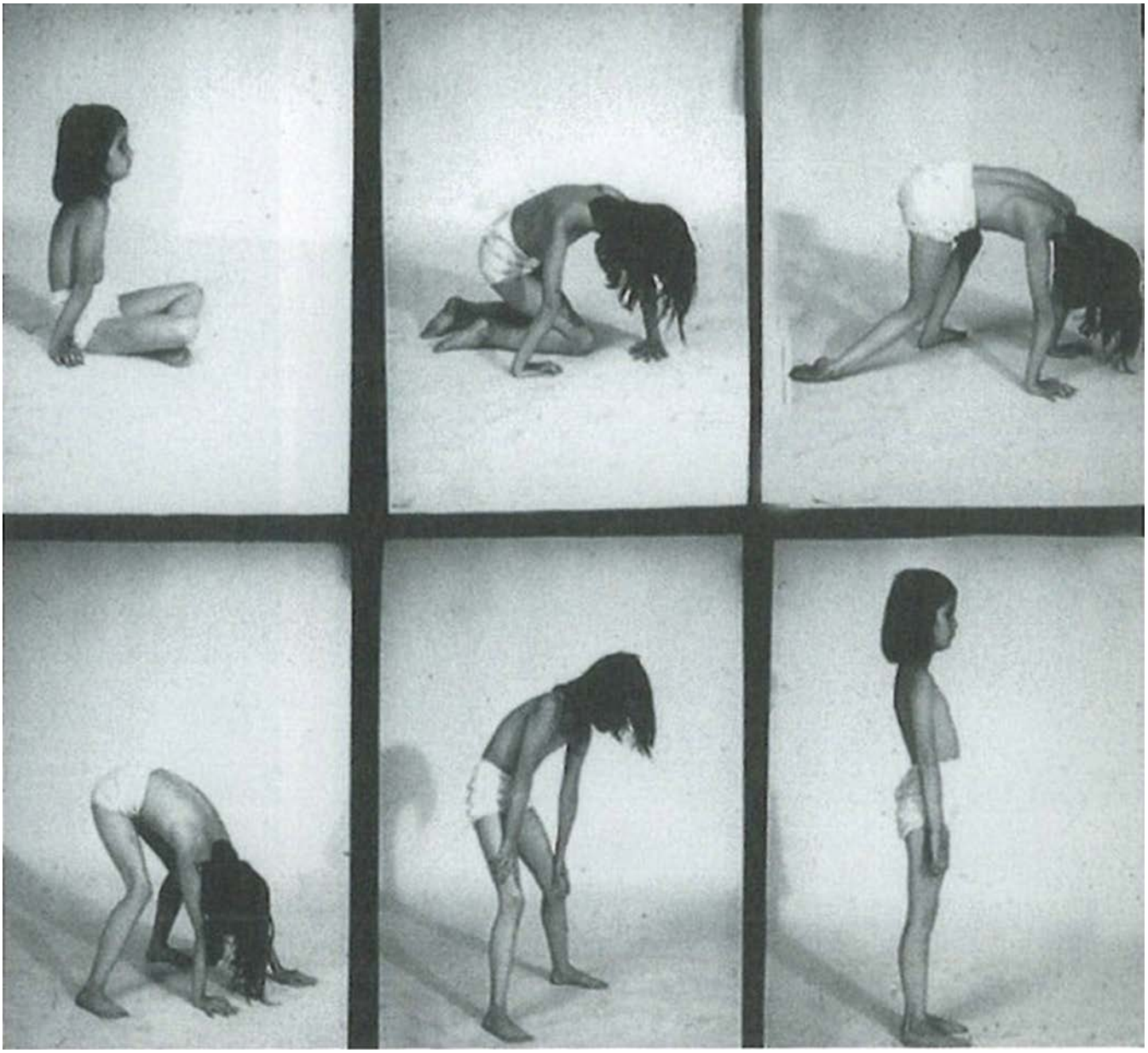


Fig. 1.4 Patient with juvenile acid maltase deficiency showing the Gower sign. Also notice the hyperextension of the elbow while sitting. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 31). Woburn, MA: Butterworth-Heinemann.)

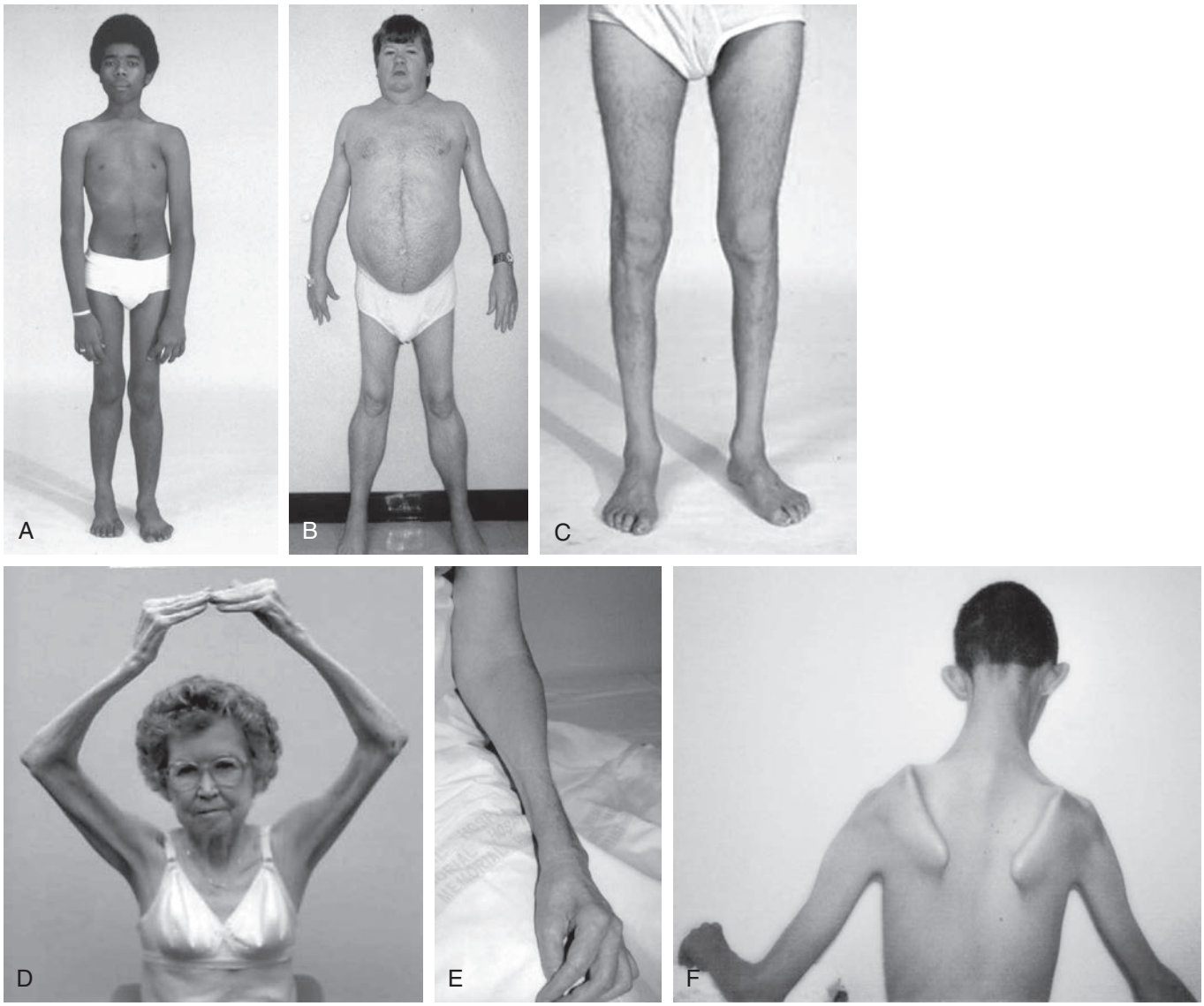


Fig. 1.5 (A) Patient with juvenile spinal muscular atrophy showing pronation of the arms with atrophy of the pectoralis and quadriceps muscles and mild calf hypertrophy. (B) Lordosis, calf hypertrophy, and atrophy of the thigh muscles in a patient with Becker muscular dystrophy. (C) Patient with peripheral neuropathy showing distal leg wasting. (D) Forearm and hand atrophy in a patient with inclusion body myositis. (E) Prominent forearm wasting and wrist extensor weakness in a patient with Welander muscular dystrophy. (F) Patient with congenital myotonic dystrophy with prominent winging and inward rotation of both scapulae.

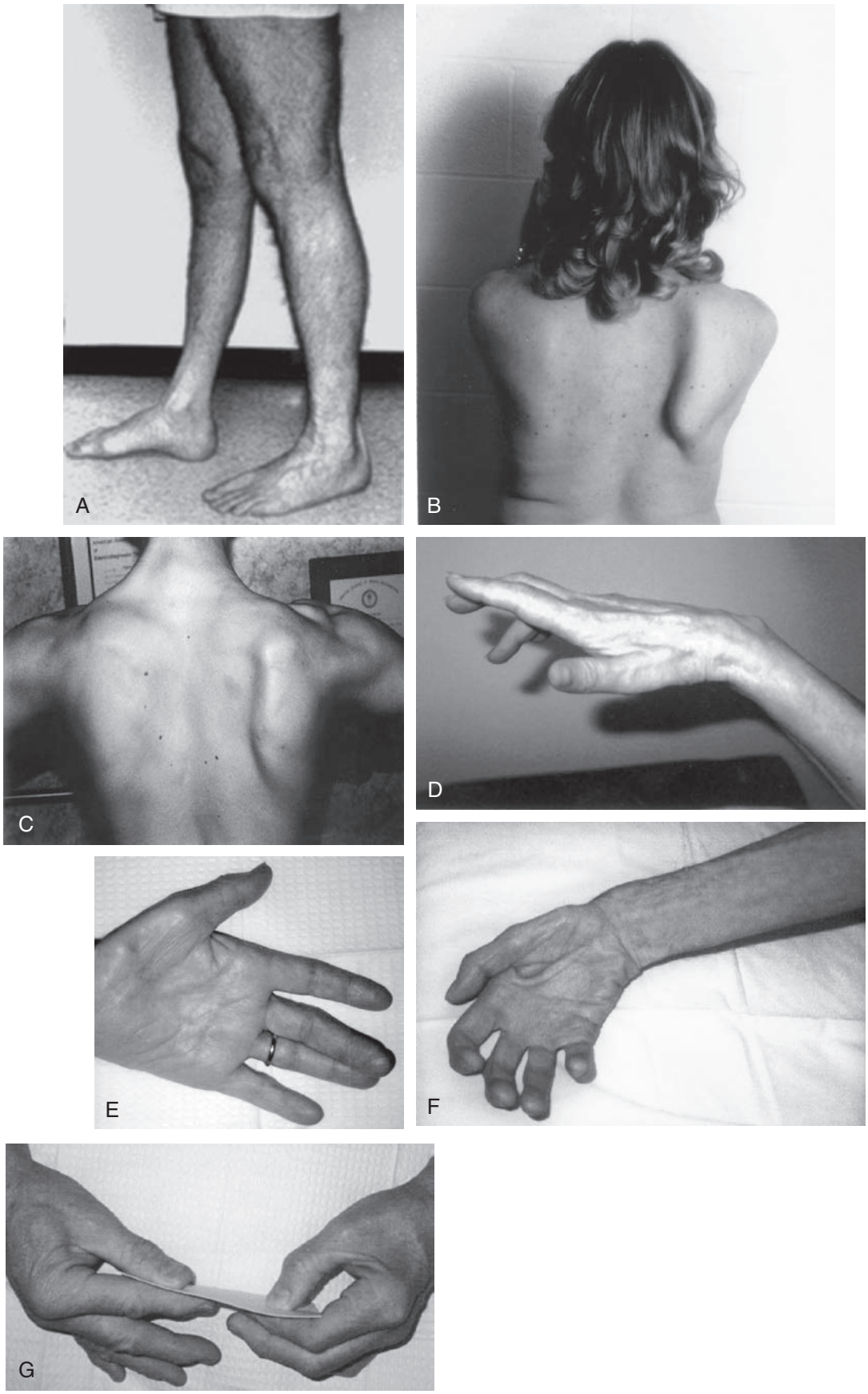


Fig. 1.6 (A) Wasting of the left calf in a patient with postmyelopathy amyotrophy from a conus medullaris lesion involving the anterior horn cells of L5 to S1 segments with chronic denervation on electromyography. (B) Patient with brachial plexopathy and serratus anterior weakness causing winging of the scapula and medial deviation of the bone. (A and B, From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, pp. 247, fig. 11.2.) (C) Patient with scapular winging secondary to spinal accessory neuropathy, showing lateral deviation of the right scapula when raising the arm from upper trapezius weakness; also notice atrophy of the upper trapezius. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, pp. 145.) (D) Patient with ulnar neuropathy attempting hand and finger extension, showing partial flexion of the last two digits and atrophy of the first dorsal interosseous muscle. (E) Median neuropathy causing thenar atrophy. (F) Claw hand and atrophy of the median and ulnar innervated muscles. (G) Froment sign. Patient has to flex the distal phalanx to hold the paper from adductor weakness. Note also muscle atrophy in the first dorsal interosseous muscle, left hand. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 125.)

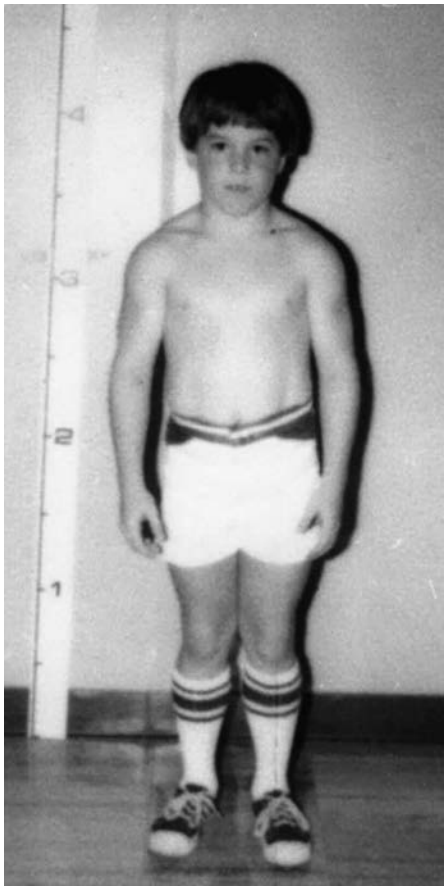


Fig. 1.7 A child with autosomal-recessive myotonia congenita. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 537.)



Fig. 1.8 Floppy infant with infantile acid maltase deficiency. Note how the limbs hang loosely and the chest is arched when the examiner holds the patient by the thorax. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 68). Woburn, MA: Butterworth-Heinemann.)

Box 1.3 Causes of Floppy Infants

Central Nervous System Disorders

Cerebral palsy
Developmental delay from primary metabolic disorders

Mixed (Central and Peripheral)

Metachromatic leukodystrophy and other lipidosis
Neuroaxonal atrophy
Giant axonal neuropathy
Merosin-deficient muscular dystrophy, other congenital muscular dystrophies (e.g., Fukuyama type)

Anterior Horn Cell Diseases

Infantile spinal muscular atrophy

Neuropathies

Charcot-Marie-Tooth disease, particularly types 3 and 4

Diseases of the neuromuscular junction

Congenital myasthenic syndromes
Infantile botulism
Neonatal transient autoimmune myasthenia gravis

Myopathies

Infantile metabolic myopathies (e.g., acid maltase deficiencies or Pompe disease, infantile phosphorylase deficiency)
Congenital muscular dystrophy
Other congenital myopathies (e.g., central core disease, myotubular myopathy, nemaline myopathy)
Congenital myotonic dystrophy
Myopathy from electrolyte and endocrine abnormalities

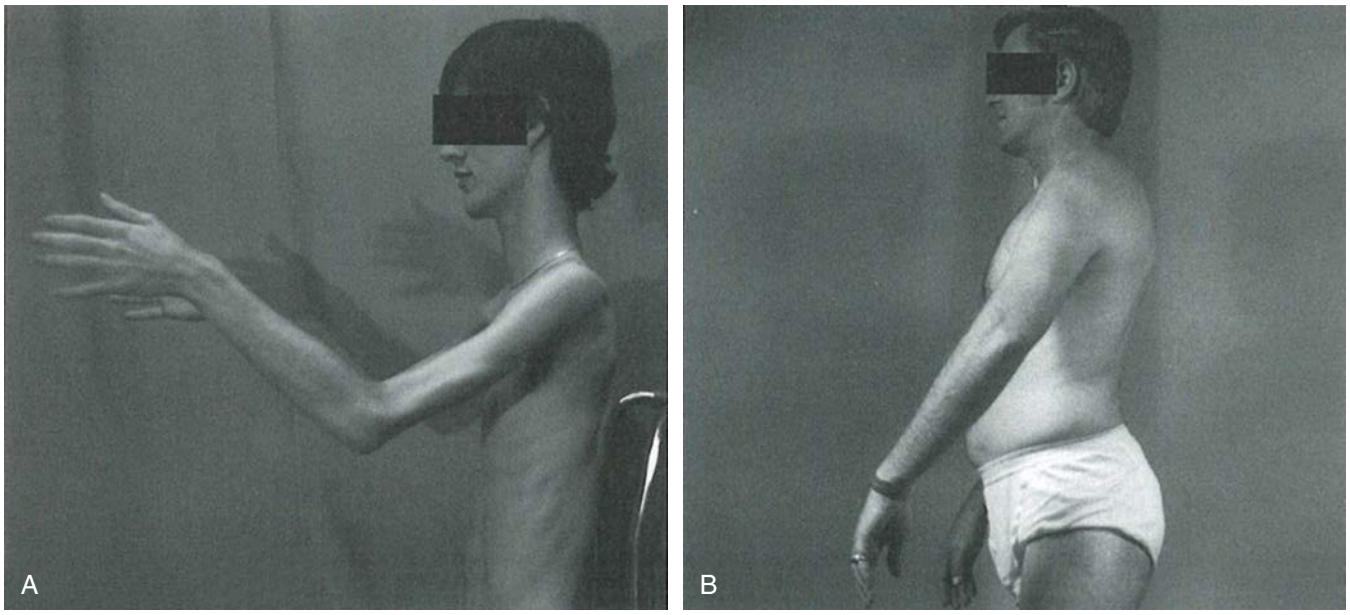


Fig. 1.9 (A) Muscle contractures from fibrosis in a patient with Emery-Dreifuss muscular dystrophy. (B) Pentazocine myopathy causing fibrosis resulting in the levitation sign with the arm. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 69). Woburn, MA: Butterworth-Heinemann.)

or both (Bertorini, 2008; Haerer & DeJong, 1992; Ochoa, 1995; Reese, Lovelace-Chandler, & Soderberg, 1999).

Quantitative sensory testing is a subjective test that evaluates perception of temperature, pain, and vibratory sense. This can be used in the assessment of patients with sensory deficits and in clinical trials (Fig 1.17).

DIAGNOSTIC TESTS

Laboratory studies should include a complete chemistry profile, which can help in the diagnosis of several disorders; for example, low or high potassium is seen in the periodic paralyses, whereas hypocalcemia and hypomagnesia are associated with tetany. Hypercalcemia could lead to the diagnosis of hyperparathyroidism. Elevated blood sugar levels could indicate diabetes as a cause of peripheral neuropathy, and if blood sugar levels are normal and the diagnosis is suspected, this testing should be followed by measurement of glucose tolerance test or 2-hour postprandial blood sugar and glycosylated hemoglobin levels. A complete blood count also is helpful to assess for anemia, as seen in connective tissue diseases; B_{12} deficiency; and leukocytosis, indicating infection or leukopenia from medication effects. An elevated erythrocyte sedimentation rate implies an inflammatory process, although it has low specificity. An increased mean corpuscular volume could suggest pernicious anemia or folate deficiency, and the results of treatment such as with azathioprine (Pruthi & Tefferi, 1994). Testing for serum muscle enzymes is important, particularly serum creatine kinase (CK), aspartate aminotransferase, alanine aminotransferase, and aldolase, which are elevated in myopathies, hypothyroidism, and sometimes to a lesser degree in motor neuron disorders (Welch & Goldberg, 1972). Elevated levels of alanine aminotransferase and aspartate aminotransferase alone suggest liver disease, and when this is considered, gamma glutamyl transpeptidase should be measured because it is affected only in liver disease. A very high CK level with myoglobulin in plasma and urine is characteristic of rhabdomyolysis (Bertorini, 1997, 2002).

Measurement of a number of antibodies is helpful in the diagnosis. These include, for example, the association of GM1 antibodies in multifocal motor neuropathy or to myelin associated glycoprotein (MAG) in older patients with distal demyelinating neuropathy. In acute autoimmune neuropathy, those with the Miller Fisher variant of Guillain-Barre syndrome usually have antibodies against GQ1b, whereas the pharyngeal brachial variant could be against GT1a and GQ1b antibodies. The acute sensory ataxic neuropathy can be associated GQ1b and GD1b antibodies (see Chapter 15 for details).

Recent data indicate that antibodies against trisulfated heparan disaccharide and fibroblast growth factor receptor 3 can be associated with chronic small fiber sensory neuropathy (Levine et al., 2020).

Assessment of autoimmune myopathies and neuropathies should also include measurement of complement, lupus and rheumatoid arthritis serology, and cryoglobulins (Agnelio, 1995). SSA and SSB antibodies should be tested if Sjögren syndrome is suspected, particularly as the cause of ganglioneuritis and myositis. An acute dysautonomia can be associated with ganglionic acetylcholine receptor antibodies. In chronic inflammatory demyelinating polyneuropathy (CIDP), there are cases with antibodies against adhesion antigens. Others include the Hu antibodies in autoimmune paraneoplastic neuropathies, and those against glutamic acid decarboxylase and antiphysin are seen in stiff person syndrome. Assessment of acetylcholine receptor and MuSK, as well as LRP4 and Agrin antibodies, if necessary, helps in those suspected of having MG, whereas elevation of voltage-gated calcium channel antibodies is seen in patients with ELS, and those against voltage-gated potassium channels (Archelos & Hartung, 2000; Narayanaswami, 2002; Sherer,



Fig. 1.10 (A) Patient with diabetic third-nerve palsy with ptosis of the left eye (*left*). Limitation of adduction of the same eye (*right*). (B) Ophthalmoplegia and ptosis in a patient with Miller-Fisher syndrome. (C) Ptosis and symmetric limitation of gaze in a patient with mitochondrial myopathy. (D) Astronomer's posture in a patient with oculopharyngeal dystrophy showing ptosis and contraction of the frontalis muscle to compensate for the ptosis. (A, C, and D, From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (pp. 15–97). Woburn, MA: Butterworth-Heinemann; B, From Bertorini, T. E. (2008). *Neuromuscular case studies.* Philadelphia: Butterworth-Heinemann, p. 288.)



Fig. 1.11 (A) Patient with myasthenia gravis. (B) Development of ptosis on sustained upward gaze.

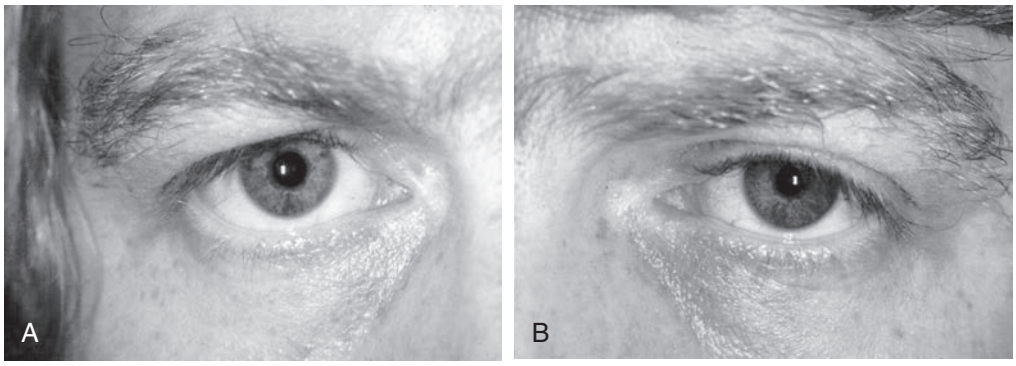


Fig. 1.12 Horner syndrome of the left eye (B) in a patient with lymphoma of the lower brachial plexus showing ptosis and a smaller pupil in the affected eye compared with the normal eye (A).



Fig. 1.13 (A) Horizontal smile in a patient with fascioscapulohumeral dystrophy. (B) Patient with fascioscapulohumeral dystrophy with a weak orbicularis oculi and positive Bell's palsy (both eyeballs rolling upward). (C) Patient with fascioscapulohumeral muscular dystrophy showing dimples in the upper lip from weakness of the orbicular oris. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 37). Woburn, MA: Butterworth-Heinemann.)

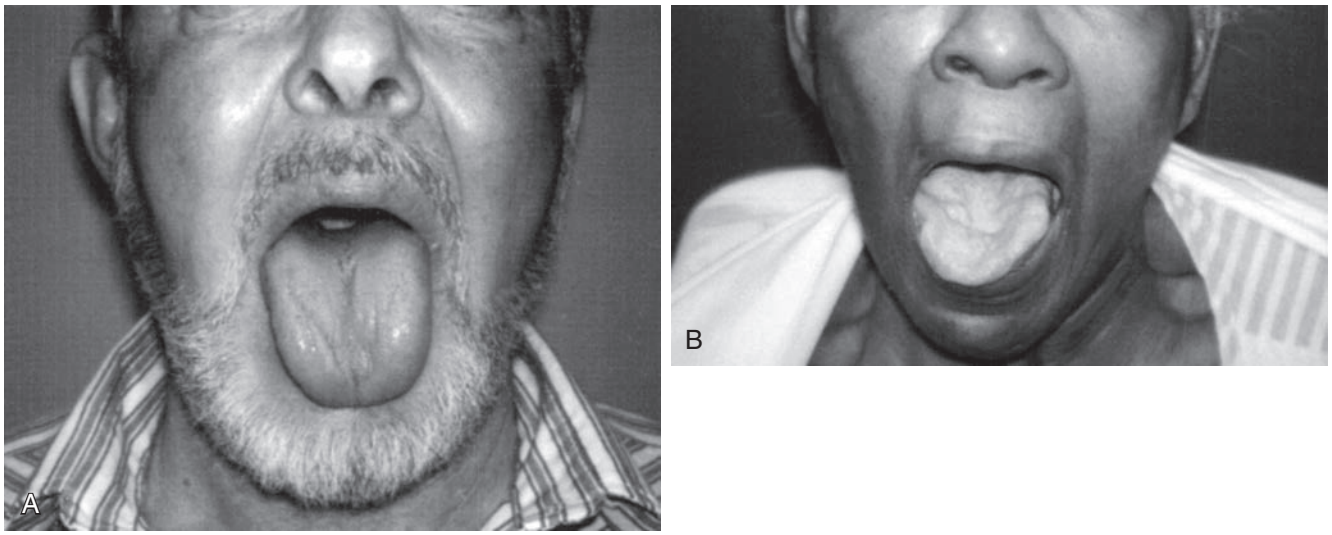


Fig. 1.14 (A) Patient with myasthenia gravis with a forked, triple furrowed tongue. (B) Amyotrophic lateral sclerosis with tongue atrophy. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (pp. 15–97). Woburn, MA: Butterworth-Heinemann.)

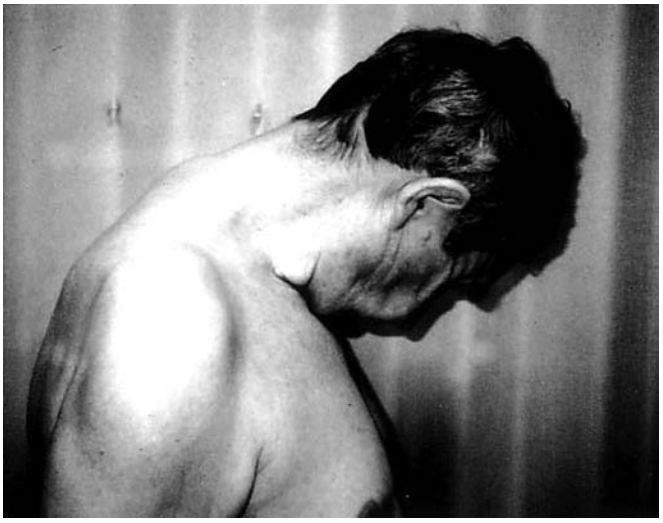


Fig. 1.15 Head drop in a patient with amyotrophic lateral sclerosis as a result of neck extensor weakness. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p 229.)

Box 1.4 Conditions Associated with Cervical Paraspinal Weakness and Dropped Head Syndrome

Prominent, Early Paraspinal Weakness in Generalized Processes

Amyotrophic lateral sclerosis
Myasthenia gravis
Polymyositis/dermatomyositis

Isolated paraspinal muscle weakness

Isolated neck extensor myopathy
Bent spine syndrome
Benign focal amyotrophy

Other diseases associated with paraspinal weakness, atrophy, or both

Chronic inflammatory demyelinating polyneuropathy
Eaton-Lambert myasthenic syndrome
Inclusion body myositis
Fascioscapulohumeral dystrophy
Nemaline myopathy
Proximal myotonic myopathy
Mitochondrial myopathy
Acid maltase deficiency
Carnitine deficiency
Hypokalemic myopathy
Hyperparathyroidism

Disorders that mimic dropped head syndrome

Cervical dystonia (anterocollis)
Fixed skeletal deformities of the spine

From Narayanaswami, P., & Bertorini, T. (2000). The dropped head syndrome. *Journal of Clinical Neuromuscular Disease, 2*, 106–112.

Table 1.1 Neuromuscular Disease: Clinical Evaluation

Clinical Parameter	Motor Neuron Disease	Polyneuropathy	Myopathy	Diseases of Neuromuscular Junction
Pattern of weakness	Variable, symmetric in most, often asymmetric in ALS	Distal > proximal	Proximal > distal; fluctuates; often involves extraocular muscles	Proximal distal in most
Fasciculations	Yes	Sometimes	No	No
Muscle stretch reflexes	Decreased or absent		Normal in postsynaptic disorders (myasthenia gravis), decreased in presynaptic disorders (Eaton-Lambert syndrome and botulism)	Normal initially, may be decreased in later stages (ankle reflexes often preserved until very late)
Sensory loss	No	Usually present	No	No

ALS, Amyotrophic lateral sclerosis.
From Bertorini, T. E. (Ed.). (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Woburn, MA: Butterworth-Heinemann.

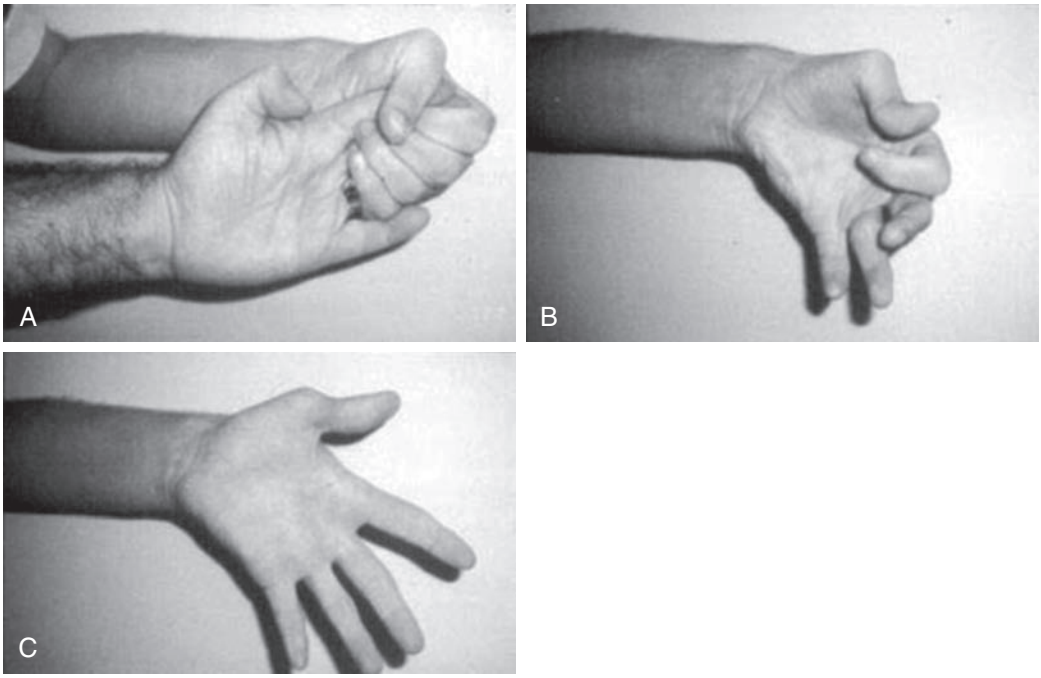


Fig. 1.16 Grip myotonia. Notice difficulty in opening of the handgrip. (A) Gripping the examiner's hand. (B) Immediately after releasing the grip. (C) After 10 seconds.

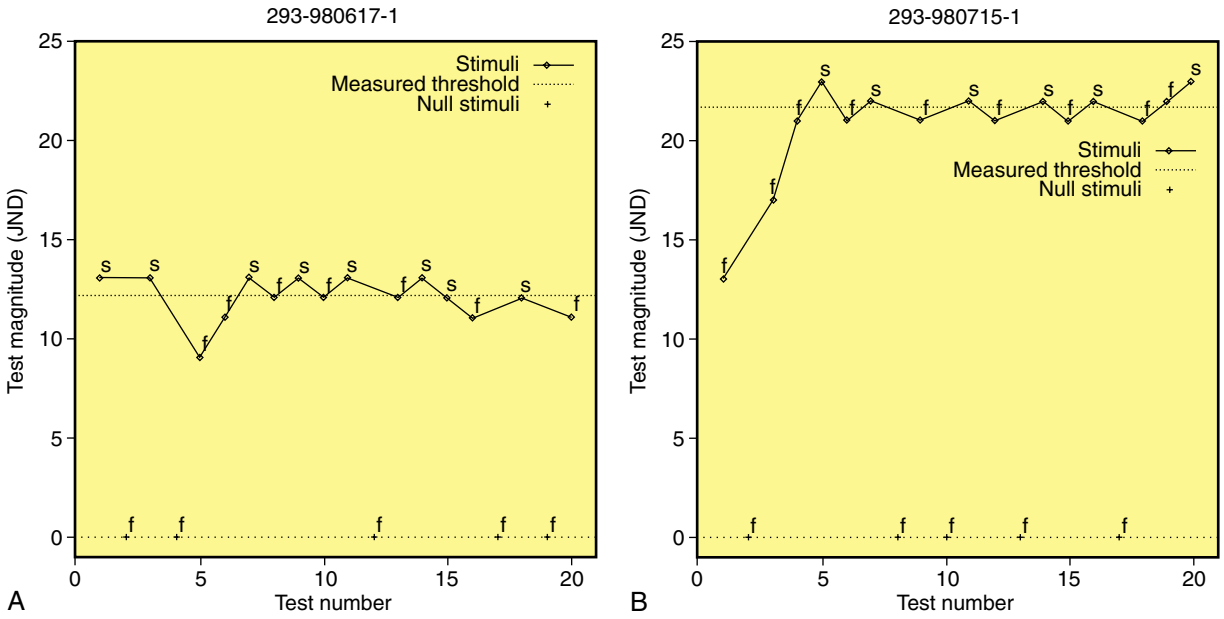


Fig. 1.17 (A) Vibration detection threshold of a normal patient (10th percentile; threshold, 12.4). (B) Vibration detection threshold on a patient with peripheral neuropathy (98th percentile). Notice the higher detection threshold. (units represent incremental and decremental steps using the CASE IV system). (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 32.)

Livneh, Levy, Shoenfeld, & Langevitz, 2000) occur in Isaac syndrome. Myositis-specific antibodies, particularly antisynthetases such as the JO, which is associated with interstitial lung disease (Lackner, Tiefenthaler, Mirzayeva, Graninger, & Stradner, 2018; Sherer et al., 2000), and also against the signal recognition particle and the 3-hydroxy-3-methylglutaryl-coenzyme A reductase in statin-induced necrotizing myositis (Wolff et al., 2018). These tests are discussed in detail in Chapters 19 and 22.

Other studies that may be appropriate, depending on the presentation, including measurement of vitamin B_{12}, folic acid, and if pernicious anemia is suspected, methylmalonic acid and homocysteine levels. Measurement of copper levels and thyroid function testing, as well urinary arsenic, porphyrins (Albers, 2001; Moore, 1993), and serum and urine immunoelectrophoresis testing are helpful for the evaluation of polyneuropathies.

Spinal fluid analysis is not always necessary; however, it can help to detect high protein levels in acquired demyelinating neuropathies or an elevated number of lymphocytes in those with human immunodeficiency virus, for whom serologic testing should be performed.

ELECTROPHYSIOLOGIC TESTS

Nerve conduction studies help to identify diseases affecting sensory or motor nerves, or both (Bertorini, 2006; Oh, 2002), assisting in the differentiation of axonal from demyelinating neuropathies, and can also localize focal entrapments. Usually, slow conduction velocities are seen in demyelinating neuropathies, whereas low amplitude compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) occur in axonal neuropathies. Measurement of latencies of proximal responses, such as the H-reflex and F-waves, helps to show more proximal demyelination. Significant conduction velocity slowing and prolonged or absent F-waves and H-reflexes are seen in acquired demyelinating neuropathies, such as GBS and in CIDP, in which there also are conduction blocks (Fig. 1.18) and temporal dispersion of the CMAP, whereas uniform slowing occurs in most hereditary demyelinating neuropathies (Bertorini, 2008) (Fig. 1.19).

Somatosensory-evoked responses also help in the diagnosis of disorders involving central pathways, such as pernicious anemia (Menkes, 2002). The blink reflex is another test applied in the diagnosis of proximal demyelination and disorders that affect the facial and trigeminal nerves (Luciano, 2002), whereas autonomic function should be tested in those with autonomic symptoms and small-fiber polyneuropathies (Wang & Kaufmann, 2002).

The repetitive nerve stimulation test is used for the evaluation of neuromuscular transmission defects, particularly MG, showing the characteristic decrement of the CMAP at slow stimulation rates (Ciafaloni & Massey, 2002; Oh et al., 1982), whereas in ELS, the initial CMAP is of low amplitude and increases (facilitation) after a tetanic contraction or during fast stimulation (Ciafaloni & Massey, 2002) (Table 1.2). A double response of the CMAP is seen in some congenital myasthenic syndromes, such as slow-channel syndrome (see Chapter 19 for details), and in overmedication with anticholinesterase drugs or organophosphate poisoning (Ciafaloni & Massey, 2002). Decremental responses could be seen in motor neuron diseases and myotonias, and because of this, routine EMG testing should be done prior to interpreting the results of repetitive stimulation testing.

Needle EMG assesses the presence of spontaneous activity and their distribution, helping in the diagnosis and localization. Fasciculations, which are spontaneous depolarizations

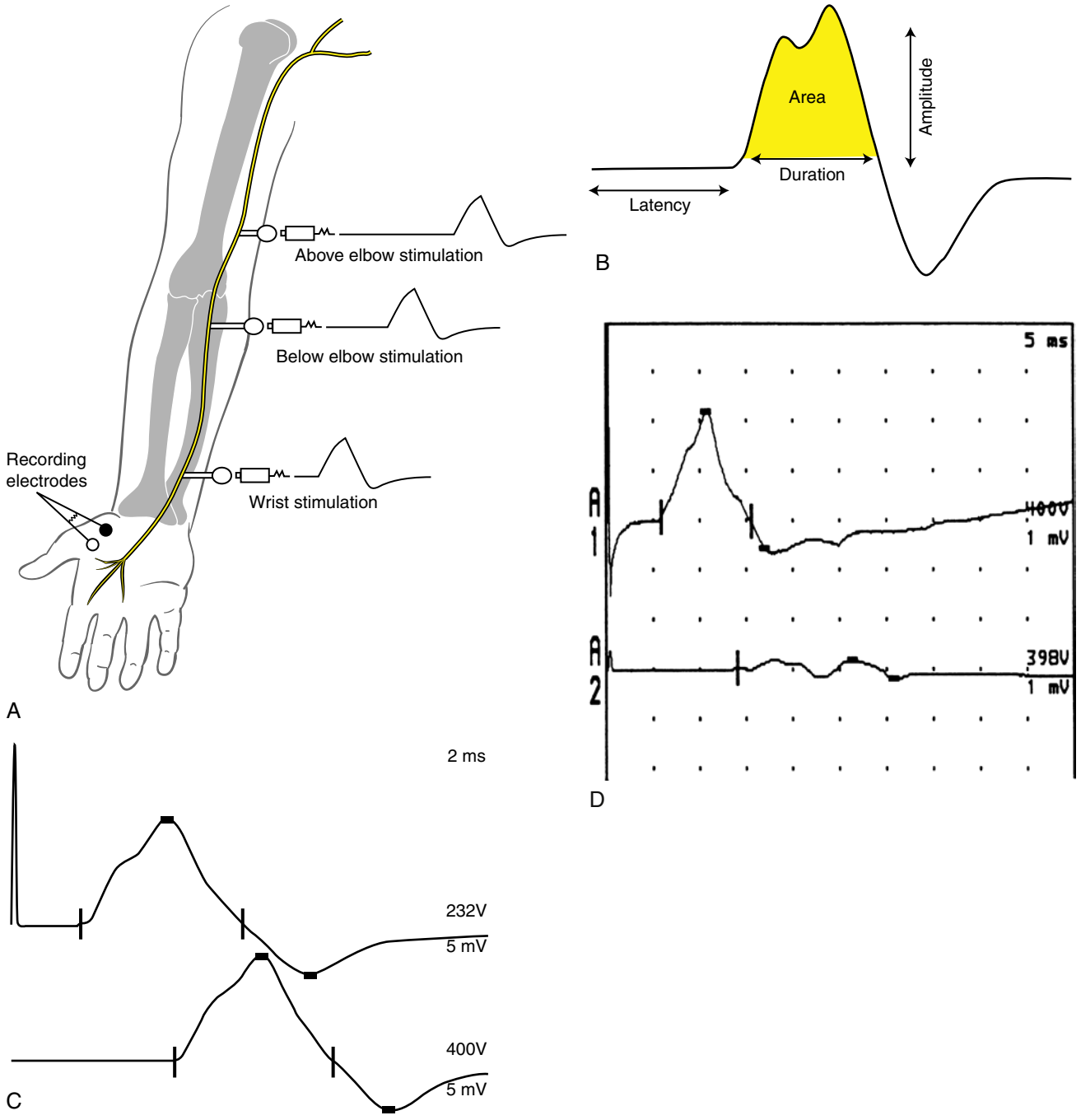


Fig. 1.18 (A) Motor nerve conduction velocity test of the median nerve showing the different compound muscle action potentials (CMAPs) obtained at various stimulation sites. (B) The elements of the CMAP. (C) Normal CMAPs of the ulnar nerve stimulating at the wrist (*top*) and at the elbow (*bottom*) (5 mV/2 milliseconds). (D) Median nerve stimulation at the wrist (*top*) and elbow (*bottom*) on a patient with a demyelinating polyneuropathy (notice temporal dispersion and partial conduction block (1 mV/5 milliseconds). (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 34.)

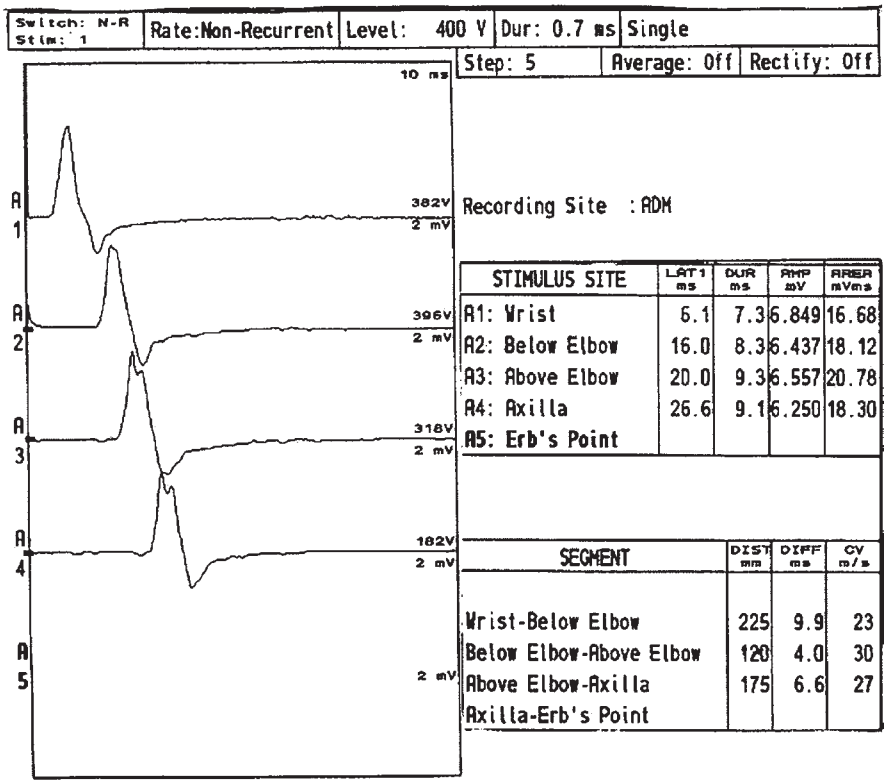


Fig. 1.19 Ulnar motor nerve conduction test in patient with Charcot-Marie-Tooth disease, type 1, showing a fairly uniform shape of a compound muscle action potential without conduction block or temporal dispersion. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 374.)

Table 1.2 Neuromuscular Disease: Laboratory Evaluation

Test	Motor Neuron Disease	Polyneuropathy	Myopathy	Disease of Neuromuscular Junction
Serum "muscle" enzymes	Normal or mild elevation	Normal	Increased	Normal
Nerve conduction studies	Normal or low-amplitude CMAPs, normal SNAPs	Usually slow nerve conduction velocities or low-amplitude CMAPs and SNAPs	Normal	Normal
Electromyography	Decreased number of MUAPs, evidence of denervation and reinnervation (large MUAPs)	Decreased number of motor units, evidence of denervation and reinnervation (large MUAPs)	Normal number of MUAPs that are of short duration and low amplitude, frequently polyphasic	Normal or small MUAPs, variability of motor unit size and shape
Repetitive nerve stimulation test	Usually normal; decremental responses of CMAPs can occur	Normal	Normal	Decrement of CMAPs at low rate of stimulation, increment at fast rates in presynaptic disorders
Muscle biopsy	Denervation (atrophic angular and target fibers, fiber type grouping, group atrophy)	Denervation (atrophic angular and target fibers, fiber type grouping	"Myopathic" (necrosis, storage material inflammation)	Normal or some type II muscle fiber atrophy

CMAPs, Compound muscle action potentials; *MUAPs*, motor unit action potentials; *SNAPs*, sensory nerve action potentials.
From Bertorini, T. E. (Ed.). (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Woburn, MA: Butterworth-Heinemann.

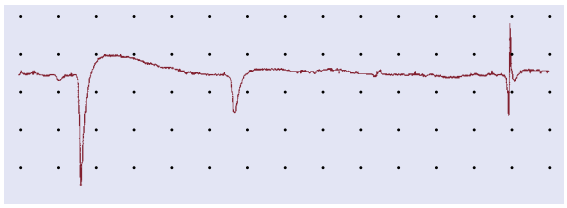


Fig. 1.20 Two positive sharp waves and one fibrillation potential, top, several sharp waves, bottom (200 μV/10 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In Bertorini, T. E. (Ed.). *Neuromuscular case studies* (p. 41, fig. 2.18). Philadelphia: Butterworth-Heinemann.)

of the motor unit, are more commonly seen in motor neuron diseases but, as discussed earlier, could also occur in some neuropathies and metabolic disorders, and even in healthy persons. Myokymic discharges are seen, particularly in radiation plexopathies and GBS. Fibrillations and positive sharp waves are spontaneous potentials originating from individual denervated muscle fibers (Fig. 1.20). These are observed in neurogenic disorders, but can also occur in the myopathies, causing membrane instability, such as polymyositis (Fig. 1.21), and some muscular dystrophies. Myotomal distribution of fibrillations or positive waves helps to localize segmental neurologic disorders, such as mononeuropathies and radiculopathies (Table 1.3) (Daube & Rubin, 2004; Dumitru, King, Rogers, & Stegeman, 1999; Kimura, 2002).

Characteristic spontaneous waxing and waning myotonic discharges (Fig. 1.22) accompanied by clinical myotonia are seen in chloride and some sodium channelopathies, whereas electrical myotonia not accompanied by clinical myotonia can sometimes be found in some myopathies, such as polymyositis and acid maltase deficiency and some toxic myopathies. Neuromyotonia and myokymic discharges are present diffusely in Isaac syndrome. Doublets, triplets, or multiplex potentials can be observed in motor neuron diseases but are characteristic of tetany. Spontaneous complex repetitive discharges occur in disorders of peripheral nerves, but also in myopathies (Fig. 1.23).

Analysis of motor unit action potentials (MUAPs) during voluntary contractions is valuable in diagnosis because large MUAPs with decreased recruitment are observed in chronic neuropathies and can be seen in motor neuron diseases (Fig. 1.24), whereas in myopathies, MUAPs are small and their recruitment is increased for the level of effort. In both types of disorders, MUAPs could be polyphasic, but small polyphasic MUAPs with decreased recruitment are seen during early reinnervation; these are called nascent motor unit potentials (Fig. 1.25) (Kimura, 2002). Satellite or late potentials occur in both neurogenic and myopathic disorders, whereas MUAPs with amplitude variability is characteristic of neuromuscular transmission diseases, but can also be seen in ALS.

Single-fiber EMG is a more sophisticated technique that is used in the diagnosis of neuromuscular transmission disorders (Fig. 1.26). This test has high sensitivity, but low specificity, because increased "jitter" (increased variability of firing of individual muscle fiber potentials in relation to others of the same motor unit) and blocking can occur in motor neuron diseases. However, when there is no evidence of other abnormalities on routine EMG, increased jitter and blocking are diagnostic of neuromuscular transmission defects (Trontelj & Stalberg, 2002).

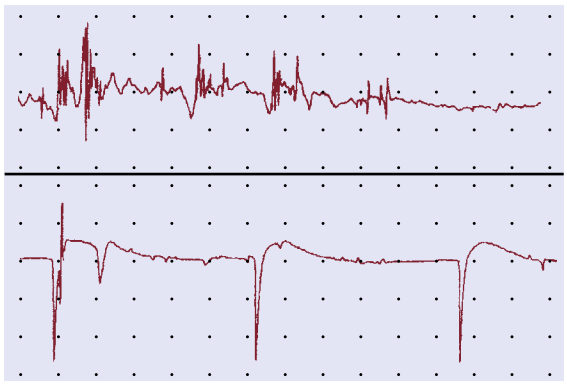


Fig. 1.21 Electromyography study of the deltoid muscle in a patient with polymyositis. Note the small polyphasic motor units (top) and tracing showing positive sharp wave (100 μV/10 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (p. 42, fig. 2.19). Philadelphia: Butterworth-Heinemann.)

Estimation of motor unit numbers is not routinely used for diagnosis but is used to monitor disease progression and in therapeutic trials in NMDs (Gawel, 2019; Gooch & Henderson, 2019; Lomen-Hoerth, 2002; Nandedkar, Barkhaus, & Stalberg, 2010).

HISTOLOGIC TESTS

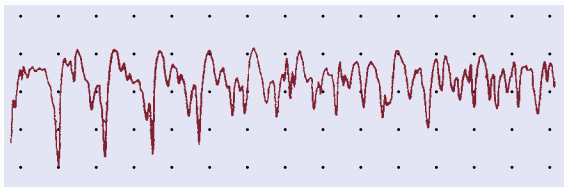
Muscle biopsy is a valuable diagnostic tool using frozen sections for histochemistry (Fig. 1.27) (DiMauro, Shanske, Naini, & Krishna, 2002), electromicroscopy, and immunohistochemistry; paraffin sections are also useful in detecting inflammation; and Western blot analysis and biochemistry are used in some specific disorders (DiMauro et al., 2002) and in some mitochondrial disorders, as well as for DNA analysis. The biopsy specimen should always be obtained from a mildly affected muscle, likely the opposite to the one with more prominent EMG abnormalities detected, ultrasound and MRI could also help to chose the muscle for biopsy. Biopsy from an end-stage muscle might not provide an accurate diagnosis, and specimens should not be taken close to a tendon, because the findings might resemble changes seen in chronic myopathies. In patients with muscle pain, a fascia biopsy helps to diagnose fasciitis (Bertorini, 1998; Bertorini & Horner, 2002).

Many histologic findings are characteristic of some conditions; for example, atrophic angular fibers that stain dark with nonspecific esterase, target fibers, fiber type grouping, and group atrophy are indicative of neurogenic disorders (Fig. 1.28 and Table 1.4) (Dubowitz, 1985). Inflammation and perifascicular atrophy are diagnostic of dermatomyositis (Fig. 1.29), whereas rimmed vacuoles and inflammation are seen in IBM, in which ragged red fibers can also be seen (Fig 1.30), but these are also characteristic of mitochondrial disorders, which also show cytochrome oxidase negative fibers in ragged red fibers. In inflammatory myopathies, the major histocompatbilty complex is upregulated (Fig. 1.31) (see Chapter 22 for details). Enzyme deficiencies and lipid or glycogen accumulation is found in metabolic myopathies (examples of findings in other myopathies are seen in Fig. 1.32 and 1.33) (also seen in Chapters 20 and 23). Otherwise, in most myopathies, the biopsy specimen may show

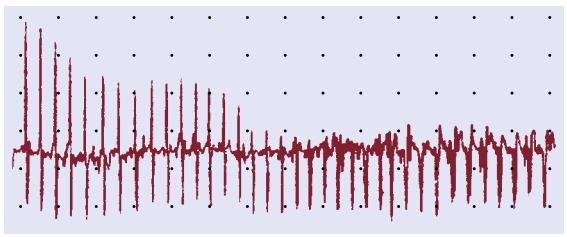
Table 1.3 Clinical and Laboratory Descriptions of Segmental Neurologic Disorders

	Mononeuropathy	Plexopathy	Radiculopathy
Muscle strength and reflexes	Weakness, decreased reflexes in muscles innervated by single nerves	Weakness or decreased reflexes in muscles innervated from affected plexus nerves	Weakness in muscles innervated by same root but different nerves
Sensory deficit	Follows a single nerve dermatome	Follows a plexus sensory territory	Follows dermatomes of affected roots
Limb needle electromyography	Signs of denervation in the myotome of one nerve	Signs of denervation in multiple nerves involved in affected plexus area (e.g., lower trunk ¼ hand muscles of ulnar, median nerves)	Signs of denervation in muscles innervated by same roots, but different nerves
Paraspinal needle	No paraspinal muscle denervation	No paraspinal muscle denervation	Paraspinal muscle denervation is common
Motor nerve	Slow in affected nerve; CMAP amplitude could be decreased when stimulating the affected nerve; conduction block could be seen	Normal (CMAP amplitude could be decreased when stimulating nerves whose axons travel through affected plexus), slowing across the Erb point (brachial plexus)	Normal (CMAP amplitude could be decreased when stimulating nerves whose axons originate in affected roots)
Sensory-evoked potentials	Low-amplitude or prolonged-latency SNAP	Low-amplitude SNAPs in nerves whose axons travel through affected plexus area	Normal SNAPs
Proximal responses	Could be slow or absent in affected nerves	Could be slow or absent in nerves from affected plexus area	Could be slow or absent in nerves from affected roots

CMAP, Compound muscle action potential; *SNAPs*, sensory nerve action potentials
Reprinted with permission from Bertorini, T. E. (Ed.). (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Woburn, MA: Butterworth-Heinemann.



A



B

Fig. 1.22 Myotonic discharges waxing and waning in amplitude: (A) 100 μV/10 milliseconds; (B) 200 μV/20 milliseconds. (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (pp. 27–76). Philadelphia: Butterworth-Heinemann.)

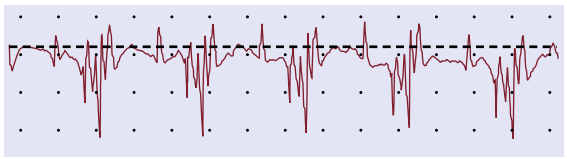


Fig. 1.23 Complex repetitive discharges, uniform spontaneous waveforms that do not change in size or shape (100 μV/20 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (pp. 27–76). Philadelphia: Butterworth-Heinemann.)

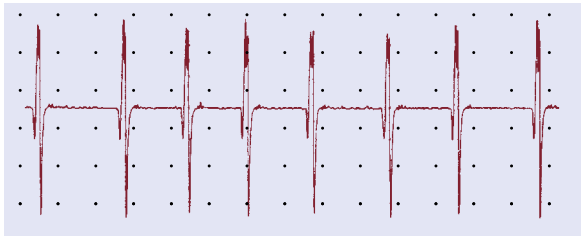


Fig. 1.24 Electromyography during muscle contraction in a patient with previous poliomyelitis showing very large motor unit action potentials firing at an increased rate of 20 Hz without recruiting a second motor unit (1 mV/20 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (pp. 27–76). Philadelphia: Butterworth-Heinemann.)

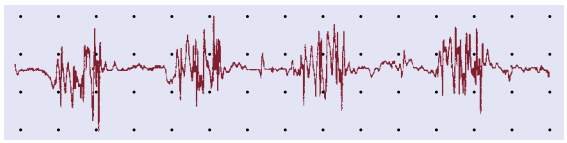


Fig. 1.25 Nascent motor unit action potential in the deltoid muscle of a patient with radiculopathy and early reinnervation. Firing occurs at a rate of 20 Hz without recruiting a second motor unit (100 μV/10 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (pp. 27–76). Philadelphia: Butterworth-Heinemann.)

hypertrophy and atrophy, internalized nuclei, and proliferation of interstitial connective tissue and fat (Bertorini & Horner, 2002; Dubowitz, 1985).

Nowadays, muscle biopsy can be avoided in some diseases. For example, in patients who present as a floppy baby with a positive family history and in whom spinal muscular atrophy is suspected, direct DNA testing may be diagnostic, and in those with suspected acid maltase deficiency, a definite diagnosis can be made by enzyme measurement in blood cells. However, in a small group of patients, this testing might not be informative, and for these patients, biopsy for histology and Western blot analysis could be necessary.

Nerve biopsy is used less frequently than muscle biopsy but can help in the evaluation of significant axonal degeneration or demyelination and for the presence of the onion bulbs in chronic demyelination (Table 1.5) (Bertorini & Horner, 2002; Dyck & Lofgren, 1968; Dyck et al., 1975; Krendel, Parks, Anthony, St Clair, & Graham, 1989; Midroni & Bilbao, 1995). Nerve biopsy shows segmental demyelination in demyelinating neuropathies and axonal degeneration in axonal neuropathies, and in other specific findings, according to the type of neuropathy. Nerve biopsy might also provide findings that are diagnostic of some disorders, such as leprosy, hereditary neuropathy with liability to pressure palsy, and storage diseases, such as amyloidosis, and vasculitis (Midroni, Bilbao, & Cohen, 1995), for which simultaneous muscle biopsy is recommended to increase the diagnostic yield (Claussen, Thomas, Goyne, Vázquez, & Oh, 2000). Fig. 1.34 shows normal nerve biopsies using different stains, and Figs. 1.35 and 1.36 show diagnostic abnormalities in routine histology and EM. Skin biopsies can be done to measure the epidermal nerve fiber numbers to determine the presence of small fiber neuropathy (Fig. 1.37).

IMAGING STUDIES

Various imaging modalities are now routinely done in patients with neuromuscular diseases, particularly in those with focal disorders. For example, magnetic resonance imaging (MRI) of the spine is performed in patients with possible ALS, to diagnose cervical spondylosis and compressive root disease, and obviously is used in patients with radiculopathies (Halford & Graves, 2002) (Figs. 1.38 and 1.39) and peripheral nerve lesions (Figs. 1.40 and 1.41). MRI also helps to assess focal nerve damage using contrast studies and are performed to demonstrate enhancement of the cauda equina roots in CIDP (Halford & Graves, 2002) (Fig. 1.42), and MR neurography shows increased signal in nerves in inflammatory neuropathies (Figs. 1.43 and 1.44) (see also Chapter 15, Fig. 6).

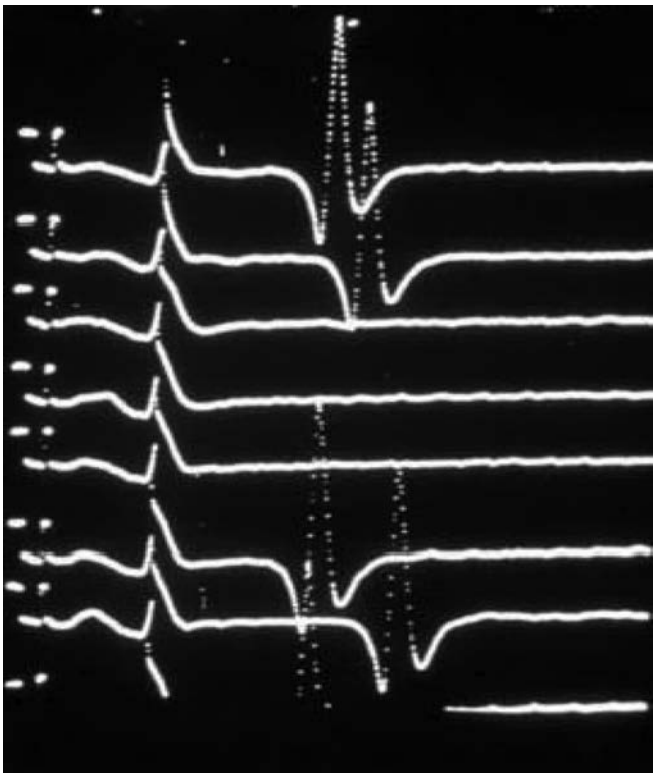


Fig. 1.26 Single-fiber electromyography recording showing a pair of single fiber potentials that belong to the same motor unit of the extensor digitorum communis muscle; jitter and blocking are seen in a patient with myasthenia gravis (200 μV/0.5 milliseconds). (From Bertorini, T. E. (2008). Neurological evaluation and diagnostic tests. In T. E. Bertorini (Ed.). *Neuromuscular case studies* (pp. 27–76). Philadelphia: Butterworth-Heinemann.)

Total-body computed tomography scans and MRI are useful in quantitating and determining selected muscle wasting in different disorders; these and magnetic resonance spectroscopy can be used to monitor disease progression (Barnard et al., 2020; Cornett et al., 2019; Kalia, Leung, Sneag, Del Grande, & Carrino, 2017; Simon, Noto, & Zaidman, 2016).

MRI helps to determine if there is evidence of fat replacement of muscle using T1 imaging (Fig. 1.45 shows a normal total-body MRI, and Fig. 1.46 shows muscle atrophy in muscular dystrophy) and increased signal using T2 imaging to determine muscle necrosis and inflammation (Fig. 1.47). This also helps in selecting muscle for biopsy.

Muscle and nerve ultrasound with portable equipment has been applied with increased frequency to study myopathies (Halford & Graves, 2002; Simon et al., 2016). Abnormal muscle typically shows increased echogenicity (Fig 1.48) in some neurogenic disorders that are associated with reduced volume of fascicles. Color and power Doppler can be used to show the degree of vascularity on inflammatory processes. The Heckmatt criteria grade the muscle echogenicity and determines the distinction of underlying bone shadow, whereas the Dock method involves counting the number of hyperechoic septa within the muscle. Muscle atrophy is demonstrated by ultrasound, and selected muscles can be seen in some disorders such as IBM (Fig. 1.49). Nerve ultrasound is used in the diagnosis of plexopathies and entrapment neuropathies (Van Rosmalen, Lieba-Samal, Pillen, & Van Alfen,

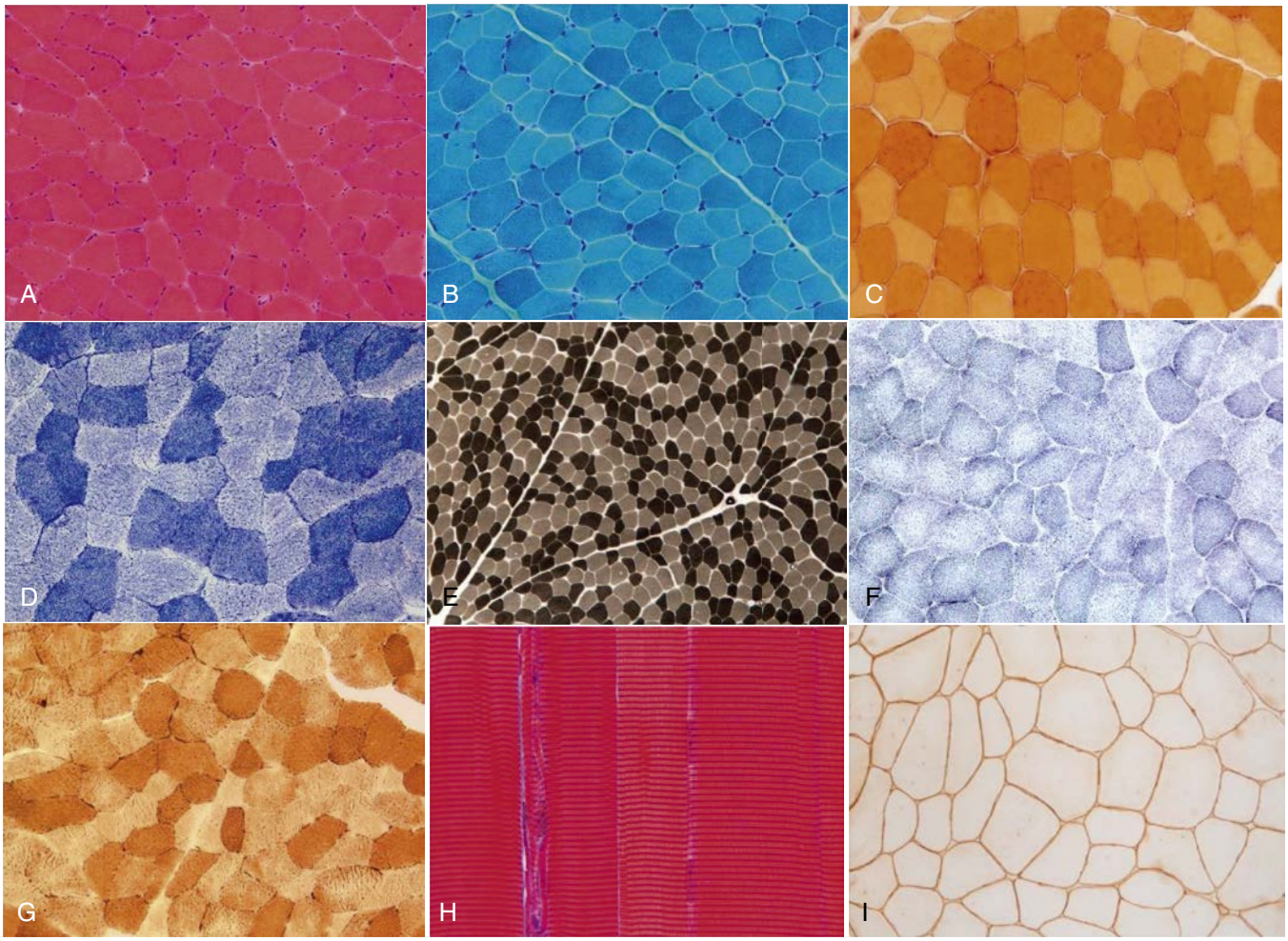


Fig. 1.27 Normal muscle histology using different stains. (A) Hematoxylin and eosin stain showing normal polygonal shape of muscle fibers with lack of internalized nuclei. There is no evidence of increased connective tissue or necrosis (×200). (B) Modified trichrome stain, also shows the normal size and shape of muscle fibers (×200). (C) Normal nonspecific esterase stain showing no evidence of atrophic angular fibers or macrophages (×200). (D) Nicotinamide adenine dinucleotide dehydrogenase–tetrazolium reductase (NADH-TR) stain also showing normal fiber type distribution, no cores or targets (×200). Type distribution and equal size of muscle fibers (×100). (E) ATPase stain, pH 9.4 showing normal fiber type distribution (×100) increasing major histocompatbilty complex (MHC) staining in immunoperoxide stain (×200). (F) SDH stain showing darker type I fibers, and no evidence of "dark blue" fibers (×200). (G) Cytochrome oxidase stain showing no evidence of cytochrome oxidase negative fibers (×200), and (also see Fig. 23.13 in Chapter 23, showing cytochrome oxidase negative fibers that stain blue with SDH). (H) Transverse longitudinal section of normal muscle stained with trichrome in paraffin showing normal striation of muscle fibers (×800). (I) Normal muscle membrane stain for dystrophin using immunoperoxidase stain (×200) in a control case.

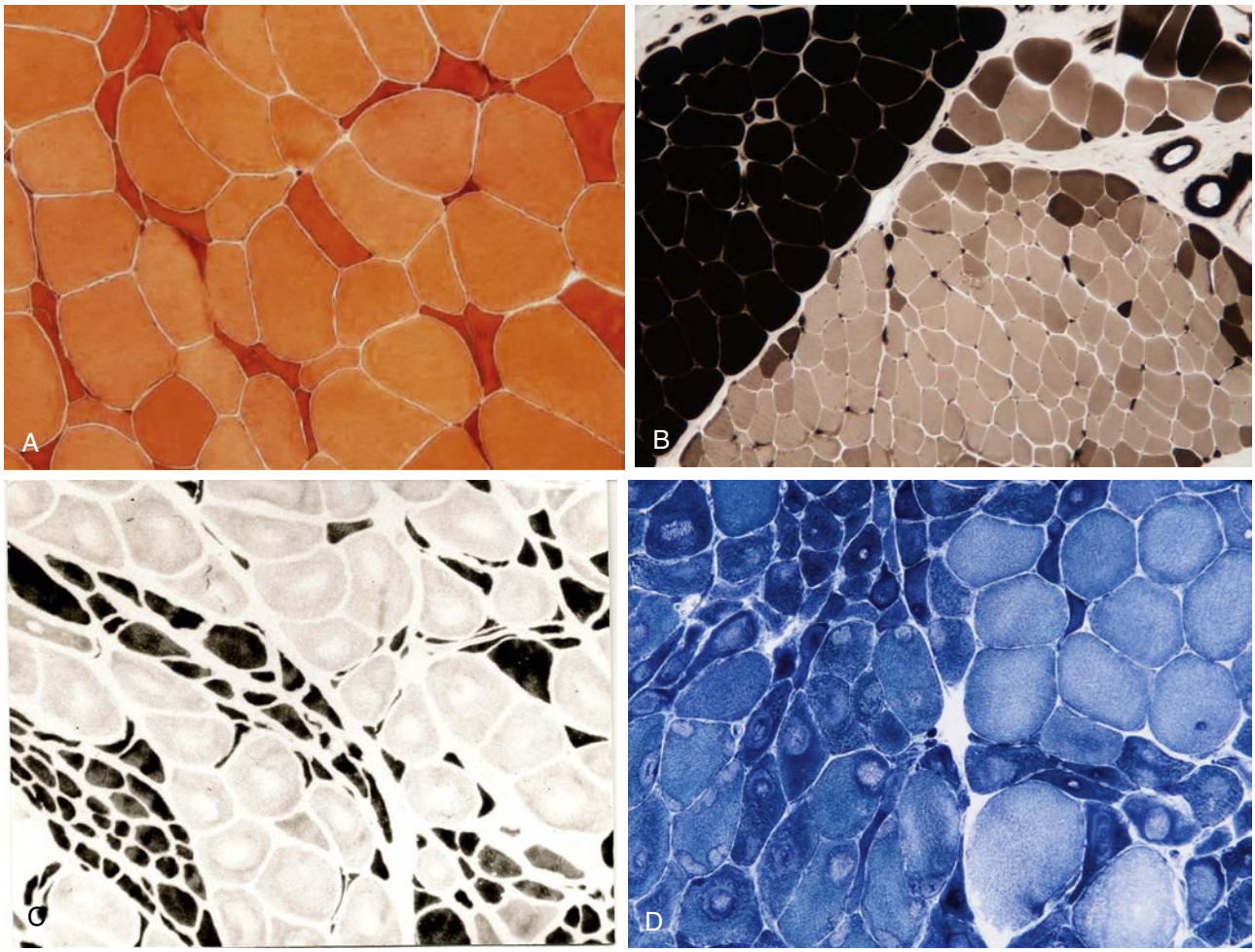


Fig. 1.28 (A) Atrophic denervated muscle fibers that stain dark with nonspecific esterase (×200). (B) Fiber type grouping in spinal muscular atrophy, ATPase stain, pH 4.6 (×100). (C) Evidence of group atrophy and angular atrophic fibers as well as pale cores in the type I fibers, ATPase, pH 9.4 (×200). (D) Many atrophic fibers with target fibers, Nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase (NADH-TR) (×200).

Table 1.4 Histologic Changes in Muscle Biopsy Found Predominantly in Neurogenic Disease and Myopathies[a]

Neurogenic Disease	Myopathy
Atrophic, esterase-positive angular fibers	Necrosis, phagocytosis
	Increased endomysial connective tissue and fat
Targets, targetoids	Regenerating fibers
Large fiber-type grouping	Round atrophic and hypertrophic fibers (variation in fiber size), fiber splitting
Group atrophy	Internalized nuclei and capillaries, lobulated fibers
Pyknotic nuclei[b]	Specific abnormalities e.g., ragged red fibers in mitochondrial disease, storage of lipid or glycogen in metabolic myopathies. Rimmed vacuoles in inclusion body myositis, and protein deficiency in dystrophies, inflammation, upregulation in complement is seen in inflammatory autoimmune myopathies

[a]Some of these can be seen in both myopathies and neurogenic diseases; the prominence of the findings would suggest one or the other.
[b]Can be prominent in some myopathies as well (e.g., myotonic dystrophy).

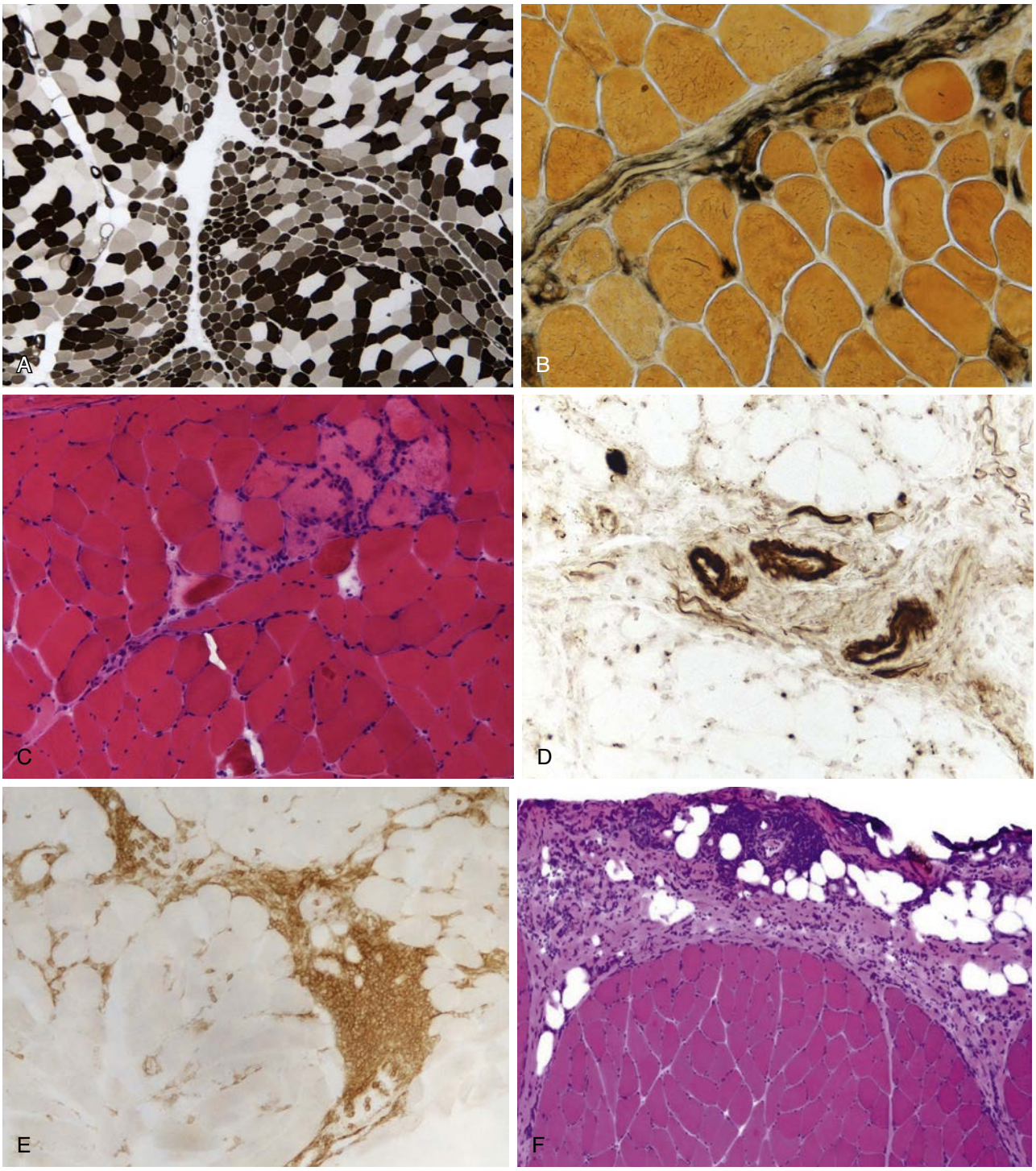


Fig. 1.29 Different features of inflammatory myopathies. (Please also see representative figures in Chapter 22.) (A) ATPase stain pH at 4.6 in dermatomyositis showing characteristic perifasicular muscle atrophy (×100). (B) Alkaline phosphatase stain showing the darker staining capillaries and connective tissue as well as necrotic fibers in dermatomyositis (×200). (C) A group of necrotic fibers which might represent an infarct in dermatomyositis, hematoxylin and eosin (H&E) stain (×100). (D) C5b-9 complement staining in capillaries and vessels in dermatomyositis, immunoperoxidase stain (×200). (E) CD45 stain with immunoperoxidase, notice the positive staining lymphocytes (×100). (F) Inflammatory infiltrates in fascia and perimysium in fasciitis H&E (×100).

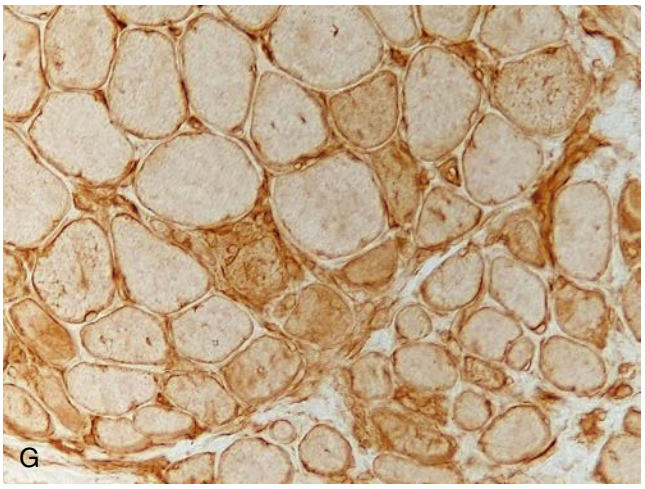


Fig. 1.29–cont'd (G) Patchy upregulation of the major histocompatibility antigen complex in muscle fibers in necrotizing myopathy, immunoperoxidase stain (×200). (H) Upregulation of major histocompatbilty complex in muscle fibers in necrotizing myopathy, immunoperoxidase stain (×200).

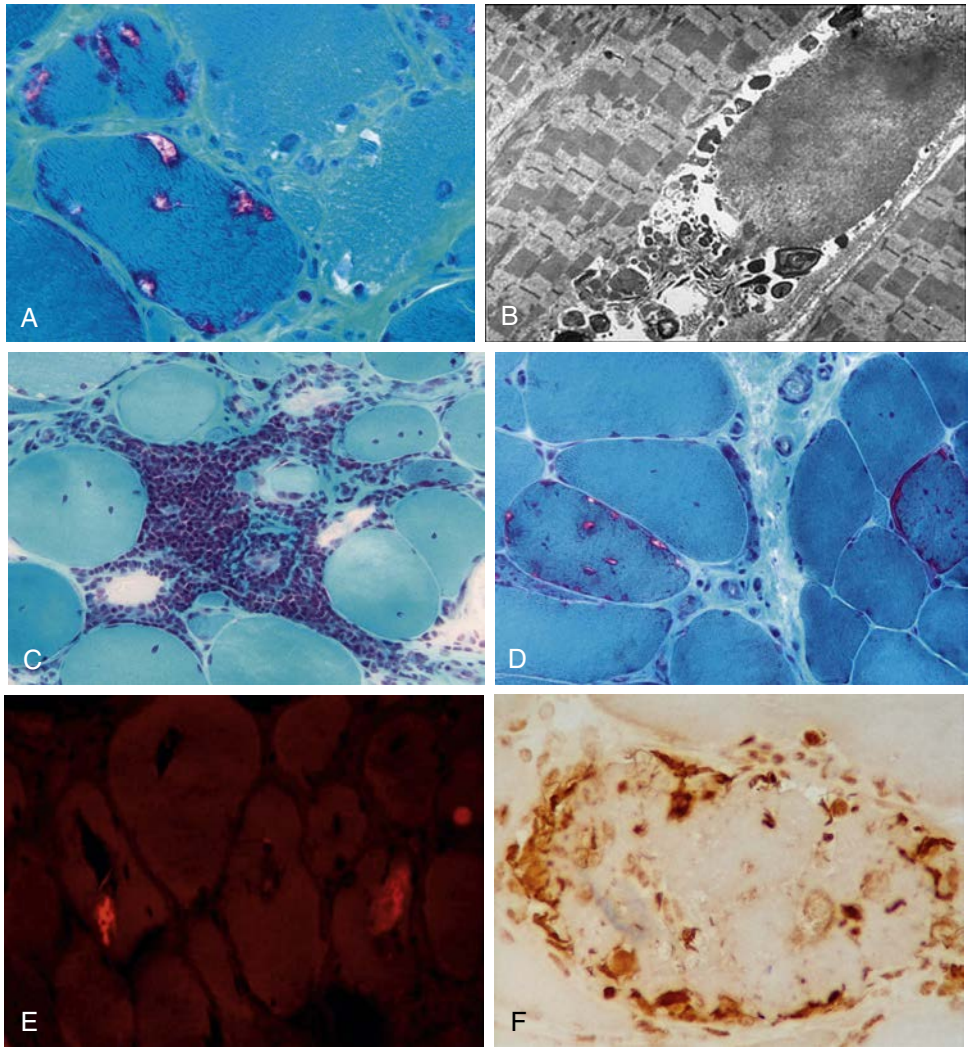


Fig. 1.30 Biopsies of inclusion body myositis. (A) Rimmed vacuoles stained with trichrome (×400). (B) Electromicroscopy showing inclusion bodies and myeloid bodies (×7000). (C) Inflammatory infiltrates, modified trichrome (×200). (D) Rimmed vacuoles and ragged red fibers, modified trichrome stain (×200). (E) Congo Red stain with fluorescent vacuoles using Texas Red filters (×400). (F) Rimmed vacuoles stain positive for SMI-31R, immunoperoxide stain (×400).

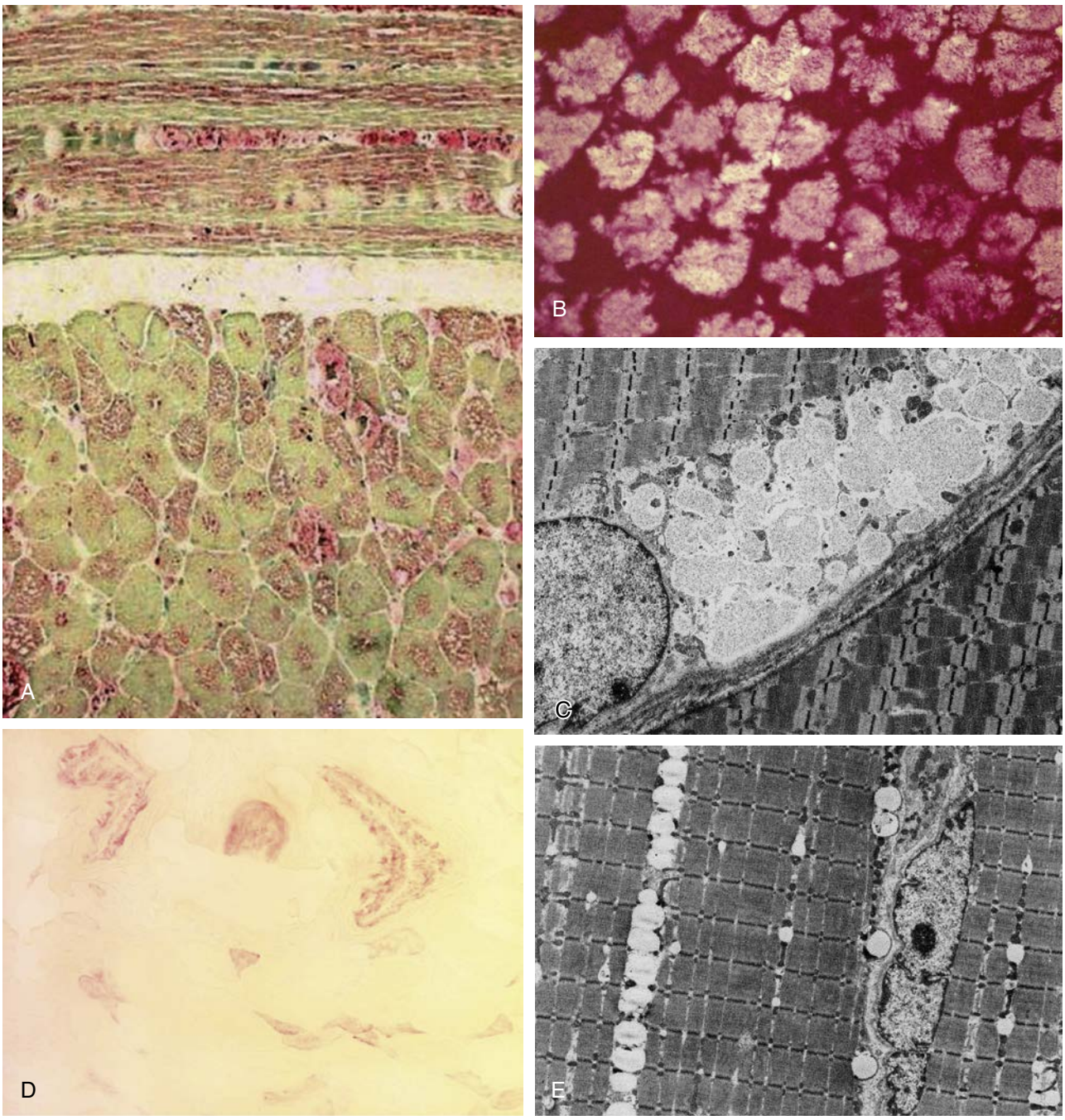


Fig. 1.31 Various findings in metabolic myopathies. (Please also see representative figures in Chapter 23.) (A) Vacuolated fibers that stain positive, red, with acid phosphatase stain, top-longitudinal, bottom-transverse section (×200). (B) Many periodic acid Schiff (PAS) positive vacuoles in a patient with debrancher enzyme deficiency (×200). (C) Lysosome accumulation next to a nuclei in a patient with Pompe disease (×3000). (D) Muscle biopsy of a patient with McArdle disease showing accumulation of staining for phosphorylase only in the vessel wall, but not in the fibers (×200). (E) Lipid vacuoles seen on electromicroscopy in lipid storage myopathy (×7000).

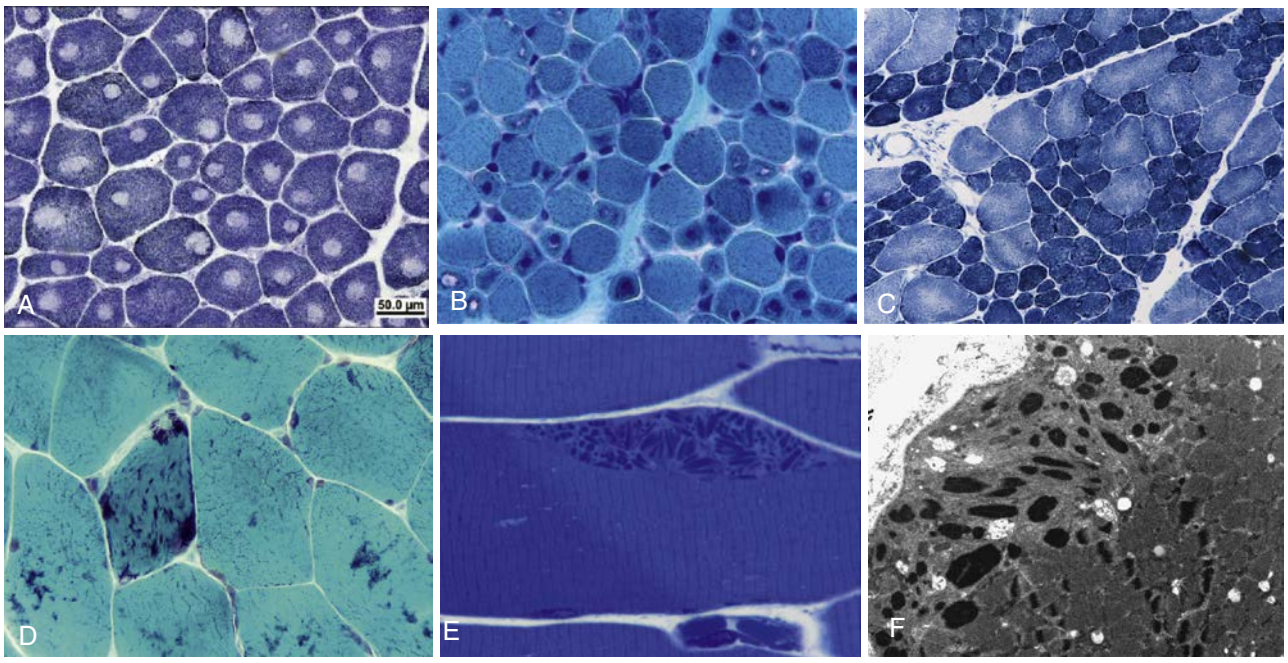


Fig. 1.32 Biopsy abnormalities in various congenital myopathies. (A) Central core disease, notice the pale cores. (B) Myotubular myopathy, modified trichrome stain showing small fibers with internalized nuclei (×200). (C) Fiber type disproportion, noticed selected type I fiber atrophy in the Nicotinamide adenine dinucleotide dehydrogenase–tetrazolium reductase (NADH-TR) stain (×200). (D) Nemaline (rod) myopathy showing dark staining rods, trichrome stain (×400). (E) Plastic embedded section showing the dark nemaline bodies, toluidine blue (×1000). (E) Nemaline (rods) on electromicroscopy (×9000).

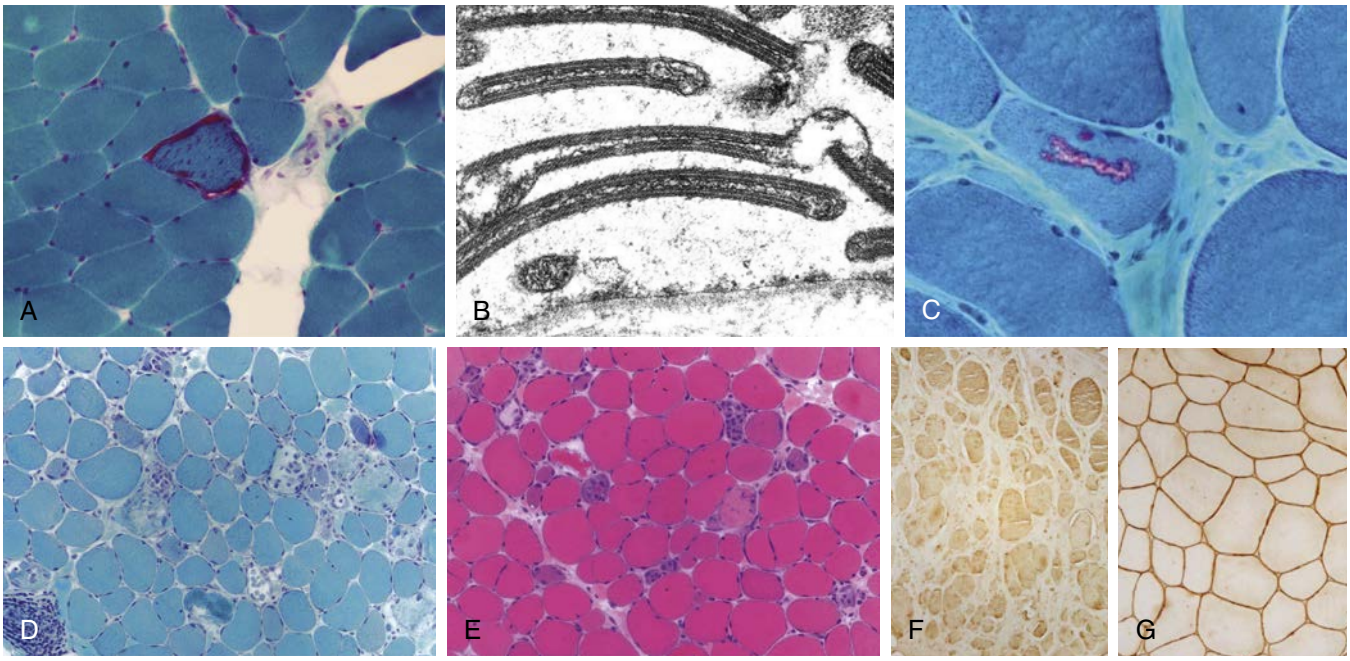


Fig. 1.33 Examples of biopsy findings in myopathies. (A) Notice the modified trichrome stain showing ragged red fibers in mitochondrial myopathy (see Chapter 23, Fig. 23.13 showing in ragged blue COX negative fibers). (B) Electromicroscopy showing paracrystalline bodies in abnormal mitochondria (×1200). (C) Small fiber with a rimmed vacuole in oculopharyngeal dystrophy, modified trichrome (×400). (D) Necrosis and inflammation in Miyoshi myopathy stain (×100), as in this, inflammation can be seen in some dystrophies (inflammatory dystrophies). (E) Many necrotic fibers on hematoxylin and eosin stain (in the same patient) (×100). (F) Lack of dysferlin stain in Miyoshi myopathy peroxidase stain (×100) compared with. (G) Normal dysferlin staining in a control (×200).

Table 1.5 Biopsy Findings That Indicate Axonal Degeneration or Demyelination[a]

Axonal Degeneration	Demyelination
May affect myelinated and unmyelinated fibers	Affects primarily myelinated fibers
Axonal degeneration of myelinated fibers seen on semithin plastic sections, teased nerve preparations (large ovoids)	Segmental demyelination Large axons with thin myelin
Axonal atrophy, inclusions	Onion-bulb formations
Denervated Schwann cell subunits	Some tiny ovoids with variation in internodal length may be seen on teased nerve preparations
Flattened, unmyelinated axons	
Bands of Bungner[b]	
Regenerating clusters of myelinated fibers	
Schwann cell processes with increased numbers of small unmyelinated axons	

[a]These changes are not definitive for diagnosis and in many neuropathies could show evidence of both axonal degeneration and demyelination, with the diagnosis based on the predominance of one or the other to determine whether the process is primarily demyelinating or an axonopathy.
[b]Groups of Schwann cell processes that were previously associated with myelinated axons.

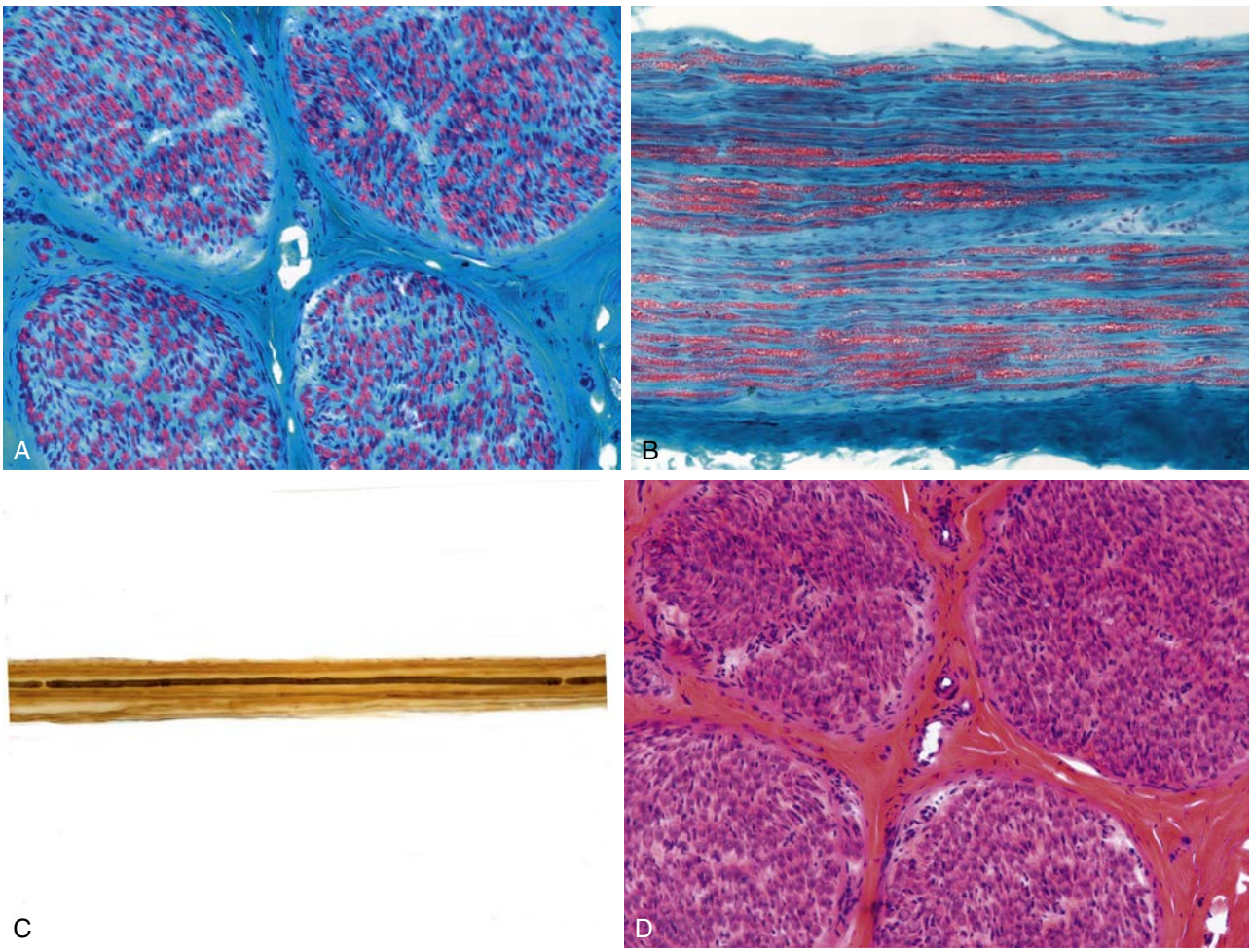


Fig. 1.34 Normal nerve biopsies. (A) Modified trichrome stain showing four nerve fascicles with normal densely populated (red) myelinated axons (×100). (B) Longitudinal section of normal nerve, modified trichrome (×100). (C) Teased nerve preparation showing a myelinated fiber and node of Ranier (×100). (D) Normal nerve on hematoxylin stain show normal vessels and no evidence of inflammation or vasculitis (×100).

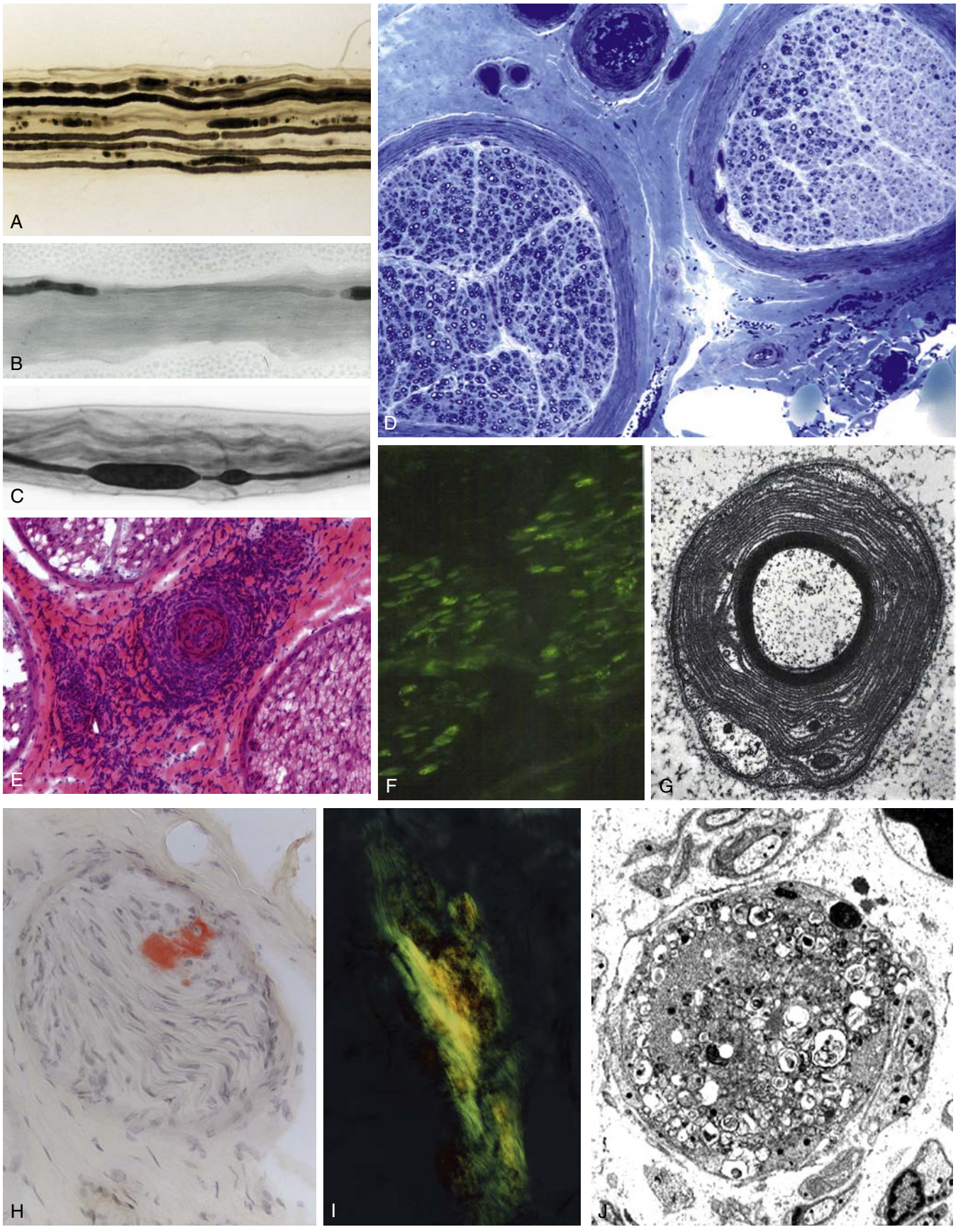


Fig. 1.35 Abnormal nerve biopsies. (A) Teased nerve preparation showing myelin ovoids from axonal degeneration (×100). (B) Teased nerve showing a small demyelinated segment in segmental demyelination (×200). (C) Teased nerve preparation showing tomaculae from a patient with hereditary neuropathy with liability to pressure palsy (HNPP) (×200). (D) Thick plastic sections showing segmental loss of myelinated axons (top right) from a patient with vasculitis, toluidine blue (×200). (E) Hematoxylin and eosin stain showing vasculitis in nerve (×200). (F) Immunofluorescent staining for immunoglobulin M (IgM) in a patient with IgM monoclonal gammopathy (×400). (Courtesy of Dr. T. O'Brien.) (G) Electromicroscopy (EM) of uncompacted myelin in neuropathy with monoclonal gammopathy (×45,360). (H) Congo Red stain showing red amyloid deposit in nerve (×200). (I) Amyloid deposits in vessel showing apple green birefringes (×400). (J) Axonal degeneration on EM (×4500)

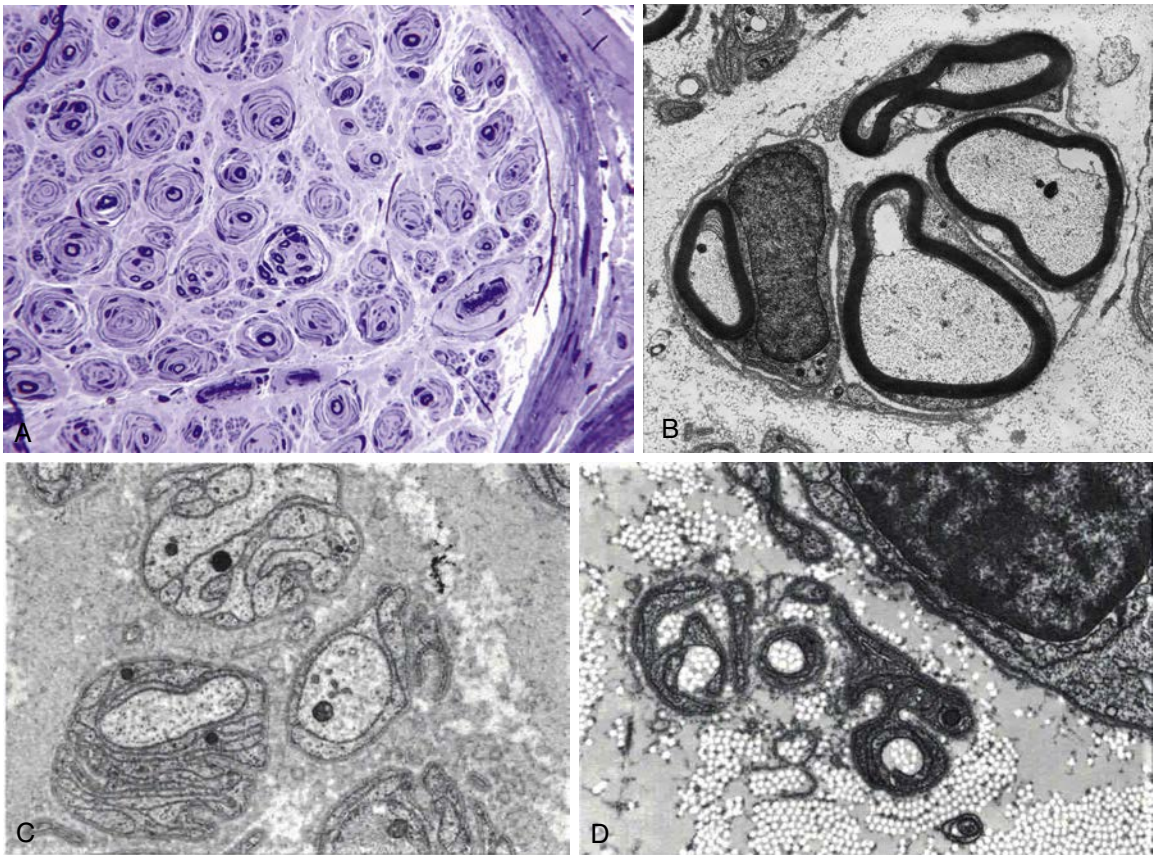


Fig. 1.36 Abnormal nerve biopsies. (A) A biopsy from a patient with Charcot-Marie-Tooth disease, type 1, evidence of onion bulbs, toluidine blue, plastic sections (×400). (B) Sprouting of small myelinated axons (×13,550). (C) Flattening unmyelinated axons on EM in small fiber neuropathy (×13,500). (D) Schwann cell processes surrounding connective tissue (collagen pockets) on electromicroscopy (×21,000).

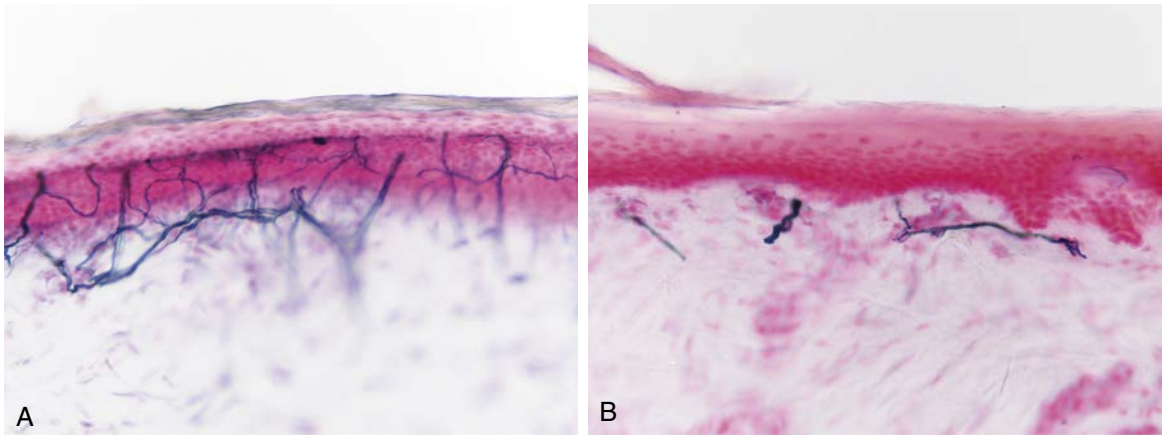


Fig. 1.37 (A) Punch skin biopsy showing axons staining with protein gene product (PGP) 9.5 antibody contrasted with nuclear fast red, left normal nerve (×200). (B) Diabetic neuropathy, notice the lack of small fibers crossing the epidermis (×200)



Fig. 1.38 (A) Sagittal view magnetic resonance imaging (MRI), T2-weighted image showing a large C6–7 herniated disc (*arrow*). (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 167.)

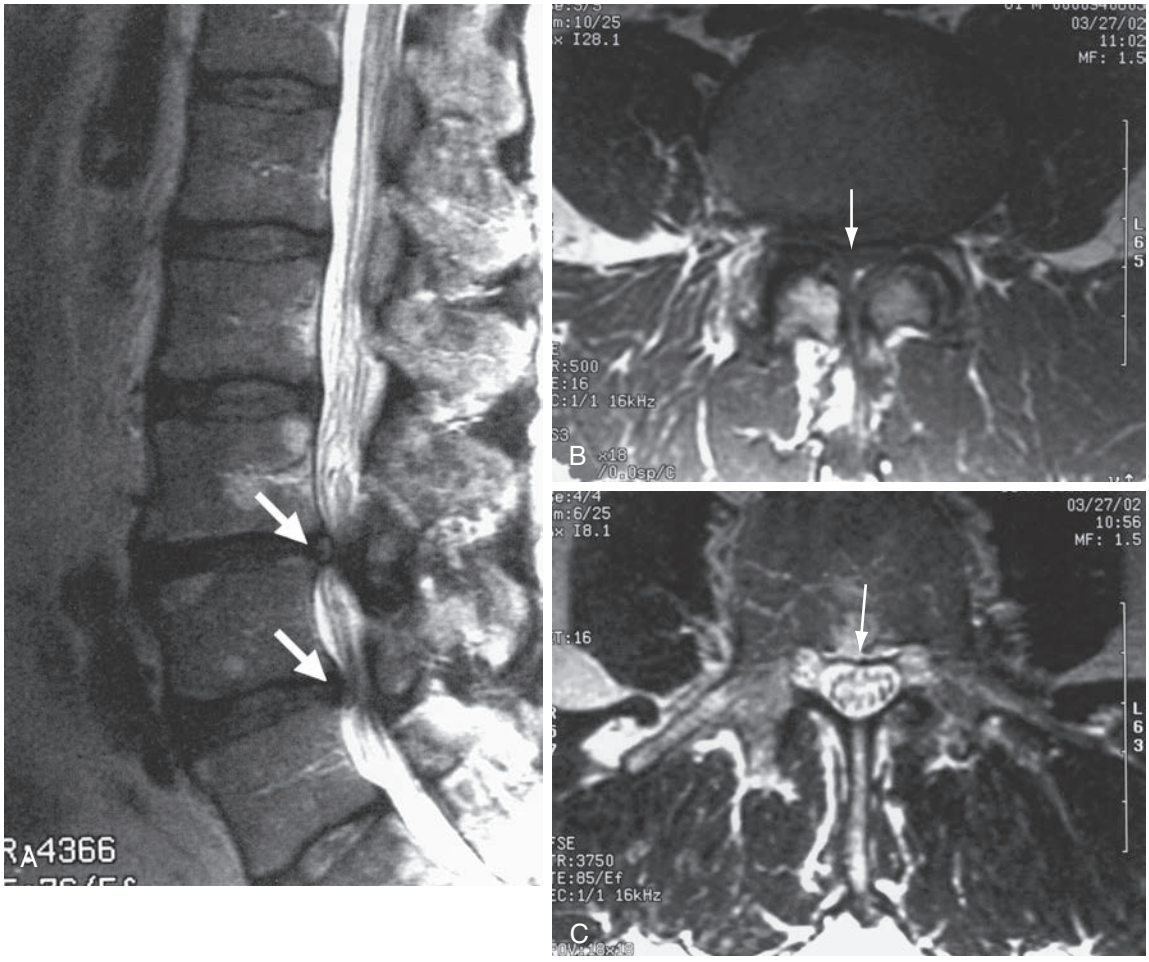


Fig. 1.39 (A) Magnetic resonance imaging (MRI), T2-weighted image (sagittal view) showing prominent disc bulging and canal stenosis at L3–4, L4–5 (*arrows*). (B) Very small canal seen in the axial view on MRI Tw-weighted image at the L4–L5 level (*arrow*). (C) Axial view MRI, T2-weighted image showing minimal stenosis at the L2 level (*arrow*). (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 193.)

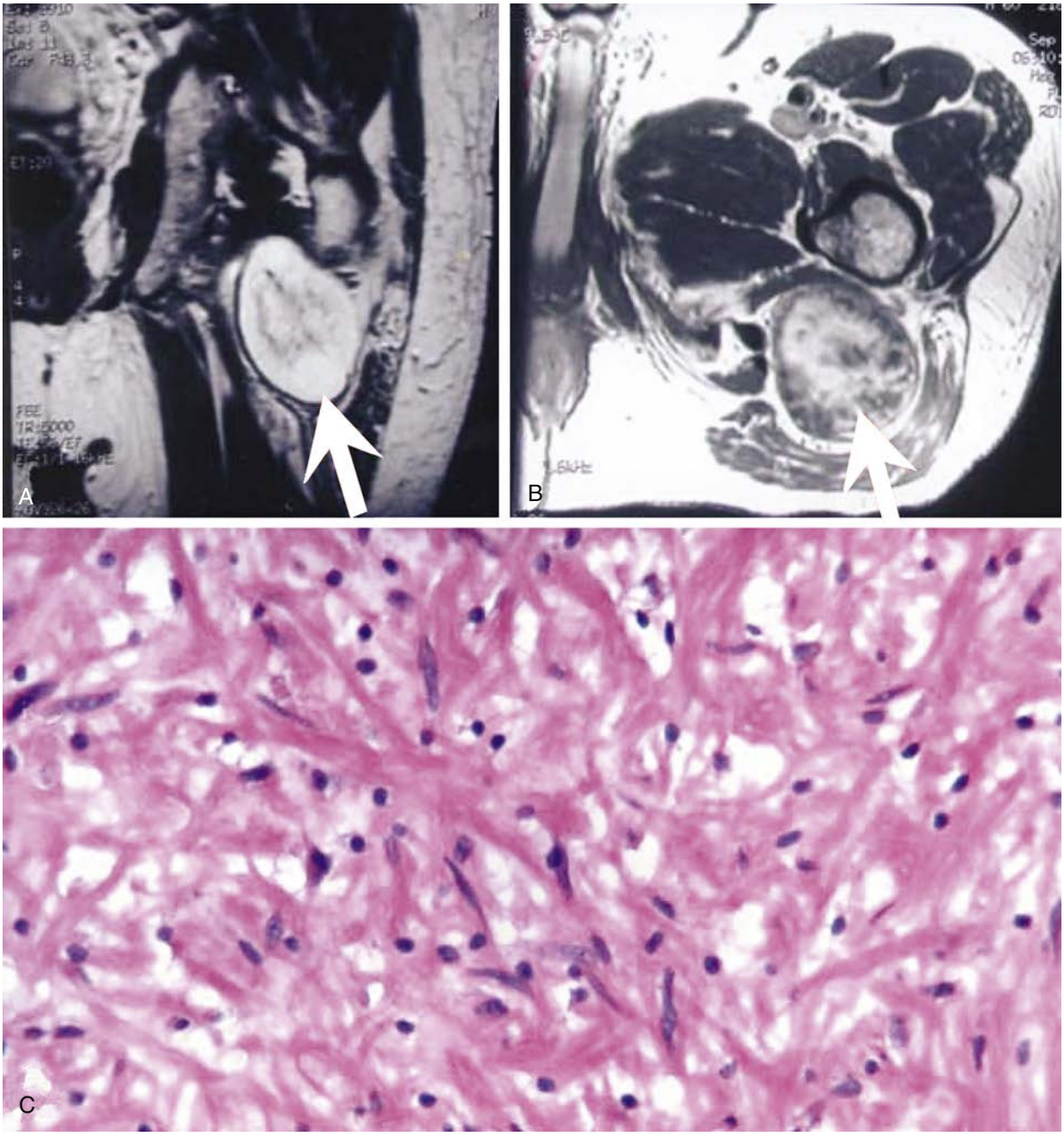


Fig. 1.40 T1-weighted image magnetic resonance imaging of the hip (coronal view) showing a neuroma in the sciatic nerve. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 198A.)



Fig. 1.41 Magnetic resonance imaging of the wrist. T1-weighted images showing a ganglion cyst (*arrow*). (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 131, fig. 8.2.)

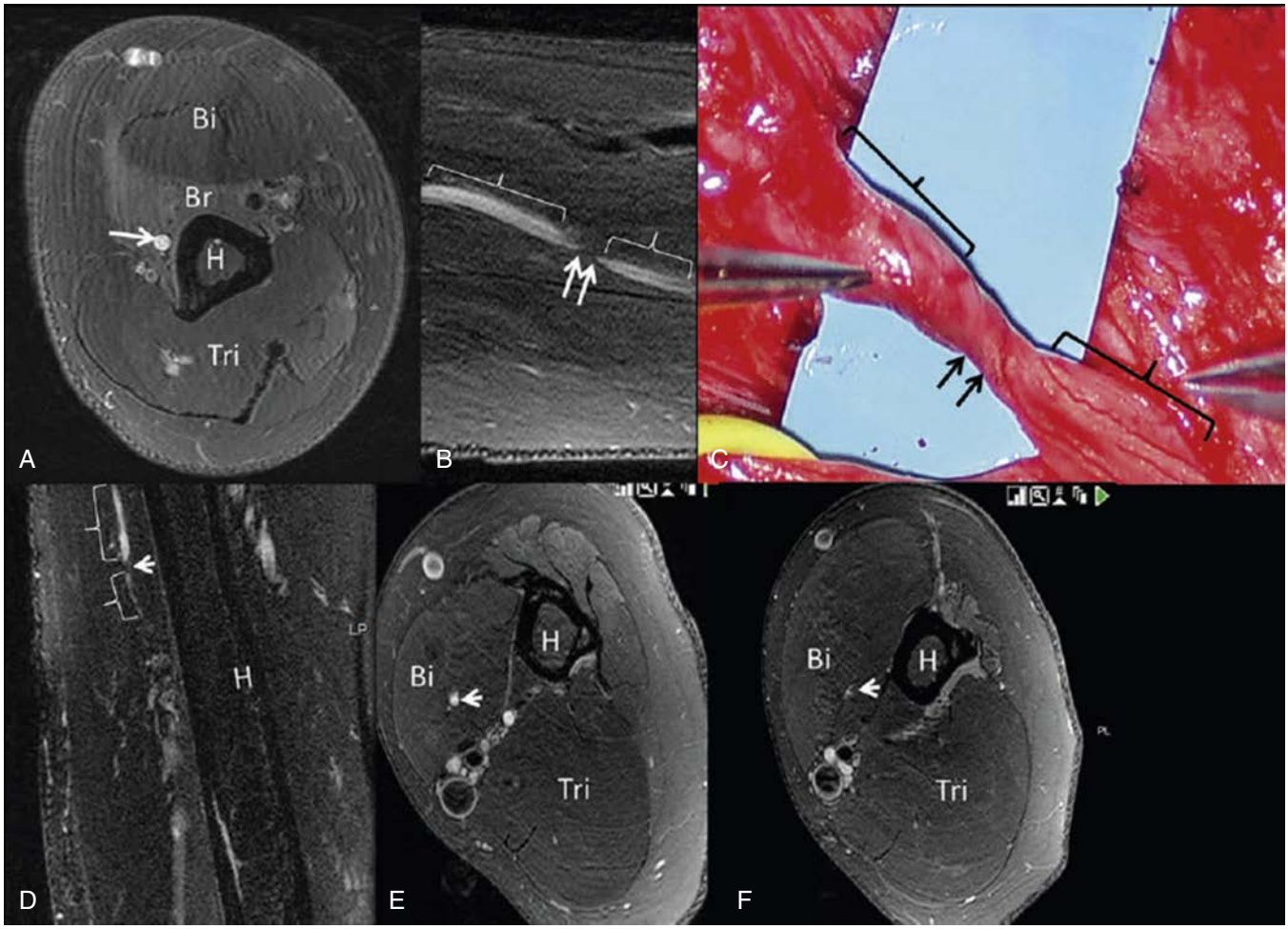


Fig. 1.42 Images from a 51-year-old man with left radial nerve and musculocutaneous nerve (MCN) palsy for 1 year. (A, B) Axial two-dimensional (2-D) T2-weighted Dixon fat-suppressed image (A) reveals enlargement, signal hyperintensity, and a "bullseye" sign of the radial nerve (*arrow*) within the distal arm, just proximal to a severe constriction (*arrows*, B) of the nerve demonstrated on the longitudinal 2D Dixon image. There is denervation edema pattern of the brachialis (Br) and sparing of the biceps (Bi) muscles, a classical finding in PTS. (C) intraoperative photograph reveals torsed appearance of the radial nerve (*brackets*) wit focal constriction (*arrows*) at the same site identified by magnetic resonance imaging (B). (D) Oblique coronal 2D T2-weighted Dixon fat-suppressed image reveals focal intrinsic constriction (*arrow*) of the MCN (brackets), likely distal to the takeoff of the biceps branch within the arm. (E, F) Axial 2-D, T2-weighted Dixon fat-suppressed images reveal MCN enlargement immediately proximal (*arrow*, E) and collapse immediately distal (*arrow*, F), to the site of constriction shown in image (D). (H) Humerus; Tri, triceps muscle. (Reproduced with permission, Sneag, D., Raney, S. K., Wolfe, S. W., Lee, S. C., Kalia, V., Lee, S. K., et al. (2018). Brachial plexitis or neuritis? *Muscle & Nerve*, *58*.)

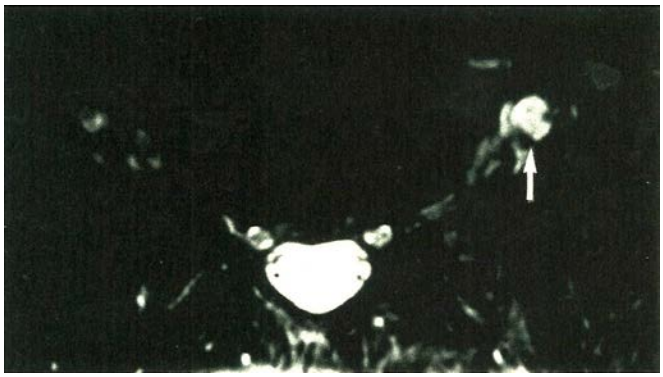


Fig. 1.43 MR neurography of a patient with neuropraxic injury. There is enlargement and increased signal intensity involving the left L4 (*large arrows*) and L3 (*small arrows*) nerve roots owing to nerve root swelling. (From Bertorini, T. E. (Ed.) (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Woburn, MA: Butterworth-Heinemann, pp. 585, Fig. 21B.)

2019). (Fig. 1.50 shows an image of the whole median nerve at the forearm. Fig. 1.51 shows an ultrasound of the wrist of a patient with carpal tunnel syndrome.) Simple ultrasound techniques to measure muscle thickness also correlate with manual muscle testing (Abraham et al., 2019).

Dual-energy x-ray absorptiometry (DEXA)scan is a radiographic method that assesses total-body mineral composition and uses scanners with an x-ray tube with K-edge filtration. Body tissues have varying degrees of absorption ratios, depending on the density, and thus, the technique detects bone mineral content, lean body mass, and fat, and this is used to diagnose osteopenia, as well as measure muscle mass, and determine disease progression in therapeutic trials, having a good correlation with manual muscle testing (Fuller, Laskey, & Elia, 1992).

Electrical bioimpendance is a new method that does not provide imaging but analyzes the response of muscles following stimuli of low-intensity electrical currents with a high frequency of 50 KHz. This measures the resistance and reactance of tissue, and increased capacitance is associated with better muscle mass. The test is done with portable equipment and is simple, safe, rapid, and reproducible (Janssen, Heymsfield, Baumgarter, & Ross, 2000; Rutkove, 2009; Rutkove et al., 2012). Different techniques are used such as measurement of the total body mass, whereas others study selected muscles. We use regional limb impendence using the Quantum 5 segmental method (Fig. 1.52), which provides appendicular (each arm and leg and torso and total body) composition results and has demonstrated lack of variability when normal subjects are tested twice at different dates. We have used the technique to monitor the progression and response to therapy in NMDs (Bertorini, Knickerbocker, & Meter, 2019; Bertorini, Zhao, et al., 2019).

GENETIC TESTING

Genetic testing is most useful in the diagnosis of hereditary NMDs, even if a positive family history is not elicited, and in establishing a genetic mutation in those who do not have a clear diagnosis (Bertorini et al., 2019; Efthymiou, Manole, & Houlden, 2016; Gorospe & Hoffman, 2002; Orengo & Murdock, 2019; Zatz, Passos-Bueno, & Vainzof, 2016). Over 500

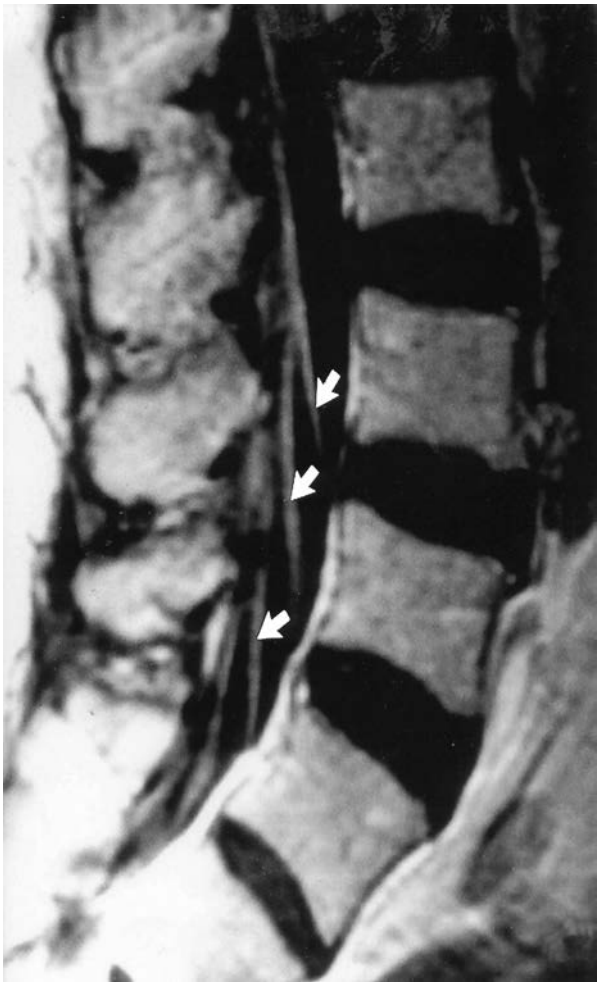


Fig. 1.44 Gadolinium enhancement of lumbosacral roots (*arrows*) a case of CIDP. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 328.)

genes have been associated with neuromuscular disease, and nowadays, as discussed, testing may be done before considering more traumatic studies such as EMG and biopsies. This is a brief introduction, and genetic testing will be covered in more detail in Chapter 11. Only DNA testing helps to determine the definite diagnosis in some disorders, particularly in cases of neuropathies and in limb girdle dystrophies in which histology or Western Blot analysis does not assess the deficient protein, for example in Fukutin-related protein mutations. Determining genetic mutations is important to find out if the patient's condition could have other organ involvement such as the heart (Efthymiou et al., 2016; Kassardjian, Amato, Boon, Childers, & Klein, 2016; Orengo & Murdock, 2019; Zatz et al., 2016); thus, proper identification could help in the determination of the risks of comorbidities and management. Furthermore, knowledge of genetic mutations could help to recognize if the patient is amendable to treatment, such as in the case of spinal muscular atrophy, Duchenne dystrophy, and those with superoxide dismutase (SOD) or C9*orf*72 ALS mutations.

If the clinician suspects a particular genetic mutation due to family history, Sanger sequencing (Sanger & Coulson, 1975) of individual genes or multiplex ligand-dependent probe amplification or Southern Blot analysis can be done and is very useful; however, these are time consuming.

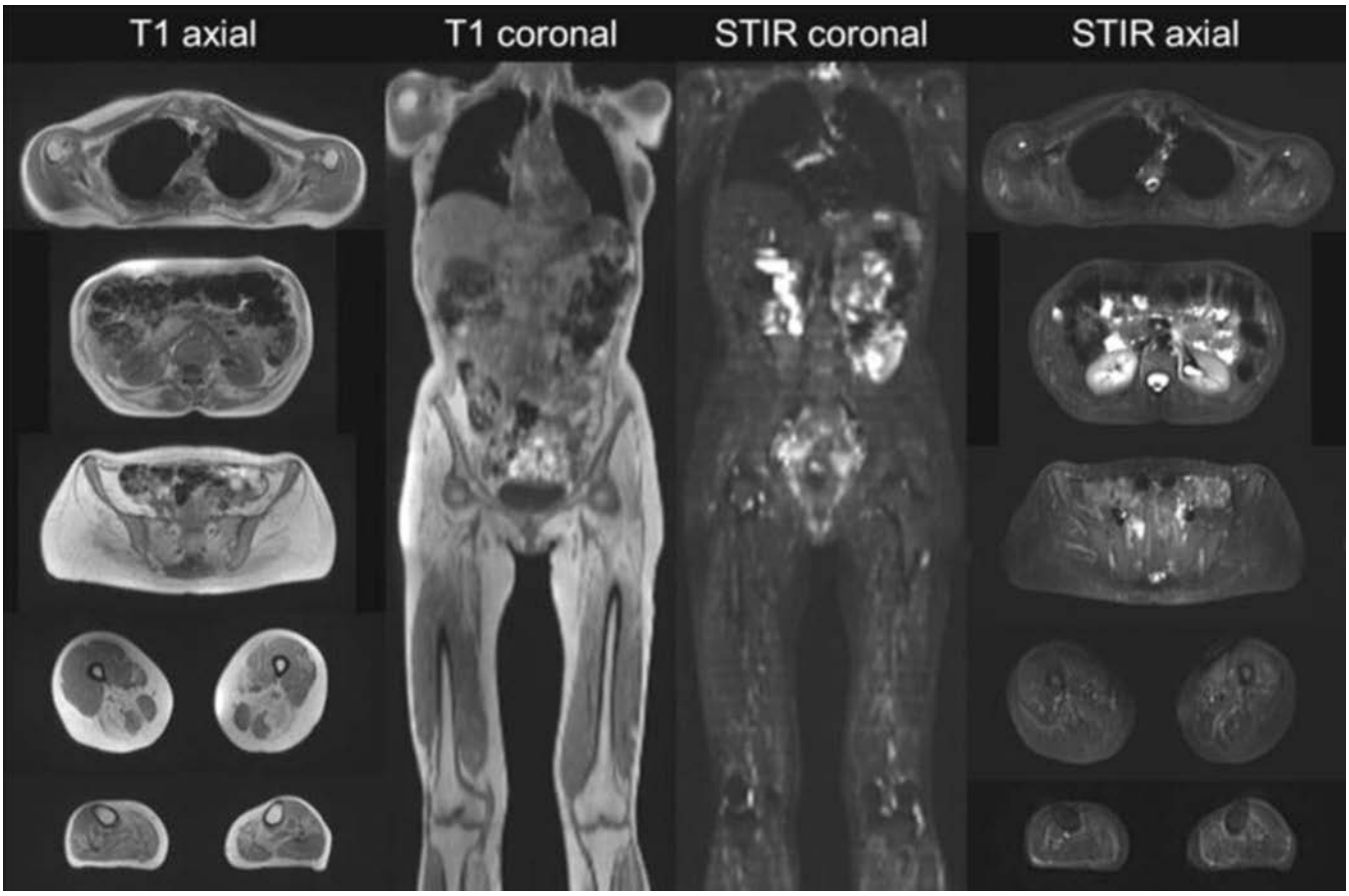


Fig. 1.45 Representative examples of T1-weighted and short tau inversion recovery whole-body magnetic resonance images in axial and coronal planes. (With permission from Kalia, V. (2017). Advanced MRI techniques for muscle imaging. *Seminars in Musculoskeletal Radiology, 21*, 459–469.)

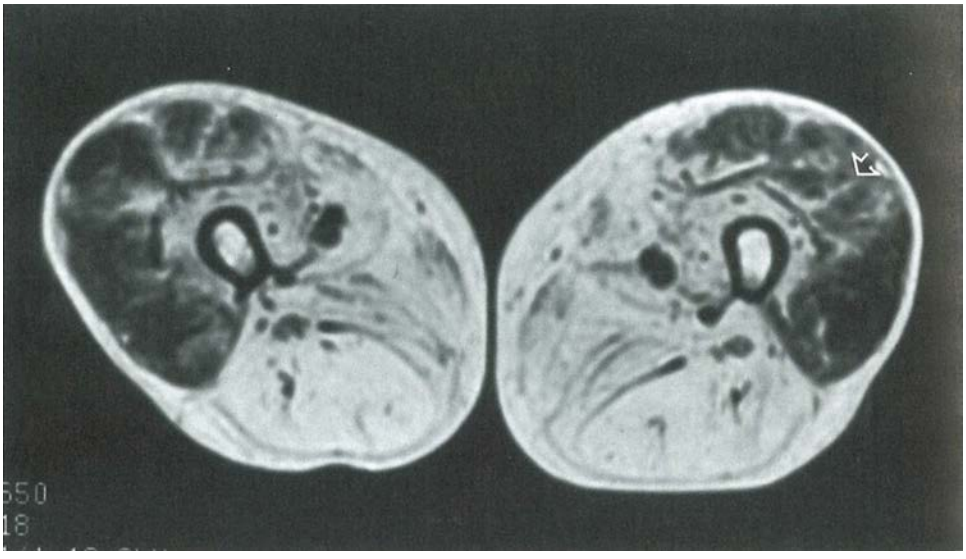


Fig. 1.46 Magnetic resonance imaging axial T1-weighted spine echo images of a patient with Becker's muscular dystrophy showing severe involvement and fat replacement in the hamstring muscle, and relatively less involvement of the vastus lateralis (*open arrow*), more involvement of the hamstrings (*arrow*). (From Bertorini, T. E. (Ed.) (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 576, fig. 18. 11b). Woburn, MA: Butterworth-Heinemann.)

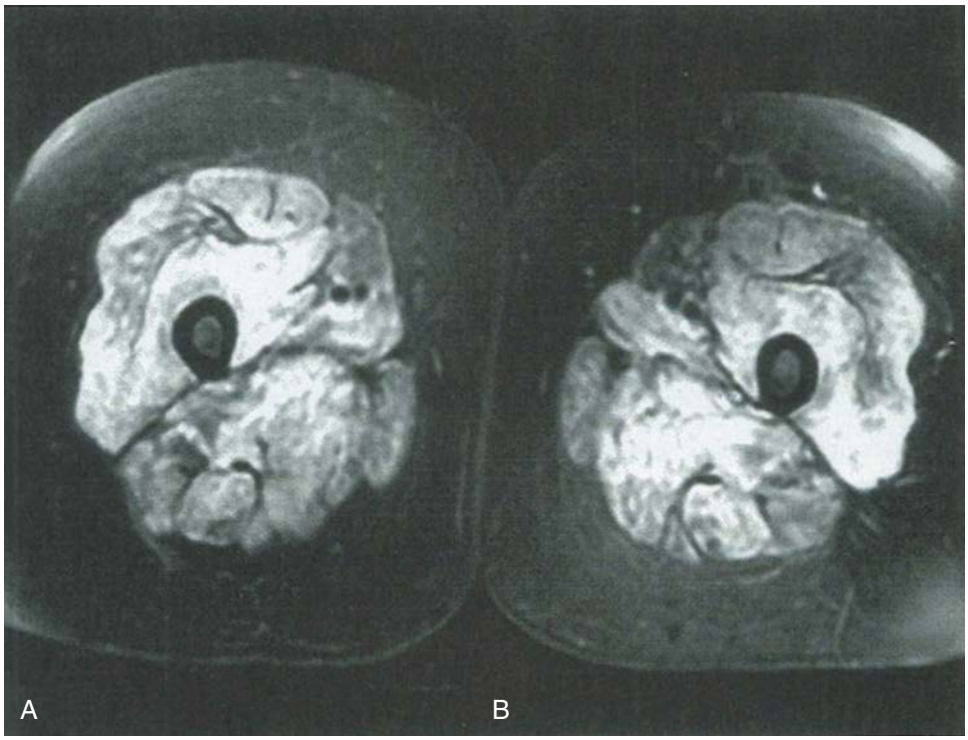


Fig. 1.47 Axial (A) and coronal (B) fast spin echo T2-weighted fat-suppressed magnetic resonance images from a patient with active polymyositis. Fat suppression was performed using a short tau inversion recovery technique (repetition time/echo time = 3500/45 milliseconds, inversion time = 160 milliseconds). There is diffuse extensive abnormal signal involving all muscle groups in the thigh. This increased signal is due to muscle edema. (From Bertorini, T. E. (2002). Clinical evaluation and clinical diagnostic tests. In T. E. Bertorini (Ed.) (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 579). Woburn, MA: Butterworth-Heinemann.)

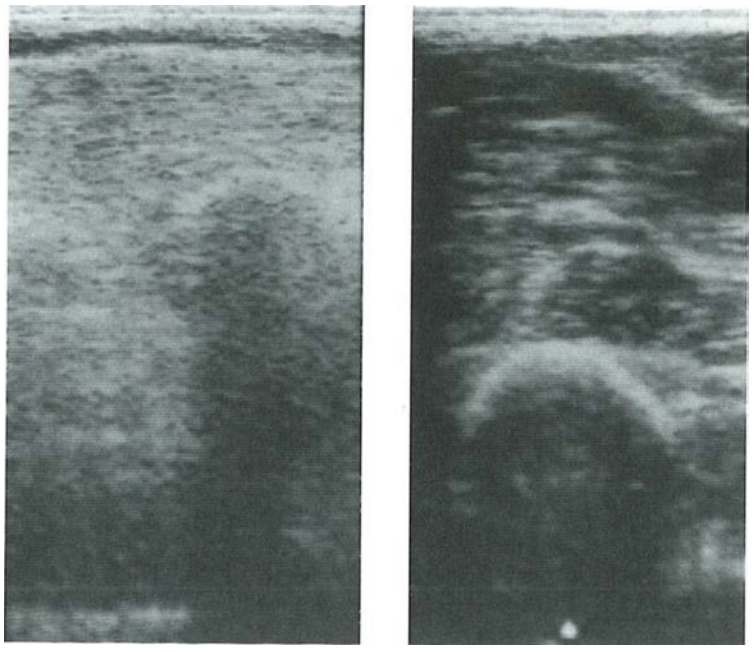


Fig. 1.48 Transverse images from biceps muscle. The image on the left is from a patient with polymyositis and muscle atrophy. Note increased muscle echogenicity and loss of bone shadowing. The muscle is also small. The biceps on the right is from a healthy control. (Courtesy of Francis Walker, Bowman Gray University. Reprinted with permission from Halford, H., Graves, A., & Bertorini, T. (2002). Muscle and nerve imaging techniques. In T. E. Bertorini (Ed.). *Clinical evaluation and diagnostic tests for neuromuscular disorders* (p. 569). Woburn, MA: Butterworth-Heinemann.)

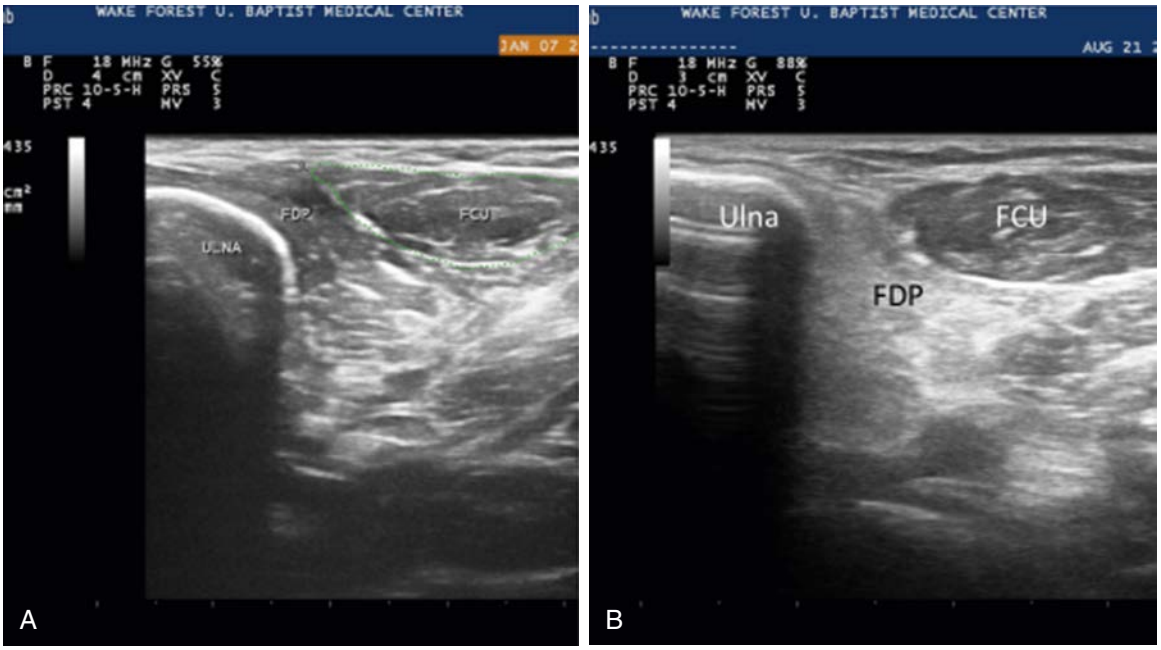


Fig. 1.49 Two cross-sectional images using an 18 MHz transducer (Esaote MyLab Gold) taken of the proximal forearm over the flexor carpi ulnaris (FCU) muscle. The left image, from a normal control (a), shows a "starry night" pattern of muscle architecture with the bulk of the muscle being hypo-echoic interspersed with fibrous tissue stroma in both FCU and the flexor digitorum profundus (FDP). The ulna has a bright edge. The right image (b), from a patient with inclusion body myositis, showing that the FDP muscle is preferentially involved, showing loss of normal architecture, and is diffusely hyperechoic consistent with chronic muscle disease. The oval shape FCU is seen with the normal "starry night" pattern with a background of very dark muscle tissue interspersed with bright (hyperechoic) punctate and curvilinear fibrous tissue stroma, but the FDP shows loss of normal architecture and is diffusely hyperechoic. (Courtesy of Dr. Michael Cartwright and Dr. Francis Walker.)

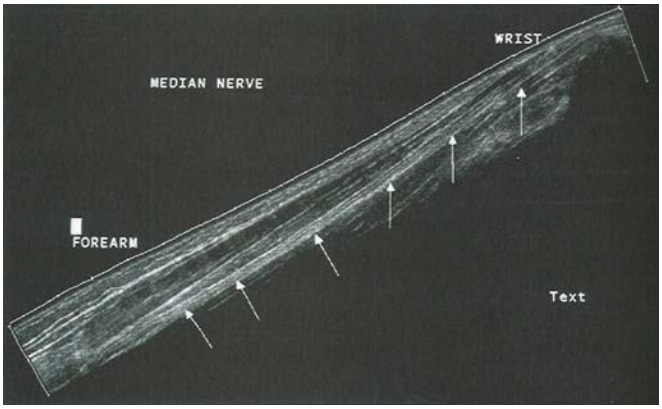


Fig. 1.50 Longitudinal image in a healthy subject of the median nerve (*arrows*), which is seen superficially. The image is obtained from the wrist to the antecubital fossa and reconstructed from the gradual movement of the transducer up the forearm using technology that displays an extended field of view with a 13.5 MTz phased array probe on a Sonoline Elegra (Siemens, Greensboro, NC). (Courtesy of Francis Walker, Bowman Gray University. Reprinted with permission from Halford, H., Graves, A., & Bertorini, T. (2000). Muscle and nerve imaging techniques in neuromuscular diseases. *Journal of Clinical Neuromuscular Disease, 2*, 41–51.)

Nowadays, next-generation sequencing is done routinely and uses massive parallel sequencing to generate a large number of reads at once and is time efficient, can be less expensive, and are used in genetic diagnostic panels (Blancalana & Laporte, 2015; Richards et al., 2015). These identify mutations providing identification of single nucleotide variations, insertions, and deletions. These methods are used for screening patients such as limb girdle muscular dystrophy and familial neuropathies. The technique has limitations as it does not detect repeat expansions, for which the standard polymerase chain reaction and Southern blot analysis are helpful. Examples of this include myotonic dystrophy and some familial forms of ALS. When the tests are not informative, then whole exon sequencing could be used, but at this time, this is very expensive and time consuming. Finally, another alternative would include whole genome sequencing techniques (Lupski et al., 2010), but these are also very expensive at this time. Karotype chromosome microarrays can be used to detect large deletions, duplications, and translocations.

With the use of next-generation sequencing, one frequently encounters variants of uncertain significance, which means that they have not been reported in a disease at the time of the test, and they may be benign and not pathogenic variations, but it is not unlikely that at later date they would be associated with particular diseases. If necessary, whole exon and gene sequencing could be considered. RNA sequencing is a promising tool in genetics, but it uses tissue samples.

The mitochondria has its own DNA whose mutations can cause neuromuscular diseases, and sequencing of mitochondrial DNA could be done in patients suspected of having these disorders (see Chapter 23).

Another consideration in testing patients is that molecular diagnosis may sometimes provide inconclusive data, for example, when there are borderline CTG repeat numbers suggestive of myotonic dystrophy and/or the diagnosis cannot be made in

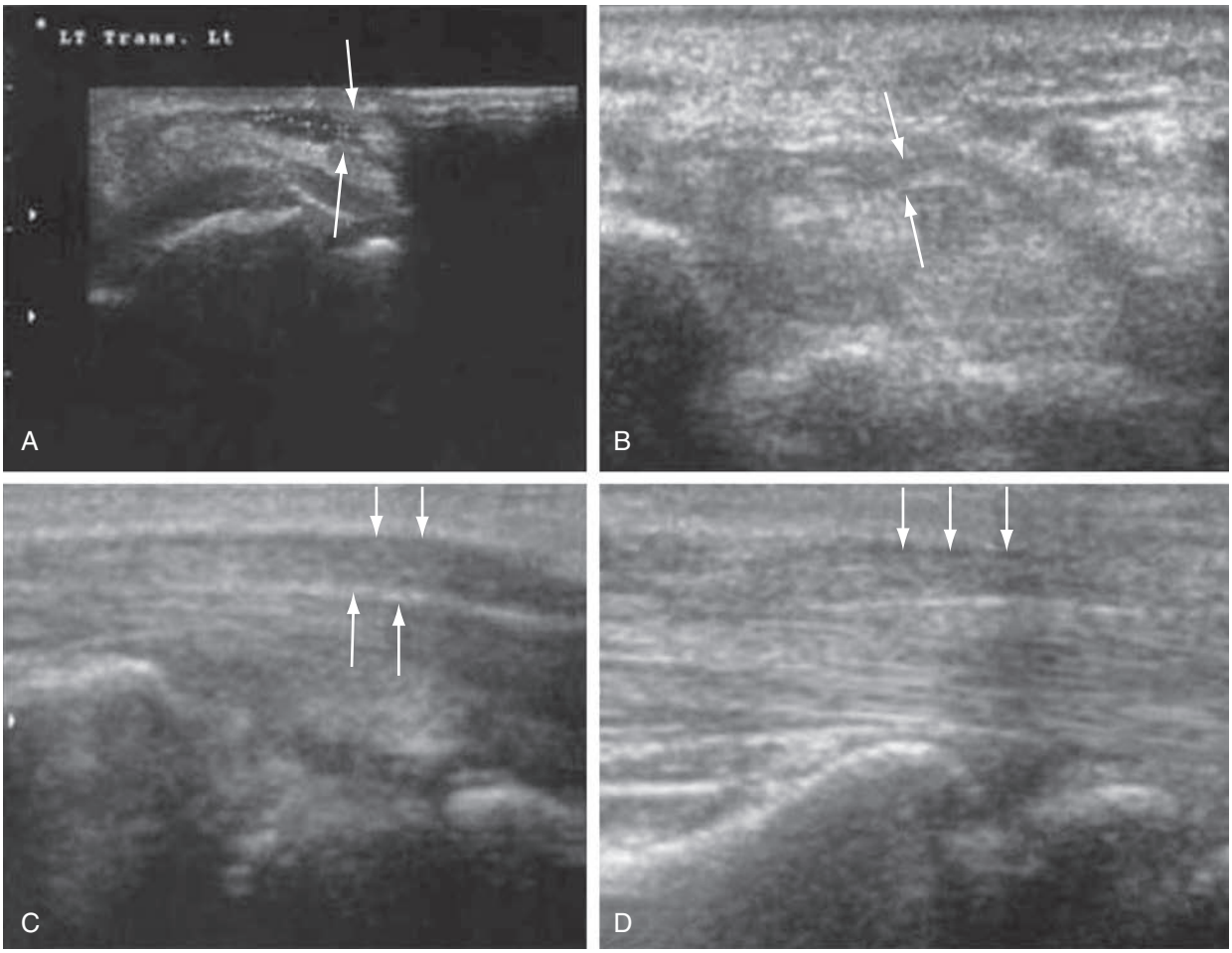


Fig. 1.51 Carpal tunnel syndrome, ultrasound of the left wrist showing narrowing of the median nerve diameter marked with *arrows* in A and B. Normal ultrasound of the median nerve in a control subject in C and D. (From Bertorini, T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann, p. 96.)

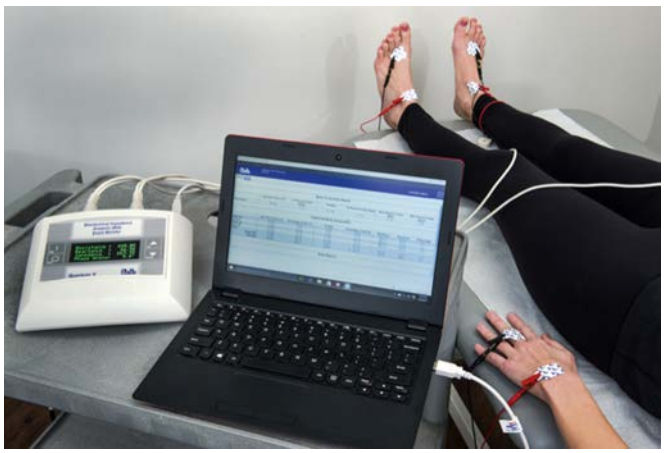


Fig. 1.52 Electrode montage and equipment used to measure segmental bioimpendance with the Quantum V Segmental BIA. Electrodes are placed in both hands and feet. (Courtesy of Rudy Liebke).

all cases of fascioscapulohumeral muscular dystrophy because some patient does not have the known causative mutation.

Finally, in some disorders, such as limb-girdle dystrophies and Charcot-Marie-Tooth disease, many patients do not have the recognizable mutation studied by commercial laboratories, and for this, the patient's proper diagnosis and clinical routine studies still remain important. Genetic testing is improving rapidly, and the cost of the testing is diminishing. It is hoped that in the future, many of these can be offered to families even when they do not have a known mutation for the disease.

More detailed descriptions of specific genetic diagnosis in hereditary neuromuscular diseases are discussed in detail in Chapters 11, 13, and 14.

The Muscular Dystrophy Association (MDA) provides excellent educational materials, as well as list sites in which genetic testing can be done for free.

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2 Respiratory Complications in Neuromuscular Disorders

Jonathan Daniel Finder, MD

Respiratory management of patients with neuromuscular diseases has changed significantly during the 21st century, aided by the development of lightweight, noninvasive technologies to assist in airway clearance and ventilation. These devices, coupled with a more aggressive approach to diseases that had previously been treated with a nihilistic approach, have resulted in reduced morbidity and greatly extended survival.

MANAGEMENT OF NEUROMUSCULAR DISEASES RESULTING IN RESPIRATORY INSUFFICIENCY

While there is a broad spectrum of neuromuscular disorders that result in respiratory insufficiency/failure, there are overarching themes to management. These themes are essentially those of assisting airway clearance and assisting ventilation. Most patients seen by a pulmonologist as outpatients fall into one of two groups: those with muscular dystrophy/myopathy and those with motor neuron disease. There has been a movement toward noninvasive approaches and avoidance of tracheostomy when possible. Management choices offered to patients and shared clinical decision making are affected by diagnosis, prognosis, physician and center experience, and personal choice. Depending on local referral patterns, ventilator-dependent patients with spinal cord injury and those with post-polio syndrome requiring ventilatory support may also be seen and will be discussed briefly. Other diseases that may have respiratory involvement include inflammatory myopathies, critical illness polyneuropathy, myasthenia gravis, Eaton-Lambert syndrome, intoxications, Guillain-Barré syndrome, botulism, and porphyria. These diseases, which cause acute, rather than chronic, respiratory failure, will be discussed in the section of the chapter on management of acute respiratory failure.

DIAPHRAGM PARESIS/PARALYSIS

Development of diaphragmatic weakness or paralysis can be insidious (with progressive disorders like Duchenne muscular dystrophy [DMD]) or rapid (such as with trauma or inflammation). Diaphragm weakness can be unilateral or bilateral, and etiology is not always clear. Diaphragm weakness can result from metabolic (hypothyroidism; Martinez, Bermudez-Gomez, & Celli, 1989), inflammatory (Guillain-Barré syndrome, systemic lupus erythematosus; vanishing lung syndrome; Laroche et al., 1989), or myopathic (DMD, Pompe disease; Moufarrej & Bertorini, 1993; Rosenow & Engel, 1978) causes. It may also be caused by phrenic nerve injury as a result of cardiac surgery (Chandler, Rozas, Kory, & Goldman, 1984), trauma, inflammation (as associated with pneumonia), hereditary neuropathy (Charcot-Marie-Tooth or Dejerine-Sottas, spinal muscular atrophy), or motor neuron disease (Niedermeyer, Murn, & Choi, 2019).

Patients with unilateral diaphragm paralysis are often asymptomatic unless there is underlying lung disease or obesity (Richman, Yeung, Bilfinger, Yang, & Stringer, 2019). Symptoms that should lead the clinician to suspect bilateral diaphragm paralysis include profound orthopnea, with which the patient is unable to lie completely flat for more than a few seconds. The patient may have mild to moderate dyspnea at rest that is severely exacerbated by bending sharply at the waist, as when tying the shoes. This results from interference with a primary compensatory mechanism. These individuals have learned to function by using their abdominal expiratory muscles to force the diaphragm upward to a level below functional residual capacity; during inspiration, the muscles relax and the abdominal viscera pulls the diaphragm down by gravity, augmenting inspiration. Physical examination varies from no change in effort but with an elevation of the hemidiaphragm on percussion of the chest to use of accessory muscles in the neck. In the supine position, paradoxical motion can be evident, with the abdomen moving in rather than out with inspiration. Careful percussion of the chest at maximal points of inspiration and expiration will demonstrate failure of normal diaphragmatic excursion.

The general history and physical examination should focus on possible underlying disease processes that may produce diaphragm paralysis. Neuralgic amyotrophy is a brachial plexitis that results in severe shoulder pain preceding the onset of dyspnea (Rice et al., 2017). Patients with adult Pompe disease may have associated proximal muscle weakness (Berger, Chan, Rom, Oppenheimer, & Goldring, 2016). Primary respiratory-onset amyotrophic lateral sclerosis (ALS) may be associated with pathologic reflexes and fasciculations. Primary underlying diseases, such as lupus, hypothyroidism, and previous trauma, including surgery, should be sought. A recent severe bacterial pneumonia on the ipsilateral side may precede idiopathic cases.

The classic confirmatory diagnostic test is fluoroscopy, during which the patient forcefully sniffs. This test is excellent for confirming the diagnosis of unilateral paralysis; the

unaffected diaphragm descends rapidly and normally, and the affected diaphragm rises while the mediastinal structures move toward the unaffected side. However, if performed while the patient is upright, it may miss bilateral paralysis; as described earlier, passive fall of the diaphragm during inspiration may confound the examiner and result in a report of normal diaphragmatic function (Minami, Manzoor, & McCool, 2018). To be effective, fluoroscopy must be performed with the patient supine; in this position, paradoxical diaphragmatic excursion will be seen. Ultrasound may also be used to assess diaphragmatic movement and is helpful to reduce radiation exposure (Minami et al., 2018).

Additional tests include pulmonary function tests, measurement of maximal inspiratory pressure, and diaphragmatic electrodiagnostic studies. Spirometry generally shows a reduction in forced vital capacity (FVC). Plethysmographic total lung capacity is reduced. Residual volume is generally preserved. Characteristically, FVC is reduced by an additional 40% or more in the supine position.

Maximum inspiratory pressure, achieved by asking the patient to inhale with greatest force from residual volume against a manometer, is typically reduced from normal and can be measured in the pulmonary function laboratory. Occasionally, an otherwise healthy patient can generate surprisingly high pressures, approaching normal. Maximum expiratory pressure (measured from total lung capacity) is generally preserved, as this reflects the abdominal musculature, not the diaphragm. Maximum transdiaphragmatic pressure, or P_{DImax} (the difference between esophageal pressure and gastric pressure, which requires balloon manometry in both organs), is always reduced, usually less than 30 cm H_2O. Sniff nasal inspiratory pressure, or SNIP, is a newly described test and is quite easy to perform. This test can be performed in a wide age range and requires little training (Kaminska, Noel, & Petrof, 2017).

Nerve conduction studies of the phrenic nerves and diaphragmatic electromyograms may be performed but are seldom necessary for clinical diagnosis. When they are believed to be required, they are best performed in a laboratory with substantial experience with the techniques.

Patients with unilateral diaphragm paralysis may present with a history of sleeping in a chair due to dyspnea while lying flat. Therapy is indicated at the time of diagnosis. Most patients can be treated successfully with noninvasive nocturnal noninvasive ventilation.

Diaphragmatic pacing is not indicated in these patients; this procedure requires both intact phrenic nerves and normal muscle function, and it is generally limited to patients with high spinal cord injuries and intact phrenic nerves and patients with central alveolar hypoventilation (DiMarco, 2018; Gonzalez-Bermejo et al., 2016; Le Pimpec-Barthes et al., 2016).

MUSCULAR DYSTROPHIES

The most common of the hereditary neuromuscular disorders requiring respiratory support is DMD. The young men with this X-linked disease have a relatively similar course, being in a wheelchair full time by roughly 12 years of age and developing respiratory failure by the late teens or occasionally as late as the early 20s. The phases of respiratory dysfunction are predictable and follow through four stages.

Patients in the first stage tend to be ambulatory or only part-time users of wheelchairs. During this stage, there is little respiratory disease but there is a higher incidence of obstructive sleep apnea due to a combination of lingual hypertrophy and decreased upper airway tone (Suresh, Wales, Dakin, Harris, & Cooper, 2005). This can be screened by history: snoring is invariably present in those patients with obstructive sleep apnea. Sleep studies are essential in identifying those patients requiring nocturnal positive pressure support in the form of constant positive airway pressure (CPAP) via mask.

The second stage occurs after the patient has become a full-time wheelchair user and is the development of insufficient cough. These patients can be easily identified before the development of symptoms by simple in-office tests including pulmonary function testing, peak cough flow, and measurement of maximal expiratory pressure. As a rule, a peak cough flow in excess of 270 L/min and peak expiratory pressure over 60 cm H_2O suggest adequate cough clearance. Values under 270 L/min for peak cough flow should prompt consideration of assisted coughing techniques, particularly mechanically assisted coughing. The goal in frequent pulmonary function testing is to predict those patients at risk for developing pneumonia and therefore prevent the need for hospitalization. Mechanically assisted cough devices can also be used for lung volume recruitment by deeply insufflating the lungs (Bach et al., 2008; Bach, 1993; Chiou, Bach, Jethani, & Gallagher, 2017; Vianello et al., 2005).

The third stage is the development of nocturnal hypoventilation. There is a correlation of inadequate nocturnal ventilation and FVC on spirometry, with a strong association of those patients with FVC less than 30% predicted requiring nocturnal ventilatory support (Lyager, Steffensen, & Juhl, 1995). Consensus recommendation has been for annual screening sleep studies on those patients with FVC less than 50% predicted (Finder et al., 2004; Sheehan et al., 2018). Often, patients have evidence of sleep disturbance or nocturnal hypoventilation, with frequent awakenings, daytime sleepiness, and morning headaches and even report nightmares of smothering. Morning headaches are characteristic and should be treated with great concern when present on awakening and clearing within 1 hour or less without intervention. These headaches are caused by nocturnal hypercapnia. Sleep studies with initiation of noninvasive positive pressure support by mask interface (bilevel positive pressure) should be titrated to normalize ventilation (CO_2 level), especially during rapid eye movement sleep. Aggressive management of nocturnal ventilation is also critical to minimize right heart strain due to alveolar hypoxia in these patients who also have cardiomyopathy.

The fourth stage is that of daytime hypoventilation, both awake and asleep. The age in which this develops is quite variable, from mid-teens to mid-20s, and is likely affected by steroid use. This stage can be quite easily diagnosed by measuring end-tidal P_{CO_2} in the ambulatory setting. A P_{CO_2} of >45 mm Hg in an awake patient is indicative of CO_2 retention and daytime respiratory insufficiency. In years past, this had been an indication for placement of tracheostomy, but more frequently, patients have been choosing noninvasive ventilation. This form of ventilation is generally delivered with a set volume delivered via an angled mouthpiece within reach of the patient's mouth, with a portable ventilator mounted behind the patient's wheelchair. The mode of ventilation used is triggered by the patient's inspiratory effort

and is delivered as a set tidal volume via a single limb open circuit. This circuit is supported by an adjustable semirigid arm, which holds the mouthpiece just in front of the patient's mouth. This technique can also allow the patient to breath stack to fully expand the lungs to achieve maximum insufflation capacity, thereby resolving atelectasis, improving airway clearance, stretching the intercostal muscles, and avoiding the development of chest wall rigidity (Bach et al., 2008). This technique has been referred to as lung volume recruitment (Chiou et al., 2017). Mouthpiece ventilation (also referred to as "sip and puff" ventilation) has been used in a broad variety of neuromuscular diseases, including ALS (Bedard & McKim, 2016), spinal cord injury, and other myopathic disorders in which there is CO_2 retention. Critical to success is the ability to understand the technique, and so significant neurocognitive dysfunction is a relative contraindication to mouthpiece ventilation. Intact bulbar function is also necessary since the patient needs to be able to form a seal around the mouthpiece.

Becker muscular dystrophy is a mild form of dystrophinopathy in which the dystrophin gene defect results in a present but reduced-function protein (generally from an in-frame deletion resulting in a shortened protein). These patients follow a course similar to that of DMD, but with each milestone, including the development of respiratory failure, delayed in onset by approximately a decade or more.

The second most common muscular dystrophy requiring ventilatory support is myotonic dystrophy, Type 1. Age of onset is variable because the severity of the symptoms is influenced by the length of the responsible CTG trinucleotide repeats. Because of trinucleotide expansion from generation to generation ("anticipation"), a physician caring for several generations of the same family can expect onset of respiratory failure progressively earlier in each successive generation. Sleep apnea is common in myotonic dystrophy, and a substantial minority of patients has excessive daytime sleepiness, even without respiratory failure. As a consequence, polysomnography should be performed in sleepy patients, even if they have normal gas exchange. Myotonia of the diaphragm is undoubtedly present, but of uncertain significance in the development of respiratory symptoms (Hawkins et al., 2019).

Other hereditary muscular dystrophies (limb-girdle, facioscapulohumeral, Emery-Dreifuss) are far less likely to result in respiratory failure but may do so on occasion.

All symptomatic patients should be evaluated. At a minimum, pulmonary function tests, including FVC, lung volumes, maximum inspiratory and expiratory pressures, oximetry, and exhaled CO_2, should be performed. Arterial puncture is no longer required given the broad availability of exhaled CO_2 monitors in the ambulatory setting; capillary blood gas is also helpful in assessing for CO_2 retention. A baseline chest x-ray will be helpful in evaluating subsequent respiratory infections, particularly if there are baseline abnormalities in heart size or in pulmonary parenchyma, spinal structure, or diaphragm. Symptoms of sleep disordered breathing should prompt a sleep study. Symptomatic dysphagia or recurrent pneumonias suggesting aspiration may be evaluated by modified barium swallow or fiberoptic evaluation of swallowing by an otolaryngologist. All patients should have appropriate influenza and pneumococcal vaccinations. If the individual has significant dysphagia or evidence of aspiration, or more commonly, weight loss associated with loss of muscles of chewing and swallowing, gastrostomy placement should be considered. Weight loss may lead to loss of soft tissue on the buttocks and back, making both bed and wheelchair use uncomfortable and placing the patient at greatly increased risk for pressure sores.

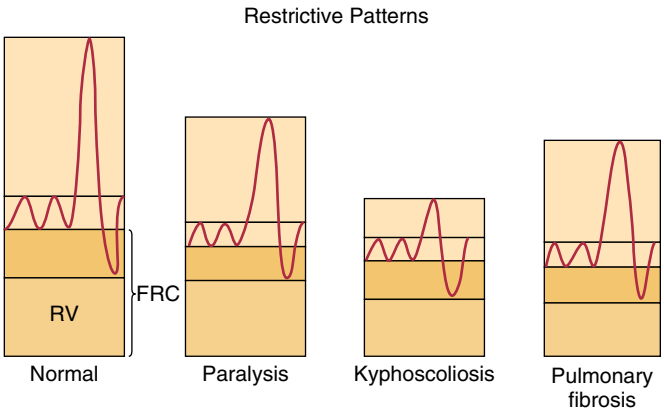


Fig. 2.1 Patterns of restriction. *FRC*, functional residual capacity; *RV*, residual volume.

Monitoring of patients who are asymptomatic is critical in order to predict those at risk for subsequent respiratory complications prior to a development of a medical crisis. The goal is prevention of illness and hospitalization. Serial monitoring of FVC is helpful in identifying those at risk for nighttime ventilatory failure. Monitoring of peak cough flows will identify those at risk for ineffective cough clearance and, therefore, pneumonia. In later stages of the disease, measuring exhaled CO_2 will identify those patients developing daytime respiratory failure, even in the absence of overt symptoms. Pulmonary evaluations should be performed at 6-month intervals, or more frequently depending on changes in status and development of new symptoms. Because of the possibility of life-threatening complications of even seemingly minor respiratory infections (discussed later), patients and their caregivers are told to seek care promptly at onset of symptoms.

Pulmonary function tests in these muscular dystrophies (Meyer & Hill, 1994) characteristically show restriction, with diminished volumes and flows and a normal-to-elevated ratio of forced expiratory volume in 1 second to FVC. The majority of volume reduction occurs in the measurements that depend on muscle strength. Thus, FVC and its subdivisions are much more reduced than functional residual capacity or residual volume (Fig. 2.1). Most of the reduction is probably the result of muscle weakness, although there is some evidence that there can also be a contribution of chest wall restriction from intercostal muscle fibrosis. As a result, functional residual capacity (determined by the relative elasticity of the lungs and chest wall) may be mildly reduced. Residual volume is increased due to the inability to fully exhale.

Maximum inspiratory and expiratory pressures have the advantage that they are easily measured with a handheld manometer and nose clips. The disadvantage is that there is a wide range of normal values, as determined by multiple studies, affected by age, sex, ability to form and maintain a tight mouth seal, and general health. Normal maximum expiratory pressure, measured from residual volume after

a full exhalation, is roughly –120 cm H_2O for men and approximately –90 cm H_2O for women, with a broad range. Corresponding values for maximal expiratory pressure, measured from total lung capacity after a full inhalation, are approximately +230 cm H_2O for men and +150 cm H_2O for women. Values of less than 60 cm for maximum expiratory pressure have been associated with a loss of "flow transients" or "cough spikes" on pulmonary function testing, suggesting inadequate cough clearance (Chaudri, Liu, Hubbard, Jefferson, & Kinnear, 2002).

Respiratory management of patients with muscular dystrophy has been described in several consensus statements, and the reader is referred to these documents (Finder et al., 2004; Sheehan et al., 2018).

Because the muscles of coughing are weak, use of mechanical insufflation-exsufflation (MI-E) is recommended to improve airway clearance (Bach, 1993; Gomez-Merino & Bach, 2002; Vianello et al., 2005). These devices rapidly inflate and then deflate the lungs, generating high airway velocities. Pressures are gradually increased as tolerated to achieve maximum pressures of approximately 40–45 cm H_2O for expiratory phase; inspiratory pressures for a healthy patient generally are sufficient in the range of 35–45, but these values can be adjusted to comfort and effect. Use of these devices has become widespread since the publication of the 2004 American Thoracic Society consensus guidelines statement on respiratory management of DMD (Finder et al., 2004). Interestingly, since the publication of these guidelines, mean survival in DMD has increased by a full decade from 18 to 28 years (Passamano et al., 2012). Use of the insufflation phase for lung volume recruitment may be of value to resolve asymptomatic atelectasis and to help stretch the intercostal muscles and avoid development of a rigid chest wall (Bach et al., 2008; Chiou et al., 2017; Kang & Bach, 2000).

Evidence of daytime hypoventilation is generally considered an indication for initiation of 24-hour ventilatory support. These factors include daytime hypercapnea (as documented in clinic visit by end-tidal capnography) and nocturnal hypoventilation (as demonstrated by sleep study). Longitudinal experience of multiple groups is unequivocal in showing that noninvasive positive pressure ventilation (NPPV) improves symptoms, quality of life, and longevity (Gomez-Merino & Bach, 2002; Villanova, Brancalion, & Mehta, 2014) compared with studies that showed very poor survival in the absence of ventilatory support once vital capacity is less than 1 L or once nocturnal hypoxemia and daytime hypercapnea occur (Phillips, Smith, Carroll, Edwards, & Calverley, 1999).

The most common approach to managing daytime respiratory failure with CO_2 retention is use of a mouthpiece ventilator (Fig. 2.2), which requires intact bulbar muscle function and the intellectual capacity to understand use of this device. This approach has been greatly aided by the development of lightweight portable ventilators (Fig. 2.3), which can be mounted behind the wheelchair. The angled mouthpiece is held in place adjacent to the patient's lips by an adjustable arm. The ventilator is set to deliver a set tidal volume, usually in the range of 750–1000 mL, when triggered by the patient's inspiratory effort (assist control mode).

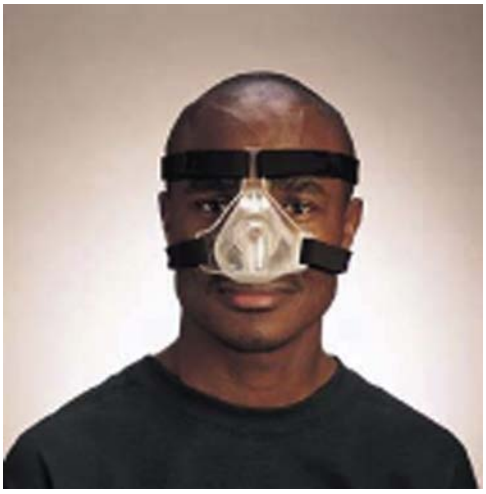


Fig. 2.2 Nasal mask interface.



Fig. 2.3 Nasal pillow interface.

Nasal pillows interface is occasionally preferred when mouthpiece ventilation is not well tolerated. Placement of a tracheostomy remains an option for patients who do not tolerate noninvasive ventilation.

For nighttime ventilation, interface selection is critical to success. It is more than a matter of individual choice and comfort: if the mask cannot be tolerated, it will not be used, and the patient will remove it in the night and have respiratory failure. Interfaces can be nasal, oronasal, full-face mask, or intranasal (Figs. 2.4 and 2.5). It may be helpful to have more than one interface to alternate pressure points.

Mask interfaces for noninvasive ventilation are designed with holes for air leak. Combined with expiratory positive pressure, the holes minimize CO_2 rebreathing. If volume ventilation is used, these masks must be modified or they cannot be used. If assist-control ventilation is used with a nasal mask leak, the patient may find it impossible to trigger the ventilator, or rapid autocycling may occur.

Bilevel positive airway pressure devices, originally designed for treatment of sleep apnea, have evolved into more sophisticated ventilators and have largely supplanted volume ventilators for noninvasive management. If pressure mode is chosen, pressures necessary to provide adequate tidal volume and rest the respiratory muscles must



Fig. 2.4 Nasal mask interface with supported tubing.



Fig. 2.5 Passy-Muir speaking valve (Passy-Muir Inc., Irvine, CA).

be chosen. The most frequent reason for unsatisfactory results from bilevel positive pressure is inadequate inspiratory pressures; the goal in the neuromuscularly weak patient is high-span bilevel positive pressure support. In other words, it is the span (the difference between inspiratory pressure and expiratory pressure) that determines the tidal volume. Expiratory pressure airway pressure (EPAP) is used for the purpose of purging carbon dioxide from the mask; 4 to 5 cm H_2O is generally adequate. Newer modes of ventilation that can be delivered to approximate a volume ventilator (without requiring an actual volume ventilator) use a technology referred to as "average volume assured pressure support." This is a combination of pressure-limited and volume-limited modes of ventilation designed to reduce barotrauma and help deliver a single tidal volume.

Tidal volumes and respiratory rates (generally as back-up rates) are initially chosen based on the patient's size and weight, to achieve tidal volumes and minute ventilation in the range described earlier. These are adjusted by well-trained respiratory therapists overnight based on comfort and compliance, ideally in a sleep laboratory. The nighttime ventilator mode is usually assist-control, although intermittent mandatory ventilation with pressure support is a comfortable alternative. Oxygen administration during this

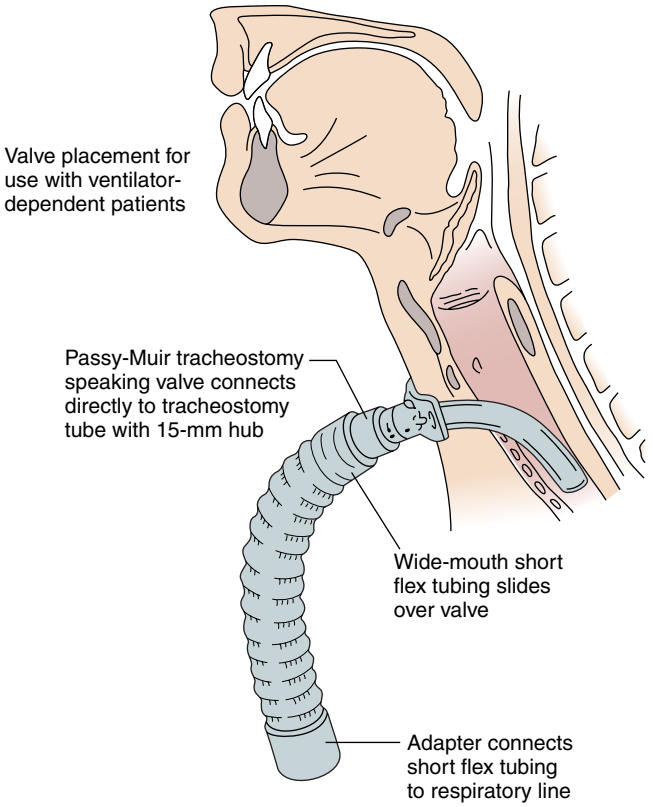


Fig. 2.6 Passy-Muir valve anatomic view.

process should be avoided, since supplemental oxygen will mask the desaturation that results from hypercarbia and will also suppress hypoxic drive.

Common problems during initiation and thereafter include mask air leak, which may result in eye irritation and exposure keratitis, skin breakdown, nasal congestion and dryness, and stomach bloating. The mask leak can usually be corrected with optimal interface selection, strap adjustment, and appropriate support of ventilator tubing (Fig. 2.6). This in turn will reduce eye irritation; early on, it may be necessary to provide eye lubricant. Skin irritation and breakdown can be helped with padding, application of moleskin, and alternating between mask and nasal pillows. Gastric distention may be treated with simethicone, but it usually abates on its own over the first 2 weeks.

In-hospital initiation allows observation for oral leaks. If they occur, they may be corrected with a chin strap. If initiation occurs on an outpatient basis and results are suboptimal, nocturnal family observation or recording oximetry may show ineffective ventilation.

Home care arrangements are crucial. If possible, the home respiratory team should meet with the patient and physician in the hospital so that expectations and instructions are fully understood by both parties. Family instruction is equally important.

Once home ventilation has been initiated, the patient is seen and evaluated after 3 to 4 weeks. With few exceptions, daytime P_{CO_2} will have diminished to less than 50 mm Hg. The mechanisms remain uncertain; reduction of chronic muscle fatigue likely plays a part, but a significant role may be played by resetting central chemoreceptors to new, lower levels of nighttime P_{CO_2} (Annane et al., 1999; Simonds,

Ward, Chatwin, & Heather, 2005; Simonds, Ward, Heather, Bush, & Muntoni, 2000).

Thereafter, the patient is seen regularly at intervals of 3 to 6 months. Early on, increases in daytime P_{CO_2} are often caused by reductions in nocturnal use and will respond to increases. Over several years, it will be necessary to increase the duration of ventilation to achieve the same results. This may be conveniently applied during an afternoon nap. Over the ensuing years, the required duration increases, and often, over a decade or so, continuous ventilation becomes necessary. Many patients can be ventilated comfortably and successfully with nasal ventilation, but as the ability to tolerate ventilator-free time decreases, ventilator failure or mask displacement becomes increasingly hazardous. Nevertheless, some choose to continue NPPV indefinitely. Current portable ventilators can be mounted to or hung from the back of a wheelchair.

The choice of noninvasive ventilation versus tracheostomy is a personal one, made after consideration of the risks and benefit of each approach. In the severely weak patient, disconnection from the noninvasive ventilator interface is a very real and life-threatening risk, and thus, these patients require a caregiver nearby at all times, with monitoring via continuous pulse oximetry in sleep. For those who prefer a nasal interface over a mouthpiece interface (as can be necessary with bulbar muscle weakness), continuous use can lead to skin breakdown. Placement of a tracheostomy will ensure a stable and reliable airway, but with some short-term pain, risks of anesthesia in a patient with possible cardiomyopathy, and risks of tracheitis and bleeding. This choice is ultimately that of the patient and family, and a well-informed pulmonologist should be able to present a balanced approach to help them with this critical decision.

If a decision is reached to choose tracheostomy, elective admission is arranged. In the postoperative period, a cuffed tracheostomy tube is used; the air leak associated with an uncuffed tube may result in subcutaneous emphysema, pneumomediastinum, and pneumothorax. This is continued for 7 to 10 days, until the tissue planes are sealed. During this time, communication may be maintained with an electrolarynx. After healing, the cuffed tube is exchanged for an uncuffed tube. This should be sized to allow adequate exhalation with the tube plugged; this may require endoscopic evaluation. Flexible silicone tracheostomy tubes (such as Bivona® Smiths Medical) are generally preferred to the rigid ones as they are less traumatic to the upper airway and generally better tolerated than rigid tracheostomy tubes.

Although it is possible for a patient to produce speech while ventilated with an uncuffed tube alone, the speech pattern is noncontinuous and occurs only during expiration, a nonintuitive process. The use of a one-way valve in line with the ventilator (Passy-Muir speaking valve; Passy-Muir Inc., Irvine, CA) allows normal speech (Figs. 2.7 and 2.8). As a beneficial side effect, speech is often stronger because greater tidal volumes are delivered. Aspiration is uncommon; severe dysphagia is unusual in the muscular dystrophies, and most patients can continue oral intake after becoming accustomed to the tracheostomy and having a confirmatory swallowing evaluation. Moreover, the positive pressure exhalation helps to clear perilaryngeal secretions. Tracheostomy further impairs the ability to cough in these patients who already have inadequate cough clearance due to weakness, and suctioning is necessary. Family members must be taught proper technique. Adequate nutrition is also important. Those who have been able to eat preoperatively are generally able to continue after a suitable interval and appropriate swallowing evaluation. Those who have been fed by gastric tube because of dyspnea and weight loss may be able to resume or increase oral feedings; given the normal expiratory flow allowed by a one-way valve, aspiration risk is reduced.



Fig. 2.7 Rocking bed.

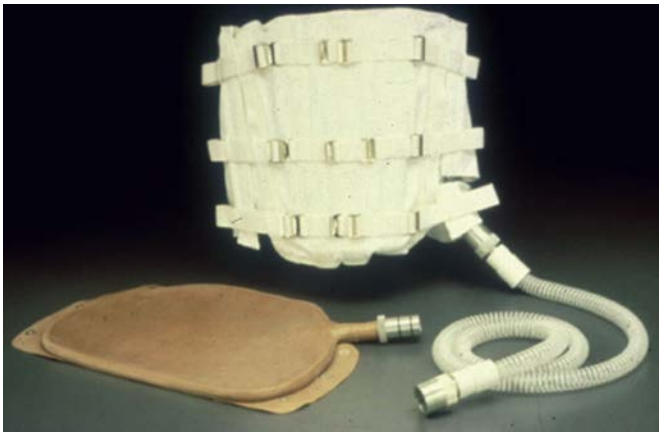


Fig. 2.8 Pneumobelt.

SPINAL CORD INJURY

Spinal cord injury above C4 often is associated with paralyzed diaphragms as well as paralysis of the scalene, intercostal, and abdominal muscles but sternocleidomastoid innervation remains intact. As a result, 40% of those with C3 injury remain ventilator dependent, as do all or nearly all of those with higher lesions. Very high lesions may leave the phrenic nerves intact but nonfunctional, with the potential for electrical stimulation later. Lesions below C5 leave the neck accessories and diaphragms intact, but lower intercostals and abdominals are nonfunctional, thereby impairing cough clearance while preserving ventilation. All patients eventually become ventilator independent, but because of impaired cough and secretion clearance, they may have problems with major atelectasis, most often in the left lower lobe. This may result in short-term respiratory failure.

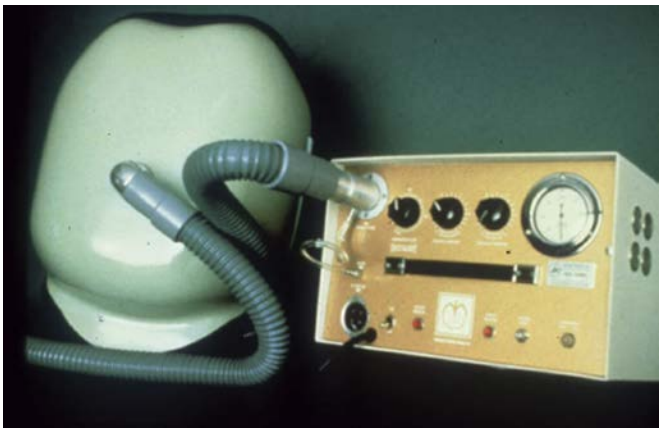


Fig. 2.9 Cuirass ventilator ("turtle shell").

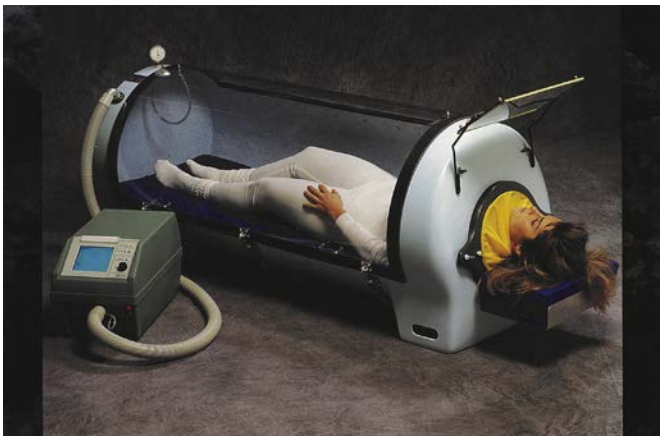


Fig. 2.10 Negative pressure ventilator (Porta-Lung™ Lakewood, CO).

For patients with permanent ventilator dependence, tracheostomy ventilation with ventilator speech, as described earlier, represents the best choice, but not all experts agree (Bach, 2012). For patients with very high lesions and demonstrable phrenic function by nerve conduction studies and diaphragmatic electromyogram, diaphragm pacing may be an option (Dalal & DiMarco, 2014).

Persistent Polio Disability and Post-Polio Syndrome

A relatively small number of patients who had polio in the 1950s with an ongoing need for ventilatory support remain. They may continue to use the noninvasive modalities described earlier, including rocking beds (Fig. 2.9), pneumobelts (Fig. 2.10), negative pressure ventilators (chest cuirass [Fig. 2.11], and tank ventilators [Fig. 2.12]). Others have converted to NPPV or may have an interest in doing so.

An increasing number of patients with recurrent symptoms resembling their original poliomyelitis began to be seen in the 1980s (Lo & Robinson, 2018a, 2018b; Shoseyov, Cohen-Kaufman, Schwartz, & Portnoy, 2017). The latent period appeared to be 20 to 30 years. Gradually progressive weakness was seen in the distribution of the original symptoms; patients requiring ventilatory assistance were generally those who had required mechanical ventilation during the original illness. These patients can be managed in a way similar to those with muscular dystrophy as described earlier. Because the polio epidemics ended with the widespread administration of the Salk polio vaccine more than 50 years ago, it can be assumed that few additional cases will be seen.

MOTOR NEURON DISEASES

Spinal Muscular Atrophy

The outlook for patients with type 1 spinal muscular atrophy (Werdnig-Hoffman) has changed since the approval of nusinersen and risdiplam, both of which are splicing modifiers that increase the levels of a functional SMN protein. While noninvasive ventilation has been used successfully in SMN-1-deficient patients (Al-Zaidy et al., 2019; Bach, 2017; Bach, Niranjan, & Weaver, 2000; Fitzgerald, Doumit, & Abel, 2018; Panitch, 2017), many of these patients whose parents chose an aggressively supportive approach have undergone tracheostomy for long-term home ventilation (Al-Zaidy et al., 2019; Bach, 2017; Bach et al., 2000; Fitzgerald et al., 2018; Panitch, 2017). Gene therapy for type I SMA is showing promising preliminary results and may alter the natural history of this disease in treated patients (Al-Zaidy et al., 2019). Type II spinal muscular atrophy is less severe in phenotype but can lead to eventual respiratory insufficiency from weakness and require ventilatory support. Most commonly, these patients are managed with just nighttime bilevel positive pressure ventilation by mask interface. As with DMD and SMA-1 patients, initiation of supported coughing is critical to maintenance of respiratory health. SMA-2 tends to be a much more slowly progressive disease than DMD, and thus it is not uncommon for respiratory function to plateau for variable periods. Without intervention, scoliosis is common and adds to the respiratory dysfunction. The management approach to SMA-2 is similar to that used for DMD as described earlier.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), a disease of both upper and lower motor neurons, differs from the muscular dystrophies in several important aspects that affect respiratory management. The course of the disease is much more rapid with the average time from onset to death approximately 3 years (Brown & Al-Chalabi, 2017; Polkey et al., 2017; van Es et al., 2017). Although approximately 80% of patients have onset in an extremity and 20% have initial bulbar involvement, all eventually have bulbar incompetence, leading to dysphagia, trouble handling oral secretions, and, eventually, aspiration. In contrast to the muscular dystrophies, all patients eventually lose the power of speech, in addition to having quadriplegia, and ultimately have great difficulty communicating by any mode.

Treating neuromuscular physicians should follow both the FVC and tests of respiratory muscle weakness, including peak inspiratory and expiratory pressures and SNIP. Patients should be referred for pulmonary evaluation when FVC approaches 50% predicted. Performance of the vital capacity is dependent on adequate seal around the mouthpiece and so is susceptible to inaccuracy with bulbar involvement. In that case, sniff nasal inspiratory force may be used to follow the patient (Capozzo et al., 2015). A value of less than 40 cm H_2O has been associated with nocturnal hypoxemia and a median 6-month survival rate of 50% (Morgan et al., 2005). Capillary

blood gases or exhaled CO_2, when available, should also be obtained when it is not possible to follow vital capacity, when there is dyspnea or orthopnea, or when there is hypoxemia on pulse oximetry. Any saturation of 95% or less should prompt an assessment for CO_2 retention.

The American Academy of Neurology consensus guidelines recommend consideration of noninvasive ventilation when one of the following is present: FVC less than 50%, orthopnea, sniff nasal pressure less than −40 cm, or maximal inspiratory pressure (MIP) less than −60 cm (Miller et al., 2009). This recommendation is based on a single randomized controlled trial comparing noninvasive ventilation to standard care in a total of 41 patients with orthopnea and MIP less than 60% predicted or symptomatic daytime hypercapnia (Bourke et al., 2006). The study design and results do not permit extrapolation to asymptomatic individuals or to those earlier in the disease course. Survival and quality of life were improved in patients without severe bulbar dysfunction. Other nonrandomized studies have shown improved survival and quality of life in those without bulbar involvement who could tolerate NPPV (Aboussouan, Khan, Meeker, Stelmach, & Mitsumoto, 1997; Bourke et al., 2006; Burkhardt, Neuwirth, Sommacal, Andersen, & Weber, 2017; Farrero et al., 2005).

The option of withdrawal of support under patient control and with comfort measures should be made explicit; that is, patients clearly understand that, having decided on tracheostomy ventilation, their rescinding that decision will not be met by opposition or legal action on the part of the treating physician (Moss et al., 1996; Phelps, Regen, Oliver, McDermott, & Faull, 2017). Quality of life appears to be improved for patients who are offered NPPV after respiratory symptoms develop (Lyall et al., 2001). The quality of life of caregivers for patients using NPPV does not appear to be negatively affected, in contrast to tracheostomy ventilation (Mustfa et al., 2006). Patients undergoing tracheostomy ventilation may be satisfied with that mode, although experience is more mixed (Cazzolli & Oppenheimer, 1996). Those choosing NPPV undergo initiation in the hospital or sleep laboratory in much the same way as those with muscular dystrophy. Hypoxemia in this patient population is generally caused by hypercapnia from hypoventilation. It is important that home and professional caregivers understand that they must not give patients oxygen without direct physician involvement because it may result in worsened CO_2 retention from diminished hypoxic drive, despite use of mask ventilation (Gay & Edmonds, 1995). For those patients with ALS and significant bulbar involvement, noninvasive ventilation tends to be unsuccessful and thus is relatively contraindicated. Those without bulbar involvement can often be supported successfully in a noninvasive manner, sometimes for up to several years. These are the exceptions, and the usual course is more rapid deterioration. Dysphagia and aspiration predispose patients to lower respiratory tract infection, which may result in acute respiratory failure. Patients should understand that this is likely to be the case.

Tracheostomy ventilation is initiated, for those desiring it, in a way similar to that described for muscular dystrophy. Because most have bulbar dysfunction, risk of aspiration, and loss of speech, ventilation with a cuffed tracheostomy tube is usually appropriate. The cuff should be inflated using minimal leak technique, and cuff pressure should be measured. Ideally, cuff pressure should be 15 to 20 mm Hg and always less than 25 mm Hg. Monitoring by caregivers at home may help to reduce the incidence of airway complications. Tracheostomy tubes may be changed on an as-needed basis, when the balloon fails. It is not necessary to change the tube on a scheduled basis because balloon failure does not generally result in significant difficulty ventilating patients with normal compliance for short periods. The caregiver should be taught to change the tracheostomy tube, but it may also be changed in the clinic or emergency room. A spare inner cannula should be kept on hand and cleaned as described earlier.

Two recent randomized controlled trials have shown excess mortality in patients with ALS who underwent laparoscopic placement diaphragmatic pacemakers and who also had noninvasive ventilation compared to a control group treated with noninvasive ventilation alone (Gonzalez-Bermejo et al., 2016; McDermott et al., 2015). The investigators concluded that diaphragmatic pacing should not be used routinely in this patient population. Impaired myofiber reinnervation appears to be the mechanism in which pacing leads to harm in this population (Guimaraes-Costa et al., 2019).

Adjuncts that may increase comfort and forestall complications are available. Control of sialorrhea may reduce microaspiration. A variety of anticholinergic agents may be used. Salivary gland injections of botulinum toxin have been used successfully to control sialorrhea and aspiration (Banfi et al., 2015; Vazquez-Costa et al., 2016; Verma & Steele, 2006). Portable suction is also useful. Gastric tube placement allows nutrition without aspiration on swallowing (although reflux aspiration may still occur).

For those desiring only symptomatic care, comfort is usually achievable. Home nursing services or home hospice care can assist the patient's family. Early involvement with a palliative care specialist is helpful in anticipating and managing late-stage complications and can guide end-of-life care (Connolly, Galvin, & Hardiman, 2015).

MANAGEMENT OF NEUROMUSCULAR DISEASES RESULTING IN ACUTE HYPERCARBIC RESPIRATORY FAILURE

Acute respiratory failure can be due to a primary failure in oxygenation from acute parenchymal lung disease, such as in severe pneumonia, but in patients with neuromuscular disease, the respiratory failure is due to loss of respiratory muscle function (ventilatory failure with CO_2 retention). Acute respiratory failure in the neuromuscular patient generally falls into one of two categories. First are the patients with an acute illness, such as Guillain-Barré syndrome, which results in respiratory failure as part of its natural history, and which, with appropriate care, is reversible, with return to normal respiratory function. Second is "acute-on-chronic" respiratory failure in patients with chronic neuromuscular disease with respiratory involvement, such as can happen in influenza infection in a patient with DMD with borderline respiratory muscle function.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is the most common neuropathy leading to new-onset acute respiratory failure. The typical

case is marked by paresthesias, ascending paralysis, and loss of deep tendon reflexes. Between 15% and 30% of patients ultimately require mechanical ventilation. Poor prognostic factors include rapid progression, bulbar dysfunction, bilateral facial weakness, and autonomic dysfunction (Goodfellow & Willison, 2016; Willison, Jacobs, & van Doorn, 2016; Yuki & Hartung, 2012). Patients with these characteristics should be admitted to an intensive care unit, with frequent neurologic and respiratory monitoring. Vital capacity should be measured with a bedside spirometer, and maximum inspiratory pressures should be monitored.

Factors associated with the development of respiratory failure and portending the need for mechanical ventilation include vital capacity of less than 20 mL/kg, maximal inspiratory pressure of less than 30 cm H_2O, maximal expiratory pressure of less than 40 cm H_2O, or a reduction of more than 30% in vital capacity, maximal inspiratory pressure, and maximal expiratory pressure (Lawn, Fletcher, Henderson, Wolter, & Wijdicks, 2001). Other factors that predict the need for mechanical ventilation include severely impaired cough and inability to clear secretions and weakness so profound that the patient cannot raise the arms or head (Sharshar, Chevret, Bourdain, Raphael, & French Cooperative on Plasma Exchange in Guillain-Barré Syndrome, 2003). Oximetry and blood gases (including end-tidal CO_2) should be monitored.

When the course strongly predicts the need for mechanical ventilation, endotracheal intubation should be performed before the patient is in crisis (Lizarraga, Lizarraga, & Benatar, 2016). The procedure can be done electively and in a controlled fashion. Orotracheal intubation is preferred to nasotracheal intubation because it allows a larger tube size and avoidance of nosocomial sinusitis. NPPV is not often successful because the need for ventilation is frequently for 2 weeks or longer and because of bulbar dysfunction, secretions, and autonomic instability.

Care from that point is supportive. The duration of need for mechanical ventilation may be shortened by plasmapheresis or intravenous immunoglobulin.

Resolution of need for mechanical ventilation is the norm, although prolonged ventilation may be required. If mechanical ventilation exceeds 10 to 14 days, particularly if there is little progress, tracheostomy will improve the patient's comfort and nursing care (Walgaard et al., 2017).

MYASTHENIA GRAVIS

Myasthenia gravis does not ordinarily require long-term respiratory support and is generally managed with noninvasive ventilatory support (Gilhus, 2016; Rabinstein, 2016). However, abrupt deterioration (myasthenic crisis) may precipitate respiratory failure. This may be caused by infection, a surgical procedure (a number of anesthetic agents and neuromuscular blockers may exacerbate myasthenia gravis), magnesium infusion, or reduction of immunosuppressive therapy (Dillon, 2004; Singh, Idowu, Malik, & Nates, 2015). It may also occur after administration of any of a large number of drugs that may interfere with neuromuscular transmission. The best known are the aminoglycoside antibiotics; however, a large number of other antibiotics, beta-adrenergic blockers, anticonvulsants, and antipsychotics may also cause deterioration. The medication list of the deteriorating patient should be reviewed carefully and compared with one of the widely available contraindicated drug lists. In earlier times, cholinergic crisis as a result of anticholinesterase therapy was a serious part of the differential diagnosis. The increasing role of immunosuppression and avoidance of high-dose anticholinesterase administration have made this much less common. As a result, edrophonium administration (Tensilon test) for differentiation is no longer used routinely.

Patients with progressive and significant weakness should be admitted to an intensive care unit. Vital capacity and maximum inspiratory pressure (also known as negative inspiratory force) should be measured frequently (Rabinstein & Wijdicks, 2003).

The goal is to avoid uncontrolled emergency intubation as well as to anticipate the need in a way that allows a controlled, elective procedure. Orotracheal intubation should be considered if the vital capacity falls to 15 to 20 mL/kg, maximum inspiratory pressure is less than 25 to 30 cm H_2O, the patient has bulbar dysfunction interfering with secretion and airway control, or the patient is in significant respiratory distress. Oximetry and blood gases should be monitored (Juel, 2004).

In general, noninvasive ventilation is not appropriate because of bulbar involvement. Once mechanical ventilation is required, anticholinesterase medication is discontinued and therapy with either plasmapheresis or intravenous immunoglobulin is begun, depending on local capabilities and preference. After this therapy, anticholinesterase medication may be resumed and high-dose steroids may be initiated or resumed. Liberation from mechanical ventilation follows standard ventilatory parameters and weaning protocols.

MISCELLANEOUS CONDITIONS

A wide variety of medical conditions may rarely precipitate acute hypercarbic respiratory failure through involvement of the neurologic system in various ways, including botulism, acute attack porphyrias, Eaton-Lambert syndrome, anticholinesterase intoxication, severe phosphate deficiency, and periodic paralysis. Respiratory care is supportive and similar to that described earlier. The principal challenges are making the diagnosis and instituting appropriate specific therapies.

ACUTE EXACERBATIONS OF CHRONIC NEUROMUSCULAR RESPIRATORY FAILURE

The first recognition of respiratory involvement in a patient with a neuromuscular disease is sometimes occasioned by acute respiratory failure. This is almost invariably precipitated by a respiratory infection. It need not be pneumonia; bronchitis or lower respiratory tract viral infection will suffice. Airway edema and mucus accumulation from respiratory viral infection may result in substantial increases in respiratory work as a result. In neuromuscular disease, the additional work of breathing may be unsupportable, and acute respiratory failure may occur rapidly.

Unexplained acute respiratory failure may reveal a previously unrecognized diagnosis of ALS (Tateno et al., 2014; Srivali, Ryu, & Rabatin, 2016). In patients with DMD, the

diagnosis may be known, but the respiratory involvement may have been unevaluated. In these cases, the patient often presents in respiratory crisis, and endotracheal intubation and mechanical ventilation vs. initiation of noninvasive ventilation will ensue.

The patient who is fortunate enough to present more subacutely is monitored in a way similar to that described earlier, after spirometry, static inspiratory pressures, oximetry, and arterial blood gases are measured, with a decision to intubate and initiate mechanical ventilation based on similar parameters. Noninvasive ventilation should be the first approach when the patient does not have significant bulbar involvement, aspiration, or altered consciousness (Vianello, Bevilacqua, Arcaro, Gallan, & Serra, 2000).

Mechanical ventilatory support is generally necessary until the infection subsides. With the first episode, the patient may wean from ventilation successfully after standard protocols. If that is not possible, extubation to noninvasive ventilatory support may be attempted. This should be undertaken when all variables are favorable: the patient's general status and strength are improved, infection is under control, secretions are minimal, and the patient is fully alert. Airway clearance must be in place (usually, MI-E) in order for extubation to be successful. If the patient does not tolerate noninvasive ventilation, a decision about long-term ventilatory support via tracheostomy must be made. This does not preclude subsequent attempts to convert to noninvasive ventilation, which may be successful (Singh, Saran, & Baronia, 2017).

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3 Cardiac Complications of Neuromuscular Disorders

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Cardiac disease has a significant association with neuromuscular diseases (Table 3.1). In all cases, early recognition of the neuromuscular diagnosis can improve timely recognition of forthcoming cardiac disease. The extent and severity of cardiac disease can vary significantly within and between specific neuromuscular disorders. In some cases, cardiac disease is the presenting symptom, long before skeletal muscle symptoms develop. In other cases, where skeletal muscle weakness occurs first, the signs and symptoms of cardiac failure can be masked by limitations in the patient's mobility and may not become apparent until cardiac failure is severe. Quality of life and longevity in some patients with muscular dystrophy are more dependent on disease of the cardiovascular system than on disease of the musculoskeletal system. Over the past 50 years, a more complete understanding of cardiac involvement in these patients has evolved. However, the specific etiologies and mechanisms of cardiac damage remain unclear. Although more data continue to emerge and improve the understanding of cardiac disease in these patients, there are still significant gaps in the etiology and best treatment practices. This chapter discusses the neuromuscular disorders most associated with cardiac disease and the current understanding of the proper diagnosis and treatment of these disorders.

DUCHENNE MUSCULAR DYSTROPHY

Cardiac involvement in Duchenne muscular dystrophy (DMD) occurs in all patients to varying degrees. Cardiac pathogenesis is similar to skeletal muscle where lack of dystrophin makes the myocyte plasma membrane susceptible to injury. Damage to the membrane leads to unregulated, calcium influxes into the cell causing inflammation, cell death, and fibrosis (Kamdar & Garry, 2016). Further, loss of dystrophin affects the L-type calcium channels and mechanical stretch-activated receptors in myocytes, further exacerbating the influx of calcium (Spurney, 2011; Spurney & Siegel, 2017). The increased intracellular calcium leads to activation of proteases that begin a pathologic process of cell injury and death.

In a large study of 328 patients with DMD by Nigro, Comi, Politano, and Bain (1990), cardiac involvement was found in 26% of patients younger than 6 years old, 62% of patients 6 to 10 years old, 81% of patients 10 to 14 years old, 95% of patients 14 to 18 years old, and 100% of patients older than 18 years. Cardiac symptoms are unrelated to the severity of skeletal muscle disease, and one study showed that patients with stronger skeletal muscles were even more likely to die of cardiac disease than those with weaker muscles (Brooke et al., 1989). In a retrospective case-matched control study of 340 patients with DMD aged 2–28 years, 27% had cardiomyopathy among all age groups and mean age of onset of 16 years. The prevalence of cardiomyopathy correlated with increasing age, with 5% of 0–5 years old, 38% of 14–17 years old, and 61% of males >18 years old (Spurney et al., 2014). A more recent review of 408 males studied over a 10-year period until 2015 found 7% all-cause mortality. Thirty percent of those deaths were due to progressive heart failure or sudden cardiac death. Risk factors for death from any cause included young age at loss of ambulation, absence of glucocorticoid therapy, left ventricular (LV) dysfunction, and higher brain natriuretic peptide (BNP) levels. Lack of glucocorticoids was associated with cardiac cause of death (Wittlieb-Weber et al., 2020).

Despite frequent myocardial involvement, most patients are free of cardiovascular symptoms. Diagnosis of cardiac dysfunction is often difficult because patients are less active and do not have early clinical symptoms (i.e., exercise intolerance) (Gilroy, Cahalan, Berman, & Newman, 1963). As treatment of the skeletal and respiratory muscle systems improves, more patients with DMD are developing symptomatic heart disease. Approximately 72% of patients younger than 18 years were asymptomatic, but only 57% of patients older than 18 years old were symptomatic, even though all patients at this age were affected (Nigro et al., 1990). Gulati et al. studied 30 patients older than 6 years, and only 10% had symptoms or signs suggestive of heart failure. However, one third had cardiomegaly, 93% had electrocardiographic (ECG) abnormalities, and left ventricular ejection fraction (LVEF) was less than 55% in 64% of patients and less than 50% in 18% of patients (normal range is 55%–65%) (Gulati, Saxena, Kumar, & Kalra, 2005). Other studies found that only 15% to 22% of patients with DMD and cardiac disease reported symptoms (D'Orsogna, O'Shea, & Miller, 1988; Kirchmann, Kececioglu, Korinthenberg, & Dittrich, 2005).

Recognition of cardiomyopathy in DMD requires active cardiac evaluation since signs and symptoms of cardiac dysfunction may be vague and nonspecific. Symptoms can include fatigue, weight loss, vomiting, sleep disturbance, inability to tolerate the daily regimen, and orthopnea. It is generally recommended that patients be referred to cardiology at diagnosis as asymptomatic children can have abnormal ejection fraction (EF) (Feingold et al., 2017; Hunt et al., 2005). Duboc et al. found that 20% of asymptomatic

Table 3.1 Summary of Cardiac Diseases Related to Specific Neuromuscular Disorders

Diagnosis	Age of Onset of Cardiac Disease	Cardiac Symptoms	Electrocardiographic Findings	Echo-cardiographic Findings	Prognosis
DMD	Preclinical disease presents at 6–8 years Clinical disease presents at 10–18 years	Asymptomatic CHF with severe DCM	*Common:* Tall R waves in V1, V2, Q waves, BBB Arrhythmias more common with DCM progression	*Common:* DCM	Death of cardiac or respiratory complications at 20–30 years
BMD	Preclinical disease presents at 10–20 years Clinical disease rare in children, progresses with age, prevalent after 40 years	Asymptomatic CHF with severe DCM	*Common:* Tall R waves, Q waves, BBB Arrhythmias more common with DCM progression	*Common:* DCM	Heart failure in the 40s Poor prognosis once heart failure is present Heart transplant eval
DMD/BMD carrier	Preclinical disease presents at 10–20 years Clinical disease presents at 30–50 years	Asymptomatic CHF with severe DCM	*Common:* Tall R waves	*Rare:* DCM can develop in 30s	Can have normal life expectancy Heart transplant eval in severe cases
XL-DCM	Clinical disease presents at 20–50 years	Asymptomatic CHF with severe DCM	*Common:* Q waves, ST/T wave changes	*Common:* DCM	Poor survival after symptomatic Heart transplant eval
LGMD (types 1B, 2C, 2D, 2E, 2F, 2I)	Clinical disease varies with diagnosis	Asymptomatic CHF with severe DCM	*Common:* Types 1B, 2E Progressive 1°, 2°, 3° AVB Tall R waves, Q waves	*Common:* DCM *Rare*: Type 2F	Variable, depending on diagnosis Heart transplant eval
Myotonic dystrophy	Clinical disease presents in adulthood	Asymptomatic Syncope Sudden death	*Common:* Type 1 1°, 2°, 3° AVB Afib/Aflutter, VT/VF	*Rare*	Progressive cardiac involvement, death in 50s Sudden death
EDMD	Arrhythmias in 30–40 years; can be earlier in XL-EDMD	Presyncope/syncope CHF (mostly AD-EDMD)	*Common:* Sinus bradycardia 1°, 2°, 3° AVB Afib/Aflutter, atrial standstill, VT/VF	*Rare:* Risk for atrial thrombus due to arrhythmia	Pacemaker placement at 30–40 years Heart transplant eval Sudden death
FSHMD	Arrhythmias in adulthood	Presyncope/syncope	*Common:* In adulthood 1°, 2°, 3° AVB SVT/VT	*Rare*	Minimal cardiac involvement
Friedreich ataxia	Uncommon in children; increases with age	Asymptomatic	*Common:* LVH with repolarization abnormalities, arrhythmias	*Common:* HCM ± LVOTO	Death occurs 30–40 years
Barth syndrome	Clinical symptoms present at 3–6 months	CHF	*Occasional:* LVH with strain LAD Prolonged QTc Arrhythmias	*Common:* DCM HCM LV noncompaction	Improvement with cardiac medications Heart transplant eval
Pompe disease	Clinical symptoms have infantile onset	CHF	*Common:* Marked LVH Short PR interval	*Common:* HCM	Death can occur by 1 year without treatment

Continued

Table 3.1 Summary of Cardiac Diseases Related to Specific Neuromuscular Disorders—cont'd

Diagnosis	Age of Onset of Cardiac Disease	Cardiac Symptoms	Electrocardiographic Findings	Echo-cardiographic Findings	Prognosis
Mitochondrial disorders	Variable onset, depending on diagnosis	CHF syncope	*Variable:* ST/T wave abnormalities 1°, 2°, 3° AVB Arrhythmias	*Variable:* DCM HCM	Variable, depending on diagnosis
Congenital myopathies	Variable onset, depending on diagnosis	Asymptomatic CHF with severe DCM	*Common:* Tall R wave Q waves	*Occasional:* DCM	Usually more dependent on skeletal and respiratory function Heart transplant eval

AD-EDMD, Autosomal dominant Emery-Dreifuss muscular dystrophy; *Afib*, atrial fibrillation; *Aflutter*, atrial flutter; *AVB*, atrioventricular block; *BBB*, bundle branch block; *BMD*, Becker muscular dystrophy; *CHF*, congestive heart failure; *DCM*, dilated cardiomyopathy; *DMD*, Duchenne muscular dystrophy; *EDMD*, Emery-Dreifuss muscular dystrophy; *eval*, evaluation; *FSHMD*, facioscapulohumeral muscular dystrophy; *HCM*, hypertrophic cardiomyopathy; *LAD*, left axis deviation; *LGMD*, limb-girdle muscular dystrophy; *LV*, left ventricular; *LVH*, left ventricular hypertrophy; *LVOTO*, left ventricular outflow tract obstruction; *SVT*, supraventricular tachycardia; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *XL-DCM*, X-linked dilated cardiomyopathy; *XL-EDMD*, X-linked Emery-Dreifuss muscular dystrophy.

children at age 10 years had abnormal EFs, further supporting early referral (Duboc et al., 2005).

BECKER MUSCULAR DYSTROPHY

In comparison to DMD, cardiac involvement in Becker muscular dystrophy (BMD) is frequently out of proportion to the skeletal muscle involvement and can be the main clinical problem (Kirchmann et al., 2005). Cardiomyopathy is rare before 16 years of age, but it increases progressively with age, eventually affecting more than 70% of patients older than 40 years (Nigro et al., 1995). There is significant variability, both within and between families, in the onset, severity, and progression of cardiac disease, as is true for skeletal muscle involvement (Hoogerwaard et al., 1997). One concern about the increased incidence of cardiac disease is the increased long-term workload on the heart because of slower progression of skeletal muscle weakness compared with DMD (Saito et al., 1996). However, this may mostly be a reflection of the heterogeneity of disease progression seen in both BMD and DMD patients.

Dilated cardiomyopathy (DCM) can sometimes be the main pathologic finding in BMD. Despite the high proportion of DCM in BMD, only one third of patients are symptomatic. Patients with BMD and severe DCM can undergo cardiac transplantation with good results (Connuck et al., 2008). Hoogerwaard et al. studied 27 patients with a mean age of 37.5 years and a mean follow-up of 12.5 years. Only 5 of 27 patients (19%) had completely normal heart evaluations. ECG abnormalities increased from 44% to 71%, and 63% of the patients showed progression of cardiac abnormalities. The presence of DCM increased from 15% to 33% over the 12 years. Five of the patients died during the follow-up period, and four of these deaths were the result of congestive heart failure. Three of these patients were able to walk at the time of death. The mean age of death in these four patients was 42 years (Hoogerwaard et al., 1997).

Melacini et al. studied 28 patients with BMD ranging in age from 6 to 48 years with subclinical or benign skeletal muscle disease. Nineteen of these patients showed myocardial involvement, but only two were symptomatic (Melacini et al., 1996). Nigro et al. reviewed the clinical history of 68 patients and found preclinical cardiac involvement in 67% of patients younger than 16 years of age. Clinically evident cardiomyopathy was found in 15% of patients younger than 16 years, increasing to 73% in patients older than 40 years (Nigro et al., 1995). These studies show a high incidence of myocardial involvement among patients with mild or subclinical skeletal muscle symptoms that progresses with time.

CARRIERS OF DUCHENNE MUSCULAR DYSTROPHY AND BECKER MUSCULAR DYSTROPHY

A percentage of female carriers of DMD and BMD can develop DCM that can progress to heart failure and even lead to heart transplantation (Hoogerwaard et al., 1999; Melacini et al., 1996). Politano et al. found preclinical or clinical evidence of myocardial involvement in 84% of DMD (n = 152) and BMD (n = 45) carriers. This increased with age, and 90% of carriers older than 16 years were affected. There were no statistically significant differences between DMD and BMD carriers. Only 11% of carriers were reported as having DCM, yet clinical symptoms were not reported (Politano et al., 1996). Hoogerwaard et al. (1999) studied 129 DMD and BMD carriers. ECG abnormalities were found in 47%, but DCM was found in seven DMD carriers (8%) and no BMD carriers. This agreed with the study of Grain et al. (2001) that found a 7% incidence of DCM in carriers. In a study of 20 carriers of DMD, evidence of cardiac fibrosis was detected in nine cases, which correlated with lower LVEF

using cardiac magnetic resonance imaging (CMRI), higher creatine kinase (CK) levels, and shorter distances in 6-minute walk tests. Further, their pro-B-type natriuretic protein (BNP) levels were also elevated (Wexberg et al., 2016). In these patients, DCM often occurs without any skeletal muscle symptoms.

X-LINKED DILATED CARDIOMYOPATHY

X-linked DCM (XL-DCM) is a rare cardiomyopathy associated with increased serum CK levels, but an absence of significant skeletal muscle weakness. Berko and Swift first described a group of affected males and their mothers. The patients presented with DCM at 15 to 21 years and survived only 5 to 12 months after diagnosis. The mothers presented in their 40s with atypical chest pain and slowly progressing heart failure (Berko & Swift, 1987). Towbin et al. (2018) found mutations in the dystrophin gene of patients with XL-DCM who had normal dystrophin levels in skeletal muscle. These patients can have mild myopathic changes on skeletal muscle biopsy but have complete loss of dystrophin in cardiac muscle (Muntoni et al., 1993, 1999). Based on reviews, prevalence ranges from 3% to 7% in male patients with nonpaternally inherited XL-DCM who had no symptoms of muscular dystrophy (Arbustini, Morbini, Pilotto, Gavazzi, & Tavazzi, 2000; Nakamura, 2015).

LIMB-GIRDLE MUSCULAR DYSTROPHY

Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of diseases with variable cardiac involvement. Cardiac presentation can be similar to that of DMD because of the loss of dystrophin-associated glycoproteins that stabilize the dystrophin complex. Autosomal dominant (AD) LGMD 1 includes LGMD1 A–H and autosomal recessive LGMD 2 includes LGMD2 A–Y. AD forms include the genes for myotilin, lamin A/C, caveolin-3, Hsp40, desmin, transportin, and heterogeneous nuclear ribonucleoprotein D-like protein. Autosomal recessive forms include sarcoglycans, telethonin, fukutin related protein, titin, fukutin, and lamin alpha 2. LGMD1B (laminopathy) is associated with DCM, conduction defects, and high risk of sudden death (Chrestian et al., 2008; van Rijsingen et al., 2012). Politano et al. studied patients with sarcoglycanopathies, and 11 of 20 patients had evidence of cardiac involvement. Patients with gamma and delta sarcoglycan deficiency had DCM, and patients with alpha and beta deficiency had preclinical involvement (Politano et al., 2001). Melacini et al. studied patients with alpha, beta, and gamma sarcoglycan deficiency, and mild cardiac abnormalities were seen in 30% of patients who had severe skeletal muscle dystrophy. Four of 13 patients showed ECG abnormalities and two showed wall motion abnormalities on echocardiography. Patients were asymptomatic, and only one had a decreased LVEF of 43%. No correlation was found between the presence of cardiac abnormalities and the type of mutation or sarcoglycan gene involved (Melacini et al., 1999). Barresi et al. described two patients with beta sarcoglycan deficiency who had severe cardiomyopathy. One died at 18 years and the other died at 26 years of age (Barresi et al., 2000). Calvo et al. showed 10 patients with LGMD 2C who had ECG and echocardiographic abnormalities, especially of the right ventricle. Only one patient had decreased LV function (Calvo et al., 2000).

LGMD 1B (lamin A/C) is an AD disease associated with conduction defects. Chrestian et al. (2008) described a large French-Canadian family in which three of seven carriers of the gene had atrioventricular (AV) conduction blocks. Ben Yaou et al. described 13 patients with LGMD 1B who had conduction defects and arrhythmias. Seven of these patients needed a pacemaker or an implantable cardioverter defibrillator (ICD), and two underwent heart transplantation (Ben Yaou et al., 2005). van der Kooi et al. studied 26 patients with LGMD 1B and 12 showed ECG abnormalities, including six cases of AV conduction block, four requiring pacemakers. Six patients also showed echocardiographic abnormalities including DCM (van der Kooi et al., 1998). Finally, van Rijsingen et al. studied a European cohort of 269 LMNA (lamin A/C) mutation carriers. A total of 48 people developed a malignant ventricular arrhythmia, of whom 11 received successful CPR and 12 died suddenly. Independent risk factors were nonsustained ventricular tachycardia (VT), LVEF <45% at first clinical contact, male sex, and non-missense mutations (van Rijsingen et al., 2012).

LGMD type 2I is related to defects in fukutin-related protein and is significantly associated with cardiac disease. Wahbi et al. studied 23 patients with an average age of 32 years and found that 60% had decreased LVEF, 8% of which were severely decreased. None of the patients had significant arrhythmias, and no sudden death was recorded (Wahbi et al., 2008). Poppe et al. studied 38 patients with LGMD 2I who were 10 to 61 years old. Overall, 55% of patients had cardiac involvement, which was defined as decreased shortening fraction, LV wall motion abnormalities, or ECG abnormalities. There was a tendency for cardiomyopathy to develop in patients with more severe skeletal muscle phenotypes, but 88% of patients with cardiac disease could still ambulate. Of 19 patients with a known clinical course, eight had symptomatic cardiac failure at 18 to 67 years of age (Poppe et al., 2004). An earlier study by the same group described 16 patients who were 11 to 53 years old. They found symptomatic cardiac failure in three patients at ages 28, 39, and 51 years and asymptomatic LV systolic dysfunction in three patients at 38, 57, and 58 years (Poppe et al., 2003). The possibility of severe cardiac disease was shown by D'Amico et al., who described the case of an 8-year-old boy who presented with LGMD 2I and severe cardiomyopathy. He required heart transplantation, with no clinical skeletal muscle weakness (D'Amico et al., 2008). Murakami et al. identified six patients in four families with fukutin gene mutations who had DCM with no significant skeletal muscle involvement. One patient died of congestive heart failure at 12 years and one patient received a heart transplant at 18 years. The other patients had cardiomyopathy at 17, 27, 30, and 46 years (Murakami et al., 2006).

These studies show that cardiac disease is significantly involved in some forms of LGMD, and a specific muscle diagnosis is required to best anticipate cardiac complications.

MYOTONIC DYSTROPHY

Myotonic dystrophy (DM) is an AD disorder that presents in adulthood with myotonia and weakness of the skeletal

muscles. There are two major subtypes: DM type I is caused by increased CTG repeats and DM type II is caused by increased CCTG repeats. The severity of cardiac disease in these patients is unrelated to the severity of skeletal muscle disease, but cardiac disease is causative in 30% of deaths in DM (Groh, 2012; Groh et al., 2008; Mathieu, Allard, Potvin, Prévost, & Bégin, 1999). Fibrosis along the conduction system leading to myocyte hypertrophy and fatty infiltration makes arrhythmia the most common complication (Finsterer, Stöllberger, & Keller, 2012; Petri, Vissing, Witting, Bundgaard, & Køber, 2012; Phillips & Harper, 1997).

Baseline ECGs frequently have QRS and PR prolongation with time. Groh et al. studied 406 patients with confirmed DM type I with abnormal CTG repeat sequences. Ninety-six of these patients had evidence of non-sinus rhythm, prolonged QRS duration (>120 milliseconds), or heart block. These patients were older, had more CTG repeats, and had more severe muscular disease. Twenty-nine of the patients with ECG abnormalities had atrial tachyarrhythmias, but only four had ventricular tachyarrhythmias, and of the patients with initially normal ECG findings (n = 310), 69 patients developed severe abnormalities. During follow-up, 81 (20%) of the 406 patients died: 27 (33%) died suddenly, 32 (40%) died of respiratory failure, and 5 (6%) died of other cardiac causes. Analysis shows that rhythm other than sinus, PR >240 milliseconds, QRS >120 milliseconds, or second- or third-degree heart block all increased the risk of sudden death (Groh et al., 2008). Ventricular tachyarrhythmias were commonly observed in patients who died suddenly. The presence of a severe ECG abnormality had a sensitivity of 74% for predicting sudden death (Mathieu et al., 1999; Phillips & Harper, 1997). Lund and colleagues reviewed 1146 patients, 485 of whom had positive genetic testing for DM type 1. The standard incidence rate for any cardiac disease was 3.41 and as high as 6.91 for cardiomyopathy, heart failure, arrhythmia, and device implantation. Any cardiac disease was present in 80% of DM patients and risk of disease increased with age (Lund et al., 2014). Petri et al. retrospectively reviewed 1828 cases of DM type I and found first-degree AV block in 28%, QTc prolongation (>440 milliseconds) in 22%, and QRS prolongation in 20%. LV dysfunction was reported in only 7% of cases (Petri et al., 2012).

In DM type II, patients can have DCM and arrhythmias. Schoser et al. described four patients with DM type II who had sudden death. Three of the patients were asymptomatic, and one had symptoms of heart failure. All of the patients had DCM, and fibrosis of the conduction system was found in two of them (Schoser et al., 2004). A case-control series of 38 DM type 2 patients showed that there were 15 patients with cardiac abnormalities, including 14 with conduction defects, six with systolic dysfunction, six with arrhythmias, and five patients with strokes. When compared to DM type 1 patients, there were fewer conduction defects, similar rates of arrhythmia, but more LV systolic dysfunction (Wahbi et al., 2009). DCM is rare, but described as well (Lee et al., 2012). In a series of 80 patients with DM and symptoms of dyspnea or exertional fatigue, 44% had functional or structural abnormalities. Abnormalities were more common in older men. LV systolic dysfunction was the most common finding, and LV dilatation, hypertrophy, and fibrosis were also commonly seen (Hermans et al., 2010).

EMERY-DREIFUSS MUSCULAR DYSTROPHY

Emery-Dreifuss muscular dystrophy (EDMD) is related to loss of the nuclear membrane proteins from XL (*STA*, *EMD*, and *FHL1*) or autosomal recessive (*LMNA*) or AD loss of lamin A/C (*LMNA, SYNE1, SYNE2*, and *TMEM43*) mutations (Arbustini et al., 2018). Almost half of patients with EDMD carry mutations in emerin, lamin A/C, nesprin1, and nesprin2. In XL-EDMD, muscle disease is milder and progresses more slowly than in AD-EDMD. In many patients, the severity of skeletal muscle disease is not significant, and the initial presentation is secondary to cardiac disease. Cardiac disease tends to start as sinus bradycardia and first-degree heart block and can evolve into third-degree (complete) heart block and atrial arrhythmias that lead to atrial paralysis. LV dysfunction can occur after the development of arrhythmias. The long-term prognosis of these patients depends significantly on the severity of cardiac involvement.

Boriani et al. studied 18 patients with EDMD as a result of both emerin and lamin deficiencies. Arrhythmias were found in 15 patients, including all of the patients with emerin deficiency. Only one patient had significant heart failure and presented with atrial flutter and AV block necessitating a pacemaker. This patient did not improve and eventually required heart transplantation. One patient had right-sided heart failure as a result of AV block that resolved with pacemaker implantation, and three other patients had mild to moderate LV dysfunction with limited or no impairment in daily activities (Boriani et al., 2003). It is generally thought that AV conduction defects and arrhythmias precede LV systolic dysfunction and pacemakers may prevent progression (Finsterer, Stöllberger, Sehnal, Rehder, & Laccone, 2015; Stoyanov, Winterfield, Varma, & Gollob, 2014).

Buckley et al. described three patients with XL-EDMD. The first presented at 19 years with atrial tachycardia and variable AV conduction. At 24 years of age, he was noted to have atrial standstill and junctional bradycardia of 37 beats per minute. A pacemaker was implanted at 29 years because of periods of atrial tachycardia and atrial arrest with junctional escape beats. The patient was then free of cardiac symptoms. His nephew was found to have junctional bradycardia at 17 years. No tachyarrhythmias were noted, and a pacemaker was implanted. He developed atrial fibrillation at 22 years, with a history of brief episodes of visual disturbances. Anticoagulants were administered and continued with intermittent atrial fibrillation. This patient's brother had junctional bradycardia at 15 years and had a pacemaker implanted. He remained asymptomatic after the pacemaker was placed (Buckley, Dean, & Mahy, 1999). An additional case report of a patient with an *FHL1* mutation with a hypertrophic cardiomyopathy phenotype is noted. The patient had LV hypertrophy (LVH) on ECG and asymmetric LVH without obstruction on echocardiogram and CMRI (Gossios, Lopes, & Elliott, 2013). Finally, a large family with an inherited *FHL1* mutation was described. There was 44% penetrance, 100% for males and 18% for females. Affected males had mild hypertrophy, systolic dysfunction, and abnormal diastolic function. Carriers had long QTc. One patient had a cardiac arrest and there were two cardiac transplants with arrhythmogenic cardiomyopathy suspected in the explanted hearts (San Román et al., 2016).

Sanna et al. studied 10 patients with AD-EDMD. The average age at the first evidence of cardiac disease was 18.3 ± 9.7 years. ECG findings were abnormal in 8 of 10 patients, showing atrial fibrillation, atrial standstill, and AV conduction abnormalities. Holter recordings showed five patients with both atrial and ventricular arrhythmias, four associated with AV conduction abnormalities. Five patients had nonsustained VT. On echocardiography, only one patient had a mild reduction in LVEF. One patient showed mild LV dilation with normal function, and another patient showed right ventricular enlargement with a ventricular filling pattern consistent with a restrictive cardiomyopathy. Pacemakers were implanted in three patients. One patient who had a pacemaker because of atrial fibrillation with a slow ventricular response died suddenly at 48 years. Four patients had various degrees of LV dysfunction (Sanna et al., 2003).

Brodsky et al. described a single family found to have a lamin A/C mutation transmitted in an AD pattern in five of 14 members. The five affected family members had minimal skeletal muscle weakness, but two had severe cardiomyopathy, AV block, and VT. One of these patients received a heart transplant, and the second had sudden death (Brodsky et al., 2000).

Fatkin et al. studied 85 members of five families with EDMD and found 44 with lamin A/C mutations and 39 with cardiovascular disease. The mean age of disease onset was 38 years (range, 19–53 years), and often the diagnosis was based on asymptomatic ECG changes. Progressive abnormalities developed with increasing age. In all, 34 of 39 had sinus node dysfunction or AV conduction disease and 23 affected members had atrial fibrillation or flutter. Twenty-one patients had pacemakers implanted, and 25 of 39 had DCM. Heart transplant was required in six members because of rapid progression of heart failure, and 11 of the 25 died suddenly between the ages of 30 and 59 years (Fatkin et al., 1999). Atrial standstill has been described in a patient with a lamin A/C mutation (Achmad et al., 2017).

FACIOSCAPULOHUMERAL DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHMD) does not appear to be a major cause of myocardial disease but is associated with conduction defects. Laforêt et al. studied 100 patients with FSHMD and found five with AV conduction defects or arrhythmias (supraventricular tachycardia, VT), but no structural or functional cardiac defects (Laforêt et al., 1998). de Visser, de Voogt, and la Rivière (1992) found no evidence of cardiac changes in 31 patients with FSHMD. Stevenson et al. studied 30 patients with well-documented FSHMD. ECG abnormalities were present in 60% of patients, and abnormal electrophysiologic (EP) findings were present in 27% of patients. Atrial flutter or fibrillation was induced in 10 of 12 patients during EP studies and sinus node function was abnormal in three patients (Stevenson, Perloff, Weiss, & Anderson, 1990).

OTHER NEUROMUSCULAR DISORDERS

FRIEDREICH ATAXIA

Friedreich ataxia is an autosomal recessive disorder caused by repeat mutations in the frataxin gene. Patients usually have ataxia with significant, but variable, progression over time. Patients have hypertrophic cardiomyopathy and show abnormal repolarization and arrhythmias on ECG findings. Tsou et al. studied 99 patients and found that the cardiac phenotype consists of LVH and fibrosis with scarring, arrhythmias, and progressive heart failure and is the most common cause of death. DCM was the most common cause of death with 59% (Tsou et al., 2011). Weidemann et al. reviewed 205 patients with multiple imaging modalities and stratified patients into four categories based on the LV septal measurement in diastole (IVSTd) and showed that 32% were normal and 40% had mild, 16% had moderate, and 12% had severe disease. Patients in the severe category had dilation of the LV, significant ECG abnormalities, and LVEF <50%. The group also found that younger patients had more advanced disease, likely signifying that more affected individuals present younger (Weidemann et al., 2012). In a series of 32 patients with genetically proven Friedreich ataxia, Weidemann and colleagues found that almost all patients had some degree of cardiac involvement, with T wave inversion as the earliest sign. There was progression of the cardiomyopathy from mild to advanced stages, with an initial increase in wall thickness and then later decreased wall thickness and LV dilatation leading to end-stage cardiomyopathy (Weidemann et al., 2015).

BARTH SYNDROME

Barth syndrome is an XL disorder caused by mutations in the taffazin gene that result in abnormal mitochondria. Patients have a spectrum of symptoms, including skeletal muscle weakness, neutropenia, growth delay, and cardiomyopathy. Cardiac disease associated with Barth syndrome has a variable presentation unrelated to neurologic symptoms. In a study by Clarke et al., 151 reported cases of Barth syndrome was found in the literature. They note descriptions of several cardiac abnormalities ranging from dilated or hypertrophic cardiomyopathy to prolonged QTc and sudden death (Clarke et al., 2013). A registry study from Roberts et al. indicated that cardiac disease is the most common presenting symptom and is typically present before age 5 years and 70% within the first year of life. Multiple cardiomyopathies are described and 12% of patients required transplantation (Roberts et al., 2012).

POMPE DISEASE

Pompe disease is a rare autosomal recessive disorder caused by a deficiency in acid alpha-glucosidase, a lysosomal enzyme that degrades glycogen. Symptoms can begin at two months of age in the infantile-onset form, and approximately 88% of these patients have hypertrophic cardiomyopathy (Kishnani et al., 2006). Death often occurs before 12 months, so long-term consequences are not known. ECGs can show large QRS complexes with short PR intervals. Nonspecific cardiac abnormalities are present in juvenile and late-onset Pompe disease but typically only present on CMRI (Boentert, Florian, Dräger, Young, & Yilmaz, 2016; Groh et al., 2008). Enzyme replacement therapy has significantly altered the disease course in treated infants.

MITOCHONDRIAL DISORDERS (MYOCLONUS EPILEPSY WITH RAGGED-RED FIBERS, MITOCHONDRIAL ENCEPHALOMYOPATHY WITH LACTIC ACIDOSIS AND STROKE-LIKE EPISODES, KEARNS-SAYRE SYNDROME, AND LEIGH SYNDROME)

Mitochondrial disorders, most often maternally inherited, are caused by specific defects in the mitochondrial respiratory transport chain or oxidative phosphorylation. Because of the high energy requirements of cardiac tissue, the heart is affected in these disorders. Cardiac manifestations include DCM and hypertrophic cardiomyopathy, AV conduction disturbances, and arrhythmias (Marin-Garcia & Goldenthal, 1997).

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies constitute a heterogeneous group of disorders with varying degrees of cardiac involvement. Generally, a primary cardiomyopathy has not yet been seen in patients with ryanodine receptor 1 (RYR1) and myotubularin (MTM1) genes. Primary cardiomyopathy has been reported in patients with actin alpha 1, dynamin 2, and tropomyosin 2 mutations (D'Amico et al., 2006). Ceviz et al. (2003) found decreased cardiac function in patients with merosin-positive congenital muscular dystrophy. Nakanishi et al. (2006) showed increasing cardiac dysfunction as a function of age in Fukuyama-type congenital muscular dystrophy. Ryan et al. (2001) published 143 cases of nemaline myopathy in which six infants had transient congestive heart failure and one had LV systolic dysfunction with congenital long QTc syndrome. Hypertrophic cardiomyopathy, DCM, and sudden cardiac death have also been reported (Gatayama et al., 2013; Marseglia et al., 2015; Mir, Lemler, Ramaciotti, Blalock, & Ikemba, 2012; Nagata et al., 2011; Nakajima et al., 2008; Skyllouriotis, Marx, Skyllouriotis, Bittner, & Wimmer, 1999; Taglia, D'Ambrosio, Palladino, & Politano, 2012). In patients with titin mutations with multi-minicore-like disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, DCM, ventricular arrhythmias, and sudden cardiac death have been reported (Bertini et al., 1990; Carmignac et al., 2007; Cullup et al., 2012; Homayoun et al., 2011; Magliocco, Mitchell, Brownell, & Lester, 1989; Ohkubo et al., 1996; Shuaib, Martin, Mitchell, & Brownell, 1988; Willemsen, van Oort, ter Laak, Sengers, & Gabreëls, 1997; Yuceyar, Baysal, Ozbay, Kocaman, & Karasoy, 2008). Heller et al. presented a series of three children with LMNA-related muscular dystrophy presenting in infancy. They described atrial level arrhythmias in all three and heart failure symptoms by the age of 5 years. Generally, children developed right heart failure symptoms including diarrhea and peripheral edema prior to a decrease in LVEF (Heller et al., 2017). In these disorders, the prognosis is usually more dependent on skeletal and respiratory muscle weakness than on cardiac disease.

In summary, cardiac disease can be a significant comorbidity in neuromuscular disorders. The recognition and proper treatment of cardiac disease are important aspects of standard of care. While the commonly associated neuromuscular disorders were discussed previously, there are a significant number of neuromuscular diseases not commonly associated with cardiac disease. However, there are occasional case reports of cardiac disease in patients with these disorders, often related to stressful events (Chai, Bertorini, & McGrew, 2011; Flöck et al., 2014). Therefore, cardiac evaluations should be a consideration in any neuromuscular patient with concerning or uncommon symptoms.

DIAGNOSIS AND EVALUATION

HISTORY AND PHYSICAL EXAMINATION

It is of vital importance to obtain a complete history of the type of muscular dystrophy and current treatments. Special attention should be given to the family history, especially in cases of undiagnosed dystrophies. Two or more affected males in a single family should raise concern about a familial inheritance pattern, as is seen with XL-DCM, especially if there is no significant history of muscle weakness. Also, a family history of sudden death should raise suspicion for inherited cardiomyopathies.

Because these patients are inactive and often do not have significant exertional symptoms, it is important for the physician to ask specifically about changes in the activities of daily living. Is there increased fatigue? Does a child now use two pillows to sleep instead of one? Are there any changes in appetite or chronic nausea? Has there been weight loss? These are subtle changes that patients and caregivers may not recognize as concerning symptoms. Has the patient had any episodes of palpitations or dizziness? Arrhythmias can be symptomatic in young patients, but because of conduction abnormalities associated with some muscular dystrophies, they can occur with normal or even low ventricular rates, causing patients to remain asymptomatic (Boriani et al., 2003; Groh, Lowe, & Zipes, 2002).

On physical examination, cardiac findings can be nonspecific but may provide initial clues to the presence and extent of cardiac disease. Vital signs can include tachycardia in patients with DMD and increased blood pressure as a result of steroid use. On examination of the neck, cannon A waves in the jugular venous pulse are suggestive of AV conduction disease, and loss of A waves can be related to atrial fibrillation or atrial standstill. Increased jugular venous distention can be present in heart failure. During palpation of the chest, displacement of the point of maximal impulse to the left and inferolaterally is caused by an enlarged left ventricle. The point of maximal impulse can also be displaced secondary to scoliosis. On auscultation, there is usually a regular rhythm, with normal S1 and S2. Irregular rhythms are associated with atrial fibrillation. A mid-systolic click secondary to mitral valve prolapse is sometimes appreciated in BMD. An S3 gallop can be heard during acute congestive heart failure and an S4 gallop can be heard secondary to LV dysfunction. Systolic ejection murmurs can be associated with DMD, and systolic regurgitant murmurs, often as a result of mitral regurgitation, can be heard in BMD (Saito et al., 1996). Gilroy et al. (1963) found systolic ejection murmurs with grade I to II intensity in approximately 10% of patients with DMD. In Friedreich ataxia, systolic ejection murmurs can be present as a result of subaortic stenosis from LVH. Hepatomegaly can be found on abdominal examination but can be difficult to palpate because of positioning and

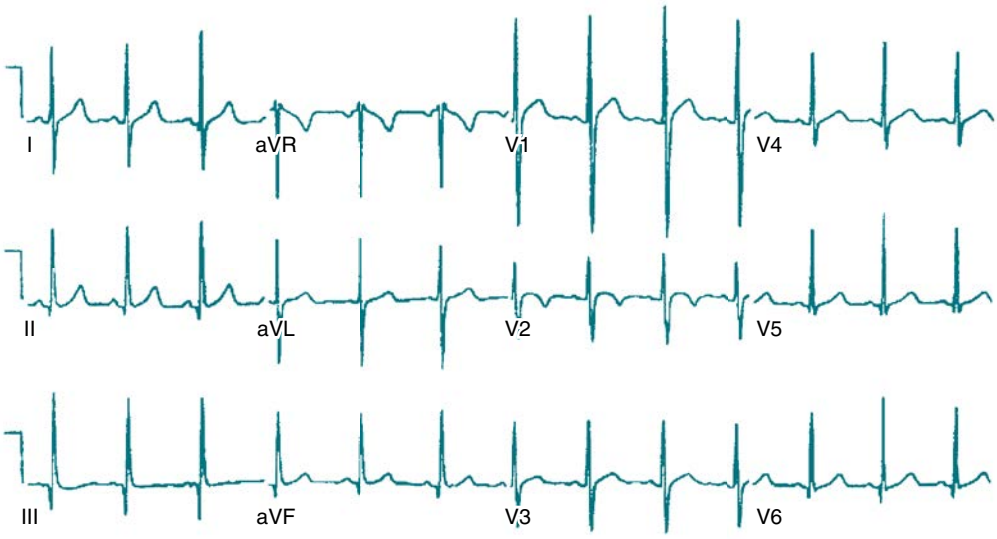


Fig. 3.1 Electrocardiogram from a 16-year-old boy with Duchenne muscular dystrophy (DMD). This tracing shows common features of DMD including sinus tachycardia with a heart rate of more than 100 beats per minute; large R waves in leads V1 and V2; and Q waves in the lateral and inferior leads (II, III, aVF, V5, and V6).

scoliosis. Examination of the extremities often shows dependent edema when heart failure develops.

ELECTROCARDIOGRAPHY

The ECG is an important tool for the diagnosis of arrhythmias, and muscular dystrophies can often have subtle early ECG changes. A 12-lead ECG examination provides noninvasive assessment of cardiac rhythm, ventricular axis, chamber enlargement, and conduction abnormalities or arrhythmias. The tracing speed can be increased (to 50 mm/second) to aid in the diagnosis of conduction abnormalities.

Sinus tachycardia is found in most (up to 75%) patients with DMD, even when these patients are nonambulatory (Gilroy et al., 1963; Dittrich et al., 2015; D'Orsogna et al., 1988; Oğuz, Olguntürk, Gücüyener, Açikgöz, & Tunaoglu, 1998). This tachycardia occurs in childhood and persists into adulthood. In an early study of DMD, Gilroy et al. presented findings in 139 patients with DMD who were four to 35 years old. The most common clinical finding was sinus tachycardia, present in 124 cases (89%). The tachycardia was labile and appeared with minimal stimulation (e.g., raising the bed) (Gilroy et al., 1963). In another study, sinus tachycardia was seen in 78% of patients with DMD (Bhattacharyya, Basu, Ray, & Maity, 1997). The exact cause is unknown, but possible etiologies include compensatory tachycardia secondary to ventricular dysfunction, autonomic dysregulation, or fibrosis of the sinoatrial node and conduction system.

Another common ECG finding is tall R waves in both DMD and BMD (Fig. 3.1). Abnormally tall R waves in leads V1 to V3 were found in a study of patients with DMD (Gilroy et al., 1963). Saito et al. (1996) also showed prominent R waves in V1 in 88% of patients with DMD and 47% of patients with BMD. Other studies confirmed the prominent R waves in patients with DMD and BMD (D'Orsogna et al., 1988; Melacini et al., 1996; Steare, Dubowitz, & Benatar, 1992). These forces represent a loss of posteriorly directed forces because of selective fibrosis of the posterobasal portion of the left ventricle that is common in dystrophic myocardium. This correlation was pathologically confirmed in a previous study (Perloff, Roberts, de Leon, & O'Doherty, 1967).



Fig. 3.2 Rhythm strip from a 17-year-old boy with Duchenne muscular dystrophy. The strip shows atrial flutter, with the (***arrows***) pointing to visible flutter waves at a rate of approximately 300 beats per minute. The atrioventricular node has variable conduction, with a ventricular rate of approximately 80 to 110 beats per minute.

This myocardial fibrosis can also extend laterally and produce large Q waves on surface ECG findings (see Fig. 3.1). Q waves are most frequently seen in the lateral leads (I, aVL, V6) and less frequently in the inferior (II, III, aVF) or anterior (V1–V4) leads (Ishikawa, 1997; Perloff et al., 1967; Steare et al., 1992). Lateral lead Q waves were seen in 73% of patients with DMD and 37% of those with BMD (Saito et al., 1996). In DMD, lateral Q waves were present in 54% of patients compared with inferior Q waves in 30% of patients (Bhattacharyya et al., 1997). Hoogerwaard et al. (1997) studied patients with BMD and found 33% with Q waves in the lateral leads and 11% with Q waves in the inferior leads. There is no correlation between baseline ECG findings and presence or absence of DCM; thus, ECG screening is insufficient and echocardiography or CMRI is required (Thrush, Allen, Viollet, & Mendell, 2009). Acute presentation with chest pain can be associated with ECG ST segment elevation, especially in the inferior and lateral precordial leads, and is related to acute exacerbation with features consistent with myocarditis (Hor et al., 2017).

Arrhythmias and conduction defects can also be present. Premature atrial contractions are common in DMD (Ishikawa, 1997). Other atrial arrhythmias, including flutter and fibrillation, and premature ventricular contractions are also seen in DMD (Fig. 3.2) (Akita, Matsuoka, & Kuroda, 1993). Corrado et al. (2002) found ventricular arrhythmias in 32% of patients with DMD who were studied. Melacini et al. found arrhythmias on ECG tracings in patients with BMD, including benign, isolated, monomorphic, and polymorphic premature ventricular contractions. Ventricular

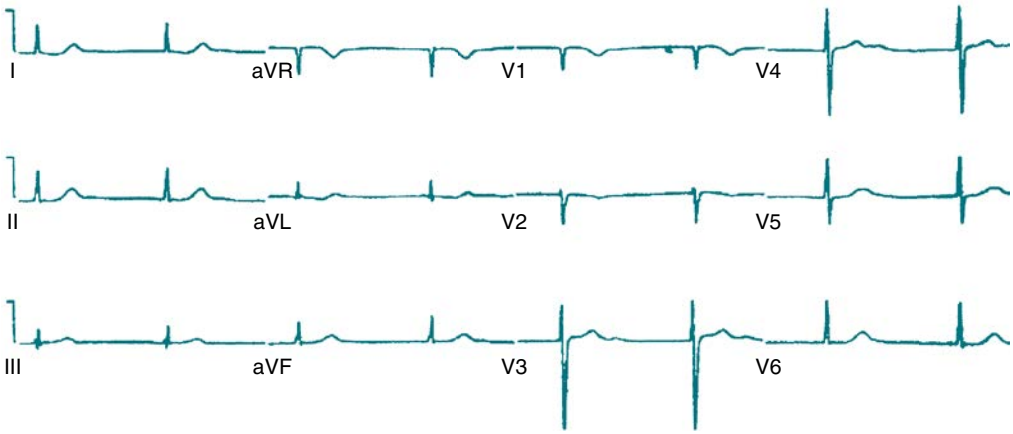


Fig. 3.3 Electrocardiogram from a 19-year-old man with myotonic dystrophy type I. The tracing shows atrial standstill. There are no P waves evident, and there is a junctional rhythm at approximately 45 beats per minute.

arrhythmias were documented in one patient who died suddenly (Melacini et al., 1996). Conduction defects are also frequent. Many patients with DMD and BMD are found to have bundle branch block patterns, but heart block is rarely seen (Gilroy et al., 1963; Hoogerwaard et al., 1997; Melacini et al., 1996).

An ECG is most important in other muscular dystrophies where conduction defects are more prevalent. In LGMD 1B, AV conduction defects are primarily seen. These defects initially begin as a prolonged PR interval but become progressively more severe over time and can develop into complete heart block. Atrial fibrillation with a variable ventricular response is seen (Chrestian et al., 2008; Ben Yaou et al., 2005; van der Kooi et al., 1998). In LGMD 2C and 2I, along with AV conduction defects, abnormal findings include dysmorphic notched P waves, tall R waves, Q waves, inverted T waves, and ectopic beats (Calvo et al., 2000; Poppe et al., 2003, 2004). MD types I and II and EDMD, both XL and AD, are significantly associated with progressive AV conduction defects. Often these are the first and only presenting symptoms because muscular weakness has not developed. In a retrospective review of 1800 patients with DM type I, the most common finding was first-degree AV block in 28% of patients, with QTc >440 milliseconds in 22% of patients. In this series, atrial fibrillation and flutter were present in 5% of patients. Pacemakers were required in 4% of patients and 1% required an ICD (Petri et al., 2012). Atrial fibrillation and flutter are present in approximately 25% of patients with DM type I (Boriani et al., 2003; Brodsky et al., 2000; Buckley et al., 1999; Fatkin et al., 1999; Groh et al., 2002, 2008; Sanna et al., 2003; Schoser et al., 2004). As a late consequence, atrial standstill can develop in patients with DM (Fig. 3.3).

The ECG results can show many other pathologic changes that indicate myocardial damage. These include ST segment and T wave changes, shortened PQ interval, increased cardiomyopathy index (QT/PQ), prolonged QTc, and increased QT dispersion (Bhattacharyya et al., 1997; Gilroy et al., 1963; Nigro et al., 1990; Steare et al., 1992; Yotsukura et al., 1995). Repolarization abnormalities are common in Friedreich ataxia (FA). In a study by Child et al., 79% of patients showed ST/T wave abnormalities, and T wave inversion was an early sign of FA cardiomyopathy progression (Child et al., 1986; Weidemann et al., 2015).

HOLTER MONITORS

Holter monitoring can provide additional important information in muscular dystrophies. As noted, depending on the type of dystrophy, the goals of Holter monitoring may differ. However, extended monitoring of the cardiac rhythm can provide greater detail of sporadic abnormalities that are not seen on the brief electrocardiogram. It is also a necessity in muscular dystrophies associated with conduction delay and heart block.

In DMD, Holter monitoring can show variations in heart rate. Autonomic dysregulation has always been evident in patients with DMD. Kirchmann et al. (2005) reported that Holter monitoring in DMD showed sinus tachycardia in 26% of patients, deprivation of circadian rhythm in 31% of patients, and reduced heart rate variability in 51% of patients. D'Orsogna et al. (1988) described labile abrupt sinus tachycardia in 11 of 18 cases. Yotsukura et al. (1995, 1998) also found a higher ratio of sympathetic to parasympathetic activity in patients with DMD compared with normal control subjects. Similarly, Lanza et al. (2001) showed impairment of cardiac autonomic function with an increased ratio of sympathetic activity. These Holter results could reflect disturbances in the cardiac autonomic nervous system as a result of focal degeneration of the conduction system or adaptation to heart failure in patients with DMD. Autonomic dysfunction is also reported in BMD (Ducceschi et al., 1997).

Holter monitoring can also capture arrhythmias (Fig. 3.4). D'Orsogna et al. (1988) reported 4 of 18 patients with DMD who had high-grade ventricular ectopy. Kirchmann et al. (2005) found premature ventricular beats in 9% of patients with DMD. Corrado et al. (2002) found more than six premature ventricular beats per hour in 32% and VT in 7% of patients with DMD who were monitored. There are less frequent arrhythmias seen in BMD. Kirchmann et al. (2005) found normal sinus rhythm with normal mean frequency in BMD, and only 1 in 17 patients had premature ventricular contractions. Hoogerwaard et al. (1997) reported only one arrhythmia (atrial fibrillation) in 21 patients with BMD who had Holter monitors. Chiang et al. reviewed 237 Holters for patients with DMD and BMD and stratified groups based on EF category (normal, mildly reduced, moderately reduced, severely reduced). Arrhythmia was defined as frequent premature atrial contractions or premature ventricular

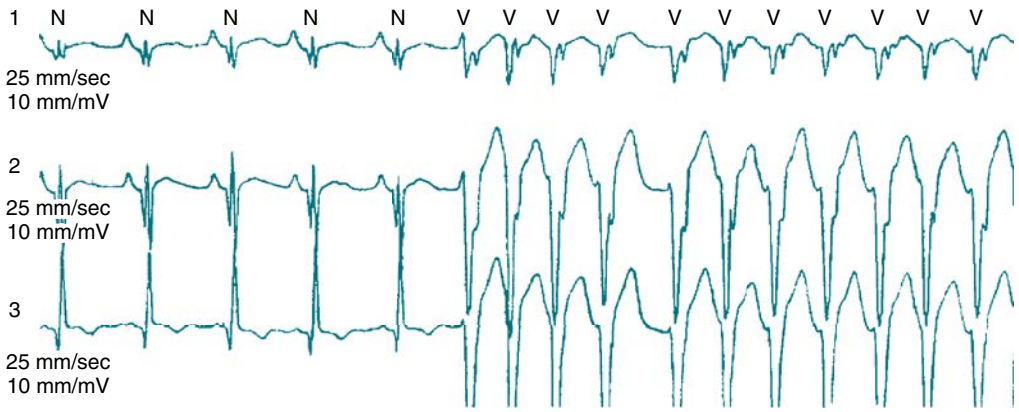


Fig. 3.4 Holter monitor tracing from an 18-year-old man with Duchenne muscular dystrophy. The tracing shows a sustained run of ventricular tachycardia at a rate of approximately 160 beats per minute. The patient was asymptomatic throughout the recording. ***N***, Normal sinus beat; ***V***, abnormal ventricular beat.

contractions (PVCs) (>10/hour), couplets, and runs of supraventricular tachycardia (SVT) or VT. Arrhythmias were present in 44% of DMD cases and 57% of BMD cases and were correlated with worsening systolic function. Clinically significant arrhythmia was seen in 10% of DMD and 25% BMD cases. There was an increase in arrhythmia in children with DMD that correlated with increased age and decreased EF (Chiang et al., 2016). This was also demonstrated by Villa et al. (2015), finding that DMD patients with LVEF <35% had more arrhythmias including nonsustained atrial tachycardia, frequent premature ventricular contractions, ventricular couplets/triplets, and nonsustained VT compared to DMD subjects with LVEF >35%. Based on these results, utilization of Holter monitoring in DMD subjects with LVEF >35% may be limited.

Patients with EDMD and DM should also have more frequent Holter monitors due to the risk of long-term conduction defects. Patients with DM who have a prolonged PR interval (>200 milliseconds), prolonged QRS interval (>100 milliseconds), or QTc >440–450 are at risk for pacemaker need and sudden death (Breton & Mathieu, 2009; Lau, Sy, Corbett, & Kritharides, 2015). For patients who might benefit from longer monitoring or who have infrequent symptoms, implantable loop recorders are a consideration. Unfortunately, normal ECG and Holter monitoring findings do not exclude the possibility of sudden death.

ECHOCARDIOGRAPHY

Echocardiography is an important diagnostic tool for cardiomyopathy in muscular dystrophies and is recommended annually in younger children (Birnkrant et al., 2018a, 2018b, 2018c; Duboc et al., 2005). As noted, many patients have few or no symptoms because of limitations in ambulation. Echocardiography provides a noninvasive assessment of cardiac structure and function that can direct therapy and future follow-up. However, standard two-dimensional echocardiography can be limited by poor imaging windows secondary to scoliosis, lung hyperinflation, and chest wall deformities. Alternative methods for the early detection of cardiac abnormalities continue to be studied.

Most patients with muscular dystrophy have normally structured hearts. Once dilation of the left ventricle occurs, patients can have mitral regurgitation and left atrial enlargement. Saito et al. showed that the LV end diastolic dimension was significantly larger in patients with BMD (5.2 ± 0.7 cm) compared with those with DMD (4.2 ± 0.7) and healthy control subjects (4.2 ± 0.7). The mitral annulus was also larger in patients with BMD, and the frequency of mitral regurgitation was significantly higher in patients with BMD (28%) compared with patients with DMD (9.3%) (Saito et al., 1996). The working hypothesis is that the increased cardiac fibrosis seen in DMD prevents dilatation in the initial phases compared to patients with BMD. Atrial enlargement can also be seen in patients with atrial arrhythmias. Atrial flutter, fibrillation, or standstill can be associated with atrial thrombi, usually in the left atrial appendage. This should be excluded, usually with transesophageal echocardiography, before restoration of normal sinus rhythm (Boriani et al., 2003).

A decrease in LV systolic function is the gold standard for the diagnosis of cardiomyopathy (Fig. 3.5). Kirchmann et al. (2005) showed that the median age of onset of decreased fractional shortening (FS) (<25%; normal is 30%–40%) was 16.8 years in DMD and 30.4 years in BMD. Corrado et al. (2002) found decreased LV systolic function to be a strong predictor of mortality in DMD during a 10-year follow-up period. Associated with decreased systolic function, two-dimensional echocardiography can also delineate DMD-related regional wall motion abnormalities. In a study by Kermadec et al., 72% of patients with DMD had at least one segment with wall motion abnormality. The most commonly involved segments were the inferior basal and inferior apical segments. Involvement of the anterior and lateral walls was usually limited to diffuse areas of hypokinesis (Kermadec, de Bécane, Chénard, Tertrain, & Weiss, 1994). Sasaki et al. (1998) also showed wall motion abnormalities in the inferior, lateral, and apical segments of patients with DMD. Hoogerwaard et al. (1997) also found hypokinesis of the inferolateral wall and global hypokinesis without dilation in patients with BMD.

However, the more important function of echocardiography is identifying preclinical cardiac disease. Markham et al. (2006) showed that patients younger than 15 years old with normal cardiac function had abnormal indices of diastolic function for ventricular relaxation and ventricular compliance at the initial visit. Evaluation of diastolic function is becoming one of the most important aspects of the cardiac evaluation. These abnormalities precede losses in systolic

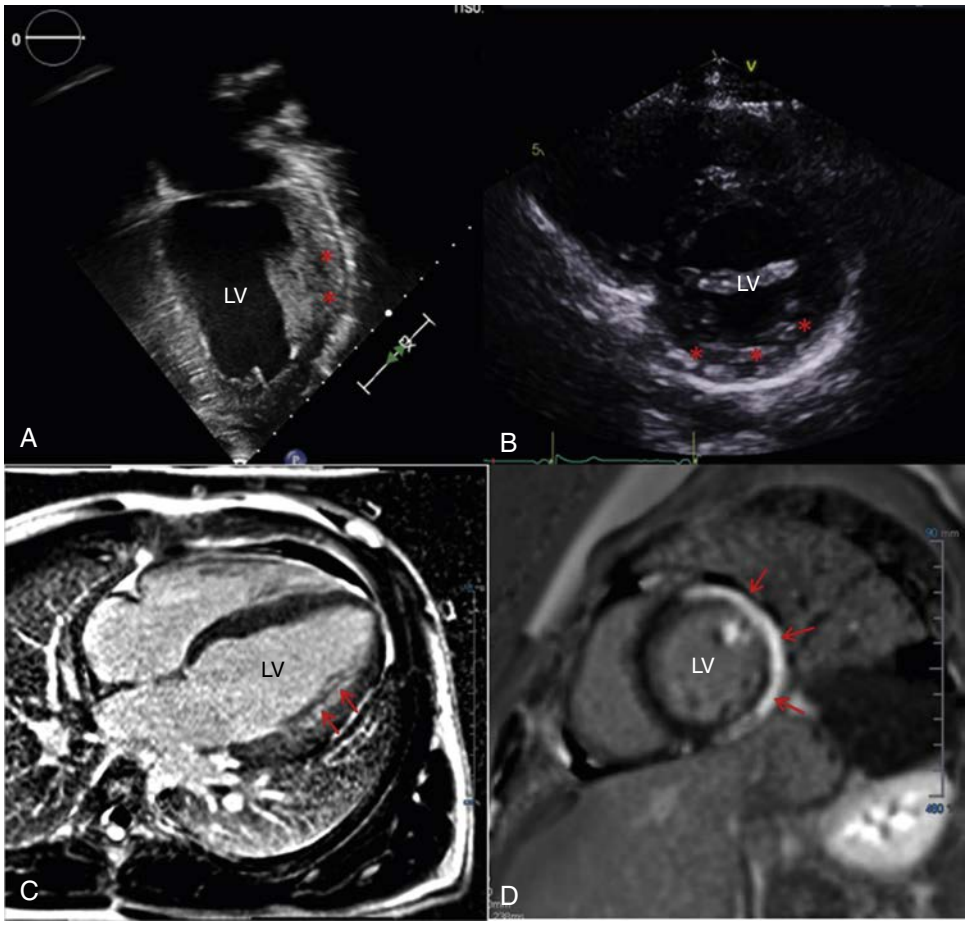


Fig. 3.5 Cardiac imaging for two patients with Duchenne muscular dystrophy, one with mild cardiomyopathy (A, C) and one with severe cardiomyopathy (B, D). (A) Two-dimensional (2D) echo apical four-chamber view of a normal sized left ventricle (***LV***). There is a normal-appearing myocardium (*) even though the cardiac magnetic resonance imaging (CMRI) of the same heart (C) demonstrates late gadolinium enhancement (LGE) (***arrows***), consistent with mild myocardial fibrosis. (B): 2D echo image of the parasternal short axis showing the mildly dilated LV in cross-section. There is a normal-appearing myocardium (*) even though the CMRI of the same heart (D) demonstrates severe LGE (***arrows***). (C) CMRI image of apical four-chamber view with normal-size LV and mild LGE (***arrows***) in the lateral wall. (D) CMRI image of parasternal short axis showing a mildly dilated LV with transmural LGE (***arrows***) in the lateral wall. There is sparing of the endomyocardial border that is a consistent finding in DMD cardiomyopathy.

function and may provide quantifiable measures for treatment initiation and evaluation. Measures of diastolic dysfunction including mitral valve E and A wave velocity, tissue Doppler imaging, and myocardial performance indices were reproducible and were different when comparing DMD patients to healthy controls (Ryan et al., 2013; Shabanian et al., 2011; Siegel, Olivieri, Gordish-Dressman, & Spurney, 2017).

Meune et al. (2006) showed that despite normal echocardiographic and radionucleotide ventriculography-derived systolic function, tissue Doppler-derived strain rates showed systolic and diastolic myocardial dysfunction in BMD. Using myocardial strain imaging, Ogata et al. showed that 10 of 13 patients with DMD, 11 to 20 years old with normal LV function, had negative strain values in the outer layer of the posterolateral wall in the parasternal short axis. In five of these 10 patients, the timing to peak systolic velocity at the inferoposterior wall was delayed more than 60 ms (Ogata et al., 2007). Mori et al. measured myocardial radial strain in the left ventricle in 25 patients with DMD who were 14.8 ± 3 years with normal LV shortening fraction. Results showed significantly decreased peak systolic strain of the LV posterior wall in patients with DMD compared with normal control subjects. Peak strain did not differ in the interventricular septum (Mori et al., 2007).

Spurney et al. (2015) showed abnormal speckle-tracking echocardiography (STE) myocardial strain prior to the development of decreased LV systolic function. Ryan et al. (2013) and Jo, Eun, Jung, Choi, and Gang (2015) confirmed that STE is abnormal between DMD patients and normal controls, indicative of early changes. Further, Soslow et al. (2016) found a moderate correlation between STE- and CMRI-derived EF. Finally, more recent measurements of tonic contraction of the left ventricle and underfilling (measurement of diastolic dysfunction) have predated systolic dysfunction in patients with DMD (Su, Ramos-Platt, & Menteer, 2016).

Hypertrophic cardiomyopathy is associated with some neuromuscular disorders. As noted, infantile Pompe disease is associated with severe hypertrophic cardiomyopathy (Kishnani et al., 2006). Patients with Friedreich ataxia also have a thickened left ventricle, and echocardiogram shows concentric (LVH or asymmetrical septal hypertrophy. Some of these patients go on to have decreased systolic function and DCM (Child et al., 1986; Dutka, Donnelly,

Nihoyannopoulos, Oakley, & Nunez, 1999). In a retrospective review of 28 patients and 113 echocardiograms in patients with Friedreich ataxia, the group had LVH and normal systolic function with an increased median mass z-score. The median EF was 61%. The last echocardiogram in this group showed systolic dysfunction in 38% of patients. There was a slow nonlinear decline in systolic function over time. There was no correlation with FAA repeat number (Kipps et al., 2009). (Child et al., 1986; Dutka et al., 1999).

Echocardiography is also used in the evaluation of the right ventricle and pulmonary pressure. Right ventricular abnormalities were seen early in 64% of asymptomatic patients with BMD, including right ventricular enlargement in 18 patients (Melacini et al., 1996). In LGMD 2C, echocardiography showed eight of 10 patients with right ventricular dilation, right ventricular free wall hypertrophy, and no evidence of increased pulmonary artery pressure. This was accompanied by abnormal right ventricle relaxation using tissue Doppler imaging (Calvo et al., 2000). Right ventricular dilation was also seen in two patients with alpha-sarcoglycan deficiency (Melacini et al., 1999).

CARDIAC MAGNETIC RESONANCE IMAGING

CMRI is another imaging modality that can provide clues to preclinical cardiac dysfunction. Due to inherent limitations in echocardiography related to neuromuscular diseases as discussed, CMRI is now the preferred noninvasive imaging modality for DMD (Birnkrant et al., 2018a, 2018b, 2018c). Several studies have demonstrated improved assessment of ventricular function with CMRI compared to echo in DMD (Buddhe, Lewin, Olson, Ferguson, & Soriano, 2016; Brunklaus et al., 2015; Soslow et al., 2016). CMRI also provides additional assessments of myocardial disease. With the use of gadolinium contrast, assessment of myocardial fibrosis is possible. A study by Silva et al. (2007) used late gadolinium enhancement (LGE) to show early myocardial fibrosis in DMD, even in patients younger than 10 years old. LGE occurs in a predictable pattern in DMD cardiomyopathy, with the primary areas affected being inferolateral, anterolateral, inferior, and other LV free wall segments (Ben Yaou et al., 2005). Only those with very advanced disease have LGE in septal segments (Kirchmann et al., 2005). Hor et al. (2013) demonstrated increased LGE in older DMD subjects and those with LVEF <55%. Studies have also shown that the extent of LGE, in particular whether it is transmural, predicts the occurrence of adverse cardiac events (Bönner et al., 2014; Silva et al., 2017). Tandon et al. (2015) showed that LGE develops prior to losses in systolic function and that the extent of LGE correlates strongly with the development of LV dysfunction. LGE has also been shown to be associated with increased arrhythmia risk and death in DMD (Menon et al., 2014).

CMRI also has the ability to assess myocardial strain measures similar to echocardiography. Tagged cine imaging, along with harmonic phase processing, allows for the measurement of cardiac strain and does not require gadolinium administration. In a study by Ashford et al., 13 patients with DMD (mean age, 10.6 years) with normal LV volume and EF manifested reduced circumferential strain compared with control subjects (Ashford et al., 2005). Hor et al. (2009) also showed that tagged strain imaging identified abnormalities prior to the development of any alteration in the LVEF that worsened with age. Tagged imaging strain measures also correlated with severity of cardiac disease, and the greatest changes were seen in the lateral segments where LGE evidence of fibrosis was detected (Hor et al., 2014; Schoser et al., 2004). Feature tracking is a CMRI measure of strain that does not require additional tagged images and can be performed on standard images. Studies showed that it correlates well with the tagged harmonic phase strain measures and is superior to echocardiographic STE measures and that abnormalities are present prior to the development of LGE (Hor et al., 2010; Siegel et al., 2017).

Newer techniques in CMRI may allow for earlier identification of myocardial disease prior to the development of myocardial fibrosis. Native T1 and extracellular volume (ECV) mapping can be used to measure the ECV expansion seen in fibrosis and edema. Olivieri et al. (2016) demonstrated that ECV and T1 measures are different in DMD patients compared to age-matched controls and the degree of changes seen in native T1 levels is proportional to the degree of cardiac disease. Soslow et al. also showed that DMD patients have abnormal ECV and native T1 values in patients both with and without LGE (Murakami et al., 2006; Soslow et al., 2016). Based on the better image quality, ability to assess myocardial fibrosis, and potential to demonstrate changes prior to fibrosis, CMRI is now the preferred imaging modality in DMD.

In LGMD 2I, magnetic resonance imaging (MRI) showed decreased cardiac function with fatty replacement and fibrosis of the myocardium (Wahbi et al., 2008). In another study of patients with 2I LGMD, eight of nine patients showed cardiac involvement with CMRI compared with only two patients using echocardiography (Gaul et al., 2006). Finally, in a case series of individuals with Friedreich ataxia, CMRI detected scarring that proceeded obvious systolic dysfunction clinically (Weidemann et al., 2015). Thus, MRI may become an important early imaging modality during preclinical cardiac disease.

CARDIAC CATHETERIZATION

There is limited use for cardiac catheterization in the diagnosis of known dystrophy-related cardiomyopathy because the structure of the heart and coronary arteries is usually normal. In cases of cardiomyopathy with absent or minimal skeletal muscle disease (i.e., XL-DCM), catheterization can confirm normal coronary angiography, and endomyocardial biopsy can be performed for pathologic analysis and dystrophin staining. Cardiac catheterization was utilized in some cases of DMD patients presenting with chest pains and acute ST segment elevations and demonstrated normal coronary angiography (Cinteza et al., 2017; Hor et al., 2017). Cardiac catheterization can also be used during acute cardiac decompensation for the placement of assistance devices to provide systolic function support to the failing myocardium.

ELECTROPHYSIOLOGIC TESTING

Invasive EP studies are indicated when certain abnormalities are present. These include pauses greater than 2.5 seconds,

sinus bradycardia less than 40 beats per minute, first-degree AV block greater than 240 milliseconds, second- or third-degree AV block, and documented atrial or ventricular arrhythmias (Finsterer & Stöllberger, 2003). DM and EDMD are known to affect the cardiac conduction system. EP testing can play a role in the diagnosis of conduction abnormalities. Lazarus et al. studied 83 patients with DM primarily with asymptomatic conduction abnormalities using invasive EP testing. AV conduction disturbances were common. Atrial arrhythmias were inducible in 41% of cases and ventricular arrhythmias were induced in 18% of cases. However, no relationship between ECG findings and EP testing abnormalities was found and the predictive value for sudden death was unclear (Lazarus et al., 1999). Negri et al. presented a case of BMD with recurrent wide complex tachycardia found to have a bundle branch reentrant VT during EP testing. This pathway was treated successfully with radiofrequency ablation (Negri & Cowan, 1998).

PATHOLOGY

Cardiomyopathy is referred to as a "final common pathway" because many different etiologies lead to a dilated, poorly functioning heart. However, pathologic specimens show specific differences in dystrophy-related cardiomyopathies. Gilroy et al. showed in DMD that the myocardium varied from areas of well-preserved fibers with slightly or moderately enlarged nuclei to areas of extensive replacement by connective tissue. Also, no inflammatory or granulation tissue was present (Gilroy et al., 1963). Most myocardiocytes were atrophic, with loss of striations and nuclear fragmentation, and there was selective scarring of the posterobasal portion of the left ventricle (James, 1962). The fibrosis appears to especially involve the outer half of the posterior LV free wall, often in a band-like distribution (Frankel & Rosser, 1976). In BMD, pathology shows marked damage in the lateral wall, consistent with the lateral ECG findings (Frankel & Rosser, 1976). In dystrophies significantly associated with arrhythmias, progressive fibrosis of the sinoatrial node, AV node, and Purkinje conduction fibers is prominent (Fatkin et al., 1999; Groh et al., 2002; Schoser et al., 2004). These differences underscore the need to further understand the specific pathways and mechanisms affected by muscular dystrophy so that more directed therapy can be developed.

TREATMENT

The treatment of cardiac disease in neuromuscular disorders depends on the neuromuscular diagnosis and stage of progression. As noted, DMD and BMD are directed by decreased cardiac function, and disease progression is treated with an increasing amount of medical therapy (Fig. 3.6 and Table 3.2). Since there are no specific therapies directed at the loss of dystrophin in cardiac muscle, traditional cardiac medications for heart failure are utilized (Yancy et al., 2017). EDMD and DM are directed by conduction system disease, and progressive disease requires pacemaker implantation (Fig. 3.7). A discussion of the benefits of specific medical and device therapies for cardiac complications in neuromuscular disease follows.

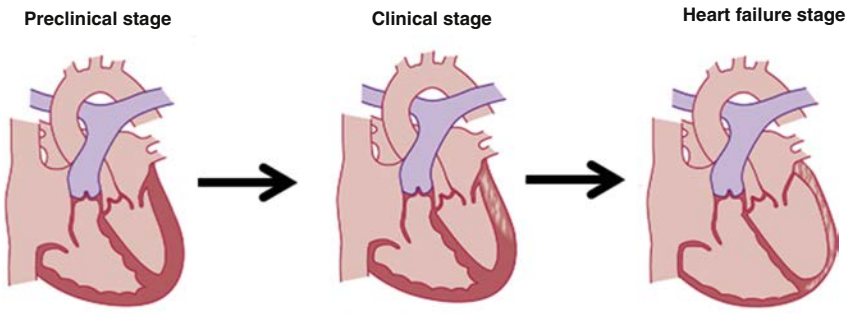
CORTICOSTEROIDS MONOTHERAPY IN DMD

The gold standard for treatment of dystrophic skeletal muscle disease is steroid therapy. However, the long-term cardiovascular effects of steroid treatment include obesity, hypertension, and cardiac hypertrophy (Bushby, Muntoni, Urtizberea, Hughes, & Griggs, 2004; Yancy et al., 2017). The effects of steroid treatment on cardiac function have also been studied. Markham et al. looked at patients with DMD who were 7.5 to 12 years old and were treated with either prednisone or deflazacort ($n = 14$) or with no steroids at all ($n = 23$). The FS decreased from 35.5% to 26.0% in the untreated group, whereas it remained unchanged (36%–34%) in the steroid-treated group. The steroid-treated patients' hearts also did not dilate as much as those of untreated patients. There were no significant differences in blood pressure between the two groups. Thus, steroids, started before there was any evidence of decreased cardiac function, delayed the onset of ventricular dysfunction in these patients (Markham, Kinnett, Wong, Benson, & Cripe, 2008). In an earlier study by the same group, untreated subjects 10 years old or younger were 4.4 more times likely to have FS of less than 28%. Untreated subjects older than 10 years were 15.2 times more likely to have decreased FS compared with steroid-treated subjects. There was no difference in FS between the prednisone and deflazacort groups (see also Chapter 20). A more recent study by Barber and colleagues demonstrated that corticosteroid treatment delayed the onset of cardiomyopathy by 2 years. By age 14 years, 63% of untreated boys had developed cardiomyopathy versus only 36% of treated boys. Further, they demonstrated that longer duration of treatment further delayed the onset of cardiomyopathy, and for every year of corticosteroid treatment, there was a 4% decrease in the probability of developing cardiomyopathy (Barber et al., 2013).

Data also suggest that the beneficial effect of steroids may persist. In patients for whom treatment was discontinued secondary to side effects, steroids appear to have helped to preserve cardiac function up to 6 years after discontinuation (Markham et al., 2005). Silversides et al. studied patients with DMD between the ages of 10 and 18 years. Patients receiving deflazacort for at least 3 years had better FS (33% vs. 21%), and only 5% of patients taking deflazacort had an LVEF of less than 45% compared with 58% for untreated subjects. Patients also showed improvement in pulmonary and skeletal muscle strength (Silversides, Webb, Harris, & Biggar, 2003). These results support a beneficial effect of steroids on cardiac function in the short term. Further understanding of the long-term effects of steroids on cardiac size and function are not yet known (Barber et al., 2013; Schram et al., 2013).

CARDIAC PHARMACOLOGIC THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY

In recent years, there has been some success in treating DMD-related cardiomyopathy. Currently, there is no specific treatment for cardiomyopathy secondary to muscular dystrophies, but consensus statements support that treatments used for other forms of cardiomyopathy are beneficial in DMD cardiomyopathy. Once decreased systolic cardiac function is found, pharmacologic therapy is



	Preclinical stage	Clinical stage	Heart failure stage
Pathology	Normal gross pathology	Mild myocardial fibrosis	Dilated cardiomyopathy
Diagnostic Testing	• ECG: Tall R waves, Q waves, ± prolonged QTc • ECHO: Normal function, ±decreased myocardial strain • CMRI: negative LGE, ± decreased myocardial strain, ± increased native T1 values	• ECG: PVCs • ECHO: Preserved to mildly decreased systolic function, decreased myocardial strain • CMRI: LGE +, decreased myocardial strain, increased native T1 values	• ECG: ST segment changes, VT • ECHO: Dilated LV, decreased systolic function • CMRI: moderate to severe LGE +, wall motion abnormalities
Treatment Goals	• Slow progression of myocardial disease	• Slow progression of myocardial disease	• Improve symptoms/quality of life • Improve cardiac function • Decrease risk of sudden death
Therapies	• Steroids for skeletal muscle • ACEi/ARB • ± MRA	• Continue steroids • ACEi/ARB • MRA • ± BB	• ACEi/ ARB • MRA • BB • Diuretics • ± Anti-arrhythmic • ±Anti-coagulation • ±IV inotropes • ±LVAD • ±Heart transplantation

Fig. 3.6 Progressive stages and treatment of cardiomyopathy in muscular dystrophies. Cardiomyopathy progresses from an asymptomatic preclinical stage to developing myocardial fibrosis, dilated left venticle, and decreased systolic function associated with heart failure symptoms. ***ACEi***, Angiotensin-converting enzyme inhibitor; ***ARB***, angiotensin receptor blocker; ***BB***, beta-blocker; ***CMRI***, cardiac magnetic resonance imaging; ***ECG***, electrocardiogram; ***Echo***, echocardiogram; ***IV***, intravenous; ***LGE***, late gadolinium enhancement; ***LV***, left ventricular; ***LVAD***, left ventricular assist device; ***MRA***, mineralocorticoid receptor blockade; ***PVC***, premature ventricular contraction; ***VT***, ventricular tachycardia.

Table 3.2 Recommended Dosages for Preventative Cardiac Medications Used in the Treatment of Duchenne Muscular Dystrophy–Related Cardiomyopathy

Medication	Initial Dosing (Age 10 years)	LGE+ (or Age 14 years)	Systolic Dysfunction
Angiotensin-Converting Enzyme Inhibitors			
Lisinopril	5 mg once daily	10 mg once daily	10 mg BID
Perindopril	2 mg once daily	4 mg once daily	4 mg BID or 8 mg daily
Mineralocorticoid Receptor Antagonists			
Spironolactone	NR	25 mg once daily	25–50 mg BID
Eplerenone	NR	25 mg once daily	25–50 mg BID
Beta-Blockers			
Carvedilol	NR	NR	0.3-0.75 mg/kg/dose BID Titrate as tolerated

BID, Twice daily; *LGE*, late gadolinium enhancement; *NR*, insufficient clinical data to recommend at this time

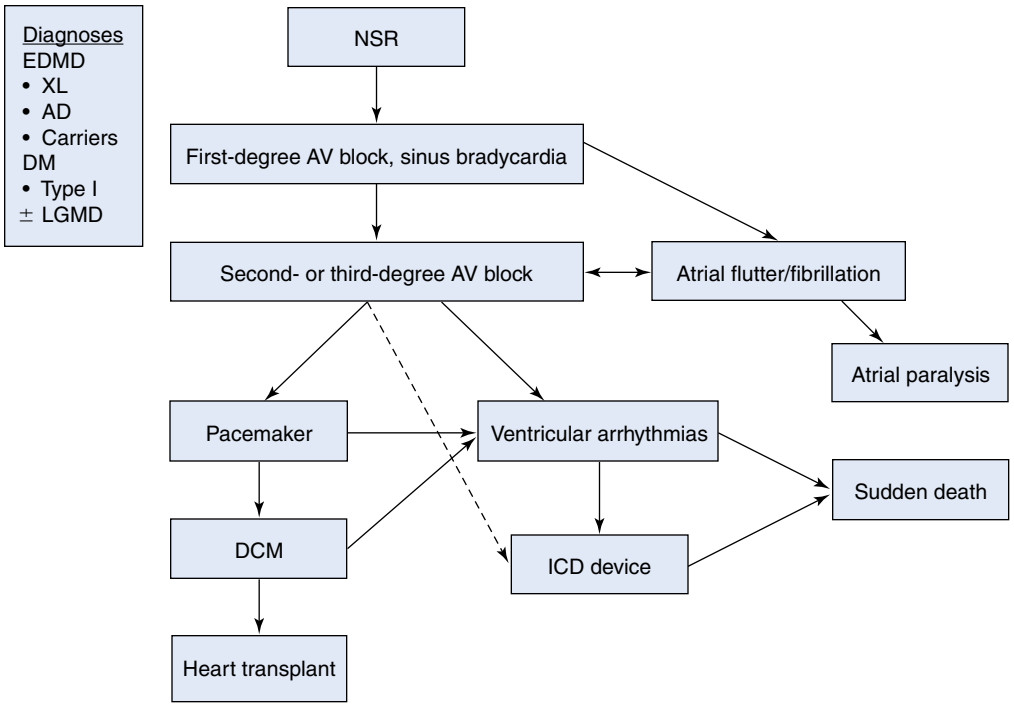


Fig. 3.7 Progression and treatment of heart rhythm abnormalities in EDMD, DM type I, and limb-girdle muscular dystrophy. ***AD***, Autosomal dominant; ***AV***, atrioventricular; ***DCM***, dilated cardiomyopathy; ***DM***, myotonic dystrophy; ***EDMD***, Emery-Dreifuss muscular dystrophy; ***ICD***, implantable cardioverter-defibrillator; ***LGMD***, limb-girdle muscular dystrophy; ***NSR***, normal sinus rhythm; ***XL***, X-linked.

recommended to slow the progression of cardiomyopathy, but multiple studies have shown benefit when therapy is initiated prior to the onset of dysfunction (Arbustini et al., 2018; Hunt et al., 2005). The main focus of medical therapy has included angiotensin-converting enzyme inhibitors (ACEis), beta-blockers (BBs), and mineralcorticoid receptor antagonists (MRAs), and this has led to some success in improving DMD-related cardiomyopathy (see Fig. 3.6 and Table 3.2).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS MONOTHERAPY

A retrospective review of 52 patients with LVEF >55% showed early and prolonged administration of fosinopril and deflazacort prevents or delays the onset of cardiomyopathy with follow-up of nearly 11 years (Politano et al., 2001). A retrospective review of boys on angiotensin-converting enzyme or angiotensin receptor blocker (ARB) plus a steroid vs. steroid alone was conducted in 136 DMD subjects. ACEi did not slow a decline in functional capacity in children already on steroids, suggesting that steroids are a key therapeutic component of DMD management (Hor et al., 2011). Finally, in a more recent study by Schram and colleagues, 86 boys treated with ACEi or ARB with and without steroids were followed prospectively starting at age 9 years for an average of 11 years. Steroids yielded a 76% lower all-cause mortality rate, which was driven mostly by fewer heart failure–related deaths. Steroids were also associated with a 62% lower rate of new onset cardiomyopathy. Further, there were reductions in dilatation and declines in LV function on echocardiogram. There was no difference in weight, blood pressure, or heart rate in the steroid treated and untreated groups (Schram et al., 2013).

In an important study, Duboc et al. studied 57 children with DMD, 9.3 to 13.0 years old, with LVEF of greater than 55%. In the initial phase, 27 children were treated with the ACEi perindopril (2–4 mg/day) and 29 children received placebo for 3 years. After this period, all patients (n = 51) received perindopril for 2 years. There were no significant differences at the start or the end of the initial 3 years. The mean EF in the treated group was 60.7% versus 64.4% in the untreated group. One patient in each group had an LVEF of less than 45%. However, at the completion of the second phase, the LVEF was 58.6% in the initially treated group versus 56% in the initially untreated group. Eight patients in the initially untreated group had an LVEF of less than 45% compared with one patient in the treated group (Duboc et al., 2005). The same group published results after 10 years of follow-up. Even though all patients started with normal cardiac function, 93% of the initially treated group were alive versus only 66% of the untreated group (Duboc et al., 2007). Ramaciotti et al. also showed a benefit from ACEi treatment. In a retrospective analysis of 50 patients with DMD who were 10 to 20 years old, 10 of 27 patients with systolic dysfunction returned to normal function after treatment with the ACEi enalapril (Ramaciotti et al., 2006). A randomized, double blind, controlled trial of the ACEi lisinopril versus. the ARB losartan showed improvement in LVEF over a 12-month period, irrespective of which arm of the study showed equipoise between the two medications (Allen et al., 2013). Finally, a randomized control trial of enalapril versus placebo in 70 boys with DMD with LVEF >55% showed decreased myocardial fibrosis progression with CMRI over a 2-year time frame (Silva et al., 2017). These studies showed that early treatment with ACEi or ARB delayed the onset and progression of LV dysfunction and led to lower mortality rates in DMD.

Multiple studies have evaluated the efficacy of ACEi alone in children with DMD, with most recent evidence suggesting initiation prior to the onset of fibrosis seen on CMRI, which is usually the first sign of cardiac involvement in children with DMD (Russo et al., 2017). ACEis are thought to work by decreasing the amount of angiotensin II stimulated renin-angiotensin-aldoseterone system (RAAS) activation and by decreasing transforming growth factor beta (TGF-beta) activation. Both RAAS and TGF-beta are thought to induce fibrosis and increased extracellular matrix in the myocardium of children with DMD, so blockade is a useful therapy to prevent this (Russo et al., 2017).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND BETA-BLOCKERS

BBs are a standard heart failure therapy and frequently used based on adult trials in heart failure. The additive effect is also seen in adult trials of medications. The first study in pediatrics to compare ACEi vs. BB therapy was done by Kwon et al. (2012), which showed that DMD patients with FS <28% had improvement of their FS over a 20-month period regardless of treatment modality, with no significant side effects. Jefferies et al. followed patients with DMD ($n = 62$) and BMD ($n = 7$) with a mean age of 12.9 years and 13.7 years, respectively. After the first abnormal echocardiogram (LVEF <55%), patients were treated with an ACEi (enalapril, captopril, or lisinopril). If no improvements in the ACEi group were seen at 3 months, BBs (carvedilol or metoprolol) were added. ACEi was the single therapy in 42% of patients, and combination therapy was required in 58% of patients. The mean age of onset for ACEi therapy was 14.1 years in BMD and 16.1 years in DMD. BBs were initiated at a mean age of 16.0 years old in BMD and 18.1 years old in DMD. ACEi or BB therapy improved cardiac function in 27 of 29 patients (Jefferies et al., 2005). Ishikawa, Bach, and Minami (1999) also reported a reduction in neuroendocrine activity and LV dilatation in patients with DMD taking ACEi and BB, and Kajimoto et al. (2006) showed that combination therapy with carvedilol and an ACEi for 2 years resulted in a significant increase in FS in a mixed muscular dystrophy cohort.

A subsequent retrospective review of 52 patients with DMD with LVEF of <45% on ACEi plus BB with follow-up of 10 years showed improved long-term survival when started before symptom onset (Ogata, Ishikawa, Ishikawa, & Minami, 2009). A repeat retrospective cohort study with 42 patients and LVEF <55% on ACEi vs. ACEi plus BB showed significant improvement in both treatment groups, but no difference between the two arms (Viollet, Thrush, Flanigan, Mendell, & Allen, 2012). Overall, there seems to be good evidence to support use of both ACEis and BB in boys with DMD. Early treatment, prior to the onset of LV dysfunction, improves survival (Russo et al., 2017).

BETA-BLOCKER MONOTHERAPY

The BB carvedilol was studied by Rhodes et al. in patients with DMD who were 14 to 46 years old and had DCM and an LVEF of less than 50%. Carvedilol was administered for 6 months and was associated with a modest but statistically significant improvement in CMRI-derived LVEF (41%–43%). There were also trends toward improved FS and diastolic function. Carvedilol also decreased the incidence of VT seen in two patients (Hunt et al., 2005). Matsumura, Tamura, Kuru, Kikuchi, and Kawai (2010) found a cardiac event free survival in patients on BB, although patients were also on ACEi, so the purity of the result is difficult to interpret. BBs are considered helpful in patients with arrhythmia (Viollet et al., 2012).

MINERALCORTICOID RECEPTOR ANTAGONISTS

MRAs, including spironolactone and eplernone, are frequently used in heart failure management to prevent fibrosis associated with heart failure. A double-blind, randomized, placebo-controlled trial of eplerenone in patients with DMD with normal CMRI EF demonstrated a significant sparing of CMRI circumferential strain (Raman et al., 2015). Follow-up studies demonstrated improved myocardial strain in younger subjects, stabilized strain measures in older subjects with no decrease in LVEF, and similar effectiveness for both spironolactone and eplerenone (Raman et al., 2017, 2019). Due to the mild side effect profile, MRAs are recommended in cases when LGE is present as an additional therapy to ACEi.

In summary, the consensus recommendations include treatment starting at 10 years of age with an ACEi or ARB or at the time of any myocardial scarring seen on CMRI with LGE (Birnkrant et al., 2018a, 2018b, 2018c; Buddhe et al., 2018; McNally et al., 2015). MRA is a potential initial treatment and should be considered when LGE is present. BB therapy is considered in patients with higher heart rates or at the onset of LV dysfunction. The initiation of therapies prior to age 10 can be considered based on provider and family discussions.

HEART FAILURE

Management of symptomatic heart failure related to dystrophic cardiomyopathy is the same as that recommended by the American Heart Association for other forms of heart failure (Hunt et al., 2005). Diuretics (furosemide), MRA (spironolactone), and salt restriction are indicated in patients with fluid retention. BBs, especially carvedilol, long-acting metoprolol, and bisoprolol, blunt the sympathetic nervous system and reduce mortality rates in heart failure. An ACEi, as noted previously, modulates the renin-angiotensin-aldosterone system and improves cardiac remodeling. Drugs that adversely affect patients, including most antiarrhythmics and calcium channel blockers, should be avoided. Digoxin is most beneficial as an adjunctive therapy in patients who remain symptomatic while receiving the previously mentioned therapies. Initiation and maintenance dosing of these medications require a cardiologist's expertise and close monitoring of blood pressure, electrolyte levels, and renal function.

ANTICOAGULATION

Oral anticoagulation therapy can be used in cases of severe cardiac dysfunction to prevent intracardiac thrombus formation; however, the efficacy of this treatment remains unclear (Hunt et al., 2005). Anticoagulation should be used in cases of atrial fibrillation and flutter or if there is any history of an embolic event. A goal international normalized ratio of 2.0 to 2.5 should be maintained. Boriani et al. showed that four of 11 patients with atrial fibrillation or flutter in EDMD had an embolic stroke. Unfortunately, stroke was the initial presentation in three of these cases. Earlier diagnosis

and anticoagulation might have prevented this outcome (Boriani et al., 2003). EDMD is also associated with atrial standstill, and even with a pacemaker these patients are still at risk for thrombus formation and should be treated with anticoagulants (Bushby, Muntoni, & Bourke, 2003).

ARRHYTHMIAS

The treatment of arrhythmias in muscular dystrophy and other neuromuscular disorders depends on the type of disorder and associated arrhythmia. Physicians must consider the proarrhythmic side effects of these drugs. Conversion of atrial arrhythmias may be attempted with medical therapy, including propafenone and ibutilide. If ventricular arrhythmias are present, treatment with amiodarone, sotalol, or carvedilol can be effective. Standard monitoring of thyroid, liver, and pulmonary function is required for prolonged use of amiodarone. Drugs that can slow cardiac conduction are contraindicated in heart block and progressive bradyarrhythmias, including digoxin, BBs, and calcium channel blockers.

CARDIOVERSION

Synchronized cardioversion is a potential treatment for stable atrial flutter or fibrillation or stable VT. Imaging studies should confirm the absence of atrial thrombi, especially in the left atrial appendage. If a thrombus is present, anticoagulation therapy should be started and conversion of the rhythm delayed. Once the rhythm has been converted to sinus, medical therapy should be considered to decrease the likelihood of recurrent arrhythmias.

PACEMAKER IMPLANTATION

Some neuromuscular diseases are a class I indication for pacemaker implantation because of acquired AV block. These include forms of DM, Kearns-Sayre syndrome, and LGMD. This indication includes both symptomatic and a symptomatic patients because of the unpredictable progression of AV conduction disease in these patients (Gregoratos et al., 2002). The placement of devices can be limited by kyphoscoliosis and muscle wasting.

Lazarus et al. studied patients with DM and a prolonged His bundle–ventricular muscle interval. These patients, even if asymptomatic, received pacemakers. During EP testing, complete AV block, sinoatrial block, and atrial or ventricular tachyarrhythmias were found. Unfortunately, pacemakers did not prevent all deaths. Ten deaths occurred during the study, and four of these deaths were sudden. Pacemaker interrogation showed no arrhythmias in two of the patients with sudden death, and the other two patients did not have an interrogation performed. Other deaths were related to respiratory failure and embolic events (Lazarus et al., 2002). There are other reports of patients with DM who die suddenly despite functioning pacemakers (Grigg, Chan, Mond, Vohra, & Downey, 1985).

Boriani et al. studied patients with EDMD, and pacemakers were required for symptomatic bradyarrhythmias in seven with XL-EDMD and three with AD-EDMD. These patients were treated successfully, and complications occurred in three of these 10 cases, including lead displacements and lead fractures. One of the patients with EDMD had a pacemaker for 24 years and was 67 years old when the report was published. This shows that, with careful monitoring, pacemaker implantation is successful and survival can be long (Boriani et al., 2003).

Biventricular pacing is a strategy to treat heart failure symptoms in patients with clear ventricular uncoupling as evidenced by a prolonged QRS duration on resting ECG. The ventricles are paced simultaneously, increasing the cardiac output and relieving some symptoms of heart failure (Yancy et al., 2017). The effective use of biventricular pacing for the treatment of DCM in muscular dystrophy is not well studied. Case reports highlight successful implantation and use in adults with DMD and BMD with improvement in heart failure symptoms, but use in children is not yet reported (Andrikopoulos et al., 2013; Fayssoil & Abasse, 2010; Kono et al., 2015).

In a retrospective study of 486 patients with DM and PR >200 milliseconds or QRS >100 milliseconds, there was long-term follow-up to compare patients managed with "invasive strategy" (EP study, prophylactic pacemaker, or ICD as appropriate) vs. "noninvasive strategy" (close surveillance and EP study or device if the patient developed high-degree AV block on a surface ECG). On follow-up, the patients managed invasively had greater overall survival after adjusting for confounders. There was a significant reduction in sudden death with absolution risk reduction of 13.5%. There is concern about selection bias, but results suggest that arrhythmias should be managed aggressively in DM if present (Wahbi et al., 2012). In a registry of 406 patients with MD, 11% had a pacemaker and 5% had an ICD. 29% of patients with pacemakers died suddenly, with most common rhythm being ventricular. A PR interval >240 milliseconds and QRS >120 milliseconds were independent predictors of second- or third-degree AV block development. Further, QRS >120 milliseconds and history of atrial tachyarrhythmia were associated with resuscitated VT/ventricular fibrillation (VF) arrest or sudden death (Bhakta et al., 2011). In another cohort study of 100 patients with MD, 49 had pacemakers, with 6-fold death reduction risk relative to expected rate (Groh et al., 2008).

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IMPLANTATION

The benefits of primary prevention with an ICD implantation compared with pacemaker implantation remain under evaluation. Generally, ICDs are recommended for patients with an EF less than 35% in congruence with adult heart failure guidelines (Al-Khatib et al., 2005; McNally et al., 2015). The devices can be considered for secondary prevention in DMD and BMD patients with evidence of VT or VF.

In EDMD, Golzio et al. described the case of a 20-year-old woman who initially had first-degree AV block and was diagnosed with EDMD at 41 years. A pacemaker was implanted because of the new diagnosis and low ventricular rate response atrial fibrillation on Holter monitoring. She had palpitations, and Holter monitoring showed nonsustained VT. The pacemaker was replaced with an ICD device. Nine months later, during a febrile illness, the patient experienced three discharges from the ICD. Interrogation of the device showed three appropriate discharges for fast

polymorphic VT that deteriorated into VF. This life-saving discharge argues for ICD placement with concern that a stressful event, such as a febrile illness, could incite lethal arrhythmias in this susceptible population (Golzio, Chiribiri, & Gaita, 2007).

In an earlier study, Meune et al. prospectively offered ICDs to patients with EDMD who were referred for cardiac pacemakers. The indication for pacemaker implantation was progressive conduction block or sinus block, and no evidence of previous ventricular arrhythmias was required. The study involved 19 patients, and during a mean follow-up period of 34 months, eight patients received appropriate ICD discharges. Six patients had VF and two had rapid VT. One patient received an inappropriate shock. No other factors, including LVEF, spontaneous or inducible VT, or drug therapy, were related to the occurrence of ventricular arrhythmias in this population (Meune et al., 2006).

Walker et al. described a 42-year-old woman and manifesting carrier of EDMD who presented with palpitations secondary to premature ventricular beats. Seven years later, she had atrial fibrillation with slow ventricular response and required pacemaker implantation. She had normal ventricular function. Later, she developed heart failure secondary to progressive DCM and also developed VT. A biventricular ICD was placed without complication. The patient improved clinically and had appropriate antitachycardia pacing function. She did not have any ICD discharges (appropriate or inappropriate). This scenario should make ICD placement at initial presentation a consideration (Walker, Levy, Rex, & Paul, 1999).

LEFT VENTRICULAR ASSIST DEVICES

Left ventricular assist devices (LVADs) are frequently used in adults with heart failure as a bridge to transplant or destination therapy. As children with DMD reach adult age, LVADs may be considered given that cardiac transplantation is not often feasible (Amodeo, Filippelli, Molfetta, Perri, & Jarvik, R. 2017). There are a few case reports describing LVAD use in adults with DMD with results as expected (Adorisio et al., 2019; Iodice et al., 2015; Perri et al., 2016; Ryan et al., 2014; Stoller et al., 2017). The decision to use LVAD in DMD is complex with significant risks and should be considered on an individual basis after discussions with the cardiologist and heart failure specialist.

CARDIAC TRANSPLANTATION

Cardiac transplantation is a viable option in muscular dystrophy when the cardiac component presents earlier and with more severity than the skeletal and respiratory muscle disease. Complete evaluation of skeletal muscle disease and respiratory function is important. Previous concerns about transplantation in this group included higher perioperative risk and potential cardiomyopathy in the transplanted heart, but these concerns are now minimal. It is an effective therapy in patients with BMD and maternal carriers of dystrophin gene mutations (Melacini et al., 1998; Piccolo et al., 1994; Rees, Schüler, Hummel, & Hetzer, 1993). Transplantation has also been reported in patients with LGMD 2I, Friedreich ataxia, DM, and EDMD (Conraads, Beckers, Vorlat, & Vrints, 2002; D'Amico et al., 2008; Fatkin et al., 1999; McCormick et al., 2017; Murakami et al., 2006; Wahbi et al., 2012). In a recent review, 27 patients with DMD ($n = 3$), BMD ($n = 19$), carrier status ($n = 3$), or XL-DCM ($n = 2$) underwent cardiac transplantation. Those with DMD underwent transplantation at ages 12, 24, and 31 years. All patients with BMD were younger than 33 years at the time of transplant, except one 45-year-old (Finsterer & Stollberger, 2003). Ruiz-Cano et al. (2003) reported five patients with muscular dystrophy who underwent transplantation at a mean age of 38 years with no significant differences in hospital course or long-term complications compared with control subjects. Wu et al. (2007) reported 29 subjects with muscular dystrophy, including 3 with DMD, who had similar outcomes compared to controls. These studies show that cardiac transplantation is a potentially successful therapy for significant heart failure in many muscular dystrophies, although there are no uniform criteria for its use.

PREOPERATIVE ASSESSMENT

A complete cardiac evaluation should be performed before major surgical procedures (Birnkrant et al., 2018a, 2018b, 2018c). Medical therapy must be optimized before surgery, and there are specific concerns in patients with muscular dystrophy. Intraoperative monitoring and anesthesia performed by anesthesiologists experienced in cardiac dysfunction and muscular dystrophy are recommended. Schmidt, Burmeister, Lilje, Wappler, and Bischoff (2003) reported a case of acute heart failure in an 11-year-old boy with DMD and normal cardiac function during elective thoracolumbar stabilization. Patients with DMD are known to be at high risk for anesthesia-associated malignant hyperthermia. Complications have also occurred in patients with BMD and in carriers (Kelfer, Singer, & Reynolds, 1983; Kerr, Durward, Hodgson, Hughes, & Robb, 2001; Sethna, Rockoff, Worthen, & Rosnow, 1988). Breucking et al. found that sudden cardiac arrest during anesthesia in DMD and BMD occurred in 6 of 221 patients, but all 6 had undiagnosed muscular dystrophy at the time. No events occurred in patients with a known diagnosis (Breucking, Reimnitz, Schara, & Mortier, 2000). These cases show how major surgical procedures should be performed in tertiary care centers using subspecialty services familiar with muscular dystrophies. This is also discussed in Chapter 10.

RESPIRATORY THERAPY

Respiratory care should be optimized since abnormal respiratory function can affect the cardiac system and overall benefits were demonstrated with home ventilation (Eagle et al., 2002; Wollinsky, Kutter, & Geiger, 2012). A complete discussion is found in Chapter 2.

GENETIC-BASED THERAPIES

In an attempt to better understand DMD cardiomyopathy, several studies have investigated genotype-phenotype correlation in cardiac disease as a possible technique to predict disease severity or treatment response. Jefferies et al. used

DNA analysis in 47 cases and found a significant association between DCM and mutations in exons 12 and 14 to 17. There was also possible protection against DCM by mutations at exon 51 to 52 and a trend toward an association between the onset of DCM and mutations in exons 31 to 42 (Jefferies et al., 2005). However, Ramaciotti et al. (2006) could not find a specific mutation that was associated with response to enalapril or predictive of systolic dysfunction. Nigro et al. studied 284 patients and showed that cardiac involvement was related to deletions in exons 48 to 49 in 38% of patients with DMD and BMD. Patients with DMD who had this deletion died 3 years earlier than those with other deletions (Nigro, Politano, Nigro, Petretta, & Comi, 1994). Melacini et al. (1996) did not show a significant relationship between specific gene mutations and the development of cardiomyopathy in BMD. With further testing, genotype may become a useful clinical tool to personalize cardiac therapy.

Exon-skipping drugs are new therapies that increase dystrophin expression through bypassing stop codons and producing a truncated dystrophin protein. The first Food and Drug Administration–approved agent was the exon skipping phosphorodiamidate morpholino oligomer (PMO) eteplirsen, which targets the most common deletion seen in approximately 13% of DMD patients (exon 51). This therapy demonstrated increased partial dystrophin expression and may improve skeletal and respiratory muscle functions (Alfano et al., 2019; Charleston et al., 2018; Ducceschi et al., 1997; Lanza et al., 2001). A second agent, golodirsen, directed as exon 53, is now also approved. However, the effectiveness of these therapies on cardiomyopathy is not studied. Without effective cardiac muscle therapy, cardiomyopathy may limit the benefits of skeletal muscle therapies (Buddhe et al., 2018).

Gene therapy continues to progress in DMD and other muscular dystrophies. Based on small and large animal models and initial human clinical trial, the field is now studying the effectiveness of micro-dystrophin gene structure, new adeno-associated virus vectors, and muscle-specific promoters/enhancers (Mendell et al., 2010; Qiao et al., 2009; Toromanoff et al., 2009). The direct benefit on cardiac disease is still unclear. Gene editing, the most recent advance in gene therapy, involves dystrophin gene editing using clustered regularly interspaced short palindromic repeats (CRISPRs). This technology has already been shown to be able to replace a dystrophin mutation in the mdx mouse model of DMD and even in isolated human DMD cells (Long et al., 2014; Ousterout et al., 2015). With potential successes in gene therapy in the near future, the evaluation of cardiac muscle responses will be most important.

MONITORING

Routine monitoring of cardiovascular disease in muscular dystrophy is important. As noninvasive methods for the quantification of cardiac function improve, certain treatments may begin at earlier ages. Consensus statements have recommended general guidelines for the routine follow-up of the cardiovascular system in muscular dystrophy (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2005; Arbustini et al., 2018; Birnkrant et al., 2018a, 2018b, 2018c; Bushby et al., 2003, 2004; Dutka et al., 1999; Hunt et al., 2005; Kajimoto et al., 2006; Kipps et al., 2009; McNally et al., 2015). A brief summary of these recommendations follows and is found in Table 3.3. Once cardiac disease is identified, follow-up is dictated by the type and severity of cardiac disease. Also, evaluation with more sophisticated tools for the detection of preclinical abnormalities, including CMRI at tertiary care centers, is recommended.

DUCHENNE MUSCULAR DYSTROPHY

A complete initial evaluation should be performed at the time of diagnosis. This evaluation should include medical history, family history, and physical examination, electrocardiogram, and echocardiogram. Consideration should be given to further testing. Holter monitoring can be used periodically or annually after the onset of abnormal cardiac function. Event monitors can be considered for episodic symptoms potentially related to arrhythmias (Birnkrant et al., 2018a, 2018b, 2018c). For DMD, patients should have a complete cardiac evaluation including echocardiogram and ECG annually (Birnkrant et al., 2018a, 2018b, 2018c). Once there are symptoms or abnormalities on imaging (LV enlargement, LV dysfunction, myocardial fibrosis), follow-up is per the patient's cardiologist and will be related to the degree of cardiac dysfunction (Birnkrant et al., 2018a, 2018b, 2018c; Bushby et al., 2010). CMRI can provide improved imaging and can initially be performed around age 6–8 years when anesthesia is not required to monitor for myocardial fibrosis.

Advances in treatment systemically have led to improvements in life expectancy (Arbustini et al., 2018). ACEis are recommended starting at age 10 years or when LGE is seen on MRI (Birnkrant et al., 2018a, 2018b, 2018c; Duboc et al., 2005; McNally et al., 2015; Russo et al., 2017). Evaluations should also be performed before any scheduled surgery.

BECKER MUSCULAR DYSTROPHY

A complete cardiac evaluation should be performed at the time of diagnosis or no later than 10 years of age and should continue every 2 to 5 years if asymptomatic. Once significant cardiac disease is diagnosed, cardiac transplantation is a viable treatment option, and referral to a cardiac transplant center is recommended.

CARRIERS OF DUCHENNE MUSCULAR DYSTROPHY OR BECKER MUSCULAR DYSTROPHY

Known carriers should be referred for cardiac evaluation in late adolescence or early adulthood as nearly 10% can develop cardiomyopathy (Wexberg et al., 2016). The patient must be informed of the risks of cardiac disease and the signs and symptoms of heart failure. Carriers should be screened with a complete evaluation at 25 to 30 years and every 5 years thereafter if asymptomatic. Evaluations may become more frequent based on symptoms and imaging results or at the cardiologists' discretion.

LIMB-GIRDLE MUSCULAR DYSTROPHY

An initial or occasional cardiac evaluation may be useful in LGMD not associated with cardiac disease (LGMD 1A, 1C,

Table 3.3 Summary of Follow-up Recommendations for Cardiac Diseases Present in Neuromuscular Disorders

Diagnosis	Cardiology Evaluation	ECG/Holter	Echocardiogram	Cardiac MRI	Other
DMD	At initial diagnosis Once every year More frequent evaluations based on clinical disease	ECG at every visit Monitor R/Q waves, conduction intervals, arrhythmias Holter when EF <35%, abn ECG, or symptomatic	Complete evaluation at every visit, including assessment of diastolic function	Once a year starting approximately age 8 Evaluate for LGE	Consider biventricular pacemaker when appropriate Consider mechanical circulatory support when appropriate
BMD	At initial diagnosis and every 2 years as child Once yearly as teenager More frequent evaluations based on clinical disease	ECG at every visit Monitor R/Q waves, conduction intervals, arrhythmias Holter when EF <35%, abn ECG, or symptomatic	Complete evaluation at every visit, including assessment of diastolic function	Once a year starting approximately age 15 Evaluate for LGE	Consider transplant evaluation when appropriate
DMD/BMD carrier	Initial evaluation at 25–30 years old Every 5 years or sooner based on clinical disease	ECG at every visit Monitor R/Q waves, conduction intervals, arrhythmias Holter when EF <35%, abn ECG, or symptomatic	Complete evaluation at every visit, including assessment of diastolic function	Initial evaluation Evaluate for LGE Based on clinical disease	Consider transplant evaluation when appropriate
LGMD (1B, 2C, 2D, 2E, 2F and 2I)	At initial diagnosis Once every year More frequent evaluations based on clinical disease	ECG at every visit Monitor R/Q waves, conduction intervals, arrhythmias Holter when EF <35%, abn ECG, or symptomatic	Complete evaluation at every visit, including assessment of diastolic function	Once a year starting approximately age 8 Evaluate for LGE	Cardiac transplant dependent on skeletal myopathy
DM	At initial diagnosis Once every year	ECG at initial diagnosis ECG once a year Monitor for AV conduction intervals, arrhythmias (especially atrial) Holter once a year or symptomatic	At initial diagnosis Every few years	Consider if symptomatic	EP testing Pacemaker placement if progressive delays
EDMD (XL and AD)	At initial diagnosis Once every year	At initial diagnosis Once every year Monitor for AV conduction intervals, arrhythmias Holter once a year or symptomatic	At initial diagnosis Every few years	Consider if symptomatic	EP testing Pacemaker/?ICD placement when progressive disease present
Friedreich ataxia	At initial diagnosis Once every year	At initial diagnosis Once every year Monitor for Q waves, ventricular hypertrophy, and repolarization abnormalities Holter if abn ECG or symptomatic	At initial diagnosis Once every year Monitor for hypertrophic cardiomyopathy with outflow obstruction and dilated cardiomyopathy	Consider if symptomatic	Genetic evaluation of GAA repeats because longer repeats are associated with more severe cardiac disease

abn, Abnormal; *AD*, autosomal dominant; *AV*, atrioventricular; *BMD*, Becker muscular dystrophy; *DM*, myotonic dystrophy; *DMD*, Duchenne muscular dystrophy; *ECG*, electrocardiogram; *EDMD*, Emery-Dreifuss muscular dystrophy; *EF*, ejection fraction; *EP*, electrophysiologic; *ICD*, implantable cardioverter-defibrillator; *LGE*, late gadolinium enhancement; *LGMD*, limb-girdle muscular dystrophy; *MRI*, magnetic resonance imaging; *XL*, X-linked.

Data from:

1) Birnkrant, D. J., Bushby, K., Bann, C. M., Alman, B. A., Apkon, S. D., Blackwell, A., et al.; DMD Care Considerations Working Group. (2018). Diagnosis and management of Duchenne muscular dystrophy, part 2: Respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurology, 17*, 347-361.
2) Arbustini, E., DiToro, A., Giuliani, L., Favalli, V., Narula, N., & Grasso, M. (2018). *JACC* state of the art review cardiac phenotypes in hereditary muscle disorders. *Journal of the American College of Cardiology, 70*, 2489-2506.
3) Feingold, B., Mahle., W., Auerbach, S., Clemens, P., Domenighetti, A. A., Jefferies, J. L., et al. (2017). Management of cardiac involvement associated with neuromuscular diseases: A Scientific Statement From the American Heart Association. *Circulation, 136*, e200-e231.
4) Hunt, S.A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., Ganiats, T. G., et al. (2005). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation, 112*, e154-e235.

2A, 2B, 2G, 2H, and 2J). LGMD 1B, 2C, 2D, 2E, 2F, and 2I can be associated with severe cardiac disease and should be monitored with the same frequency as DMD. Complete evaluations, including ECG testing, echocardiography, Holter monitoring, and additional testing as indicated, are recommended. Because of different skeletal muscle manifestations, cardiac transplantation may be indicated in selected patients.

MYOTONIC DYSTROPHY

A complete cardiac evaluation, including ECG examination, echocardiogram, and Holter monitoring, should be performed at diagnosis. Annual ECG testing should be performed after diagnosis, with echocardiography performed less frequently, depending on arrhythmias or symptoms. Holter monitors should be placed if any progressive changes are seen on ECG findings. Referral to a tertiary cardiac center for EP testing may further elucidate AV conduction abnormalities. Treatment with a pacemaker is indicated when a progressive arrhythmia is detected, even if it is asymptomatic. The value of ICD use is not clear at this time. No prospective trials have been done to evaluate ACEi in DM; however, there is suggestion that ACEi may inhibit fibrosis and prevent arrhythmias (Russo et al., 2017). Further studies are required. Although cardiac disease is seen in DM type II, there are no current recommendations, but evaluation similar to that for DM type I is likely prudent (Lau et al., 2015).

X-LINKED EMERY-DREIFUSS MUSCULAR DYSTROPHY

The major cardiac defect in XL-EDMD is AV conduction defect seen in all cases before age 40 (Groh, 2012). Complete cardiac evaluation, including ECG examination, echocardiogram, and Holter monitoring, should be performed at diagnosis. ECG testing and Holter monitoring should be performed annually. Atrial level tachyarrhythmias including Wolff-Parkinson-White (WPW) syndrome are present in slightly less than half of patients irrespective of any septal hypertrophy (Gueneau et al., 2009). Referral to a tertiary cardiac center for EP testing may further elucidate AV conduction abnormalities. Treatment with a pacemaker is indicated when a progressive arrhythmia is detected, even if the patient is asymptomatic. The value of ICD use is not clear at this time. DCM is less frequent, and echocardiograms are not required on a yearly basis. Again, there is suggestion that ACEi may prevent fibrosis and arrhythmia risk, but prospective trials are needed prior to recommending them fully (Russo et al., 2017). Follow-up for EDMD carriers is not clear, but they can have abnormal echocardiograms (Gueneau et al., 2009).

AUTOSOMAL DOMINANT EMERY-DREIFUSS MUSCULAR DYSTROPHY

In patients with AD-EDMD, the concerns are similar to those with XL-EDMD; however, there is stronger evidence of progressive cardiac involvement and DCM. Complete cardiac evaluation, including ECG examination, echocardiogram, and Holter monitoring, should be conducted at diagnosis and annually. ECG derangements are generally seen before age 40 and typically present in ages 20s–30s. Sudden death has been reported to account for 30% of all deaths in these patients and is associated with nonsustained VT, LVEF <45%, male gender, and lamin A or C nonmissense mutations (Groh, 2012). Referral to a tertiary cardiac center for EP testing may help to further elucidate AV conduction abnormalities. Treatment with a pacemaker is indicated when a progressive arrhythmia is detected. Sudden death is also seen, even after pacemaker implantation, so ICD may be a more appropriate device in these patients.

FRIEDREICH ATAXIA

There is significant variation in the degree of cardiac involvement in Friedreich ataxia. Most patients are asymptomatic, but cardiac hypertrophy can become severe enough to obstruct blood flow out of the left ventricle. Patients can also progress from a hypertrophic cardiomyopathy to a DCM. Cardiac evaluation should be performed at diagnosis and yearly to monitor for progression of disease. Genetic testing may be valuable because studies have shown increased cardiac hypertrophy with a larger number of GAA repeats (Dutka et al., 1999; Isnard et al., 1997).

CONGENITAL MUSCULAR DYSTROPHY

Cardiac evaluation every 2 years is generally recommended unless patients have MTM1 and RYR1 mutations without previous cardiac involvement. Patients with MTM1 and RYR1 mutations without previous cardiac history need not be followed (Wang et al., 2011).

SUMMARY

Outcomes for neuromuscular disease vary significantly, and some patients present early in the course of disease with cardiac complications. However, in many cases, the severity of cardiac disease is mild and secondary to skeletal muscle disease. Yet, with improvements in the recognition and treatment of skeletal and respiratory muscle systems, cardiac disease will account for a greater proportion of morbidity and mortality in these cases. It seems logical that early diagnosis and treatment of cardiac disease will lead to improved patient quality of life and outcomes. Unfortunately, there are limited studies and conflicting evidence to completely support this theory. Although some studies have shown benefits of early treatment in DMD and BMD, the sample sizes are small and the treatment paradigms varied. As the ability to diagnose preclinical changes in myocardial function improves with echocardiography, CMRI, and other modalities, the benefits of different pharmacologic therapies will require further investigation. Corrado et al. showed that even after following ECG findings, ventricular late potentials, and ventricular arrhythmias in DMD patients, only the late finding of decreased ventricular systolic function was a significant predictor of outcome (Corrado et al., 2002; Dittrich et al., 2015). Connuck et al. studied outcomes in DMD and BMD cardiomyopathy and found a significantly worse mortality rate in DMD compared with BMD and other forms of cardiomyopathy. More importantly, the authors also found a lower rate of medical therapy with ACEi and BB in DMD

(Connuck et al., 2008). Thus, to improve outcomes, further study of early diagnosis and the benefits of early treatment is needed.

For muscular dystrophies significantly associated with AV conduction block and arrhythmias, there is clear benefit from early diagnosis and treatment. These patients benefit from pacemaker implantation and show improved quality of life and prognosis. Unfortunately, even with the use of ICDs, these measures cannot prevent sudden death in these patients (Grigg et al., 1985; Lazarus et al., 2002).

CONCLUSION

Neuromuscular disorders are significantly associated with cardiac disease. Involvement of a cardiologist who is an integral member of a multidisciplinary care team is recommended (Birnkrant et al., 2018a, 2018b, 2018c). Early proactive recognition and treatment of cardiac dysfunction or abnormal electrical conduction can have a profound effect on the long-term quality of life for these patients. With improved imaging techniques, a more complete understanding of myocardial dysfunction may help to reduce morbidity and mortality rates. However, to improve the diagnosis and treatment of cardiac disease in muscular dystrophy, further multi-institutional studies with specific treatment protocols are required to better establish revised guidelines using evidence. These studies, combined with continued advances in genotyping and new experimental therapies, will lead to improved treatment and outcomes for patients.

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Gastrointestinal Complications of Neuromuscular Disorders

4

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INTRODUCTION

The gastrointestinal (GI) tract is an extremely dynamic organ with its extensive muscle regulated not only by enteric nervous system but also by the central nervous system, autonomic nervous system, as well as humoral factors. It is therefore not surprising that many neuromuscular diseases affect the GI tract (Chaudhry, Umapathi, & Ravich, 2002).

GI symptoms occur commonly in neurological diseases, usually as transfer/oropharyngeal dysphagia, nausea, early satiety, constipation, or incontinence (Tieleman et al., 2008; Toepfer, Folwaczny, Klauser, et al., 1999) (Box 4.1). GI manifestations have also been reported in neurological autoimmune disorders like neuromyelitis optica and other autoimmune enteric neuropathies (Blackburn, Kubiliun, Harris, & Vernino, 2019).

PHARYNX AND ESOPHAGUS

IMPAIRMENT OF DEGLUTITION (DYSPHAGIA)

Dysphagia is one of the most disabling conditions arising from neuromuscular disorders, with high morbidity, mortality, and cost (Costantini et al., 1996; Janzen, Rae, & Hudson, 1988). Dysphagia typically refers to difficulty in eating as a result of disruption in the swallowing process. It is a subjective sensation that suggests the presence of an organic abnormality in the passage of liquids or solids from the oral cavity to the stomach. Patients' complaints range from the inability to initiate a swallow to the sensation of solids or liquids being hindered during their passage through the esophagus into the stomach. The prevalence of dysphagia in selected neuromuscular disorders is depicted in Table 4.1 (Britton, Karam, & Schindler, 2018).

Dysphagia can be classified as either oropharyngeal or esophageal. Oropharyngeal dysphagia, also called transfer dysphagia, arises from disorders that affect the function of the oropharynx, larynx, and upper esophageal sphincter (UES). Neurogenic and myogenic disorders as well as oropharyngeal tumors are the most common underlying causes for oropharyngeal dysphagia. Esophageal dysphagia arises within the body of the esophagus, the lower esophageal sphincter, or cardia and is most commonly due to mechanical causes or a motility disturbance. However, some neuromuscular disorders affect the esophagus as inflammatory myopathies.

Normal swallowing consists of three phases (oral, pharyngeal, and esophageal), which are usually performed effortlessly up to 600 times a day. A total of five cranial nerves (V, VII, IX, X, and XII) and 26 muscle groups are involved in coordinating the act of swallowing. In the oral phase, the food is chewed and the bolus is pushed to the pharynx under voluntary control. In the pharyngeal phase, the nasopharynx closes to prevent food entry into the nasal passages. The vocal cords approximate and the epiglottis tilts downward to prevent entry of food into the airway. Relaxation of the upper esophageal sphincter and progressive waves of muscular contraction propel the food bolus into the esophagus. In the esophageal phase, peristalsis moves the food bolus through the esophagus and the lower esophageal sphincter into the stomach.

PATHOGENESIS

Oropharyngeal dysphagia can arise from the abnormalities of the oral or pharyngeal phase of swallowing. A variety of disorders from neurologic and muscular diseases affecting the strength and coordination of orofacial muscles can lead to disrupted swallowing. As described earlier, a coordinated neuromuscular event in the pharyngeal phase is required for successful transit of a bolus in the esophagus, and any disruption caused by neuromuscular disease can lead to failure of swallowing and result in dysphagia (Box 4.2). Patients with these groups of disorders are also particularly at risk for postextubation dysphagia following a critical illness, with occurrence rates as high as 33% (Smithard, 2013).

CLINICAL MANIFESTATIONS

Like any other medical conditions, a detailed history is useful in elucidating the cause of the dysphagia.

Patients affected with dysphagia often present with subjective complaints of either choking on solids or inability

Box 4.1 Gastrointestinal Manifestations of Neuromuscular Diseases

Dysphagia
Dyspepsia
Gastroparesis
Chronic intestinal pseudo-obstruction
Bacterial overgrowth
Weight loss
Constipation
Incontinence

Table 4.1 Prevalence of Dysphagia in Selected Neuromuscular Diseases

Examples	Prevalence
Inclusion body myositis	65% to 80%
Duchenne muscular dystrophy (muscle level)	Unknown; <30% report dysphagia, >95% based on modified barium swallow study findings—greater with advancing age
Myasthenia gravis (neuromuscular junction disease)	30% as an early symptom. Up to two thirds of individuals with myasthenia gravis
Amyotrophic lateral sclerosis	95%–98% bulbar onset. 35%–73% spinal onset

Adapted from Britton, D., Karam, C., & Schindler, J. S. (2018). Swallowing and secretion management in neuromuscular disease. *Clinics in Chest Medicine*, *39*(2), 449-457.

Box 4.2 Neurological and Myopathic Etiologies of Dysphagia

Neurological	*Myopathic*
Stroke	Connective tissue disorders
Head injury	Dermatomyositis
Brain stem tumors	Oculopharyngeal dystrophy
Cerebral palsy	Muscular dystrophy, e.g., oculopharyngeal dystrophy, Duchenne muscular dystrophy, myotonic dystrophy, and others
Guillian-Barre syndrome	Polymyositis
Huntington's disease	Sarcoidosis
Polio	Myasthenia gravis
Postpolio syndrome	Paraneoplastic syndromes
Amyotrophic lateral sclerosis (ALS)	
Parkinson's disease	
Multiple sclerosis	
Tardive dyskinesia	
Dementia	
Metabolic encephalopathies	

Box 4.3 Neuromuscular Disease Swallowing Status Scale (NdSSS)

Level 1 Tube feeding with saliva suctioning in the oral cavity necessary. A patient can neither discharge nor swallow saliva.
Level 2 Tube feeding without suctioning. Although a patient cannot take anything by mouth, can discharge and/or swallow saliva.
Level 3 Tube feeding with occasional oral intake. A patient sometimes take orally for fun, not for nourishment.
Level 4 Totally orally fed and tube-free with supplemental nutrients, such as enteral solution. A patient usually takes supplemental nutrients by mouth although does not take general food.
Level 5 Totally orally fed with easy-to-swallow food and supplemental nutrients, such as enteral solution. A patient sometimes/often takes supplemental nutrients by mouth.
Level 6 Totally orally fed with only easy-to-swallow food. A patient eats foods processed in a mixer and drinks thickened water.
Level 7 Totally orally fed with no difficulties. A patient eats without something difficult to eat.
Level 8 Totally orally fed with no restrictions. A patient eats all kinds of food.

"Tube feeding" modes include feeding by a nasogastric tube, a gastrostomy tube, and so on.
Adapted from Wada, A., Kawakami, M., Liu, M., Otaka, E., Nishimura, A, Liu, F., et al. (2015). Development of a new scale for dysphagia in patients with progressive neuromuscular diseases: The Neuromuscular Disease Swallowing Status Scale (NdSSS). *Journal of Neurology*, *262*(10), 2225–2231.

to swallow food. Associated symptoms including coughing, choking, nasal regurgitation, and dysarthria are suggestive of oropharyngeal dysphagia. Neuromuscular disorders tend to be progressive in nature, with GI complications manifesting later in the course of the disease. Scoring systems like the Neuromuscular Disease Swallowing Status Scale (NdSSS) (Box 4.3) can be utilized to monitor the progression of dysphagia (Wada et al., 2015).

DYSPHAGIA IN MOTOR NEURON DISORDERS

Dysphagia due to bulbar or pseudobulbar palsy occurs in up to 25% of amyotrophic lateral sclerosis (ALS) patients at the onset of the disease (Caroscio, Mulvihill, Sterling, & Abrams, 1987). Dysphagia occurs very early in patients with bulbar onset as compared to those with spinal onset, in which the disease duration influences the occurrence of dysphagia (Andrenelli et al., 2018). Eventually, almost all patients with ALS have at least some degree of dysphagia (Leighton, Burton, Lund, & Cochrane, 1994). In motor neuron disorder (MND), weakness of the orolingual as well as the pharyngeal muscles leads to swallowing difficulties. Pharyngeal constrictor muscle weakness results in choking or coughing during or immediately after swallowing. Sialorrhea (drooling) is common and results from impaired pharyngeal clearance and weakness of oral muscles rather than an increase in salivation. Progression of dysphagia results in weight loss because of the patient's inability to maintain adequate caloric intake with oral feedings alone. Dysphagia affects not only caloric intake but also the delivery of effective disease-modifying drug therapy like Riluzole in patients with ALS. Riluzole is available in an oral suspension, which can be used as an alternative to tablets for patients with dysphagia. Riluzole did not impact survival either in dysphagic or in nondysphagic ALS patients (Onesti et al., 2017).

DYSPHAGIA IN PRIMARY MUSCULAR DISORDERS

Dysphagia in myopathies arises from impairment of pharyngeal and esophageal phases (Jaffe, McDonald, Ingman, & Haas, 1990).

Unlike neurogenic disorders (neuropathies and motor neuron disease) and disorders of neuromuscular transmission, there is usually no significant impairment of

mastication. However, to avoid aspiration, patients may spend a long time chewing their food. Nasal regurgitation and dysarthria are also less frequent (Bellini et al., 2006).

Although in theory any muscular disorder may present with impairment of swallowing, abnormalities of deglutition tend to predominate in some types of muscle disease. These include certain muscular dystrophies such as oculopharyngeal muscular dystrophy (OPMD) (Tiomny et al., 1996), myotonic dystrophy (MD) and patients with advanced stages of Duchenne muscular dystrophy (DMD), and fascioscapulohumeral myopathy (Hill, Hughes, & Milford, 2004; Jaffe et al., 1990; Jequier & Todorov, 1967; Wohlgemuth et al., 2006). Inflammatory disorders such as polymyositis (PM), dermatomyositis (DM), and inclusion body myositis can involve the muscles of deglutition. Metabolic myopathies, particularly mitochondrial myopathies, may present with impairment of swallowing as well (Mueller, Camilleri, & Emslie-Smith, 1999). Some patients who have cricopharyngeal (CP) achalasia with associated impairment of the CP muscle function and its ability to relax can present with oropharyngeal dysphagia.

Recently, some authors have suggested that a combined myopathic-neuropathic etiology could provide a more satisfactory explanation for the pharyngo-esophageal symptoms of MD, but at present, this remains speculative (Modolell et al., 1999). Marked atrophy of the esophageal striated muscle, but only small changes in the smooth muscle, was observed in one study (Jequier & Todorov, 1967), and using electron microscopy in another study, Ludatscher, Kerner, Amikam, and Gellei (1978) detected mild degenerative changes with disoriented filaments of the smooth muscle.

MD (Steinert disease) is the most common adult-onset form of muscular dystrophy. There are frequent dysarthria and dysphagia owing to weakness of the palatal and pharyngeal muscles (Costantini et al., 1996). In MD, different studies have reported a prevalence of dysphagia ranging from 25% to 80% (Lecointe-Besancon et al., 1999; Nowak, Ionasescu, & Anuras, 1982; Ronnblom, Forsberg, & Danielsson, 1996).

OPMD, an autosomal dominant disorder, manifests as bilateral symmetrical ptosis, external ophthalmoparesis, and dysphagia (Tiomny et al., 1996). Dysphagia is frequent and may be the presenting symptom with impairment mainly of the pharyngeal phase, although lingual and oral phases can also be affected. Patients usually develop symptoms between the fourth and fifth decades. In one study, retroflexion of the head because of ptosis was noted to deteriorate preexisting dysphagia in OPMD patients. Subjective and objective reduction of swallowing problems was found when patients were instructed to eat and drink with a slightly flexed head position (de Swart et al., 2006). Complications including dysphonia and aspiration can develop after years of progression.

In DMD, there is some involvement of the oropharyngeal muscles (Jaffe et al., 1990). The occurrence of macroglossia further complicates the oral phase of swallowing. In the oral preparatory phase, occasional difficulties in bringing food to the mouth, chewing difficulty, and malocclusion have been observed in patients with DMD, including tongue biting due to macroglossia.

DYSPHAGIA IN INFLAMMATORY MYOPATHIES AND NEUROMUSCULAR JUNCTION DISORDERS

Among inflammatory myopathies, PM associated with connective tissue disease and inclusion body myositis (IBM) are most likely associated with dysphagia (van der Meulen et al., 2003; Verma et al., 1991). Of all the inflammatory myopathies, IBM is notorious for esophageal involvement and a steroid resistant disease course (Hilton-Jones & Brady, 2016; Schneider, Thumfart, Pototschnig, & Eckel, 1994). Dysphagia occurs primarily from the involvement of striated muscles, but in some cases the upper third of the esophagus may be affected. Dysphagia is often an early presenting symptom in older patients affected with inflammatory myopathy. Disorders affecting neuromuscular junction including myasthenia gravis can present with intermittent swallowing problem and are often associated with oculomotor abnormalities, including diplopia, and facial muscle weakness. Clinical symptoms range from problems with chewing food or moving it in their mouth to problems related to the pharyngeal phase. Involvement of the pharyngeal muscles in Lambert-Eaton syndrome has been described, and only a small number of patients develop dysphagia.

DYSPHAGIA IN PERIPHERAL NEUROPATHY

Peripheral neuropathy seldom involves the pharyngeal muscles. However, polyradiculoneuropathies, both acute (Guillain-Barre Syndrome) and chronic inflammatory demyelinating neuropathy involving cranial nerves, can lead to pharyngeal and cervical muscle weakness.

NUTRITION

Failure to gain weight and associated weight loss are commonly associated with feeding and nutritional problems in patients with neuromuscular diseases. Feeding difficulties have been reported in approximately 30% of DMD patients younger than 25 years (Willig, Bach, Venance, & Navarro, 1995). Weight loss is another common symptom in ALS (Cameron & Rosenfeld, 2002; Slowie, Paige, & Antel, 1983; Worwood & Leigh, 1998) and usually relates to the progression of dysphagia, which results in the patient's inability to maintain adequate caloric intake with oral feedings alone (Hardiman, 2000). Weight loss may also develop in patients with and without bulbar involvement because of generalized fatigue, poor appetite, and associated depression (Heffernan et al., 2004). Malnutrition is a poor prognostic factor and correlates with increased risk of death; therefore, once a patient has lost 5%–10% of normal body weight, consider enteric feeding and discuss options with the patient and caregivers. Assessment of a patient's nutrition status should involve referral to a nutrition specialist soon after diagnosis, facilitating careful monitoring of caloric intake and body mass.

Malnutrition can be indicated by the triceps skin fold and arm muscle circumference measurements being below the 30th percentile, with measurements below the 24th percentile indicating severe malnutrition (Slowie et al., 1983). The upper extremity anthropometrics of mid-arm circumference, triceps skin fold thickens, and mid-arm muscle circumference are argued to be precise indicators of nutritional status (Kasarskis et al., 1996; Worwood & Leigh, 1998).

A combination of body composition measures (body weight dietary histories, body mass index [BMI], biochemical tests, anthropometry) is recommended to achieve accurate assessment of nutritional status. Assessment of lean body mass by dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) is useful, but each method has its own limitations. Laboratory values for hemoglobin, hematocrit, serum iron, transferrin, glucose, blood urea nitrogen, creatinine, lipid profile, and protein stores of albumin and transthyretin (prealbumin) should be evaluated and monitored. Given the evidence demonstrating a direct relationship between survival and nutritional status, early nutrition intervention should be a standard component of care in the patient with neuromuscular diseases (Cameron & Rosenfeld, 2002).

While at risk for undernutrition, patients with neuromuscular disorders are at risk for overnutrition as well, risk factors being decreased caloric needs, decreased resting energy expenditure, decreased physical activity, and increased appetite because of medications (Davis, Samuels, & Mullins, 2015). These patients are at risk for acceleration of disease progression, worsening of pulmonary and cardiac functions, and deterioration of skeletal malformations. Hence, optimal nutritional status must be checked time and again in these groups of disorders (Davis et al., 2015; Davidson & Truby, 2009).

DYSPHAGIA DIAGNOSIS AND EVALUATION

Various noninstrumental examinations (volume-viscosity swallow test, Eating Assessment Tool 10) as well as instrumental examinations (videofluoroscopic swallowing study [VFSS] or fiberoptic endoscopic evaluation of swallowing [FEES]) can be utilized to evaluate and screen patients with MND for dysphagia. VFSS, in conjunction with an oropharyngeal examination by a speech pathologist, can provide a more objective measurement of swallowing (Barbiera et al., 2006). Videofluoroscopy involves the swallowing by the patient of barium suspension of varying consistency, fluid and semisolid. An analysis of the various stages of swallowing is made, and laryngeal penetration can be reliably detected by videofluoroscopy. Videofluoroscopy can also help guide decisions about feeding regimes and estimate the patient's risk of respiratory complications from oral feeding. Videofluoroscopy could be used to assess risks of aspiration. The presence of laryngeal penetration on videofluoroscopy in the setting of clinical dysphagia indicates a high risk of aspiration pneumonia (Figs. 4.1 and 4.2). Cineradiographic studies of the pharynx in MD patients have revealed abnormalities such as weak and asymmetric contractions of the pharynx and cricopharyngeus, myotonia of the tongue and pharynx with stasis, and pooling of contrast in the pyriform sinuses and valleculae. The combined techniques of videofibrolaryngoscopy and videofluoroscopy can be the best methods for evaluating dysphagia.

Manometry is useful in detecting motility disturbances, which show in the form of asymmetric contractions of the pharynx and weak contractions of the upper esophageal sphincter. In the esophageal body, significant decreases in the peristaltic amplitude and/or simultaneous waves have often been reported among patients with MD (Costantini et al., 1996; Eckardt, Nix, Kraus, & Bohl, 1986; Hila, Castell, & Castell, 2001; Lecointe-Besancon et al., 1999; Modolell et al., 1999; Swick et al., 1981). However, manometric findings are not significantly different between symptomatic and asymptomatic patients or in patients with different degrees of striated muscular involvement. Eleven patients with an established diagnosis of OPMD were studied by Castell, Castell, Duranceau, and Topart (1995). They found that nine of these patients showed abnormal UES and pharyngeal manometrics, with the most common abnormalities found in the pharynx (UES and pharyngeal incoordination, prolonged pharyngeal contraction, low pharyngeal pressure, and low

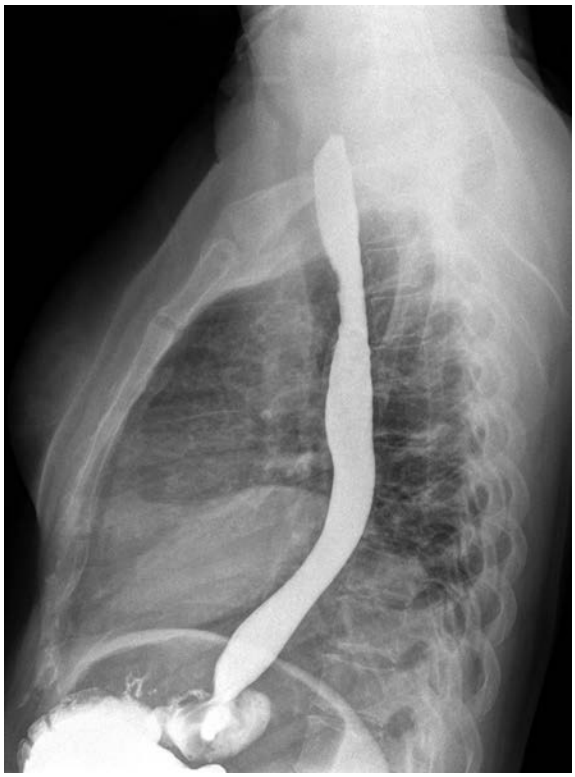


Fig. 4.1 Normal esophagogram.

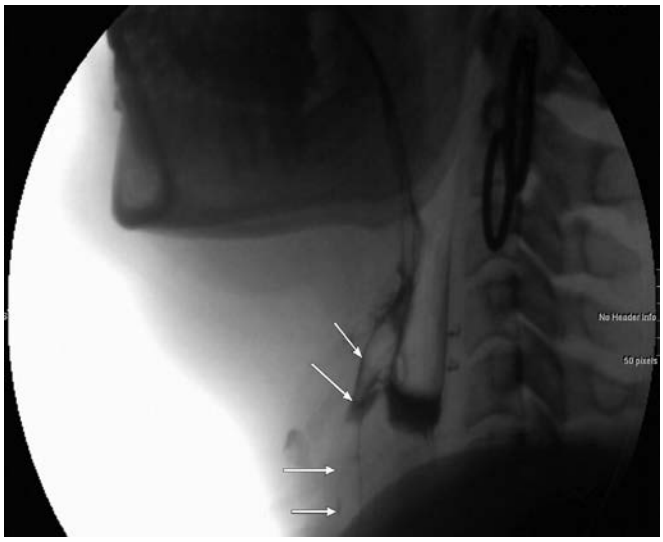


Fig. 4.2 Modified barium swallow with aspiration: on the lateral image, *arrows* show abnormal spillover with aspiration.

pharyngeal contraction rate). Another procedure that has been used for evaluation of dysphagia in MND patients is the use of electromyographic (EMG) techniques.

Routine endoscopy is not helpful in the majority of patients unless underlying esophageal inflammation with complications related to reflux needs endoscopic evaluation. A study comparing VFSS with FEES found that VFSS had a significantly greater sensitivity in detecting swallowing alterations as compared to FEES (Briani et al., 1998). The authors of the paper also recommended FEES only if VFSS is not available or if the patient cannot be positioned for the study or is bedridden.

Noninvasive studies are quick, cost-effective, highly sensitive, and specific tools for screening, which can be confirmed using instrumental examinations when the aspiration status is still unclear from noninvasive studies (Audag, Goubau, Toussaint, & Reychler, 2019).

MANAGEMENT

Initial management of dysphagia includes modification of food and fluid consistency and coaching by a speech pathologist (Leigh et al., 2003). The use of thicker liquids and semisolid foods with a high water content, such as gelatin, can help alleviate aspiration (Hillel & Miller, 1989). In relation to liquids, drinking through straws can help swallowing (Andersen et al., 2005).

It is usually advised that patients should eat more slowly, take smaller bites, and alternate bites of solid food with sips of liquid to ensure adequate oral and pharyngeal clearing. In this regard, involvement of a speech and language therapist in assessing the patient and providing advice on the consistency and quantity of food and fluid in the diet and various positioning techniques (chin tuck) to improve swallowing is very helpful. If these initial measures fail, then evaluation for an alternative route for nutrition is warranted. Enteral nutrition can be achieved through various means, including nasogastric or nasoenteric tube percutaneous endoscopic (or radiologic placed) gastrostomy (PEG/PRG) and/or jejunostomy tubes, which are entered into the stomach (gastrostomy) through the abdominal wall or into the intestine (jejunostomy) (Stellato, 1992). Nasoenteric feeding tubes are commonly used for short-term nutritional support and can be placed more reliably using endoscopic or fluoroscopic guidance (Park et al., 1991). PEG is the recommended choice for long-term maintenance of good nutrition in patients with myopathies (Ramelli, Aloysius, King, Davis, & Muntoni, 2007; Seguy et al., 2002) and MND/ALS patients with pronounced dysphagia (Hill et al., 2004; Mathus-Vliegen et al., 1994; Mazzini et al., 1995; Miller et al., 1999).

ROLE OF FEEDING TUBES

The timing of PEG/PRG is based on an individual approach taking into account bulbar symptoms, malnutrition (weight loss >10%), respiratory function, and the patient's general condition. Thus, early placement is highly recommended (Andersen et al., 2005; Miller et al., 1999). A study performed by Jackson-Tarlton, Benstead, and Doucette (2016) on 654 ALS patients showed that abnormal ALS Functional Rating Scale–Revised dysphagia scores and use of noninvasive ventilation (NIV) were associated with a higher rate of feeding tube referrals.

The literature specifies a number of factors that influence the timing of PEG: forced vital capacity (FVC), accelerated weight loss, and dysphagia symptoms (Jackson-Tarlton et al., 2016). The 2009 American Academy of Neurology guidelines on ALS do not provide any ALS-specific indications for PEG but do mention that the risk of PEG placement increased when the FVC declined by 50% of predicted (Miller et al., 2009). Specifically, PEG is indicated when patients with ALS have symptomatic dysphagia with accelerated weight loss due to insufficient caloric intake, dehydration or end meals prematurely because of dysphagia or choking on food. Although a barium swallow study may provide supportive evidence for dysphagia (Akpunonu et al., 1997), the indication for PEG in ALS depends on the presence of inadequate oral intake and diminished quality of life due to choking rather than the result of a swallowing study.

Because PEG tube insertion typically employs procedural sedation, knowledge of a patient's respiratory capacity and monitoring of oxygen saturation are essential (Forbes, Colville, & Swingler, 2004; Gregory, Siderowf, Golaszewski, & McCluskey, 2002). Novel use of noninvasive positive pressure ventilation (NIPPV) to provide respiratory support during sedation for percutaneous placement has been described for patients with MND (Boitano, Jordan, & Benditt, 2001; Birnkrant, Pope, Martin, Repucci, & Eiben, 1998; Pope, Birnkrant, Martin, & Repucci, 1997). In a retrospective study performed by Strijbos, Hofstede, Keszthelyi, Masclee, and Gilissen (2017), conscious sedation with midazolam in ALS patients was not associated with increased respiratory complications and other PEG-related complications when compared to patients with other indications. However, the majority of patients (42.2%) in this study had a mild to moderate impairment in their FVC. In patients with moderate to severe impairment in ventilation, NIV before, during, and after PEG tube insertion reduces complications when compared to PEG tube without NIV (Czell, Bauer, Binek, Schoch, & Weber, 2012). Multiple case series of uncomplicated PEG tube placement with NIPPV assistance has been reported in patients with advanced ALS and with FVC of <50% (Boitano et al., 2001; Gregory et al., 2002).

Endoscopic placement required upper endoscopy usually under conscious sedation and includes inspection of the stomach and identification of the placement site by using transillumination and finger indentation technique. Safe performance of PEG depends on adequate transillumination of the anterior abdominal wall by the gastroscope light. Inability to optimally transilluminate the anterior abdominal wall is a common cause of endoscopic gastrostomy tube placement failure. In some patients with ALS, because of intrinsic weakness of the diaphragm, the stomach migrates high under the costal margin, which can make placement difficult.

PRG techniques have been used successfully in patients with ALS where endoscopic tube placement was not feasible (Thornton et al., 2002). In PRG, gastropexy with T-fasteners fixes the anterior wall of the stomach to the anterior abdominal wall, which stabilizes the anterior wall of the stomach and allows safe dilation of the gastrostomy tract. T-fastener gastropexy enables routine use of larger gastrostomy tubes and ready replacement of a displaced tube even before the development of a mature tract. As PRG did not involve passage of scope through the pharynx, local anesthesia of the

pharynx is not needed and may be safer in patients with borderline respiratory status with less requirement of sedation (Birnkrant et al., 1998; Boitano et al., 2001). However, higher tube dislodgement rates (26.5% vs. 2.4%) have been reported with PRG, which could be secondary to the design of the tubes used for PRG (Vidhya, Phoebe, Dhina, Jayne, & Robert, 2018). PEG should be the procedure of choice when considering gastrostomy insertion, and PRG should be reserved as an alternative in those in whom PEG is technically difficult or contraindicated (Laskaratos et al., 2013).

Contraindications for PEG Placement

Absolute contraindications to PEG placement include the inability to bring the anterior abdominal wall in apposition to the abdominal wall, pharyngeal or esophageal obstruction, uncontrolled coagulopathy, interposition of organs, infection of the abdominal wall at the site of placement, gastric varices, peritoneal carcinomatosis, sepsis, hemodynamic instability, and history of total gastrectomy. Prior gastric resection, ascites, hepatomegaly, and obesity are some conditions that may impede gastric transillumination and subsequent PEG placement. PEG should not be used for nutritional support when GI tract obstruction is present. Relative contraindications of PEG include neoplastic, inflammatory, or infiltrative diseases of the gastric or abdominal wall (Eisen et al., 2002).

Although nutritional goals and hydration can be successfully achieved with PEG, it does not prevent aspiration. Therefore, prevention of aspiration pneumonia is not an indication for PEG. Recognized risk factors for aspiration include history of previous aspiration pneumonia, evidence of reflux esophagitis at the time of endoscopy, older age, male gender, and the presence of infection (Hassett, Sunby, & Flint, 1988; Light, Slezak, Porter, Gerson, & McCord, 1995; Park et al., 1991).

Patients undergoing PEG are often at high risk for complications caused by associated comorbidity. Minor complications associated with PEG placement occur in 13% to 43% of patients and include tube occlusion, maceration from leakage of gastric contents around the tube, and peristomal pain. Major complications, reported in 0.4% to 8.4% of procedures, include transient laryngeal spasm (7.2%), localized infection (6.6%), gastric hemorrhage (1%–4%), failure to place PEG due to technical difficulties (1%–9%), necrotizing fasciitis, aspiration, bleeding, perforation, ileus, injury of internal organs, and death due to respiratory arrest (1.9%), with a 30-day mortality in the range of 6.7% to 26%. This may be due, in part, to patients' underlying comorbidities (Hull et al., 1993; Larson, Burton, Schroeder, & DiMagno, 1987; Mathus-Vliegen & Koning, 1999).

The most common complication is wound infection. Antimicrobial prophylaxis is recommended because it may reduce the frequency of peristomal wound infection and is cost-effective. Parenteral cefazolin (or an antibiotic with equivalent coverage) should be administered to all patients 30 minutes before they undergo PEG tube placement. Such prophylaxis is necessary only in those patients not already receiving appropriate antibiotic treatment at the time of the PEG insertion (Dormann et al., 1999; Gossner, Keymling, Hahn, & Ell, 1999; Jafri et al., 2007).

Buried bumper syndrome is a rare complication (1.5%–1.9%) when the internal bumper impacts and erodes on the gastric wall and is secondary to increased tension between the internal and external bumpers (El et al., 2011). It manifests clinically with increased pain, malfunctioning of the tube, and sometimes with extravasation of the nutritional formula.

A mature fistulous tract is required to safely replace a percutaneous gastrostomy tube/button. Nonendoscopic replacement of a dislodged tube/button is contraindicated in the absence of a mature tract. It takes 4–6 weeks following the procedure for the tract to fully form. Therefore, if a PEG tube gets dislodged within a month, endoscopic replacement is recommended versus if it gets dislodged after 4–6 weeks, where bedside replacement is sufficient (Shah & Shah, 2019). Pneumoperitoneum occurs commonly after PEG and is of no clinical significance unless accompanied by signs and symptoms of peritonitis (Gottfried, Plumser, & Clair, 1986).

Gastrostomy in Children

Since its first use in children in 1980 by Gauderer, Ponsky, and Izant (1980), studies of children with neurodevelopmental disorders have shown that receiving nutrition through a gastrostomy can improve clinical outcomes and quality of life. Two major groups of feeding-related problems before gastrostomy were identified among children with muscular dystrophies and other neuromuscular disorders. The most common group presented primarily with poor growth and nutrition, and the second group had swallowing difficulties resulting in aspiration. After gastrostomy, the improvement in growth velocity was marked for weight and height. The procedure was well tolerated, with minimal postoperative complications. It also seemed to improve quality of life (Brant, Stanich, & Ferrari, 1999; Ramelli et al., 2007; Seguy et al., 2002). Complication rates seem to be fairly low (4%) in the pediatric population following PEG placement before hospital discharge (Fortunato et al., 2010). Wound infection, pneumoperitoneum, and skin necrosis were the commonly reported minor complications (Fortunato et al., 2010). However, in patients with severe congenital myopathy, severe gastroesophageal reflux, or severe respiratory deficiency that requires intensive care, or when patients have a poor short-term prognosis with a high risk of death, it is difficult to know if gastrostomy feeding will have a similar impact or not.

Survival after PEG

In one study, the frequency of PEG tube placement among patients with ALS was 11%, with a mean duration of disease of around 24 months. The 1-month mortality after gastrostomy was 25% (Forbes et al., 2004). In a postmortem study on ALS patients by Burkhardt, Neuwirth, Sommacal, Andersen, and Weber (2017), the 6-month survival rate following PEG tube insertion was 75%. PEG insertion revealed a significant survival benefit in ALS patients compared to those without PEG (Burkhardt et al., 2017). After radiologic gastrojejunostomy tube placement, the 30-day mortality was reported to be 9.6%, with median survival of 22 months (Gregory et al., 2002). A positive impact of PEG was noted in 79% of PEG patients (Mitsumoto et al., 2003). The best evidence to date, based on controlled prospective cohort studies, suggests an advantage for survival in all people with ALS/motor neuron disease, but these conclusions are tentative (Langmore, Kasarskis, Manca, & Olney, 2006).

ENTERAL NUTRITION

Nutrition plays a critical role in the prognosis of patients with neuromuscular disease. It has been well studied in patients with ALS/motor neuron disease; however, studies on other neuromuscular disease are lacking. Enteral nutrition by PEG tube is recommended once patients have lost 10% of their premorbid weight (Greenwood, 2013). Moderate obesity (BMI 30–35 kg/m^2) has also been associated with slower disease progression and longer survival (Paganoni, Deng, Jaffa, Cudkowicz, & Wills, 2011). High carbohydrate hypercaloric tube feeding formula with a goal of weight gain was less likely to have serious adverse events including death (Wills et al., 2014). PEG tube placement and enteral nutrition have been associated with improved survival outcomes in prospective studies in an ALS cohort of patients (Chiò et al., 2006; Mazzini et al., 1995). ALS patients on enteral nutrition were also reported to have improvements in nutritional parameters like weight gain, BMI, and triceps skinfold thickness as compared to the nonenteral control group (Desport et al., 2000; Mazzini et al., 1995).

Enteral formulas, also termed as *medical foods*, are products that are developed to meet the nutritional requirement of patients who cannot meet their nutrition orally or those who are at risk for complications from oral intake. They are generally nutritionally complete emulsions of macronutrients and micronutrients that consist of intact protein, glucose polymers, and a mixture of long-chain and medium-chain triglycerides. In the past few years, many enteral nutrition products have been created, adding to the overall large pool of commercial formulas already available. However, these formulas can be broadly categorized into one of the categories in Table 4.2. Formula methods of administration include bolus, intermittent, or continuous feeding. In bolus feeding, 300–400 mL is infused with a syringe via feeding tube over 5 to 10 minutes several times per day. The bolus and gravity methods are ideal for infusion into the stomach and may be initiated with full-strength formula three to eight times per day with increases of 60–120 mL every 8–12 hours as tolerated up to the goal volume (Bankhead et al., 2009). The formula does not require dilution; when additional water is necessary, it can be administered intermittently as flushes throughout the day. Bolus feedings are administered by gravity through a syringe over approximately 15 minutes, whereas intermittent feedings are administered through a feeding container or bag over 30–45 minutes with or without an enteral feeding pump. Pump-assisted feedings are required for small bowel feedings and can be administered with slower administration rates and often enhance tolerance. It is usually initiated at full strength of 10–40 mL/h and advanced to the goal rate in increments of 10–20 mL/h every 8–12 hours as tolerated. Gravity, especially continuous feeding, provides intermittent and more controlled delivery of feeding and recommended when a reduction in risk of gastroesophageal reflux and aspiration is needed. Feeding tubes can get clogged, especially with slow rates of administration, and calorically dense formulas and should be flushed with 30 mL of water every 4 hours during continuous feeding or before and after intermittent feedings in an adult patient (Kohn-Keeth, 2000).

Initiating enteral nutrition increases the risk for aspiration and aspiration pneumonia; hence, all patients receiving enteral nutrition should have the backrest elevated to a minimum of 30 degrees and preferably to 45 degrees (Bankhead et al., 2009). The fluid and electrolyte status of the patients should be closely monitored for refeeding syndrome, especially during the initial phases of initiating enteral feeding in patients with a negative caloric balance.

TREATMENT FOR CRICOPHARYNGEAL DYSFUNCTION

Cricopharyngeal (CP) muscle, which is the main muscle of the UES, is affected in a number of anatomic, neuromuscular, and inflammatory conditions resulting in oropharyngeal dysphagia. Dilation, injection of botulinum toxin, and CP myotomy are the three main treatment modalities for patients affected with this disorder. The average success rates for myotomy, botulinum injections, and dilation are 75%, 76%, and 81%, respectively (Kocdor, Siegel, & Tulunay-Ugur, 2016). The average complication rates for these procedures are between 5% and 6% (Kocdor et al., 2016). CP myotomy (Brouillette, Martel, Chen, & Duranceau, 1997), a surgical procedure in which the CP muscle is severed, may be useful in selected patients. It is best suited when there is documented dysfunction at the pharyngo-esophageal junction, but adequate laryngeal/hyoid elevation and pharyngeal propulsion were present (Janzen et al., 1988). This procedure is found to be beneficial in OPMD, IBM, ALS, multiple sclerosis (MS), and OPMD. In one surgical series, the overall mortality rate after CP myotomy was 1.6% (Brigand, Ferraro, Martin, & Duranceau, 2007). In one series, oropharyngeal symptoms improved in 75% of these patients. CP myotomy was performed in 139 patients for dysphagia secondary to OPMD. Complication was seen in 16 patients. Four of these patients, all with respiratory distress syndrome, eventually died of lung infection. Permanent tracheostomy with laryngeal exclusion was required in two with muscular dystrophy, because of infection. Pulmonary infection was the most common complication after CP myotomy in patients with muscular dystrophy.

TREATMENT OPTIONS FOR ASPIRATION

Prevention of aspiration episodes should be a key management strategy. A behavioral management approach like dietary modification, posture adjustments, and swallowing maneuvers should be the focus early on in the disease process. Sialorrhea can be minimized with the help of medications like amitriptyline, scopolamine, atropine, glycopyrolate, and guaifenesin. Surgical methods like tracheostomy with an inflated cuff, laryngectomy, and larygotracheal separation should be considered only for those with severe bulbar impairments (Britton et al., 2018; Lewis & Daniel, 1981).

STOMACH AND DUODENUM

DYSPEPSIA AND GASTRIC EMPTYING ISSUES

MD patients frequently complain of dyspeptic symptoms such as early satiety, nausea, vomiting, and epigastric pain. Rare cases of gastric bezoar and retention have been reported as well (Kuiper, 1971).

Gastric emptying delay, gastroparesis, and acute GI dilatation have been shown to characterize the clinical course of MD (Bellini et al., 2006). The delayed gastric emptying in muscular dystrophy can be explained by the muscular

Table 4.2 Summary of Characteristics of Enteral Formulations and Recommendations for Use

Formula Type	Summary of Characteristics	Recommendations for Use
Polymeric (Boost, Ensure)	- Contain macronutrients as nonhydrolyzed protein, fat, and carbohydrate - Range in concentration from 1 to 2 kcal/mL - 1–1.5 L usually meet RDA for vitamins and minerals - May be disease specific and/or contain pre- and probiotics	- Intended for use among patients without severe malabsorptive disorders
Fiber containing (Fibersource, Glucerna, Jevity)	- Fiber content intended to improve the health of the GI tract regulating frequency and/or consistency of stool by maintaining healthy GI flora - Fiber content is typically well below total daily fiber recommendations - May contain prebiotics in the form of fructooligosaccharides, oligofructose, or inulin - May also contain probiotics	- Recommended for use among patients with diarrhea and/or to promote/maintain gut microbiota
Whole food/blenderized	- Blenderized whole foods designed to allow patients to receive qualities of food not found in standard enteral formulas, such as phytochemicals	- Considered for use only in medically stable patients with a healed feeding tube site and no signs of infection - Best suited for patients with safe food practices and tube maintenance techniques - Should be provided as bolus feeds to maintain safe food practices (hang time ≤2 hours) - RD should be involved in development of feeding composition to ensure adequate nutrient delivery
Diabetes/glucose intolerance (DiabetiSource AC, Glucerna Select, Resource Diabetic)	- Intended to reduce hyperglycemia with macronutrient composition of 40% carbohydrate, 40% fat, and 20% protein - Fat and soluble fiber content may slow gastric emptying and prevent elevated blood glucose	- Use of DM-specific enteral formulas is not currently supported by strong research; instead, efforts should be made to prevent overfeeding
Renal (Nepro, Novasource Renal)	- Fluid restricted - Contain lower amounts of electrolytes, specifically potassium and phosphorous to prevent excessive delivery to patients with renal insufficiency - Protein content varies	- Standard enteral formula should be the first line for patients with renal insufficiency - If significant electrolyte abnormalities exist or develop, a renal formula should be considered until electrolytes stabilize - Standard, high-protein formulas without fluid restriction should be used among critically ill patients receiving dialysis; if electrolyte abnormalities exist without dialysis, renal formulas should be considered
Hepatic (Hepatic-Aid II, NutriHep)	- Contain lower protein content with higher percentage of branched-chain amino acids, lower aromatic amino acids to prevent hepatic encephalopathy - Low protein content may result in inadequate protein delivery - Fluid and sodium restricted to attenuate effects of ascites	- Standard EN formula should be administered as first line among patients with hepatic encephalopathy - Reserve only for use among encephalopathic patients in whom standard therapy with luminal acting antibiotics and lactulose does not improve encephalopathy
Bariatric (Peptamen Bariatric)	- Contain approximately 37% kcal from protein in efforts to maintain positive nitrogen balance, modest carbohydrate content for glucose control, and EPA/DHA in efforts to modulate inflammatory response	- Intended for patients with BMI >30 kg/m - Goal enteral delivery should not exceed 60%–70% of target energy requirements, but provide adequate protein
Elemental/semielemental (Peptamen, Vivonex T.E.N.)	- Macronutrients are hydrolyzed to maximize absorption	- Intended for use among patients with malabsorptive disorders; not intended for routine use

Table 4.2 Summary of Characteristics of Enteral Formulations and Recommendations for Use—cont'd

Formula Type	Summary of Characteristics	Recommendations for Use
Pulmonary	- In efforts to reduce carbon dioxide production, these formulas contain >50% total calories from fat, with lower carbohydrate (<30%) and similar protein content (16%–18%) - Typically also contain ω-3 fatty acids derived from fish oil to increase delivery of anti-inflammatory properties of EPA/DHA	- Efforts to prevent excessive EN delivery should be employed to reduce complications associated with overfeeding - Pulmonary formulas should be used with caution among septic, critically ill patients
Immunonutrition/immune modulating	- Contain pharmacologically active substances, such as arginine, glutamine, ω-3 fatty acids, γ-linolenic acid, nucleotides, and/or antioxidants in efforts to modulate immune function	- Administration of immune-modulating substances as components of EN is potentially beneficial when used for patients undergoing elective surgery; however, research is not sufficient to recommend immune-modulating formulas for routine use among critically ill patients

Adapted from Brown, B., Roehl, K., & Betz, M. (2015). Enteral nutrition formula selection: Current evidence and implications for practice. *Nutrition in Clinical Practice*, *30*(1), 72-85.
BMI, Body mass index; *DHA*, docosahexaenoic acid, *DM*, dermatomyositis; *EN*, enteral nutrition; *EPA*, eicosapentaenoic acid; *GI*, gastrointestinal; *RD*, registered dietitian; *RDA*, Recommended Dietary Allowance.

disease with associated fatty infiltration and dystrophy of smooth muscle; however, histological evidence remains limited. A malfunctioning electrical control of gastric activity may be the cause of slow gastric emptying (Lewis & Daniel, 1981). Abnormalities have been noted on electrogastrography in MD patients when compared to controls, and studies have demonstrated a partial deregulation of the GI endocrine system in MD patients with decreased postprandial secretion of motilin and glucagon-like peptide-1 (Ronnblom, Andersson, Hellström, & Danielsson, 2002; Ronnblom et al., 1996). Similar problems with gastric emptying have been reported in patients with DMD and Becker muscular dystrophy. Delayed gastric emptying for solids has been shown in patients with ALS, which was attributed to subclinical involvement of the autonomic system (Hillemand, 1979; Toepfer, Folwaczny, Klauser, et al., 1999; Toepfer, Folwaczny, Lochmüller, et al., 1999).

DIAGNOSIS

Patients with dyspepsia, nausea, and vomiting usually require radiologic and endoscopic evaluation to rule out peptic ulcer disease, *Helicobacter pylori* infection, and gastric outlet obstruction followed by gastric emptying study. Routine laboratory testing is not useful for the diagnosis of gastric stasis itself, although it may help to identify diseases that are associated with delayed gastric emptying or to rule out other disorders and related electrolyte disturbances. The most widely available and robust technique to confirm the presence of postprandial gastric stasis is scintigraphic gastric emptying. Consensus standards for performing and reporting gastric emptying scintigraphy have been published by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine (Abell et al., 2008). This involves consumption of a low-fat, egg-white meal labeled with 99mTc-Amberlite, with imaging at 0, 1, 2, and 4 hours after meal ingestion, which provides standardized information about normal and delayed gastric emptying. A gastric residual of >10% at 4 hours is most accurate for detecting delayed gastric emptying. A scintigraphic study by Ronnblom et al. indicated delayed emptying of the stomach in MD patients with dyspeptic symptoms, although patients without dyspeptic symptoms may have delayed gastric emptying as well. In addition, there is no significant difference in gastric emptying between patients with different degrees of skeletal muscle involvement (Ronnblom et al., 1996, 2002). Similar gastric motor abnormalities were demonstrated in a group of children with recent diagnosis of muscular dystrophy (DMD and Becker muscular dystrophy) at the initial phases of the disease, where worsening of gastric motor activity paralleled a progressive derangement of neuromuscular function during the 3-year follow-up of the disease (Borrelli et al., 2005; Horowitz, 1987). Other tests available to evaluate patients with suspected gastroparesis are stable isotope breath test, wireless motor capsules (Smart Pill; Giving Imaging), and gastroduodenal manometry.

TREATMENT

Dietary modification like small meals and avoiding meals high in fat and indigestible fibers is the first line of treatment (Camilleri et al., 2018). Different drugs, particularly prokinetics, have been proposed to treat the dyspeptic symptoms and motor disturbances in patients with muscular dystrophy. In a small series of 16 patients with delayed gastric emptying of solids and liquids, Horowitz et al. (1987a) showed that oral administration of 10 mg of metoclopramide 3 times per day can improve solid gastric emptying. Its mechanism of action involves local release of acetylcholine. Patients should be informed of extrapyramidal side effects and the risk of tardive dyskinesia, which, although rare, can be irreversible.

Cisapride stimulates 5-hydroxytryptamine 4 receptor (5HT4), resulting in release of acetylcholine from the neurons in the myenteric plexus. It has also reported to improve both gastric emptying and digestive symptoms such

as nausea, vomiting, early satiety, abdominal distension, and pain (Horowitz et al., 1987b), but availability in the United States is severely restricted due to significant drug interactions (e.g., macrolide antibiotics, antifungals, and phenothiazines) that have caused cardiac arrhythmias and death (Wysowski, Corken, Gallo-Torres, Talarico, & Rodriguez, 2001), but it remains available in several other countries. In the United States, prescriptions for the drug can be filled directly only through the manufacturer after providing documentation as to the need for the drug and assessment of risk factors for cardiac arrhythmias in the individual patient through a Food and Drug Administration (FDA) investigational protocol only.

Use of erythromycin in small doses (100 mg, twice daily orally) in dyspeptic MD patients over a period of 4 weeks was shown to minimally improve nausea and early satiety, but marked improvement in diarrhea was noted by some patients (Ronnblom et al., 2002). Its clinical effect lies in its agonistic action on the motilin receptors, inducing high-amplitude gastric propulsive contractions. It can be used only for a short period of time as long-term use is associated with tachyphylaxis. However, no trials using intravenous erythromycin are available in MD patients, where it has shown to improve gastric emptying in acute episodes of gastric stasis where oral intake is not tolerated.

Domperidone has been used in patients with gastroparesis. It is a dopamine receptor antagonist with gastric prokinetic and antiemetic actions. It is not approved for use by the FDA in the United States but is available in Canada and other countries. The FDA encourages physicians who would like to prescribe domperidone for their patients with severe GI disorders that are refractory to standard therapy to open an Investigational New Drug Application. QT prolongation has also been reported with domperidone, which may also increase the risk of cardiac arrhythmias. Ghrelin agonists are a new class of prokinetic drugs with potent prokinetic effects currently under development. Relamorelin, a ghrelin agonist, was found to decrease vomiting frequency by 75% and accelerate gastric emptying from baseline in a phase 2 study (Camilleri et al., 2017). Pyloric interventions like botulinum injection, pyloroplasty, or pyloromyotomy can be performed for patients with gastroparesis resistant to pharmacologic agents (Camilleri et al., 2018).

Gastric pacing using gastric electrical stimulator has received humanitarian device exemption approval for the treatment of refractory diabetic and idiopathic gastroparesis; however, the use of this technology in patients with gastroparesis secondary to other conditions is not well known. In a single-center prospective study, gastric electrical stimulation was found to at least moderately improve symptoms in 43% of patients (Heckert, Sankineni, Hughes, Harbison, & Parkman, 2016).

Gastric peroral endoscopic myotomy (G-POEM) is an advanced endoscopic procedure that can be performed for patients with refractory diabetic gastroparesis, particularly those with pyloric dysfunction. There is increasing evidence that G-POEM is not only safe but also effective for the treatment of patients with severe refractory gastroparesis, with clinical success in 68%–90% of patients and overall 8.3% risk of major complications like capnomediastinum and capnoperitoneum (Podboy et al., 2018).

SMALL INTESTINE

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a severe digestive syndrome characterized by derangement of gut propulsive motility, which resembles mechanical obstruction, in the absence of any obstructive process (Camilleri, 2003; De Giorgio & Camilleri, 2004; Nowak et al., 1982). There are various etiologies of intestinal pseudo-obstruction (Antonucci et al., 2008; Krishnamurthy & Schuffler, 1987). CIPO is considered primary/idiopathic, when no underlying disorder can be demonstrated, or secondary, when related to a variety of systemic diseases, such as infections, autoimmune processes, mitochondrial dysfunction, either sporadic or familial, as well as side effects of medications.

Based on tissue examination, CIPO can be classified into three major entities: neuropathies, "enteric mesenchymopathies," and myopathies (De Giorgio, Sarnelli, Corinaldesi, & Stanghellini, 2004).

Inflammatory neuropathies related to several diseases including paraneoplastic syndrome, infectious disease (Chagas disease), and idiopathic cases are characterized by a dense lymphocytic and plasma cell infiltrate involving myenteric plexus and axons of the enteric nervous system. Degenerative noninflammatory neuropathies occur secondary to damage or loss of enteric neurons. This can be of familial or primary idiopathic form or acquired as a result of radiation injury, diabetes, vinca alkaloids, and amyloidosis. Typical neuropathological findings include neuronal damage and hpo-ganglionosis. Enteric mesenchymopathies are associated with alteration in the interstitial cells of Cajal network (Sanders, Ordög, & Ward, 2002).

Myopathic etiologies include primary visceral myopathy, muscular dystrophies, PM (Takakusaki et al., 2008), and scleroderma. Primary visceral myopathy, including familial visceral myopathy is characterized by degeneration and fibrosis of smooth muscle layer of GI system (Anuras et al., 1986). The GI system showed marked dilatation of the entire digestive tract, especially the duodenum (megaduodenum), which has been reported in hollow visceral myopathy as well (Mansell, Tattersall, Balsitis, Lowe, & Spiller, 1991). Adult patients with spinal motor atrophy can also develop CIPO (Ionasescu, Christensen, & Hart, 1994). In scleroderma, altered function of enteric neurons and progressive loss of smooth muscle with fibrosis involving the GI tract lead to impaired motility, intestinal stasis, and secondary bacterial overgrowth. In both MD and DMD, marked damage to enteric smooth muscle cells has been described (De Giorgio & Camilleri, 2004; Harvey, Sherbourne, & Siegel, 1965). Histopathological analysis of the enteric muscle layer may reveal the existence of muscular abnormalities of the circular and longitudinal layers in patients with primary visceral myopathy. Smooth muscle actin deficiency in the external muscular layer of the ileum, with features of eosinophilic plexitis and eosinophilic muscle infiltration in the colon, has been described in DM patients with CIPO (Pelizzo, Calcaterra, Villanacci, Mura, & Bassotti, 2018). In a study of 115 patients with CIPO who underwent full-thickness jejunal biopsy, 24% showed absent or reduced α-actin staining in the circular muscle of the jejunum, in the absence of other structural abnormalities of muscle and nerve when compared with controls (Knowles et al., 2004).

GI smooth muscle involvement, manifested pathologically as muscle cell hypereosinophilia, nuclear pyknosis, and cell fragmentation, was reported in three cases of DMD (Pruzanski & Huvos, 1967).

The typical clinical manifestation of CIPO is dependent upon whether functional derangement affected the upper GI tract when nausea and vomiting with abdominal pain are more predominant, while abdominal distension and constipation are suggestive of a more distal involvement of the gut. Diarrhea and steatorrhea can occur as a consequence of small bowel bacterial overgrowth (Faure et al., 1999).

Mitochondrial diseases like MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), also known as POLIP (polyneuropathy, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction) or MEPOP (mitochondrial encephalomyopathy, polyneuropathy, ophthalmoplegia, and pseudo-obstruction) syndrome, are a condition characterized by moderate to severe sensorimotor polyneuropathy, ophthalmoplegia, and severe, sometimes fatal, GI dysmotility (Giordano et al., 2006; Uncini et al., 1994). The pathophysiological mechanisms underlying CIPO in mitochondrial disorders are likely related to mitochondrial dysfunction, energy metabolism imbalance, and reduced/disturbed pool of interstitial cells of Cajal (Gagliardi et al., 2019; Yadak, Breur, & Bugiani, 2019). The initial presentation is usually of GI symptoms that include dyspepsia, bloating, eructation, cramps, intolerance of large meals, and episodic vomiting and diarrhea. The disease is usually presented before the age of 20 years, ranging between 2.5 and 32 years. Esophageal motility is variably affected, the smooth muscle of the small intestine does not function normally, and intestinal pseudo-obstruction is the rule. An upper GI manometric study demonstrated diminished amplitude of contractions in the small bowel during the fasting and fed states (Mueller et al., 1999). Helpful screening tests include elevated serum lactate-to-pyruvate ratios that result from relative excess of reduced nicotinamide adenine dinucleotide and lack of nicotinamide adenine dinucleotide. Glucose loading may unmask hyperlactatemia and may give rise to a paradoxical increase in ketone bodies (Gillis & Sokol, 2003; Munnich et al., 1996; Simon et al., 1990). CIPO has been associated with diffuse involvement of all parts of the GI tract. In one retrospective study involving 116 patients, CIPO was found to be associated with esophageal motor disorders in 73% and abnormal gastric emptying in 61% of the cases (Amiot et al., 2012). The presence of esophageal motor disorders was associated with a lower survival; hence, esophageal manometry should be performed in CIPO patients whenever indicated for early diagnosis and treatment (Amiot et al., 2012).

DIAGNOSIS

Diagnosis of CIPO is mainly clinical, and diagnostic tests in patients with suspected CIPO are necessary to exclude mechanical occlusion. Plain abdominal films usually show signs of intestinal occlusion such as distended bowel loop with air-fluid levels, and small bowel barium studies or computed tomography/magnetic resonance enterography is necessary to exclude the presence of organic lesions. Endoscopic evaluation based on symptoms and radiologic evaluation may be indicated to evaluate the exclusion of mechanical occlusions and evaluating intestinal biopsies to rule out inflammatory bowel disease and celiac sprue (Ravindra et al., 2008). Diagnosis may require small bowel transit studies using scintigraphy (von der Ohe & Camilleri, 1992). Small bowel manometry is usually not required when associated with known etiologic conditions but is helpful in selected cases, although it is not widely available (Stanghellini, Camilleri, & Malagelada, 1987). Manometric findings described in myopathic form as normally coordinated motor patterns with low amplitude. In neuropathic CIPO, contractions are uncoordinated but have normal amplitude (Faure et al., 1999). Endoscopic full-thickness wall resection using a full-thickness resection device has been utilized to harvest full-thickness tissue samples for accurate histological diagnosis in patients with suspicion of these neuromuscular gut disorders (Valli, Pohl, Fried, Caduff, & Bauerfeind, 2018).

TREATMENT

The cornerstones for the management of patients with CIPO are maintenance of nutritional support, fluid and electrolyte restoration, symptom control with medications, and avoidance of surgery as much as possible. A multidisciplinary team, primarily including a gastroenterologist, a neurologist, a nutritionist, and surgeons who cooperate with the other medical specialists (psychologist, urologist, geneticist/metabolic medicine, general practitioner/pediatrician) and health care professionals (nurses, social workers, pharmacists) according to specific requirements of the single patient, is mandatory to optimize the result of treatment (Di Nardo et al., 2017).

Medical therapy of CIPO in patients with neuromuscular disease is aimed at controlling symptoms and avoiding complications (De Giorgio et al., 2001). Use of antiemetics, antisecretory, antispasmodics, prokinetics (Abell et al., 1991), laxatives, or antidiarrheal (based on dominant symptoms) and analgesic drugs is often necessary.

Small intestinal bacterial overgrowth (SIBO), which causes mucosal inflammation and further impairs GI motility, is a frequent complication in these patients. SIBO should be treated with use of antibiotics (Attar et al., 1999), and alternating cycles with metronidazole and tetracycline is sometimes necessary to reduce the chance of developing resistance. Commonly used antibiotics include amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, and aminoglycosides. Octreotide, a long-acting somatostatin analog that increases intestinal motor activity, has shown to decrease bacterial overgrowth and can be used in selected cases (Soudah, Hasler, & Owyang, 1991). Patients may require medication to relieve visceral pain. Low doses of antidepressants (tricyclic antidepressants or the noradrenergic serotonergic reuptake inhibitors) and/or gabapentin are usually prescribed.

Gastrostomy for gastric decompression along with feeding jejunostomy (Di Lorenzo, Flores, Buie, & Hyman, 1995) may be helpful in patients with recurrent hospitalization with vomiting and abdominal distension and represents a possible option in patients who can be fed by enteral nutrition. PEG-jejunostomy was found to result in a significant decrease in the number of days without abdominal symptoms, along with improvement of wasting and malnutrition in patients with CIPO (Di Nardo, Karunaratne, Frediani, & De Giorgio, 2017). The majority of patients with CIPO will require nutritional support, and some may require total parenteral nutrition as well (Koretz, Lipman, & Klein, 2001).

Explorative laparotomy may be required to exclude mechanical obstruction in some cases, and a decompressive ileostomy or colostomy may reduce the degree of abdominal distension and alleviate obstructive symptoms and increase tolerance of enteral feeding. However, it is recommended to avoid unnecessary surgeries, because of the high risk of dense adhesions after surgery and prolonged postsurgical paralytic ileus observed in these patients.

Drug therapy, surgical procedures, dietary counseling, and nutritional tube feedings are successful in maintaining nutritional status in around two thirds of patients with CIPO, whereas one third develop chronic intestinal failure, requiring long-term home parental nutrition (HPN) (Vasant et al., 2018). The European Society for Parenteral and Enteral Nutrition (ESPEN) gives recommendations for the management of HPN for chronic intestinal failure (CIF) as well as for the management of the underlying intestinal pathology and the prevention and treatment of major HPN-related complications (Pironi et al., 2016).

Intestinal transplantation has been increasingly used for the management of advanced CIPO after failure of HPN and different conventional modalities of treatment, with 5-year survival around 60% (Abu-Elmagd et al., 2012).

LARGE INTESTINE AND ANAL SPHINCTER CONSTIPATION

Constipation is defined as infrequent/incomplete evacuation or the passage of excessively hard stools. Constipation is a common complication of neuromuscular diseases, especially as the disease progresses. In a study of 120 patients with DMD, 46.7% of the patients were found to have constipation (Kraus, Wong, Horn, & Kaul, 2016). It is highly prevalent but yet underdiagnosed and undertreated in patients with DMD (Kraus et al., 2016). Patients with ALS were found to have a similar prevalence of constipation, ~46% (Nubling et al., 2014). Various abnormalities including megacolon, loss of haustration, absence of segmental contractions, and loss of peristaltic activity, sigmoid volvulus, and segmental narrowing have been published among patients with muscular dystrophy (Kark & Greenstein, 1972; Weiner, 1978). Light microscopy showed atrophy of the individual muscle fibers similar to that seen in skeletal muscle (Pruzanski & Huvos, 1967). Apart from histopathological changes on the GI musculature, loss of mobility and stature, and weakness of abdominal wall musculature, use of certain medical treatments that slow colonic transit and decrease appetite and fluid intake also plays a big role in slowing the colonic transit time.

Constipation plays an important role in malnutrition because it can exacerbate appetite loss. There has been evidence of autonomic dysfunction among patients with ALS that might be associated with GI symptoms (Baltadzhieva, Gurevich, & Korczyn, 2005). A study using radio-opaque markers to measure colonic transit time showed markedly delayed colonic transit time in ALS patients as compared to controls (Toepfer et al., 1997). Colonoscopy is usually indicated in patients with alarming symptoms, including changes in bowel habits, rectal bleeding, and iron deficiency.

TREATMENT

Lo Cascio et al. (2016) demonstrated that objective measures such as a prolonged colonic transit time did not correlate with symptoms of constipation. Hence, measures to treat constipation should be taken regardless of the patient's perception to prevent disabling constipation (Lo Cascio et al., 2016). Treatment is generally supportive, and close attention should be paid to medications commonly prescribed to these patients, such as scopolamine among patients with ALS (reduces excessive salivation), that may exacerbate constipation. Fiber-enriched formulas should be preferred in patients on tube feeding to prevent constipation. Management suggestions include use of osmotic laxatives (such as lactulose), bulk-forming laxatives (such as methyl cellulose), suppositories, enemas, and the augmentation of fluid and fiber intake (Borasio & Miller, 2001). However, in patients with poor colonic transit, excessive bulking of stools may have the opposite effect of worsening constipation or increasing obstruction potential. Additionally, psyllium-based supplements are degraded by colonic bacteria, which can lead to a worsening of bloating and flatus. For severe constipation, newer polyethylene glycol solution can be used. Use of intestinal secretagogues including lubiprostone (Amitiza), a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion, and linaclotide (Linzess), a guanylate cyclase-C agonist (GCC), was found to have a similar efficacy and tolerability without any significant difference in odds of diarrhea when compared with plecanatide (Trulance, another GCC agonist therapy for constipation) in a meta-analysis with more than 10,000 patients (Shah, Kim, & Schoenfeld, 2018). Prucalopride (Motegrity), a selective, high-affinity 5HT4 agonist, has been shown to be effective for the treatment of chronic idiopathic constipation in adults (Camilleri, Kerstens, Rykx, & Vandeplassche, 2007; Johanson, Morton, Geenen, & Ueno, 2008). However, these new agents, i.e., GCC agonists and 5HT4 agonists, have not been studied in patients with neuromuscular diseases, but so far, they appear to be relatively safe and effective in the general population.

INCONTINENCE

In healthy individuals, the internal anal sphincter normally contributes about 80% of the manometrically determined resting pressure. The most burdensome and disabling problem affecting MD patients may be fecal incontinence (FI) due to sphincter involvement. Up to 66% of MD patients suffer occasional FI, while more than 10% report FI one or more times a week (Herbaut, Nogueira, Panzer, & Zegers de Beyl, 1992). Prevalence rates as high as 52% have been reported in MS patients as well (Nusrat, Gulick, Levinthal, & Bielefeldt, 2012). Anorectal dysfunction has a significant impact not only on the patients but also on the caregivers, resulting in nursing home admissions (Cheung & Hocking, 2004). Anorectal manometry with or without balloon expulsion test is considered the first-line diagnostic test that assesses anal sphincter function, rectal compliance, rectal reflexes, and rectal sensation (Guillaume, Salem, Garcia, & Chander Roland, 2017).

Studies using manometry report a decrease in both the resting pressure (based on the tonic activity of the internal anal sphincter) and the squeezing pressure (exerted by the phasic activity of the external anal sphincter) (Abercrombie, Rogers, & Swash, 1998; Lecointe-Besancon et al., 1999).

Pudendal nerve terminal motor latencies are normal in these patients, confirming the absence of a neurogenic lesion (Kiff & Swash, 1984). Eckardt et al. studied the external anal sphincter using EMG and have found myopathic potentials with myotonia (Eckardt & Nix, 1991). Herbaut et al. (1992) reported decreased duration and amplitude of the motor units in the external anal sphincter and the puborectalis muscle of MD patients with FI. One study using electron microscopy to evaluate the anal sphincter in two siblings with MD found that the external anal sphincter is atrophic in both patients, with marked fibrosis and a high variation in the diameter of the fibers, as well as the striated muscle almost entirely substituted by smooth muscle cells deriving from the internal sphincter (Abercrombie et al., 1998). In ALS, the Onufrowicz nucleus in the medial sacral spinal cord, which innervates sphincter and pelvic floor muscles, is spared; therefore, urinary and bowel incontinence is not a feature of even advanced cases (Holstege & Tan, 1987).

TREATMENT

Mild FI can be treated with high-fiber diet and antidiarrheal agents like loperamide and diphenoxylate. Medical treatment with procainamide (300 mg twice a day) has been proposed for FI (Pelliccioni, Scarpino, & Piloni, 1999).

Rehabilitation involving a combination of volumetric rehabilitation, electroanal stimulation, kinesiotherapy, and biofeedback can be effective in those patients not suffering from severe damage to the pelvic floor muscle (Buntzen et al., 2004; Coggrave, Wiesel, & Norton, 2006; Pucciani, Iozzi, Masi, Cianchi, & Cortesini, 2003). Parker, Henry, and Liu (2019) demonstrated a 79.6% overall response in terms of anorectal manometry and subjective symptom improvement in patients with FI treated with biofeedback therapy. Bulking injection with nonanimal stabilized hyaluronic acid/dextranomer is an FDA-approved treatment for FI. A preliminary study done by Gourcerol et al. (2016) in 26 patients with FI treated with endoscopic botulinum injection of the rectum showed improvement in severity and quality of life scores at the end of 3 months. However, experience with these treatment options among patients with neuromuscular disorder is very limited.

LIVER AND THE HEPATOBILIARY SYSTEM

Liver manifestations have been reported in myotonic dystrophy and can range from elevated transaminases, steatosis, to liver cirrhosis (Finsterer et al., 2015). In one study, the occurrence of cholecystectomy was found in 16.5% of patients with myotonic dystrophy type 1 and 12.8% in those with myotonic dystrophy type 2 (Hilbert et al., 2017).

PERIPHERAL NEUROPATHY AND THE GASTROINTESTINAL SYSTEM

Most generalized peripheral polyneuropathies are accompanied by clinical or subclinical autonomic dysfunction. In these neuropathies, autonomic dysfunction affecting gut motility is the most prominent manifestation.

Diabetic enteropathy is a pan enteric disorder resulting from loss of neurons causing dysmotility and altered secretion. Esophageal motor disorder has been reported with a prevalence rate of up to 63% leading to gastroesophageal reflux disease and is more common than gastroparesis, with a prevalence rate of 13% (Gustafsson et al., 2011). Other GI manifestations are abnormal small bowel motility, abdominal pain, constipation, diarrhea, and FI (Bytzer et al., 2001, 2002). The diarrhea is watery and painless, occurs at night, and may be associated with FI. The prevalence is estimated to vary between 8% and 22% (Dandona, Fonseca, Mier, & Beckett, 1983; Feldman, & Schiller, 1983). Therapy is usually directed toward predominant symptoms. Diarrhea is usually treated with antidiarrheal drugs (loperamide and diphenoxylate). Use of antibiotics to treat small bowel bacterial overgrowth and octreotide (50 to 75 μg subcutaneously BID to TID) has been found to be somewhat helpful in the treatment of diabetic diarrhea (Mourad, Gorard, Thillainayagam, Colin-Jones, & Farthing, 1992; Walker & Kaplan, 1993). Antidepressants like tricyclics, selective serotonin reuptake inhibitors, and gabapentin can be used in the treatment of nonspecific abdominal pain secondary to diabetic enteropathy.

Autonomic dysfunction is present in patients with Guillain-Barre syndrome, amyloidosis, and hepatic porphyrias with peripheral neuropathy. MNGIE, discussed earlier in the chapter, is associated with peripheral neuropathy with severe visceral neuropathy and secondary GI dysfunction. Segmental demyelination, myelin sheath abnormalities, and axonal degeneration and depletion have been found on nerve biopsies in patients with MNGIE (Bedlack et al., 2004).

CONCLUSIONS

GI involvement is frequently observed in patients with neuromuscular diseases, and digestive complaints may be the first sign of the disease. Problems with swallowing and motility disorders are two main GI manifestations usually observed in these patient groups. Collaboration between gastroenterologists and neurologists is essential for the appropriate understanding, diagnosis, and management of patients.

After exclusion of intrinsic mucosal disease of the gut, the presence of these symptoms in patients with established neurological disorders suggests that the underlying condition is responsible for the patient's symptoms. Recognition of these complications is imperative, and early intervention with hydration and nutritional support, including appropriate timing of feeding tube placement, is necessary. Principles of management also include treatment of neurological disease itself, suppression of bacterial overgrowth, correction of dysmotility with medical therapy, and multidisciplinary approach toward the management of these patients.

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Autonomic Dysfunction in Neuromuscular Disorders

5

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OVERVIEW OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system extends to every organ in the human body, creating a dizzying array of central and peripheral nerves, nuclei, ganglia, and neurotransmitters that often defy conventional attempts at learning through memorization. Although colloquial understanding of the autonomic nervous system is discovered in the medical students' mantra of "fight or flight," true comprehension of the system often occurs only after disease-specific disturbances of autonomic function are encountered in clinical practice. The autonomic nervous system modulates blood pressure, heart rate, thermoregulation, motility of the gastrointestinal system, micturition, pupillary function, and salivary gland secretion, among other things (Benarroch, 2007). Dysfunction of one, or all, of these processes may occur in neuromuscular disorders that affect the autonomic nervous system. This chapter briefly reviews the anatomic structure and clinical implications of autonomic dysfunction, the evaluation of the autonomic nervous system, neuromuscular diseases that result in autonomic disturbances, and treatment options in patients with dysautonomia. A graphic overview of the autonomic nervous system is shown in Fig. 5.1.

SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system is composed of cells located in the lateral horn of the spinal cord (thoracic to lumbar levels), and for this reason it has been referred to as the *thoracolumbar system*. The cell bodies of sympathetic preganglionic neurons are located from T1 to L3 in the intermediolateral columns (Benarroch, 2007). The preganglionic neurons project ipsilaterally out the white rami to the paravertebral chain, where they synapse on postganglionic neurons in adjacent ganglia. There is a rough anatomic distribution to the ganglia, with the upper thoracic ganglia projecting to the head and the lumbar ganglia projecting to the lower extremities and lower trunk. The axons of the preganglionic sympathetic neurons are relatively short because of the close proximity of the paravertebral ganglia, and they use acetylcholine as their neurotransmitter. In contrast, the postganglionic neurons have longer axons that stimulate directly on their target end-organ through the neurotransmitter norepinephrine. One notable exception to this rule is the innervation to the postganglionic sudomotor system (i.e., the sweat glands), which also uses acetylcholine as the postganglionic neurotransmitter (Benarroch, 2007).

Activation of the sympathetic nervous system facilitates energy expenditure in urgent situations. Bronchial dilation occurs to improve respiratory capacity. There is constriction of the arrector pili muscles, resulting in hairs standing on end. The piloerection response is seen prominently in households cohabitated by feline and canine species as the domesticated cat attempts to frighten the dog by appearing larger. Sphincters of the anus and bladder tighten (to prevent fluid release), with simultaneous relaxation of the detrusor muscle (to prevent fluid expulsion). Activation of the cardiovascular system results in increased heart rate and contractility, and vasodilation occurs in blood vessels to the lungs, heart, and striated muscle. Conversely, vasoconstriction occurs in the skin and gastrointestinal tract to improve blood flow to the other organ systems. During sympathetic activation, the pupil widens as a result of constriction of the dilator muscle, the tarsal muscle of the eyelid contracts, elevating the eyelid, and tightening of the orbital muscle results in protrusion of the eyeball. These ocular adjustments result in an increase in visual field size but are well suited to stereotyping for cartoonists who create a caricature of a face with retracted eyelids and bulging eyes.

PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system is composed of cells located in the brain stem and the sacral region of the spinal cord, and for this reason it has been referred to as the craniosacral system. The cranial preganglionic neurons project to the cranial nerves (CNs) with autonomic activity: III, VII, IX, and X. Unlike the sympathetic nervous system, the parasympathetic postganglionic neurons are located near end-organ systems, resulting in long preganglionic axons and relatively short postganglionic axons (Benarroch, 2007).

The brain stem nuclei involved in CN parasympathetic innervation include the following. (1) CN III: Preganglionic neurons from the Edinger-Westphal nucleus extend down the oculomotor nerve and synapse at the orbital ciliary ganglion, where postganglionic neurons extend to the ciliary muscles and iris, resulting in accommodation and pupillary constriction. (2) CN VII: Pontine preganglionic fibers from the superior salivatory nucleus extend down the facial nerve to the pterygopalatine ganglion, with postganglionic fibers extending to the lacrimal gland (tear production) and the cranial vasculature (resulting in vasodilation).

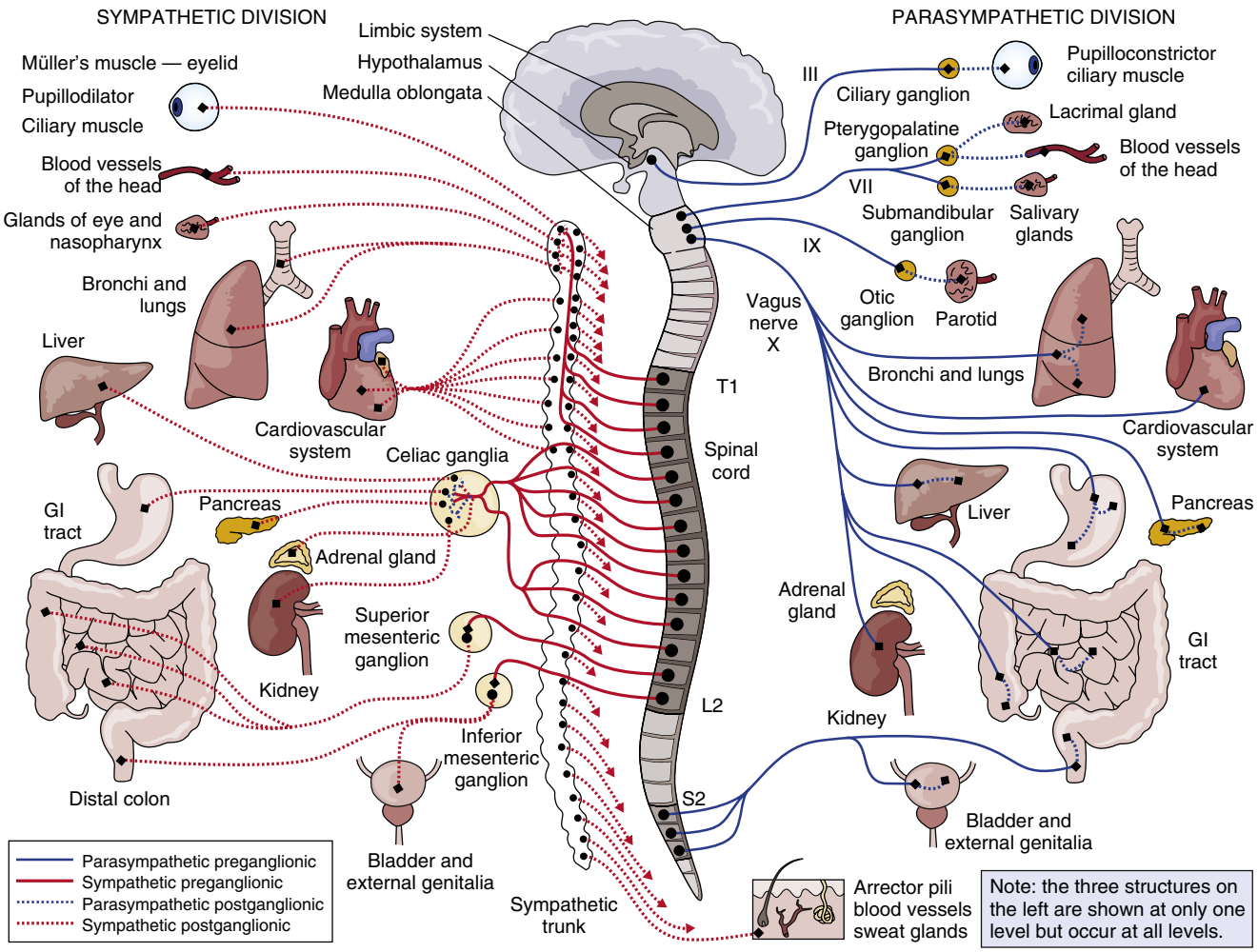


Fig. 5.1 Major pathways of the autonomic nervous system, with sympathetic innervation shown in *red* and parasympathetic innervation shown in *blue.* Preganglionic fibers are shown as *solid lines,* and postganglionic fibers are represented by *dotted lines. GI*, Gastrointestinal.

Pontine preganglionic fibers also extend to the submandibular ganglion, with postganglionic fibers continuing on to the salivary glands (resulting in salivation). (3) CN IX: Medullary preganglionic fibers from the inferior salivatory nucleus extend down the glossopharyngeal nerve to the otic ganglion, where postganglionic fibers continue on to the parotid gland (resulting in salivation). (4) CN X: By far the largest parasympathetic output, the preganglionic fibers from the dorsal motor nucleus of the vagus and the ventrolateral portion of the nucleus ambiguus extend down the vagus nerve to various ganglia. The fibers extending from the dorsal motor nucleus of the vagus provide input to the gastrointestinal tract (enteric system, described in more detail later), the respiratory tract, and some cardiac input, whereas fibers extending from the nucleus ambiguus extend primarily to the heart. The primary response to vagal activation is cardiac inhibition, visceromotor activation, and salivation (Benarroch, 2007).

Sacral parasympathetic output begins in the lateral gray matter of segments S2–S3, with preganglionic fibers extending down the ventral roots to the splanchnic nerves. The parasympathetic fibers extend to the colon, bladder, and sexual organs. The Onuf nucleus innervates the rectal and urethral sphincters and the pelvic floor. Selective denervation of the Onuf nucleus in Parkinson disease enables differentiation (in some cases) from multiple system atrophy, although this has not been found to be widely reproduced (Palace, Chandiramani, & Fowler, 1997).

The overall effect achieved with activation of the sacral parasympathetic system results is urination (relaxation of the bladder sphincter with simultaneous contraction of the detrusor muscle to facilitate micturition), defecation (relaxation of the rectal sphincter with increased peristalsis), and penile erection (ejaculation is mediated via sympathetic innervation). Unlike the sympathetic nervous system, the parasympathetic nervous system uses acetylcholine for both preganglionic and postganglionic neural transmission.

ENTERIC NERVOUS SYSTEM

Although it was historically subsumed under the auspices of the parasympathetic nervous system, recent evidence suggests that the enteric nervous system is a discrete component of the autonomic nervous system. The enteric system is made up of two interconnected ganglia influenced by both sympathetic and parasympathetic pathways. The first ganglia are located between the longitudinal and circular muscle layers of the gastrointestinal tract, known as the

myenteric or Auerbach plexus, and project to both external and internal muscle layers. The second ganglia are located in the submucosal layer, known as the submucosal or Meissner plexus, and project to the mucosal layer. Neurons from both the myenteric plexus and the submucosal plexus innervate nearby tissue as well as anteriorly and posteriorly along adjacent regions of the gastrointestinal tract. The enteric nervous system controls peristalsis, secretion, and absorption along the gastrointestinal tract (Benarroch, 2007).

EVALUATION OF THE AUTONOMIC NERVOUS SYSTEM

A number of testing techniques are available for clinical evaluation of the autonomic nervous system; far more are used for research investigation. This chapter describes the most commonly used clinical tests but does not provide a comprehensive review. For additional details on evaluation of the autonomic nervous system, more comprehensive references are suggested (Low & Benarroch, 2008). The overall utility of autonomic testing has been reviewed and given a level B recommendation (probably effective) by an expert panel for the evaluation of autonomic neuropathy and a level C recommendation (possibly effective) in the evaluation of distal small fiber neuropathy (England et al., 2009).

INDICATIONS FOR AUTONOMIC TESTING

Autonomic testing provides functional information on the parasympathetic, sympathetic adrenergic, and sympathetic cholinergic systems. Any patient presenting with suspected dysfunction of the autonomic nervous system resulting in orthostatic hypotension, syncope, postural tachycardia syndrome, peripheral neuropathy, or thermoregulatory abnormalities is a candidate for tests of autonomic function. Other common symptoms that suggest autonomic dysfunction include postural dizziness, visual graying in the upright position, impaired cognition, coat hanger headache (due to ischemia of the strap muscles of the neck and shoulders), lightheadedness, platypnea (shortness of breath in the upright position), weakness, and lethargy (Gibbons & Freeman, 2005).

PREPARATION FOR AUTONOMIC TESTING

Adequate preparation for autonomic testing is critical to obtain reliable and reproducible results. All medications that affect autonomic function should be discontinued for five half-lives before testing, if clinically appropriate, with guidance from the patient's treating physician as necessary. All patients referred for autonomic evaluation should avoid caffeine and nicotine on the day of testing. Food intake should be kept to a minimum, with no food 3 hours before testing.

Medications that commonly interfere with testing include anticholinergics (antihistamines, antidepressants, decongestants), antihypertensives, volume expanders (e.g., fludrocortisone), and volume contractors (e.g., diuretics) and should be discontinued for five half-lives, if possible. Analgesics (opioids or over-the-counter) and items that cause structural changes to blood flow (e.g., compression stockings or corsets) should be avoided the day of testing (Low, 1997b).

Table 5.1 Definitions of Frequently Used Terms

Term	Definition
Orthostatic intolerance	Symptoms that develop in the upright position that are relieved by recumbancy. No physiologic measurements required.
Orthostatic hypotension	A sustained drop in systolic blood pressure of ≥20 mm Hg, or diastolic blood pressure of ≥10 mm Hg within 3 minutes of moving from the supine to standing position or head up tilt to ≥60 degrees.
Postural tachycardia	A sustained increase in pulse of ≥30 beats per minute within the first 10 minutes of moving from the supine to standing position or head up tilt to ≥60 degrees.

TESTS OF AUTONOMIC FUNCTION

A number of terms are frequently used when describing symptoms related to autonomic dysfunction, such as *orthostatic hypotension*, *orthostatic intolerance*, and *postural tachycardia*. A brief overview of these terms is provided in Table 5.1.

HEMODYNAMIC RESPONSE TO STANDING

The transition from supine to standing causes hemodynamic stress on the cardiovascular system as approximately 500 to 1000 mL of blood moves from the central to the peripheral vasculature (Borst, Van Brederode, Wieling, van Montfrans, & Dunning, 1984). The immediate response to orthostatic stress occurs in the first 30 seconds, beginning with a rapid decrease in blood pressure and systemic resistance, followed by a rapid increase in peripheral vascular resistance, cardioacceleration, and blood pressure overshoot (Borst et al., 1984). These dynamic changes allow two tests of autonomic function to be determined: (1) orthostatic vital signs and (2) the 30:15 ratio.

To measure orthostatic vital signs, blood pressure and heart rate should be measured in the supine position after an adequate period of recumbency (typically, at least 5 minutes). Patients then move to the standing position, where blood pressure and heart rate are monitored again after 3 minutes. A diagnosis of orthostatic hypotension is made when a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg occurs from the supine to the standing position (Gibbons et al., 2017). There is a frequent misunderstanding among practitioners that an increase in pulse of 25 points or greater leads to a diagnosis of "orthostatic by pulse." In the appropriate clinical setting, this finding suggests that the patient may be hypovolemic, but there is appropriate tachycardia preventing orthostatic hypotension from occurring. However, in a normovolemic patient, a sustained increase in pulse of 30 points or greater (to a maximum of 120 beats per minute) from the supine to the standing position within 10 minutes results in a diagnosis of postural tachycardia syndrome (if the appropriate symptoms occur with standing and have been present for a

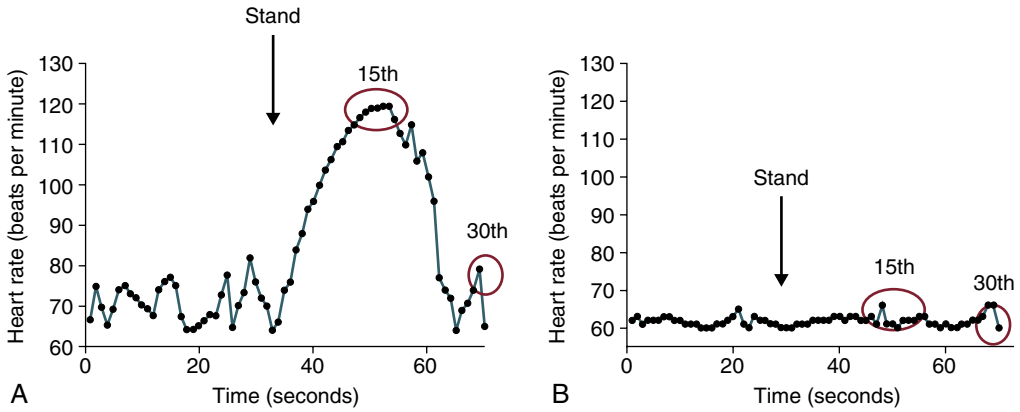


Fig. 5.2 The 30:15 ratio. (A) The patient moves rapidly from a supine to a standing position, causing initial tachycardia at approximately the 15th heartbeat, followed by bradycardia at approximately the 30th heartbeat. The RR interval at the 30th heartbeat is 0.89 seconds, and at the 15th beat it is 0.5 seconds, leading to a 30:15 ratio of 1.78. (B) The same test is performed in a patient with severe diabetic autonomic neuropathy. There is no noticeable change in heart rate on standing, and the 30:15 ratio approaches 1.

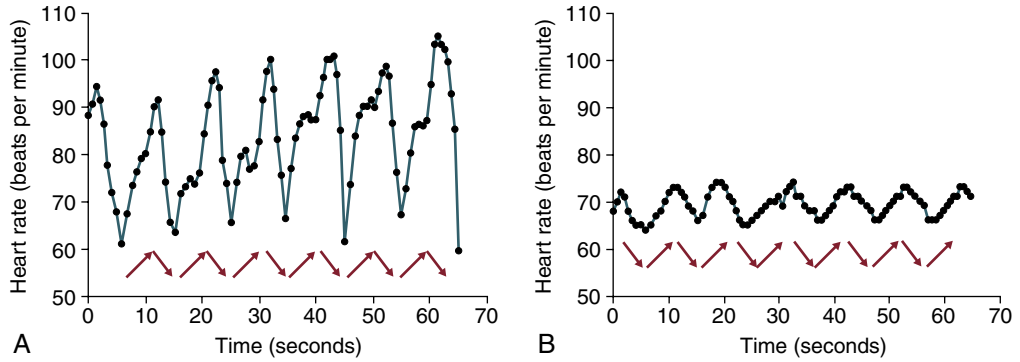


Fig. 5.3 Heart rate response to deep breathing. (A) A healthy subject takes slow, deep breaths (*up arrows* denote inspiration; *down arrows* denote expiration) with auditory or visual cues while the heart rate is monitored. The average variation in heart rate is calculated and can be expressed as the mean difference in heart rate (in this example, an average of 29), or the RR interval ratio between mean minimum and maximum heart rates (in this example, 1.52). This is a normal response. (B) The heart rate response to deep breathing is seen in a patient with diabetic autonomic neuropathy. The average variation in heart rate is substantially reduced compared with the healthy individual shown in A. In this example, the average variation in heart rate is eight beats, with an RR interval ratio of 1.1.

sufficient duration of time) (Arnold, Ng, & Raj, 2018; Low, Schondorf, Novak, Opfer-Gehrking, & Novak, 1997).

The 30:15 ratio is a measure of parasympathetic function that occurs when subjects move from the supine to the standing position. The immediate response to orthostatic stress is tachycardia, typically maximal at the 15th heartbeat after standing, followed by bradycardia, most pronounced at the 30th heartbeat after standing. The ratio of the RR interval at beat 30 to the RR interval at beat 15, called the 30:15 ratio, is an index of cardiovagal function (Fig. 5.2) (Low, 2003).

TILT-TABLE TESTING

The tilt-table is an important tool in the evaluation of the autonomic nervous system. When a subject is tilted to an angle of 60 to 70 degrees, the orthostatic stress that occurs is similar to that of standing, but the muscles of the legs are relaxed. The "muscle pump" effect that occurs with the legs during standing is a powerful countermaneuver to prevent orthostatic hypotension (Gibbons & Freeman, 2004).

Testing requires a period of recumbency, typically 20 minutes, followed by a gradual rise to a head-up tilt angle of 60 to 70 degrees. Testing for many laboratories extends to 45 minutes for adequate assessment of autonomic function (Low, 1997b). Testing combines the use of oscillometric blood pressure recording at regular intervals and noninvasive beat-to-beat blood pressure recordings (Low, 2003). A diagnosis of orthostatic hypotension is made when a sustained decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg occurs from the supine to the upright position within the first 3 minutes of head-up tilt. Decreases in blood pressure after 3 minutes have been described as delayed orthostatic hypotension (Gibbons & Freeman, 2006a; Gibbons et al., 2017). A sustained increase in pulse of 30 points or greater (to a maximum of 120 beats per minute) from the supine to the standing position within 10 minutes, in a normovolemic patient, results in a diagnosis of postural tachycardia syndrome (Schondorf & Low, 1993).

HEART RATE RESPONSE TO DEEP BREATHING

The heart rate varies during inspiration and expiration and has been described as the sinus arrhythmia. The maximal heart rate variation with respiration occurs at a breathing rate of 5 to 10 breaths per minute. Patients are provided with a visual or auditory cue to regulate their breathing in combination with continuous electrocardiographic monitoring. Approximately 1 minute of respiration is recorded, and the average variation between the maximal and minimal heart rates is described (Fig. 5.3). This test provides a measure of

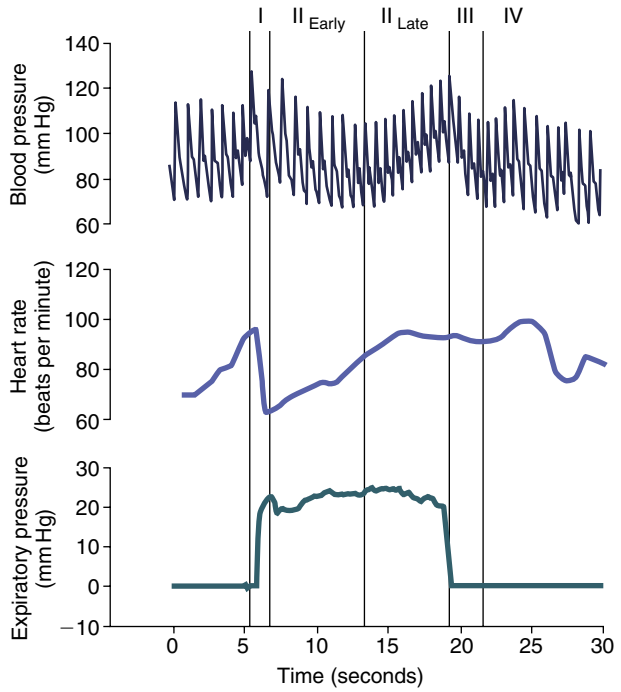


Fig. 5.4 Valsalva maneuver. The patient exhales forcefully for 15 seconds. Expiratory pressure is shown at the bottom of the graph. The heart rate response is shown in the middle of the graph, whereas the beat-to-beat blood pressure response is shown at the top of the figure. The four phases of the Valsalva maneuver are as follows. Phase 1 occurs during the onset of exhalation with straining against resistance. The increase in intrathoracic pressure causes compression of the great vessels (with a transient increase in venous flow to the heart) and an increase in blood pressure. Phase 2 begins with decreased venous return (because of increased intrathoracic pressure compressing the great vessels and reducing venous flow) and decreased stroke volume, cardiac output, and blood pressure (phase 2 early), followed by sympathetically mediated peripheral vasoconstriction and an increase in blood pressure and heart rate (phase 2 late). Phase 3 occurs with cessation of forced exhalation, resulting in decreased intrathoracic pressure and a transient decrease in blood pressure. Phase 4 may extend for several minutes from the end of phase 3 and leads to an increase in blood pressure over baseline levels secondary to increases in stroke volume and cardiac output with peripheral vasoconstriction.

parasympathetic function and can be compared with age- and sex-matched normative values (Bennett et al., 1977).

VALSALVA MANEUVER

The Valsalva maneuver is a relatively simple test to perform, but it results in rapid and complex hemodynamic shifts that require continuous electrocardiographic and beat-to-beat blood pressure recordings to measure. The subject, in a supine position, blows into a tube with a pressure of approximately 40 mm Hg for 15 seconds (Low, 2003). The procedure is similar to blowing up a stiff balloon. The breathing tube should have an air leak to prevent glottic closure.

The Valsalva maneuver has four parts, as seen in Fig. 5.4. Phase 1 occurs during the onset of exhalation with straining against resistance. The increase in intrathoracic pressure causes compression of the great vessels and an increase in blood pressure. Phase 2 of the Valsalva maneuver begins with decreased venous return (because of increased intrathoracic pressure) and decreased stroke volume, cardiac output, and blood pressure (phase 2 early), followed by sympathetically mediated peripheral vasoconstriction and an increase in blood pressure and heart rate (phase 2 late). Phase 3 occurs with cessation of forced exhalation, resulting in decreased intrathoracic pressure and a transient decrease in blood pressure. Phase 4 may extend for several minutes from the end of phase 3 and leads to an increase in blood pressure over baseline levels secondary to increases in stroke volume and cardiac output with peripheral vasoconstriction (Low, 2003).

TESTS OF SYMPATHETIC CHOLINERGIC FUNCTION

SYMPATHETIC SKIN RESPONSE

The sympathetic skin response detects electrical potential changes between the dorsal and ventral surfaces of the hands and feet. A stimulus, such as an inspiratory gasp or electric shock, results in electrical potential changes to the palms of the hands and soles of the feet. This test can be easily performed with any electromyogram or evoked potential device. A typical example in a healthy individual and a patient with neuropathy is shown in Fig. 5.5. The sympathetic skin response is a surrogate measure of sudomotor function but does not actually measure sweat production (Illigens & Gibbons, 2009). Attempts to correlate response amplitude and latency with disease severity have met with mixed results. The absence of a sympathetic skin response is usually considered abnormal, although age-related changes occur

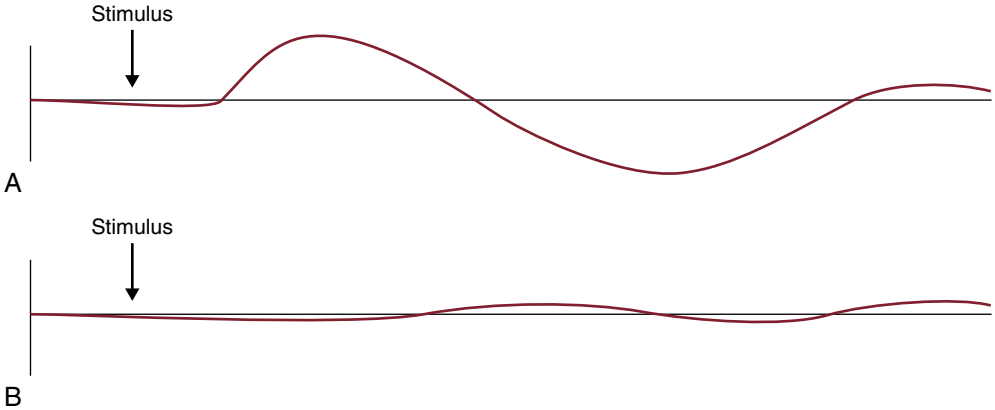


Fig. 5.5 Sympathetic skin response. (A) After a stimulus (a deep breath or an electric shock), a normal sympathetic skin response is shown, with negative and positive deflection noted. The onset latency and magnitude of response can be quantified. (B) A patient with neuropathy has a much smaller magnitude of response and longer onset latency.

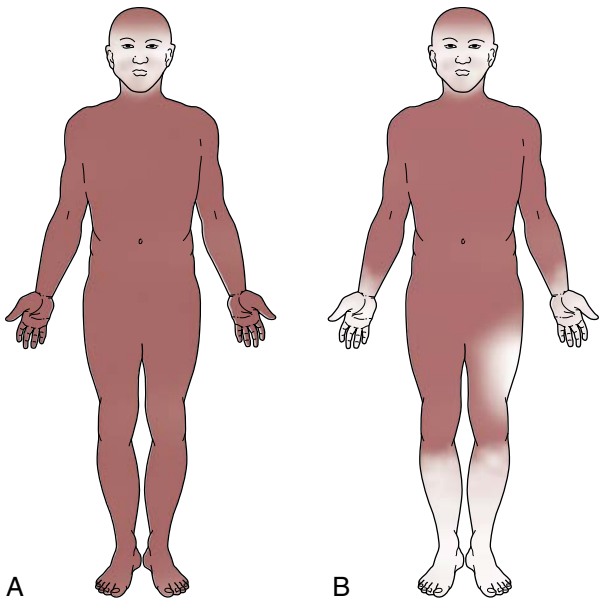


Fig. 5.6 Thermoregulatory sweat testing. Two patients are shown after thermoregulatory sweat testing. The *dark areas* correspond to regions where sweating has occurred. (A) Normal response. (B) Loss of sweating in a stocking-glove distribution (length-dependent neuropathy, in this case, secondary to diabetes), with additional loss in the left lateral cutaneous nerve distribution.

in the lower extremities of individuals older than 50 years (Illigens & Gibbons, 2009). In addition, some central disorders, such as stroke, may result in loss of the sympathetic skin response (Illigens & Gibbons, 2009). More recent efforts to improve upon measurements of sweat function through use of an electrochemical skin conductance device (Sudoscan) have provided very mixed results (Rajan, Campagnolo, Callaghan, & Gibbons, 2019). At the present time, electrochemical skin conductance is not recommended for clinical use.

THERMOREGULATORY SWEAT TESTING

The thermoregulatory sweat test detects the host's ability to generate sweat in response to an increase in core temperature. The subject is placed in a chamber where the external temperature is increased to a degree sufficient to increase the core temperature by 1°C to 1.5°C (Fealey, Low, & Thomas, 1989). An indicator dye, typically alizarin red or iodinated corn starch, covers the individual and changes color in the presence of sweat. Photographic mapping of sweat patterns can determine patterns of abnormalities. A normal response is seen with symmetrical sweat production over the entire body (there is individual variation in maximal sweat production), as shown in Fig. 5.6. Specific abnormalities can be seen in diseases of both the central nervous system and the peripheral nervous system because the thermoregulatory sweat test measures both the preganglionic and postganglionic response to an increase in core temperature. An abnormal response may suggest a specific diagnosis through a distribution of sweat loss but cannot differentiate a preganglionic lesion from a postganglionic lesion (Fealey et al., 1989).

QUANTITATIVE SUDOMOTOR AXON REFLEX TESTING

Quantitative sudomotor axon reflex testing provides a measure of postganglionic sweat production. Activation of local sudomotor fibers through iontophoresis of a cholinergic agonist (typically, acetylcholine) results in the direct stimulation of local sweat glands. However, a local axon reflex occurs when an antidromic response is generated, travels to a more proximal nerve branch point, and then travels orthodromically to neighboring sweat glands that were not directly activated by the cholinergic agonist (Low, 2003). A small capsule over the skin is used to detect changes in humidity and provide a quantifiable measure of postganglionic sweat production. Well-established normative values have been published, and abnormalities can be seen early in distal small fiber neuropathies of many causes (Low, Caskey, Tuck, Fealey, & Dyck, 1983).

SUMMARY OF AUTONOMIC TESTING

Tests of sympathetic adrenergic, sympathetic cholinergic, and parasympathetic function are shown in Table 5.2. Many tests fall under both sympathetic adrenergic and parasympathetic categories because of their effects on both heart rate and blood pressure. A large number of additional tests can be performed by other subspecialty groups in ophthalmology, gastroenterology, urology, cardiology, and others. For a complete review of available tests, the reader is referred to a number of excellent texts devoted entirely to these topics (Low & Benarroch, 2008; Mathias & Bannister, 1999).

One of the challenges inherent in autonomic testing is the differentiation of peripheral and central disorders of autonomic regulation, a problem compounded by the frequently overlapping test results. Most autonomic tests cannot differentiate between peripheral and central causes of autonomic disturbance in isolation; the results are usually combined with a detailed history and examination by a specialist to narrow the differential diagnosis. A few tests are more likely to differentiate central from peripheral autonomic disorders and are described in Table 5.3.

TYPES OF AUTONOMIC NEUROPATHY

CHRONIC AUTONOMIC NEUROPATHIES

DIABETIC AUTONOMIC NEUROPATHY

Diabetic autonomic neuropathy is the most common form of autonomic neuropathy in the developed world (Freeman, 2005). It is a system-wide disorder, affecting all parts of the autonomic nervous system (Pop-Busui et al., 2017). The incidence of this form of neuropathy increases with age, with duration of disease, and with chronic hyperglycemia, and it is almost universally accompanied by features of concomitant distal sensorimotor polyneuropathy (Freeman, 2005). The symptoms of autonomic neuropathy generally occur well after the onset of the endocrinologic manifestations of diabetes mellitus. However, evidence of subclinical autonomic dysfunction may be seen as early as 1 year after initial diagnosis (Freeman, 2014). The prevalence of diabetic autonomic neuropathy is dependent on the criteria used for diagnosis and the population studied. A population-based study in the United States found that symptomatic diabetic autonomic neuropathy affected 5.5% of patients with diabetes mellitus (Dyck et al., 1993). In a multicenter study in Europe involving nearly 1200 patients, there was evidence of abnormalities in the results of tests of autonomic function in 25.3% of patients with type 1 diabetes mellitus and in 34.3% of patients with type 2 diabetes mellitus (Ziegler, Gries, Spuler, & Lessmann, 1992).

Table 5.2 Autonomic Testing

Sympathetic Adrenergic	Parasympathetic	Sympathetic Cholinergic
Blood pressure response standing	Heart rate response to standing (30:15 ratio)	Sympathetic skin response
Blood pressure response to tilt table testing	Heart rate response to tilt table testing	Thermoregulatory sweat testing
Valsalva maneuver: phase 2 blood pressure recovery and phase 4 overshoot	Valsalva heart rate ratio	Quantitative sudomotor axon reflex testing
Isometric exercise: blood pressure response[a]	Isometric exercise: heart rate response[a]	Silicone impression testing[a]
Cold pressor test: blood pressure response[a]	Cold pressor test: heart rate response[a]	Quantitative direct and indirect axon reflex testing[a]
Plasma catecholamine levels[a]	Deep breathing: heart rate response	Acetylcholine sweat-spot[a]

[a]Tests not described in detail in this chapter.
For further information, the following references are suggested: Low, P. A. (1997). *Clinical autonomic disorders: Evaluation and management*. Philadelphia: Lippincott–Raven; Low, P. A. (1997). Laboratory evaluation of autonomic function. In *Clinical autonomic disorders: Evaluation and management* (2nd ed., pp. 179–208). Philadelphia: Lipincott-Raven; Mathias, C. J., & Bannister, R. (1999). *Autonomic failure*. Oxford: Oxford University Press.

Table 5.3 Findings Suggestive of Central or Peripheral Autonomic Dysfunction

Test	Central Autonomic Disorder	Peripheral Autonomic Disorder
Plasma catecholamines[a]	Normal or slightly elevated (150–300 pg/mL plasma norepinephrine)	Low (≤100 pg/mL of plasma norepinephrine)
Thermoregulatory sweat test[b]	Abnormal	Abnormal
Quantitative sudomotor axon reflex test[b,c]	Normal	Abnormal

[a]A minority (up to 20%) of patients will have plasma catecholamine levels that fall between the two ranges, resulting in diagnostic ambiguity.
[b]Thermoregulatory sweat testing and postganglionic tests of sudomotor function can be combined to identify central or peripheral disorders. If both tests are abnormal, it is a peripheral disorder; if only the thermoregulatory sweat test is abnormal, it is central.
[c]Any postganglionic test of sudomotor function can be used (Quantitative sudomotor axon reflex testing (QSART), silicone impressions, acetylcholine sweat-spot testing or quantitative direct and indirect reflex testing (QDIRT)).

Autonomic neuropathy is associated with an increase in overall mortality and with a higher likelihood of sudden death, especially when cardiovascular autonomic neuropathy is present (Maser, Mitchell, Vinik, & Freeman, 2003). In a prospective study (Ewing, Campbell, & Clarke, 1981), 56% of patients with diabetic cardiovascular autonomic neuropathy were dead at 5 years, and half of them died unexpectedly and possibly of causes related to underlying dysautonomia.

There are multiple hypotheses as to the pathogenesis of diabetic autonomic neuropathy, and the etiology is likely multifactorial. A metabolic injury to nerve fibers secondary to hyperglycemia, neurovascular insufficiency, autoimmune damage, and a neurohormonal growth factor deficiency are among the processes implicated (Feldman et al., 2019). As with most neuropathies, diabetic autonomic neuropathy is a length-dependent process and clinical manifestations are first seen in processes affecting longer nerves. Accordingly, the vagus nerve (the longest of the autonomic nerves) is affected early in the disease course. Because this nerve is responsible for approximately 75% of parasympathetic function, symptoms may occur from the beginning and may be widespread (Freeman, 2014). The clinical features of diabetic autonomic neuropathy are reflective of the multiple organ systems that it affects. Accordingly, these are discussed on a system-by-system basis.

Cardiovascular Autonomic Neuropathy in Diabetes

Cardiovascular autonomic neuropathy results from damage to autonomic nerves that innervate the heart and blood vessels, thereby leading to abnormalities in heart rate control and peripheral vascular dynamics. The prevalence is estimated to be approximately 17% of patients with type 1 diabetes mellitus and 22% with type 2 diabetes mellitus (Ziegler et al., 1993). The 5-year mortality rate among diabetic patients with symptomatic cardiovascular autonomic neuropathy is estimated to be five times higher than that of those without cardiovascular autonomic neuropathy (Ziegler et al., 1993). The manifestations of cardiovascular autonomic neuropathy are multiple and reflect both parasympathetic and sympathetic dysfunction.

Exercise intolerance is frequently seen in patients with cardiovascular autonomic neuropathy. Early in the course of the disease, an increase in resting heart rate is often observed as a result of vagal neuropathy and unopposed sympathetic activity and may be the first sign of autonomic neuropathy. As the disease progresses, a fixed heart rate is observed (Ewing et al., 1981). Eventually, reduced response in heart rate and blood pressure during physical activity

leads to decreased cardiac output, reflecting impairment of both parasympathetic and sympathetic responses that typically augment cardiac output during exercise.

Orthostatic hypotension is also a typical feature of cardiovascular autonomic neuropathy and is defined as a decrease in blood pressure of greater than 20 mm Hg systolic or greater than 10 mm Hg diastolic in response to postural change (Gibbons et al., 2017). Orthostatic hypotension occurs secondary to damage to efferent sympathetic vasomotor fibers, predominantly in the splanchnic vasculature, reduced cardiac output, and a reduction in the normal increase in plasma norepinephrine (Low, Walsh, Huang, & McLeod, 1975). Patients typically present with symptoms of lightheadedness or presyncope on change of position. Other symptoms may include nonspecific dizziness, weakness, fatigue, visual blurring, and neck pain (Gibbons & Freeman, 2005). Many patients may remain asymptomatic despite significant decreases in blood pressure on change of position (Freeman et al., 2018).

Other symptoms seen in cardiovascular autonomic neuropathy are intraoperative cardiovascular lability and sudden death, possibly as a result of malignant arrhythmogenesis (Freeman, 2014). In addition, silent myocardial infarction, likely as a result of cardiac denervation, is estimated to occur in approximately one third of patients with diabetes mellitus (Pop-Busui et al., 2017).

Gastrointestinal Autonomic Neuropathy in Diabetes

Gastrointestinal symptoms are relatively common in patients with diabetes mellitus and are often caused by underlying autonomic neuropathy. The prevalence of gastrointestinal symptoms was reported to be as high as 76% in patients with type 2 diabetes mellitus in one series (Maleki et al., 2000). Symptoms are reflective of widespread disease and include esophageal dysfunction secondary to vagal neuropathy. This may manifest as heartburn or dysphagia for solids. Gastroparesis diabeticorum is seen in up to 50% of patients with diabetes mellitus. This can produce such symptoms as early satiety, anorexia, postprandial nausea and vomiting, and epigastric discomfort. In addition, delayed gastric emptying interferes with nutrient delivery to the small bowel and can have far-reaching implications (Kong, Horowitz, Jones, Wishart, & Harding, 1999). Diarrhea, which is typically nocturnal, watery, and profuse, is frequently seen in those with diabetes. This may alternate with constipation as a result of gut dysmotility and is estimated to occur in approximately 60% of patients with diabetes (Maleki et al., 2000). Fecal incontinence may also occur as a result of anal sphincter incompetence or reduced rectal sensation.

Genitourinary Autonomic Neuropathy in Diabetes

Neurogenic bladder is seen in approximately one third to one half of patients with diabetes mellitus. Early on, deafferentation leads to impaired bladder sensation and an increased threshold for initiating the micturition reflex. This leads to an increase in bladder capacity with urinary retention. Later, parasympathetic dysfunction results in reduced detrusor activity with urinary hesitancy and incomplete emptying. This causes further retention and overflow incontinence, as well as predisposing patients to urinary tract infections (Ellenberg, 1980).

Erectile dysfunction may actually be the earliest sign of diabetic autonomic neuropathy and is seen in 35% to 75% of men with diabetes mellitus (Freeman, 2005). The pathogenesis is likely multifactorial and due to neuropathy (leading to reduced cholinergic activation), vascular, metabolic, endocrinologic, pharmacologic, and psychological factors (Freeman, 2005). In addition to erectile dysfunction, ejaculatory failure and retrograde ejaculation may be seen (Freeman, 2005).

Sudomotor Dysfunction in Diabetes

Sudomotor dysfunction is a common feature of diabetic autonomic neuropathy. It typically manifests first as anhidrosis of the extremities in a stocking-glove distribution, conforming to the length dependency of the neuropathy. This progresses to involve the upper aspects of the limbs, the anterior abdomen, and the top of the head and may ultimately result in global anhidrosis (Freeman, 2005). Hyperhidrosis of the trunk may be seen early in the disease as a compensatory phenomenon. Gustatory sweating (abnormal production of sweat over the face, head, neck, shoulders, and chest after eating) is also occasionally observed (Fealey et al., 1989). The gustatory pattern of sweating is believed to occur secondary to cervical sympathetic denervation and aberrant reinnervation (Low, Vernino, & Suarez, 2003).

OTHER MANIFESTATIONS OF DIABETIC AUTONOMIC NEUROPATHY

Other manifestations of diabetic autonomic neuropathy include reduced or absent pupillary response to light and lacrimal gland dysfunction (resulting in dry eyes). Although impaired awareness of hypoglycemia as a result of blunting of the normal catecholamine surge has long been believed to be secondary to autonomic neuropathy in patients with diabetes, the literature on this topic is controversial. Some studies found that peripheral neuropathy was a risk factor for episodes of severe hypoglycemia (Akram, Pedersen-Bjergaard, Borch-Johnsen, & Thorsteinsson, 2006; Pedersen-Bjergaard et al., 2004), although others looking specifically at the presence of autonomic neuropathy found that neuropathy produced at best a modest increase in the risk of severe hypoglycemia because of a reduction in counter-regulatory catecholamine responses (Meyer et al., 1998; Stephenson, Kempler, Perin, & Fuller, 1996).

AMYLOID AUTONOMIC NEUROPATHY

Overall, amyloidosis is a rare disease (Falk, Comenzo, & Skinner, 1997). There are multiple forms of amyloidosis, including primary (AL) amyloidosis (typically caused by a plasma cell dyscrasia), secondary (AA) amyloidosis (typically caused by an underlying chronic inflammatory condition), and hereditary amyloidosis (Falk et al., 1997). Of these, dysautonomia is seen in the primary and hereditary forms (Freeman, 2005). Neuropathy is present in 20% to 50% of patients with amyloidosis. The typical presentation is that of a distal painful small-fiber sensory neuropathy (Chao et al., 2019; Ebenezer et al., 2017). Autonomic neuropathy is also frequently observed and involves both sympathetic and parasympathetic nerve fibers (Low et al., 2003). Symptoms of autonomic dysfunction typically manifest early in the disease process and may be the presenting symptom in approximately 40% of cases (Falk et al., 1997). These include orthostatic hypotension, heart block, anhidrosis, erectile dysfunction, gastroparesis, pupillary abnormalities, constipation, and diarrhea.

The pathogenesis of the neuropathy in amyloidosis involves the deposition of insoluble beta-fibrillar proteins in the epineurium, perineurium, and endoneurium, as well as in the vasa nervorum, with resultant infiltrative, inflammatory, toxic, or ischemic damage to axons (Freeman, 2005).

Primary amyloidosis is most commonly of the amyloid light chain (AL) type and is a plasma cell dyscrasia whereby monoclonal immunoglobulin light chains are deposited as amyloid (Falk et al., 1997). Patients typically present in the sixth or seventh decade. The survival is poor (median range, 13–35 months), despite treatment with prednisone and melphalan (Freeman, 2005).

There are many forms of hereditary amyloidosis, and the most common cause is mutant production of transthyretin protein (Falk et al., 1997). Inheritance is autosomal dominant, and the disease usually presents in the third to fifth decade (Low et al., 2003). Autonomic symptoms are usually prominent. Survival is better than in the primary form of amyloidosis, but death generally occurs 5 to 15 years after diagnosis. There are reports of increased survival with orthotopic liver transplantation, although the autonomic symptoms typically do not improve (Freeman, 2005). The exciting development of novel therapies that target transthyretin (TTR) formation or TTR deposition for hereditary amyloidosis (hATTR) is one of the first major breakthroughs in treating a progressive neuropathy. The TTR therapies target different stages of protein formation or misfolding, with several now available for clinical use. The treatments for TTR amyloidosis generally fall into one of two categories: (1) they stabilize TTR amyloid or (2) they knock down TTR through a reduction in RNA degradation or gene silencing (although several novel therapies with additional mechanisms of action are in development) (Gertz, Mauermann, Grogan, & Coelho, 2019).

Tafamidis is a drug that binds to TTR at the thyroxine binding sites and stabilizes the tetramer of the TTR transport protein, slowing the breakdown of the TTR into monomers and slowing the development of amyloid deposition in tissues. Tafamidis has proven efficacy in the treatment of TTR cardiomyopathy and has received Food and Drug Administration (FDA) approval for a reduction in cardiovascular mortality and hospitalizations related to cardiomyopathy (Maurer et al., 2018). Tafamidis also has shown benefits in the treatment of early polyneuropathy through slowing of disease progression; however, it has not demonstrated efficacy in moderate- to late-stage polyneuropathy and does not have FDA approval for this treatment. The results for tafamidis do vary across TTR mutation subtypes, and therefore it is difficult to make general recommendations regarding therapy.

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that stabilizes TTR tetramers and reduces the rate of disease progression. Diflunisal has shown a reduction in the rate of neuropathy progression over 2 years compared to placebo, although the adverse events related to chronic NSAID use have raised concerns about chronic treatment (Berk et al., 2013). Diflunisal does not currently have FDA approval for treatment of hATTR.

Inotersen is an antisense oligonucleotide therapy that reduces the TTR amyloid RNA and protein levels. It has been FDA approved for the treatment of early-stage polyneuropathy in individuals with hATTR (Gertz et al., 2019). In a longitudinal study of 172 patients treated with either inotersen or placebo, there was a significant an improvement in symptoms and signs of neuropathy progression in the inotersen-treated group (Benson et al., 2018).

Patisiran is a double-stranded small interfering RNA (ribonuclein acid) that targets TTR. Patisiran has been FDA approved for the treatment of polyneuropathy in hATTR. In a study of 225 patients with hATTR polyneuropathy, there was a significant improvement in symptoms and signs of neuropathy development with patisiran compared to placebo after 18 months of treatment (Adams et al., 2018).

Direct comparisons between treatment for hATTR polyneuropathy have not been conducted; therefore, specific treatment recommendations are limited (Gertz et al., 2019). Treatment recommendations will largely vary by availability, cost, formulation (oral vs. intravenous), side effect profiles, and comorbidities. However, despite the gaps in knowledge, the development of therapies for hATTR polyneuropathy is an enormous scientific and clinical advance.

AUTONOMIC NEUROPATHIES IN ASSOCIATION WITH METABOLIC DISEASE

RENAL DISEASE

Up to 60% of patients with chronic uremia show evidence of abnormalities on testing of autonomic function (Vita, Messina, Savica, & Bellinghieri, 1990). Parasympathetic dysfunction occurs more frequently than sympathetic dysfunction; the exact pathogenesis is unknown but presumably involves damage to axons of autonomic fibers by toxic compounds. Symptomatic autonomic neuropathy appears to be most severe in older patients with concomitant diabetes mellitus. Symptoms include gastrointestinal dysmotility, orthostatic hypotension, and anhidrosis (Vita et al., 1990). It has also been hypothesized that dysautonomia contributes to instances of intradialytic hypotension (Toth & Zochodne, 2003; Vita et al., 1990).

HEPATIC DISEASE

In one study of patients with hepatic failure, 48% showed evidence of autonomic neuropathy, often subclinical. Most patients with symptoms reported gastrointestinal dysfunction and cardiovascular symptoms. The mechanism of the development of peripheral nerve damage is unclear (Chaudhry et al., 1999).

PORPHYRIA

The porphyrias are autosomal dominant disorders of heme biosynthesis. The neuropathic syndrome has an acute to subacute onset, with a predominantly distal motor polyneuropathy. Autonomic symptoms are common in acute intermittent porphyria and reflect sympathetic overactivity as opposed to failure. Symptoms include tachycardia (which may go on to produce malignant cardiac arrhythmias), abdominal pain and cramping, nausea and vomiting, obstipation, bladder dysfunction, and anhidrosis (Sack, 1990).

NUTRITIONAL DEFICIENCIES

Finally, autonomic neuropathy is infrequently seen in patients with nutritional deficiencies, such as vitamin B_{12} deficiency. One study of 21 patients with documented vitamin B_{12} deficiency found abnormalities on testing of sympathetic

and parasympathetic function, with patterns similar to those of patients with diabetic autonomic neuropathy (Beitzke, Pfister, Fortin, & Skrabal, 2002). It is unclear how frequently autonomic neuropathy is seen in conjunction with the more typical large-fiber deficits seen in patients with vitamin B_{12} deficiency.

Autonomic neuropathy has been described in two patients with concomitant sensory neuronopathy as a result of pyridoxine (vitamin B_6) intoxication. The autonomic symptoms were primarily of gastrointestinal and genitourinary dysfunction. Although changes in the autonomic ganglia have not been observed in animal models of pyridoxine excess, it has been posited that they are susceptible to damage by very high doses of pyridoxine because they lie outside the blood-brain barrier (Albin et al., 1987).

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

A group of rare disorders known as hereditary sensory and autonomic neuropathies are characterized by prominent sensory loss and autonomic symptoms with minimal motor involvement. There are currently five types of hereditary sensory and autonomic neuropathy (HSAN), with several subtypes recognized. HSAN I is the most common form (with subtypes 1A–1D) and has by far the most extensive list of historic names, including hereditary sensory radiculoneuropathy, Thévenard syndrome, familial trophoneurosis, familial syringomyelia, and ulceromutilating neuropathy. HSAN I presents in an autosomal dominant fashion during late childhood or early adolescence (Axelrod, Chelimsky, & Weese-Mayer, 2006). The primary deficit is in small unmyelinated fibers, leading to loss of pain sensitivity, although peroneal motor atrophy and auditory nerve deafness may be seen. HSAN II, or congenital sensory neuropathy, is autosomal recessive and presents in infancy or early childhood with loss of pain sensation. Multiple ulcerations and injuries to joints and extremities are common (Axelrod & Gold-von Simson, 2007). HSAN III, familial dysautonomia or Riley-Day syndrome, is an autosomal recessive disorder that presents at birth. In addition to impaired pain sensation, affected individuals have orthostatic hypotension, hypothermia, hypotonia, reduced tearing, and absent corneal reflexes (Axelrod & Gold-von Simson, 2007). HSAN IV, or congenital insensitivity to pain with anhidrosis, is an autosomal recessive condition presenting in infancy with hyperthermia, impaired pain sensation, and anhidrosis (Axelrod & Gold-von Simson, 2007). HSAN V, or congenital insensitivity to pain with partial anhidrosis, is autosomal recessive and presents in a similar fashion to HSAN IV, with the exception that anhidrosis is not complete (Axelrod et al., 2006; Axelrod & Gold-von Simson, 2007). A summary of HSAN I to V is shown in Table 5.4. Other inherited causes of autonomic neuropathy include Fabry disease, triple A syndrome, Navajo Indian neuropathy, Tangier disease, and the neuropathy seen in multiple endocrine neoplasia (MEN) type 2B (Freeman, 2005). MEN type 2B consists of pheochromocytoma, medullary thyroid carcinoma, mucocutaneous neuroma, gastrointestinal symptoms (e.g., constipation and flatulence), and muscular hypotonia.

SUBACUTE AUTONOMIC NEUROPATHIES

PARANEOPLASTIC AUTONOMIC NEUROPATHY

Autonomic neuropathy may occur in association with the development of anti-Hu antibodies in patients with malignancy, most commonly small cell lung cancer, but it is also seen with ovarian and breast cancer, lymphoma, and thymoma. Peripheral neuropathy eventually occurs in 60% to 95% of patients with anti-Hu antibodies (Dalmau, Graus, Rosenblum, & Posner, 1992). As is the case with a majority of paraneoplastic phenomena, neurologic symptoms typically antedate the diagnosis of malignancy. Although the most common manifestation is subacute sensory neuronopathy with a progressive course (Lucchinetti, Kimmel, & Lennon, 1998), autonomic neuropathy is present in 10% to 30% of patients and may be the presenting symptom in 4% to 9% (Dalmau et al., 1992). The pathogenesis involves autoimmune targeting of postganglionic sympathetic and parasympathetic and myenteric neurons. Accordingly, symptoms include bowel dysmotility (which may be the sole autonomic symptom), orthostatic hypotension, and

Table 5.4 Hereditary Sensory and Autonomic Neuropathies

HSAN Type	Nomenclature	Inheritance	Onset	Chromosomal Locus	Gene
HSAN IA	Hereditary sensory neuropathy	AD	Childhood–adolescence	9q22.1	SPTLC1
HSAN IB		AD	Childhood–adolescence	3p24-p22	Unknown
HSAN IC	CMT 2B, HMSN 2B	AD	Childhood–adolescence	3q21	RAB7A
HSAN ID		AD	Childhood–adolescence	Unknown	Unknown
HSAN II	Congenital sensory neuropathy	AR	Childhood	12p13.33	Unknown
HSAN III	Familial dysautonomia/Riley-Day syndrome	AR	Childhood	9q31	IKBKAP
HSAN IV	Congenital insensitivity to pain with anhidrosis	AR	Childhood	1q21-q22	NRTK1
HSAN V	Congenital insensitivity to pain with partial anhidrosis	AR	Childhood	1p13.1	NGFβ NTRK1

HSAN, Hereditary sensory and autonomic neuropathy.

erectile, bladder, pupillomotor, and sudomotor dysfunction (Freeman, 2005).

AUTONOMIC NEUROPATHIES ASSOCIATED WITH RHEUMATOLOGIC DISEASES

Autonomic neuropathy has been best illustrated in patients with Sjögren syndrome but has also been described in association with rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, and scleroderma. Various forms of peripheral neuropathy have been seen in association with Sjögren syndrome, and the pathogenesis is unresolved. Autonomic symptoms were seen in a majority of patients with Sjögren syndrome in one study (Mori et al., 2005), and a purely autonomic neuropathy was the predominant form in 3 of 92 patients who showed striking involvement of the sympathetic nervous system. In this series, symptoms of autonomic dysfunction included orthostatic hypotension, anhidrosis, evidence of cardiac sympathetic dysfunction, pupillary abnormalities, diarrhea, constipation, and urinary dysfunction. In the one patient who went to autopsy, pathologic evaluation showed T cell invasion of the sympathetic ganglion cells (Mori et al., 2005),

TOXIC AUTONOMIC NEUROPATHIES

Autonomic neuropathies have been described with the use of a variety of prescription medications and industrial, organic, and environmental toxins. With regard to medications, chemotherapeutic agents are notable offenders. Cisplatin and other platinum-containing agents usually lead to large-fiber sensory neuropathy, but the development of autonomic neuropathy with prominent orthostatic hypotension and ileus has been described (Rosenfeld & Broder, 1984). Vinca alkaloids (e.g., vincristine, vinblastine) characteristically cause motor neuropathy more than sensory neuropathy, but autonomic involvement has been reported (Legha, 1986). The use of paclitaxel has also been associated with autonomic neuropathy (Jerian et al., 1993). Long-term use of the antiarrhythmic agent amiodarone may lead to a sensorimotor or motor neuropathy, but autonomic neuropathy has been reported (Manolis, Tordjman, Mack, & Estes, 1987). Arsenic poisoning and thallium poisoning have been associated with autonomic neuropathy. Distal sudomotor dysfunction in combination with painful sensory neuropathy is the characteristic presentation of arsenic intoxication (LeQuesne & McLeod, 1977). Hypertension and tachycardia, also in association with painful sensory neuropathy, have been described with thallium intoxication (Bank, Suzuki, Nigro, & Katz, 1972). Exposure to organic solvents, vacor (a rat poison), hexacarbon compounds (inhaled when sniffing glue), acrylamide, and marine toxins (e.g., ciguatoxic fish) may lead to prominent autonomic symptoms, with or without evidence of distal sensory polyneuropathy (Freeman, 2005; Matikainen & Juntunen, 1985).

INFECTIOUS AUTONOMIC NEUROPATHIES

A number of infectious processes are associated with the development of autonomic neuropathy, including HIV/AIDS, leprosy, Chagas disease, and diphtheria.

The severity of autonomic symptoms seems to increase as HIV/AIDS progresses in severity, and these symptoms are usually seen in association with other signs of HIV-related neurologic disease, such as sensory polyneuropathy (Toth & Zochodne, 2003). Patients with early HIV infection have abnormalities in autonomic testing, but symptoms are more severe in those with AIDS and low CD4 count (Freeman, Roberts, Friedman, & Broadbridge, 1990). The pathogenesis includes direct viral effects on small nerve fibers, but concomitant nutritional deficiencies and medications may have a role. Symptoms reflect both parasympathetic and sympathetic dysfunction and include resting tachycardia, orthostatic hypotension, bowel and bladder dysfunction, impotence, and sweating disturbances (Freeman et al., 1990).

Leprosy is caused by infection with *Mycobacterium leprae* and is a common cause of autonomic neuropathy in endemic regions. Focal anhidrosis in association with impaired pain and temperature perception is seen in cooler parts of the body and is usually the first sign of disease. This correlates with the loss of cutaneous innervation in these areas (Facer et al., 1998). More widespread involvement of the autonomic nerves may occur and lead to orthostatic intolerance, impotence, and gustatory sweating (Freeman, 2005). Chagas disease is caused by infection with *Trypanosoma cruzi* and is found primarily in Central and South America. Autonomic (particularly parasympathetic) dysfunction may be seen in the chronic phase of the disease and manifests as cardiac conduction abnormalities and dysrhythmias, orthostatic intolerance, and bowel dysmotility (Iosa et al., 1990).

Diphtheria is caused by *Corynebacterium diphtheriae*. A toxin-mediated sensorimotor neuropathy characterized by multiple cranial neuropathies, a descending pattern of weakness, and absent reflexes is typically seen weeks after either pharyngeal or cutaneous diphtheria. Accommodation paralysis with preserved light reflex, cardiac vagal abnormalities, and bowel and bladder dysfunction may also be seen (Idiaquez, 1992).

ACUTE AUTONOMIC NEUROPATHIES

DYSAUTONOMIA ASSOCIATED WITH GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome, or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is an acute monophasic illness associated with sensorimotor neuropathy of variable severity. The sensorimotor symptoms are commonly accompanied by autonomic manifestations. As early as 1892, Osler observed that some patients with "acute febrile neuritis" died of "paralysis of the heart" (Osler, 1892). Some form of dysautonomia is seen in approximately two thirds of cases of AIDP (Hughes & Cornblath, 2005). Rarely, autonomic symptoms are the presenting feature of AIDP. Autonomic symptoms are more prominent in patients with respiratory failure, severe paresis, and the axonal variant of the disease (Winer & Hughes, 1988). With the availability of mechanical ventilation, autonomic symptoms are a major cause of mortality in AIDP (Zochodne, 1994), which ranges from 3% to 7% (Hughes & Cornblath, 2005).

The clinical manifestations of dysautonomia in AIDP reflect both sympathetic and parasympathetic dysfunction.

Cardiovascular abnormalities occur in as many as two-thirds of patients with AIDP, although they are mild in most cases (Ropper, Wijdicks, & Truax, 1991). Blood pressure lability (hypertension alternating with hypotension), often in an unpredictable manner, may be observed and is believed to be primarily due to excessive sympathetic outflow (Asahina, Kuwabara, Suzuki, & Hattori, 2002). Orthostatic hypotension as a result of sympathetic hypofunction may also be seen, occurring in 19% to 43% of patients (Singh, Jaiswal, Misra, & Srivastava, 1987). Cardiac arrhythmias are frequently seen and are primarily caused by parasympathetic dysfunction. Vagal neuropathy may lead to the development of ectopic activity in the diseased nerve, manifesting as sudden bradyarrhythmias and even asystole (Zochodne, 1994). These arrhythmias may be spontaneous or provoked by suctioning or Valsalva maneuvers. Tachyarrhythmias are also seen as a result of an overall reduction in vagal activity. Sinus tachycardia is the most frequently observed abnormality on cardiac telemetry. If bradyarrhythmias or tachyarrhythmias are problematic, temporary pacemaker insertion may be required (Zochodne, 1994). A wide range of abnormalities may be observed on 12-lead electrocardiogram, including atrial fibrillation, atrial flutter, supraventricular tachycardia, ST segment depression, QT interval prolongation, and conduction block (Asahina et al., 2002).

In addition to cardiovascular abnormalities, other symptoms of dysautonomia are frequently seen in AIDP. Anhidrosis as a result of sympathetic hypofunction is often observed, and hyperhidrosis has been described. Gastrointestinal manifestations are relatively infrequent, but gastroparesis, ileus, and constipation may be seen in a minority of patients (Asahina et al., 2002; Zochodne, 1994). Urinary retention is seen in approximately one third of patients. Sexual dysfunction and pupillomotor abnormalities have also been observed (Zochodne, 1994).

The management of patients with AIDP should include vigilance and awareness of the possibility of dysautonomia, especially in those with severe weakness. Routine cardiac telemetry and 12-lead electrocardiogram to evaluate for rhythm disturbances or conduction abnormalities should be performed. As discussed earlier, if malignant arrhythmias occur, temporary pacemaker insertion may be needed. In addition, attentive blood pressure monitoring should be performed with the knowledge that lability may occur. Patients with AIDP are usually very sensitive to most vasoactive drugs, and low doses of short-acting agents should be used only if absolutely necessary (Zochodne, 1994).

The outcome of AIDP and associated autonomic symptoms is usually good. Typically, the autonomic neuropathy improves in concert with the motor and sensory nerve improvement, and long-term autonomic sequelae are uncommon (Low et al., 2003).

DYSAUTONOMIA IN CHRONIC DEMYELINATING POLYRADICULONEUROPATHY

Although much less common than in AIDP, autonomic dysfunction has also been described in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Dysautonomia in CIDP is rare because of the involvement of predominantly large myelinated nerve fibers and has been attributed by some to concomitant involvement of postganglionic unmyelinated autonomic fibers, perhaps because of an immune-mediated attack on nonmyelin proteins (Stamboulis et al., 2006).

DYSAUTONOMIA IN AUTOIMMUNE AUTONOMIC GANGLIONOPATHY

A syndrome affecting predominantly autonomic nerves has been referred to as *acute pandysautonomia* or *autoimmune autonomic neuropathy*. An antecedent (usually viral) illness is followed by subacute onset of autonomic failure. A more chronic form is also seen and is more aptly referred to as *autoimmune autonomic ganglionopathy* (Gibbons & Freeman, 2009; Klein et al., 2003). The disease is secondary to antibodies to the nicotinic acetylcholine receptor of the autonomic ganglia, not the neuromuscular junction, as is seen in myasthenia gravis (Vernino et al., 2000). Sensory symptoms are reported in some patients, but not motor involvement.

Most commonly, patients present with profound orthostatic hypotension resulting in syncope, anhidrosis, fixed and dilated pupils, urinary retention, and severe constipation (Sandroni et al., 2004). Purely cholinergic and adrenergic forms have been described (Sandroni et al., 2004). In the acute form, some patients improve spontaneously but incompletely (Vernino et al., 2000). There is no proven treatment, although there are reports of a beneficial effect of intravenous immunoglobulin or plasmapheresis (Gibbons, Vernino, & Freeman, 2008). In the chronic form, these therapies have also been shown to be effective (Gibbons et al., 2008).

DYSAUTONOMIA IN DISEASES OF THE NEUROMUSCULAR JUNCTION

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is an acquired disorder of the neuromuscular junction as a result of antibody-mediated attack against the voltage-gated P/Q-type calcium channel. This syndrome is associated with an underlying malignancy (usually small cell lung cancer) in one half to two thirds of cases. Although proximal weakness, particularly in the lower extremities, is the most common presenting symptom, autonomic complaints are frequent. It has been estimated that 74% to 93% of patients with LEMS have some evidence of dysautonomia (O'Suilleabhain, Low, & Lennon, 1998; Toth & Zochodne, 2003). Although it is mild in most cases, autonomic dysfunction is severe in approximately 20% of cases, typically older patients with an underlying malignancy (O'Suilleabhain et al., 1998). Autonomic symptoms reflect cholinergic dysfunction in LEMS. These include xerostomia (the most common symptom), blurred vision, pupillomotor dysfunction, impaired sweating, erectile dysfunction, constipation, and, much less commonly, orthostatic hypotension (Toth & Zochodne, 2003). The mechanism of autonomic dysfunction is believed to be secondary to a cross-reaction of the pathogenic antibody against N-type calcium channels in autonomic ganglia, which have approximately 60% homology with the P/Q type of channel (O'Suilleabhain et al., 1998). As with all paraneoplastic diseases, treatment is directed against the underlying malignancy. There are reports, however, that treatment with 3,4-diaminopyridine

leads to symptomatic improvement in the autonomic features of LEMS (Toth & Zochodne, 2003).

DYSAUTONOMIA IN MYASTHENIA GRAVIS

Autonomic dysfunction in association with myasthenia gravis is rare, with only 12 cases reported in the literature (Vernino, Cheshire, & Lennon, 2001). All patients were found to have thymomas and all were acetylcholine receptor antibody positive. These patients experienced subacute onset of symptoms ranging from isolated gastrointestinal dysmotility (the most commonly observed symptom) to severe panautonomic failure, including cardiovascular dysfunction (Vernino et al., 2001). Symptoms improved with acetylcholinesterase inhibitors in a majority of patients, supporting the concept of impaired cholinergic transmission as the underlying mechanism of dysautonomia (Vernino et al., 2001).

BOTULISM

Botulism is another important infectious cause of dysautonomia. Binding of the toxin released by *Clostridium botulinum* to the presynaptic nerve terminal prevents release of synaptic vesicles at the neuromuscular junction. This leads to the acute onset of ptosis, extraocular muscle weakness, and diplopia, dysphagia, and bulbar dysfunction, followed by progressive generalized limb weakness in a characteristically descending pattern. Autonomic symptoms reflect acute, severe cholinergic failure as a result of a similar mechanism of failed synaptic vesicle release in autonomic ganglia. This results in symptoms of blurred vision, xerophthalmia, xerostomia, anhidrosis, constipation, and urinary retention. Orthostatic intolerance has also been described (Merz, Bigalke, Stoll, & Naumann, 2003). Examination classically shows mydriasis with poor or absent reactivity to light or accommodation. Autonomic symptoms may rarely occur in the absence of evidence of concomitant neuromuscular disease (Merz et al., 2003). In the more typical form of the disease, the autonomic symptoms generally improve in conjunction with other neuromuscular symptoms.

AUTONOMIC DISORDERS—OTHER

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous disorder of orthostatic intolerance. The initial description of the disorder in 1982 highlighted an association between orthostatic intolerance and autonomic dysfunction in a small group of well-characterized patients (Schondorf & Low, 1993). POTS has an exaggerated heart rate response to postural stress, with associated symptoms of orthostatic intolerance, of at least 6 months duration without identifiable cause (Freeman et al., 2011). Unfortunately, the diagnostic criteria over time have expanded to become more sensitive but less specific (Olshansky et al., 2020). At present, the literature on POTS has become very difficult to interpret due to the intermixing of vague symptoms overlapping with a number of different underlying conditions.

At present, POTS is defined as primary POTS (which is considered idiopathic) and secondary POTS (with the tachycardia due to an underlying medical condition, medication effect, or altered physiologic parameter such as dehydration). The first step in the evaluation of patients presenting with a postural tachycardia is to investigate the potential underlying cause. In many cases, patients with secondary POTS will not necessarily have an autonomic disorder unless the underlying medical condition predisposes to this (e.g., such as diabetes presenting with an early autonomic neuropathy causing a tachycardia). Primary POTS is generally considered as either (1) due to a partial dysautonomia or (2) due to a hyperadrenergic state (Olshansky et al., 2020). Both forms of primary POTS have been linked to mild autonomic dysfunction, although there has been no clear benefit to outcome measures when defining the form of primary POTS. At present, the most effective treatment for patients with POTS is a cardiovascular reconditioning program (Fu & Levine, 2018; George et al., 2016).

In contrast, patients with secondary POTS are a more heterogeneous group that would be better served by identification of the underlying problem, with the appropriate treatment. For example, many patients carry a diagnosis of POTS while taking medications that are likely responsible for the postural tachycardia (such as tricyclic antidepressants, simulants, or antihypertensive medications). The simple removal of the offending medication can resolve the postural tachycardia, although in many cases the vague underlying symptoms will typically still be present (Olshansky et al., 2020).

SYMPTOMATIC TREATMENT OF AUTONOMIC DISORDERS

TREATMENT OF ORTHOSTATIC HYPOTENSION

NONPHARMACOLOGIC THERAPIES

The mainstay of treatment of orthostatic hypotension is education (Gibbons et al., 2017). Patients need to develop the practical skills that will enable them to function independently in the face of dramatic decreases in blood pressure. Gradual transitions from the supine to the standing position will reduce symptoms of orthostatic intolerance. Maintaining adequate hydration, especially if subjected to unusual heat or humidity, is an absolute requirement. Individuals who enjoy vacationing in warmer climates often experience dramatic worsening of symptoms if intravascular volume is not maintained.

Physical countermaneuvers, such as leg crossing, fist clenching, or squatting, can improve venous return and increase cerebral perfusion with a decrease in orthostatic intolerance (Wieling, van Lieshout, & van Leeuwen, 1993). The use of thigh-high or waist-high compression stockings, in combination with an abdominal binder, will reduce peripheral venous pooling (Gibbons & Freeman, 2006b). Sleeping with the head of the bed elevated activates the renin-angiotensin-aldosterone system, reducing nocturia and improving hydration in the morning.

Additional nonpharmacologic therapies include sodium chloride ingestion. Adequate dietary intake in symptomatic individuals is typically 10 g/day or more, with sodium chloride tablets used as a supplement if necessary (Freeman, 2008). Adequate fluid intake is necessary for sodium chloride to result in an increase in plasma volume. In general, 2 L/day is appropriate for most individuals, although those

with greater activity levels or living in warmer environments may require greater daily fluid intake. Caffeinated beverages may augment blood pressure transiently but tend to worsen orthostatic hypotension secondary to the diuretic effect of caffeine, so they should not be counted as part of the total volume of daily fluid intake.

The rapid ingestion of pure water (approximately 500 mL) can result in a transient pressor effect in patients with dysautonomia. Water can increase systolic blood pressure by 30 mm Hg in the upright position for more than 1 hour and will work within 5 minutes (Jordan et al., 2000). This effect is unique to water, does not appear to work with other ingested liquids, and will not work in individuals without autonomic disturbance (Raj et al., 2006). This "water effect" can be used by patients to counterbalance postprandial hypotension or to provide a brief pressor response for a short period of upright activity. A common scenario in which this might be used is while shopping. In this scenario, a patient experiences orthostatic hypotension and is forced to sit down. The patient does not have the necessary medications handy (or does not have time to wait for the medication to take effect) and is unable to walk back to the car. The ingestion of water will take effect quickly and will provide a brief period in which the patient can return to the car or can return home safely.

Finally, many patients with mild orthostatic intolerance have symptoms that worsen to a large degree after medication adjustments (Gibbons et al. 2017). Avoiding the use of the many iatrogenic causes of orthostatic hypotension, such as diuretics, antidepressants, antihypertensives, alpha blockers, and peripheral vasodilators, will frequently improve orthostatic tolerance (Meredith, 2001). The concomitant supine hypertension that is often seen in patients with orthostatic hypotension frequently results in overuse of long-acting antihypertensive medications. Short-acting antihypertensives dosed only at night may decrease supine hypertension without worsening orthostatic hypotension during the day.

PRIMARY THERAPY

An overview of pharmacologic therapies for the symptomatic treatment of orthostatic hypotension is shown in Table 5.5.

Fludrocortisone

Fludrocortisone, a mineralocorticoid, results in modest volume expansion and improvements in orthostatic tolerance and is often considered first-line therapy for the treatment of orthostatic hypotension. Fludrocortisone has demonstrated effectiveness in several observational studies of patients with orthostatic hypotension and in patients with orthostatic intolerance (van Lieshout, ten Harkel, & Wieling, 2000). Fludrocortisone may also enhance the sensitivity of blood vessels to circulating catecholamines (Hickler, Thompson, Fox, & Hamlin, 1959). Fludrocortisone is given at 0.1 to 0.5 mg daily; however, with a half-life of 36 hours, a clinical effect typically is not seen for several days. Monotherapy is often inadequate for patients with more severe orthostatic hypotension. Supine hypertension is a common and dose-limiting side effect of treatment. Other side effects may include peripheral edema, congestive heart failure, and hypokalemia (Gibbons & Freeman, 2006b).

Midodrine Hydrochloride

Midodrine is approved by the US FDA for the treatment of orthostatic hypotension. Midodrine is an alpha-1 adrenoceptor agonist, resulting in both arterial and venous constriction and an increase in blood pressure. The efficacy of this agent was shown in double-blind placebo-controlled studies (Low, Gilden, Freeman, Sheng, & McElligott, 1997; Wright et al., 1998). The minimum effective

Table 5.5 Pharmacologic Treatment of Orthostatic Hypotension

Drug	Dose	Side Effects	Monitoring/Special Points
Fludrocortisone	0.1–0.4 mg daily	Supine hypertension, peripheral edema, congestive heart failure, hypokalemia	Potassium levels, supine blood pressure
Midodrine hydrochloride	2.5–10 mg qd–tid	Severe supine hypertension, urinary retention, headache	Supine blood pressure
Droxidopa	100–600 mg tid	Headache, dizziness, nausea	Supine blood pressure
Ephedrine	25–50 mg tid	Supine hypertension, anxiety, restlessness, nervousness, tachycardia	Supine blood pressure
Pseudoephedrine	30–60 mg tid	Supine hypertension, anxiety, restlessness, nervousness, tachycardia	Supine blood pressure
Pyridostigmine	60 mg tid	Cramps, diarrhea, nausea, vomiting, miosis, salivation	Cholinergic overdose
Desmopressin acetate	Nasal spray (5–40 μg qhs) Orally (0.1–0.8 mg qhs) Intramuscularly (2–4 μg qhs)	Water intoxication, hyponatremia, supine hypertension	Sodium levels, supine blood pressure
Erythropoietin	25–75 units/kg tiw starting, 25 units/kg tiw maintenance	Edema, injection site reactions, headache, supine hypertension, constipation	CBC with platelets and differential, supine blood pressure

CBC, Complete blood count; *qd*, once a day; *qhs*, before bedtime; *tid*, three times a day; *tiw*, three times a week.

dose for symptomatic relief should be used, starting with 2.5 mg and titrating to clinical effect. The medication has a clinical effect within 30 minutes and lasts for approximately 4 to 6 hours. The medication can be dosed three times daily but is often written as TID, typically resulting in the last dose at bedtime. Doses should be administered only when patients are required to maintain the upright position. Midodrine given within 6 hours of sleep can result in severe supine hypertension, forced nocturnal diuresis, volume depletion, and more severe orthostatic hypotension in the morning. Doses are typically given at 8 AM, 12 noon, and 4 PM. The maximum recommended dose of 30 mg/day may be exceeded in rare patients with severe orthostatic hypotension. Supine hypertension is common and may require dose reductions in the latter part of the day and sleeping with the head of the bed elevated. Other side effects include piloerection, urinary retention, and headache. Concomitant use of digoxin can lead to bradycardia and atrioventricular block. Monoamine oxidase inhibitors can result in hypertensive crisis.

Droxidopa

Droxidopa is approved by the US FDA for the treatment of neurogenic orthostatic hypotension. The term *neurogenic* implies that this is due to a neurological disease and not to some other reversible or treatable condition. The efficacy of droxidopa has been demonstrated in double-blind placebo controlled trials (Hauser, Hewitt, & Isaacson, 2014; Kaufmann et al., 2014). The dose is started at 100 mg three times per day and titrated upward to clinical effect. The medication lasts approximately 5 hours but also carries a significant risk of supine hypertension. Doses later in the day should be avoided to reduce the complications of supine hypertension. The maximum recommended dose is 600 mg three times per day. The most common side effects are headaches, nausea, and dizziness. Supine hypertension is common and may require monitoring and reduction in evening doses.

Ephedrine and Pseudoephedrine

Ephedrine and pseudoephedrine are mixed α-adrenoreceptor agonists that act through direct and indirect mechanisms to release norepinephrine from the postganglionic sympathetic neuron and increase blood pressure (Freeman, 2003; Gibbons & Freeman, 2006b). Both medications cross the blood-brain barrier, resulting in dose-dependent and dose-limiting side effects of anxiety, restlessness, nervousness, and tachycardia. Pseudoephedrine, a stereoisomer of ephedrine, may have less β-adrenoreceptor agonist activity than ephedrine and fewer central sympathomimetic effects (Freeman, 2003; Jordan et al., 1998). As with other sympathomimetic agents, these medications should not be given within several hours of bedtime to prevent severe supine hypertension. Typical doses of pseudoephedrine are 30 to 60 mg three times daily, and for ephedrine, 25 to 50 mg three times daily.

SECONDARY THERAPY

Pyridostigmine

Pyridostigmine has improved orthostatic tolerance and blood pressure in patients with orthostatic hypotension in recent studies (Singer et al., 2006). The mechanism of action is believed to be augmentation of autonomic ganglionic transmission. Theoretically, pyridostigmine has a lower risk of supine hypertension than sympathomimetic or volume-expanding agents by potentiating ganglionic transmission selectively during orthostatic stress. Typical doses are 60 mg up to three times daily. The clinical impact of pyridostimine is modest, and therefore it is not generally recommended as a first-line therapy. Cholinergic side effects are common (cramps, diarrhea, nausea, vomiting, increased salivation, and miosis) and may be dose-limiting.

Vasopressin Analogs

Desmopressin acetate is a synthetic analog of the natural pituitary hormone 8-arginine vasopressin, an antidiuretic hormone affecting renal water conservation. The postural release of arginine vasopressin is reduced in some patients with autonomic failure, in part because of loss of vasopressin neurons in the suprachiasmatic nucleus of the hypothalamus (Ozawa et al., 1998). Desmopressin acetate acts on the V2 receptors in the collecting ducts of the renal tubules, prevents nocturia and weight loss, and reduces the morning postural decrease in blood pressure in patients with autonomic failure when administered at bedtime (Freeman, 2003). Fluid and electrolyte status must be monitored because there is a risk of water intoxication and hyponatremia (Mathias, Fosbraey, da Costa, Thornley, & Bannister, 1986). Desmopressin acetate can be administered as a nasal spray (5–40 μg), orally (0.1–0.8 mg), or intramuscularly (2–4 μg). A typical oral starting dose is 0.1 to 0.2 mg only at bedtime.

Erythropoietin

Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension (Hoeldtke, Streeten, & Streeten, 1993). This agent corrects the normochromic normocytic anemia that frequently accompanies autonomic failure and diabetic autonomic neuropathy (Hoeldtke et al., 1993). The mechanism of action for the pressor effect of this agent is unresolved. Possibilities include an increase in red cell mass and central blood volume, alterations in blood viscosity, and direct or indirect neurohumoral effects on the vascular wall. There is also evidence that the effect of erythropoietin is related to vascular tone regulation mediated by the interaction between hemoglobin and the vasodilator nitric oxide (Rao & Stamler, 2002). Standard doses are 25 to 75 units/kg three times weekly until a normal hematocrit is achieved. Lower maintenance doses (approximately 25 units/kg three times weekly) should then be used. Iron supplementation is usually required, particularly during the period when the hematocrit is increasing.

TREATMENT OF GENITOURINARY DISORDERS

TREATMENT OF URINARY RETENTION

Although pharmacologic therapy for urinary retention is frequently used, many patients with complete urinary retention require clean intermittent catheterization or chronic indwelling catheterization as the primary treatment (Apostolidis & Fowler, 2003). Sacral nerve stimulation has been touted as an effective alternative to catheterization, although most patients must continue to catheterize, albeit at a lower frequency (White, Dobmeyer-Dittrich, Klein, & Wallace, 2008).

Table 5.6 Pharmacologic Treatment of Erectile Dysfunction

Drug	Dose	Side Effects	Monitoring/Special Points
Sildenafil	50 mg	Headache, flushing, dyspepsia, rhinitis	Contraindicated in patients with active cardiovascular disease or severe orthostatic hypotension
Tadalafil	10 mg	Headache, flushing, dyspepsia, rhinitis	Contraindicated in patients with active cardiovascular disease or severe orthostatic hypotension
Vardenafil	5–10 mg	Headache, flushing, dyspepsia, rhinitis	Contraindicated in patients with active cardiovascular disease or severe orthostatic hypotension
Alprostadil	2.5–40 μg injection	Pain, headache, hypotension	Contraindicated in patients with severe orthostatic hypotension

Bethanechol

Bethanechol can augment urination in patients with residual bladder activity. For those with complete bladder atony, the medication is unlikely to be effective. Medication doses of 5 to 50 mg four times daily are used to induce urination on a scheduled basis (Apostolidis & Fowler, 2003).

Common side effects are anticholinergic and include lightheadedness, diarrhea, abdominal cramps, salivation, and flushing.

TREATMENT OF ERECTILE DYSFUNCTION

An overview of pharmacologic therapies for the symptomatic treatment of erectile dysfunction is provided in Table 5.6.

Phosphodiesterase Type 5 Inhibitors

The phosphodiesterase type 5 inhibitors (i.e., sildenafil, tadalafil, vardenafil) have dramatically altered the treatment of erectile dysfunction. The mechanism of action is the relaxation of smooth muscle in the corpora cavernosa, resulting in increased penile arterial blood flow and erection. The phosphodiesterase type 5 inhibitors are effective in the treatment of erectile dysfunction as a result of diabetes, postradiation therapy for prostate cancer, spinal cord injury, and multiple sclerosis (Carson & Lue, 2005; Boulton, Selam, Sweeney, & Ziegler, 2001; Derry et al., 1998). These medications are contraindicated in patients with active cardiovascular disease, those taking nitrates, and those with uncontrolled hypertension. Additionally, these medications should not be used in patients with autonomic dysfunction and orthostatic hypotension (Hussain, Brady, Swinn, Mathias, & Fowler, 2001). Doses per use are as follows: sildenafil, 50 mg with a 4- to 5-hour half-life; tadalafil, 10 mg with a 17- to 18-hour half-life; and vardenafil, 5 to 10 mg with a 4- to 5-hour half-life.

Alprostadil

For those unresponsive to oral phosphodiesterase type 5 inhibitors, alprostadil is a naturally occurring form of prostaglandin E_1 used in an intracavernous injection for the treatment of erectile dysfunction. The mechanism of action is relaxation of smooth muscle in the corpora cavernosa and resulting erection. Although it is effective in up to 80% of patients, it is rarely used because of the route of administration (Linet & Ogrinc, 1996).

TREATMENT OF GASTROINTESTINAL DISORDERS

Patients with dysautonomia may experience gastrointestinal disorders that include esophageal dysmotility, delayed gastric emptying, gastroparesis, constipation, diarrhea, and incontinence.

TREATMENT OF GASTROPARESIS

Nonpharmacologic therapies are used in the management of gastroparesis, including eating smaller, more frequent meals. In addition, diet modification may provide some relief. More invasive nonpharmacologic therapies have been suggested, and a number of small case reports have touted gastric pacemakers as effective treatments for gastroparesis. However, attempts to rigorously evaluate the value of these treatments have not been as successful (Park & Camilleri, 2006). Until controlled trials provide hard data, this treatment should be considered experimental. An overview of pharmacologic therapies for the symptomatic treatment of gastroparesis is provided in Table 5.7.

Metoclopramide

Metoclopramide improves the symptoms of gastroparesis through a number of different mechanisms. It reduces nausea by acting on serotonergic (5-HT3) receptors, increases gastrointestinal motility by facilitating acetylcholine release, and improves gastric emptying through an antidopaminergic effect on the fundus (Parkman, Hasler, & Fisher, 2004). Typical doses are 5 to 10 mg one half hour before meals, with additional dosing at bedtime. Although it is highly effective, there are concerns about tardive dyskinesia, parkinsonism, myelosuppression, and cardiac arrhythmias with use.

Erythromycin

Erythromycin is a motilin receptor agonist (a G-protein-coupled receptor that stimulates contractions of smooth muscle in the gut) and has been used in the treatment of diabetic gastroparesis. The use of erythromycin immediately after meals leads to improved contraction and gastric emptying (Parkman et al., 2004). Typical doses are 250 to 500 mg given immediately after meals. Side effects include nausea, vomiting, and diarrhea.

Domperidone

Domperidone is a selective antagonist of the dopamine (D2) receptor. It stimulates antral contractions and has

Table 5.7 Pharmacologic Treatment of Gastroparesis

Drug	Dose	Side Effects	Monitoring/Special Points
Metoclopramide	5–10 mg before meals and bedtime	Tardive dyskinesia, parkinsonism, myelosuppression, cardiac arrhythmias, drowsiness, fatigue, anxiety, headache, depression	Extrapyramidal side effects, Parkinsonism
Erythromycin	250–500 mg after meals	Nausea, vomiting, abdominal pain, diarrhea	Rare QTc prolongation
Domperidone	10 mg before meals	Menstrual irregularities, galactorrhea, breast engorgement	Not available in the United States
Clonidine	0.2–1 mg every 12 hours	Confusion, hypotension, dry mouth, hallucinations, somnolence, dizziness	Sudden discontinuation can result in rebound hypertension

Table 5.8 Pharmacologic Treatment of Diarrhea

Drug	Dose	Side Effects	Monitoring/Special Points
Loperamide	4 mg initial dose, 2 mg after each loose stool (up to 16 mg/day)	Constipation, drowsiness, dizziness, fatigue	Rare reports of anaphylactic reactions.
Clonidine	0.2–1 mg every 12 hours	Confusion, hypotension, dry mouth, hallucinations, somnolence, dizziness	Sudden discontinuation can result in rebound hypertension. Monitor orthostatic hypotension, mental status.
Diphenoxylate	5 mg four times per day until diarrhea is controlled	Nausea, dizziness, sedation, euphoria, miosis	Controlled substance, category V.

promotility activity similar to that of metoclopramide. It does not cross the blood-brain barrier, so it is less likely to cause extrapyramidal side effects. Unfortunately, however, this medication is not available within the United States (Parkman et al., 2004). Domperidone is also dosed at 10 mg one half hour before meals and at bedtime.

Clonidine

Clonidine is an alpha-2 adrenergic agonist that reduces symptoms related to gastroparesis and dyspepsia by relaxing the fundus (Thumshirn, Camilleri, Choi, & Zinsmeister, 1999). Typical doses of clonidine are 0.2 to 1.0 mg every 12 hours. Side effects may be dose-limiting and include confusion, hypotension, dry mouth, hallucinations, somnolence, and dizziness.

TREATMENT OF DIARRHEA

An overview of pharmacologic therapies for the symptomatic treatment of diarrhea is provided in Table 5.8.

Loperamide

Loperamide is US FDA approved for the treatment of diarrhea. Loperamide reduces watery stool by altering electrolyte and fluid absorption and inhibiting peristaltic activity (Abrahamsson, 1995). The standard dose is 4 mg for the initial dose, followed by 2 mg after each loose stool (16 mg daily maximum).

Clonidine

Despite its use in gastroparesis, clonidine inhibits intestinal electrolyte secretion and may reduce diarrhea. Typical doses of clonidine are 0.2 to 1.0 mg every 12 hours. Side effects may be dose-limiting and include confusion, hypotension, dry mouth, hallucinations, somnolence, and dizziness.

Diphenoxylate

Diphenoxylate is FDA approved for the treatment of diarrhea. It is a synthetic opiate related to meperidine and is considered a controlled substance (Harford, Krejs, Santa Ana, & Fordtran, 1980). The medication is dosed at 5 mg four times daily until diarrhea is controlled. Side effects include nausea, dizziness, sedation, euphoria, and miosis.

TREATMENT OF CONSTIPATION

An overview of pharmacologic therapies for the symptomatic treatment of constipation is shown in Table 5.9.

Docusate Sodium

Docusate sodium is a stool softener often used as the initial treatment for chronic constipation, and it is FDA approved for this purpose. Although useful only as a single agent in mild to moderate constipation, it can be used in conjunction with other agents in cases of refractory constipation (Hurdon, Viola, & Schroder, 2000). The medication is typically dosed at 100 mg twice daily.

Laxatives

Polyethylene glycol and lactulose are FDA-approved agents for the treatment of constipation. They are osmotic agents that increase the water content of stool (Rao, 2003). The standard dose of polyethylene glycol is one heaping spoonful (17 g) and the standard dose of lactulose is two to three spoonfuls (20–30 g) administered as needed (up to four

Table 5.9 Pharmacologic Treatment of Constipation

Drug	Dose	Side Effects	Monitoring/Special Points
Docusate sodium	50–200 mg twice daily	Abnormal taste, diarrhea, nausea, muscle cramps	Rare hepatotoxicity has been noted.
Polyethylene glycol	17 g as needed (up to four times per day)	Diarrhea, flatulence, nausea, abdominal cramping, muscle cramping	Monitor electrolytes with chronic use.
Lactulose	20–30 g as needed (up to four times per day)	Diarrhea, flatulence, nausea, abdominal cramping, muscle cramping	Contains galactose, which may alter blood glucose levels in patients with diabetes. Bowel movements may not occur for 24–48 hours. Monitor electrolytes with chronic use.
Senna	15 mg daily	Nausea, vomiting, diarrhea, abdominal cramps	May discolor feces.
Bisacodyl	5–15 mg daily	Electrolyte and fluid imbalance, nausea, rectal burning, vomiting, abdominal cramps	Should be taken with water on an empty stomach.

times daily). Osmotic laxatives that contain sodium or magnesium salts should be avoided in patients with chronic constipation because of the risk of electrolyte imbalance (Parkman et al., 2004).

Stimulant Laxatives

Stimulant laxatives are available both over the counter and by prescription. Many of the side effects and contraindications are similar. Two of the most commonly used are senna and bisacodyl (Rao, 2003). Senna is an herbal supplement available in liquid or tablet form that causes mild colon-specific stimulation and changes in electrolyte absorption to produce bowel movements in 6 to 12 hours (Rao, 2003). Bisacodyl is an FDA-approved treatment for chronic constipation. The mechanism of action is likely altered absorption and intestinal fluid accumulation, although it was initially assumed to be direct colonic stimulation (Rao, 2003). There are concerns that long-term use of any stimulant laxative can result in physical dependence.

Pyridostigmine

In addition to use in orthostatic hypotension, there is limited evidence that pyridostigmine provides relief in patients with chronic constipation secondary to autonomic dysfunction (Bharucha et al., 2008). A pilot study suggested doses of 60 mg three times daily or greater, but additional study is required before clinical conclusions on effectiveness can be made.

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6 A Practical Approach to the Treatment of Painful Polyneuropathies

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The prevalence of neuropathic pain (NP) in the US population has yet to be determined precisely. One conservative estimate predicted that between 1% and 2% of the population will eventually experience NP (Bennet, 1998). A higher estimate of 10% of the population, with 5% reporting severe pain, has been reported by other authors (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008; DiBonaventura et al., 2017; Torrance, Smith, Bennett, & Lee, 2006). Even using the more conservative estimate, more people are afflicted with NP than with multiple sclerosis, myasthenia gravis, and amyotrophic lateral sclerosis combined. Given these statistics, every health care provider must have a working knowledge of the pathophysiology of NP as well as its treatment, supported by evidence-based medicine (EBM). NP and painful polyneuropathies (PPs) are not synonymous, as pain management specialists consider NP to result from many types of dysfunction within the sensory nervous system or its central connections. Even if NP were restricted to conditions affecting the peripheral nervous system (PNS), numerous other entities other than polyneuropathy would be included, such as traumatic mononeuropathies, plexopathies, radiculopathies, and cranial neuropathies (e.g., trigeminal neuralgia). Many studies that assess the treatment of NP combine one or more of these entities, such that an "effective" NP treatment cannot necessarily be extrapolated to the treatment of PPs. Because there are numerous textbooks, book chapters, medical reviews, and editorials on the treatment of NP in general, this topic is not addressed in this chapter. Two related publications summarized the available evidence on topical and oral agents used in the treatment of NP (Dworkin et al., 2007, 2010). Neither these articles nor this chapter discusses invasive methods to treat NP, such as spinal stimulators, intrathecal delivery systems, or radioablation techniques, as these methods are rarely used in a neuromuscular consultant's practice. Furthermore, this chapter addresses only the treatment of PP in adults (i.e., those who are 18 years and older). As such, these data cannot be used to guide treatment decisions in younger individuals. Medications used in the pediatric population should be adjusted for the patient's age, height, and weight and should be prescribed by pediatric neurologists who specialize in the treatment of PP in children.

This chapter provides a practical approach to the treatment of an adult patient presenting with a PP. It describes the available medical literature and clinical practice experience. Ideally, EBM should guide all treatment decisions, but EBM is useful only when the requisite studies have been conducted in an appropriate manner. Thus, EBM is limited when discussing the management of PP for numerous reasons. One is that pain management experts tend to subdivide pain based on its presumed mechanism of action. Studies that evaluate "neuropathic pain" can assess a variety of conditions, such as post–herpetic neuralgia (PHN), diabetic peripheral neuropathic pain (DPNP), and even central nervous system (CNS) syndromes such as post–spinal cord injury pain. Most studies of PP tend to focus on common disorders, such as DPNP, because a significant number of patients must be recruited in order to have an adequately powered study designed to detect a statistically significant difference. For this reason, there are far more studies on the treatment of DPNP and HIV-related neuropathy than there are of patients with unclassified small fiber neuropathies. Additionally, older medications such as the tricyclic antidepressants (TCAs) or opioids, were not studied to the same standards as modern-day trials. Furthermore, there are few head-to-head trials of older generic medications versus newer brand name medications whose patents have not yet expired. Finally, there are few studies that allow for an accurate assessment of the use of combinations of agents versus monotherapy, especially with the newer proprietary drugs.

Previous publications tended to focus on the pharmacologic management of NP without specifically addressing commonly associated comorbid disorders, such as obstructive sleep apnea (OSA), major depressive disorder (MDD), generalized anxiety disorder (GAD), sleep/wake disorders, and fibromyalgia (FM). These comorbid conditions have a significant negative effect on the patient's quality of life (QOL) such that the clinician should specifically assess for their presence. Treatment of the entire constellation of symptoms associated with PPs is required to obtain optimal outcomes as these symptoms will affect/modulate the patient's pain perception. Given the paucity of EBM guidance, clinicians should assess all relevant clinical data in order to generate a patient-specific treatment plan. For example, a thin patient with insomnia would be a better candidate for TCAs as opposed to an obese elderly patient with cardiac arrhythmias.

This chapter reviews the definition of NP and the concept of EBM and discusses some of the potential mechanisms that may be responsible for the pain associated with PP. Although the cranial nerves may be considered part of the PNS, this chapter restricts itself to the management of PP and does not address trigeminal neuralgia (Gronseth et al., 2008). As with any disorder, the clinician should attempt to identify a

Table 6.1 Recommended Workup for Painful Polyneuropathy

Evaluation	Comments
Routine testing	
Complete blood count with differential	↑ White blood cell count may indicate infection Eosinophilia may indicate Churg-Strauss syndrome ↑Mean corpuscular volume may reflect B_{12} deficiency
Electrolyte panel	Abnormalities may indicate renal disease Hyponatremia may also indicate SIADH
Hemoglobin A1c (known diabetic) Fasting blood sugar Glucose tolerance test	Goal is <7 (6.5%–8% depending on multiple factors) in diabetics (<5.7% in patients without diabetes; American Diabetes Association, 2019) Fasting blood sugar ≥126 mg/dL (7 mmol/L) 2-hour PG ≥200 mg/dL (11.1 mmol/L) = impaired glucose tolerance
Renal function studies (24-hour urine is preferred)	Consider urea clearance with impaired renal function (<50% of predicted)
Liver function studies	AST ALT
Serum B_{12} and methylmalonic acid levels	↑ Methylmalonic acid levels may warrant B_{12} treatment even with normal B_{12} level
Folate levels	Rarely observed in isolation
Serum and urine immunoelectrophoresis	Immunoelectrophoresis is more sensitive
Thyroid-stimulating hormone	Complete thyroid panel rarely needed
Antinuclear antibody	Titers <1:160 are nonspecific
Rheumatoid factor	May be first indication of HCV infection
Erythrocyte sedimentation rate ± C-reactive protein	Nonspecific indicators of inflammation
Workup for painful polyneuropathy (when clinical history warrants) (Tyrer et al., 2008; Narrow, 1998)	
History of IV drug abuse, needle-stick, blood transfusion, "increased risk" sexual behavior	HBV, HCV, HIV, serum cryoglobulins
Severe gastroenteritis preceding the neuropathy	24-hour urine test for heavy metals, porphyrins
Suspected rheumatologic condition	ACE level, ANCA, ENA, SS-A, SS-B
Suspected inherited neuropathy	DNA analysis
Dysautonomia	Autonomic testing Fat pad or skin biopsy for amyloidosis Transthyretin-related DNA testing in selected patients
Asymmetric polyneuropathy (suspected vasculitis)	Sural nerve ± muscle biopsy

ACE, Angiotensin-converting enzyme; *ALT*, alanine aminotransferase; *ANCA*, antineutrophil cytoplasmic antibody; *AST*, aspartate aminotransferase; *ENA*, extractable nuclear antigen; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *IV*, intravenous; *PG*, postprandial glucose; *SS-A*, Sjögren syndrome (specific) antibody A (also known as anti-Ro); *SS-B*, Sjögren syndrome (specific) antibody B (also known as anti-La); *SIADH*, syndrome of inappropriate antidiuretic hormone.

potentially reversible cause for the PP (Table 6.1). If no specific etiology is identified, the treating practitioner should improve the patient's QOL by identifying and aggressively treating any comorbid conditions. This chapter discusses only oral and topical medications that have the highest level of EBM that supports their use for the treatment of at least one disease entity that manifests with a PP.

DEFINITIONS AND OVERVIEW

Pain has been defined by the International Association for the Study of Pain (IASP, 2019) as "an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury." Restated, pain can occur even in the absence of an actual tissue injury. All that is required to experience pain is for the affected person to believe that such an injury is imminent or has occurred. The IASP also recently updated its definition of NP as indicative of a direct consequence of diseases that affect the somatosensory system (Treede et al., 2008). Many pain management experts further subdivide NP into noninflammatory and inflammatory subtypes. Examples of inflammatory NP include herpes zoster neuritis, cancer pain, and complex regional pain syndrome, whereas noninflammatory pain would include conditions such as trigeminal neuralgia and phantom limb pain. PP cannot be as readily classified because the underlying etiology is not always identified. Even when the underlying cause is identified, pain may occur as a result of both inflammatory and noninflammatory

mechanisms (e.g., inflammatory vasculitis with secondary axonal loss from ischemia). This is one of many reasons why the EBM recommendations regarding the treatment of NP in general do not necessarily apply to the treatment of PP.

Varying definitions of chronic pain have existed over the last decade. Acute pain was differentiated from chronic pain by stating that acute pain lasted less than 3 to 6 months (SPINE-health, 2020). However, this definition has fallen out of favor because of its arbitrary nature and because many patients with acute pain eventually develop chronic pain. For these reasons, the American Pain Society revised this definition by stating, "Acute pain follows injury to the body and generally disappears when the bodily injury heals. It is often, but not always, associated with objective physical signs of autonomic nervous system activity. Chronic pain, in contrast to acute pain, is rarely accompanied by signs of sympathetic nervous system arousal" (Miaskowski et al., 2008). Expert opinion has come full circle as most recently the IASP defined chronic pain as pain that persists or recurs for more than 3 months (Treede et al., 2019).

Turk and Okifuji (2001) proposed a different definition of pain that integrates its duration and perceived physical intensity. They describe NP in terms of a "strength-duration curve" in which pain intensity is reported as severe over a relatively short period, whereas chronic pain tends to be reported as less severe but more persistent. From this perspective, they define acute pain as pain elicited by the injury of bodily tissues and activation of nociceptive transducers at the site of local tissue injury. They also opined that the nociceptive transmission may be altered through central processing and that coexistent autonomic phenomena are often observed. In contrast, chronic pain is usually elicited by an injury but may be augmented by other factors that are not necessarily related to the precipitating cause. Turk and Okifuji (2001) remarked, "Chronic pain extends for a long period of time, represents low levels of underlying pathology that does not explain the presence and extent of the pain, or both." They also wrote that acute pain often responds to treatment, whereas chronic pain is "rarely effectively treated." Turk and Okifuji (2001) concluded that "cure" may be a reasonable goal for acute pain processes, whereas "setting realistic expectations" would be more appropriate in patients with chronic pain. Within the patient-physician relationship, it is important to establish realistic expectations for each person in the relationship with shared decision making. This collaboration helps foster a patient- and family-centered care practice model. Paired with objective function-based goals, therapeutic interventions will be more effective.

The division between acute and chronic pain should not lead to the misconception that one cannot transform into the other. One prospective study from New Zealand reported that acute NP accounted for 1% to 3% of consults on an acute pain service (Hayes, Brown, Lantry, & Burstal, 2002). The same study reported that 78% of patients had persistent pain after 6 months and that 56% still had pain after 1 year. Thus, failure to treat acute NP may lead to chronic NP, implying that early intervention is the best course of action. Therefore, it is recommended that NP be treated as early and comprehensively as possible because a "wait and see" attitude is less likely to be effective than one in which the underlying disorder is treated in short order. Dworkin et al. (2007) advised that moderate to severe pain must be treated quickly and aggressively in an attempt to reduce the probability that a chronic pain syndrome will result. Although early and aggressive intervention in a patient with an acute pain process may not result in a "cure," it may mitigate the severity of the chronic pain syndrome. Patients with chronic pain syndromes rarely experience complete relief and may require long-term medication management, a course of action that should be viewed as a double-edged sword for reasons that are discussed subsequently.

NERVE ANATOMY

A simplified view of the peripheral nerve is to subdivide it into its three main structural components: Schwann cells with the myelin sheath that they produce, the vasa nervorum, and the axons. The axons are further classified as afferent or efferent fibers. The afferent, or sensory, fibers can be further subdivided into large, heavily myelinated fibers (Aβ), thinly myelinated fibers (Aδ), and unmyelinated fibers (C fibers). Most sensory fibers within a sensory nerve are the "small fibers" that are either thinly myelinated or unmyelinated. Further, these small fibers tend to be clustered toward the center of the nerve. The blood vessels to the nerves (vasa nervorum) do not penetrate the nerve itself but stop at the epineurium so that the axons receive their nutrients and eliminate their wastes through diffusion. For this reason, the large, heavily myelinated axons at the edge of the nerve are at less risk from hypoxic-ischemic issues than are the small fibers that tend to be clustered in the center of the nerve. The myelinated fibers have an additional advantage in that the myelin sheath acts as an electrical insulator such that the electrical impulse along these nerve fibers only needs to be boosted by firing an action potential at the nodes of Ranvier. In contrast, the unmyelinated fibers must fire an action potential at every contiguous membrane segment. After an action potential is generated, energy must be expended to reestablish the electrochemical gradient. The net result is that lesser myelinated and unmyelinated sensory axons are much more susceptible to toxic-metabolic pathologic processes than are the more heavily myelinated Aβ fibers. Because these "myelin-deficient" fibers must generate an action potential more frequently than their heavily myelinated counterparts, they are also more prone to ischemic processes. These smaller, less myelinated fibers require more energy per unit length than do the heavily myelinated fibers. Viewed from this perspective, the small fibers serve an important purpose as an early warning system indicative of an underlying ischemic or toxic-metabolic process. The smaller fibers thus serve a similar function to the "check engine" light on a car. Either the engine is fully functional or it is not. When nerve function is suboptimal, the "check engine" light is illuminated, advising the operator that there is a problem. In the same way that an illuminated "check engine" light cannot specify the severity of a problem, the severity of the patient's NP does not necessarily correlate with the severity of the underlying pathology. The presence of a PP usually indicates dysfunction of the smaller fibers or their central connections, often as a result of an ischemic or toxic-metabolic process. Contrast these disorders with those in which the small fibers are relatively spared, as in acquired demyelinating polyneuropathy. Although pain may be a

feature of acquired demyelinating polyneuropathies, this is less common and often indicates collateral damage of small fibers secondary to inflammatory processes. The presence of a PP should initiate an investigation for potentially reversible causes, as suggested in Table 6.1.

OVERVIEW OF PERIPHERAL NEUROPATHIC PAIN PATHOPHYSIOLOGY

The precise mechanisms by which NP occurs are not completely understood. One early hypothesis advanced by Melzack and Wall (1965) was the "gate control theory." They postulated both large and small fiber input onto a wide dynamic range (WDR) neuron remained quiescent until an imbalance in sensory input developed. This would result in the activation of a previously quiescent nociceptive WDR neuron. The WDR neuron would then engage in central NP transmission. This simplistic hypothesis has flaws because it does not predict what is observed in clinical practice. The activation of a WDR neuron as a result of small and large fiber imbalance predicts that loss of one or the other of these fiber types would result in NP. However, patients with hereditary sensory and autonomic neuropathies do not always experience pain. In fact, many have mutilated limbs because of an absence of small fiber function, the exact opposite of what the gate control theory would predict. Another example would be acquired demyelinating polyneuropathies, such as chronic inflammatory demyelinating polyradiculoneuropathy, wherein there is significant large fiber dysfunction, yet pain is not a common feature of this illness. For these reasons, the gate control hypothesis had to be modified.

No optimum theory can explain all the mechanisms involved in NP, let alone the pain experienced in PP. As a first approximation, one can view this process as one in which there is a real or perceived injury to the sensory nervous system such that various mechanisms are activated. At every level of this process, there will be events that favor nociceptive transmission and those that oppose it. From the periphery to the most rostral regions of the CNS, there will be a wider degree and an ever more complex series of inputs on this process. Even though the current understanding of this process is incomplete, some of these mechanisms have been elucidated, as summarized in Tables 6.2 to 6.4.

There is also some consensus that pain in polyneuropathy likely results from some change in the previous level of functioning of the sensory afferent pathways. Most NP conditions associated with PP develop after an injury to the PNS. Several potential mechanisms are responsible for peripheral NP, including phenotypic switch of nociceptors, ectopic activity in damaged axons, abnormal firing of dorsal root ganglion (DRG) cells, unmaking of silent nociceptors, collateral sprouting, and invasion of dorsal root ganglia (Nurmikko, Nash, & Wiles, 1998). Each of these potential mechanisms provides a rationale for the use of the medications available for the treatment of pain in polyneuropathy.

Table 6.2 summarizes the various mechanisms by which NP can be generated in the PNS. These include direct pain impulse transduction by the transient receptor potential vanilloid channels and tyrosine kinase A (TrkA) receptors activated by nerve growth factor (NGF). In addition, they may induce previously dormant receptor subtypes that include purine receptors ($P2X_3$, $P2X_{2/3}$), the proteinase-activated receptor (PAR-2), and the bradykinin receptors B1 and B2 (Pappagallo & Werner, 2007). Ion channels that regulate electrochemical transmission, such as voltage-gated sodium, potassium, and calcium channels, are also involved in the transmission of NP (Cox et al., 2006; Nagasako, Oaklander, & Dworkin, 2003; Wada, Wanke, Gullo, & Sciavon, 2008). In most instances, activation of sodium and calcium channels tends to depolarize the membrane and lead to electrical impulse propagation, whereas activation of potassium channels has the opposite effect. Several available medications modify ion conductance, and a more in-depth discussion of these channels is in order.

SODIUM CHANNELS

Sodium channels may be divided into tetrodotoxin-resistant and tetrodotoxin-sensitive subtypes, although chronic inflammation activates both. Primary nociceptive neurons express multiple voltage-gated sodium channels. There are nine alpha unit isoforms of the sodium channel, designated $Na_v1.1$ through $Na_v1.9$. Of these, pathologic mutations in $Na_v1.7$ have been shown to be responsible for certain specific disease states. Gain-of-function pathologic mutations in $Na_v1.7$ have been reported to result in the clinical syndromes of erythromelalgia and paroxysmal extreme pain disorder (Wada et al., 2008). Conversely, an autosomal recessive "loss-of-function" mutation mapped to 2q24.3 in three northern Pakistani families resulted in a "'channelopathy-associated insensitivity to pain" (Cox et al., 2006). Affected persons experience painless injuries beginning in infancy but have otherwise normal sensory function. Proprioception, joint vibratory sensation, tactile thresholds, and light touch perception are normal, as are reflexes and autonomic responses. The axonal flare response after an intradermal histamine injection is normal in these persons, a feature that distinguishes this condition from hereditary sensory and autonomic neuropathy (Nagasako et al., 2003). Wada et al. (2008) noted that mutations in the $Na_v1.7$ isoform of the sodium channel are not required because the aberrant upregulation/hyperactivity of even the native $Na_v1.7$ can produce pain associated with inflammation and nerve injury, as noted in rodents.

POTASSIUM CHANNELS

Voltage-gated potassium channels may be viewed as the "brakes" on the sensory system in that they repolarize active neurons to the resting state (Bee & Dickenson, 2007). Potassium channel, voltage-gated KQT-like subfamily (KCNQ) (K_v7) channels are responsible for the inhibitory M current in DRG neurons (Passmore et al. 2002). The agent retigabine, a Food and Drug Administration (FDA)–approved anticonvulsant, has been shown to facilitate the inhibitory M current through the opening of K_v7 channels in a dose-dependent manner (Rivera-Arconada, Martinez-Gomez, & Lopez-Garcia, 2004). A recent publication reported that this agent could reduce the severity of paclitaxel-induced peripheral neuropathy and its associated NP (Li et al., 2019). There are also hyperpolarization-activated cyclic nucleotide-gated pacemaker cells that have structural similarities to potassium channels that are located in cardiac tissue

Table 6.2 Mechanisms Involved in Peripheral Neuropathic Pain

Channels/Receptors	Activated by	Function	Comments
TRPV channels (types 1, 2, and 3)	Noxious heat, low pH, capsaicin	Neuropeptide release	Proinflammatory
TRPV channels (other types)	Neuropeptides[a]	Nerve growth factor and cytokine release	Proinflammatory
TrkA receptors	Nerve growth factor	Up regulation of ion channels, receptors, and neuropeptides	Proinflammatory
	Creates NGF:TrkA complex		Channel activation
Sodium channels	Chronic inflammation	Linked to familial erythromelalgia and PEPD	$Na_v1.7$ has key role
TTX-R and TTX-S	Membrane voltage changes		Alters membrane potential
Calcium channel α2δ subunit	Membrane voltage changes	Calcium influx and cell damage	Gabapentinoids block calcium influx
Potassium channels	Membrane voltage changes	Membrane repolarization	Opening of K_v7 channels inhibits conduction
Purine receptors ($P2X_3$, $P2X_{2/3}$)	ATP	Neuropeptide release	Proinflammatory
Proteinase-activated receptor (PAR-2)	Tryptases/proteinases	Hyperalgesia	Proinflammatory?
Bradykinin receptor (B1 and B2)	Tissue injury	Inflammatory hyperalgesia	Proinflammatory

[a]Neuropeptides are neither receptors nor channels; they are proteins (e.g., substance P).
ATP, Adenosine triphosphate; *NGF*, nerve growth factor; *PEPD*, paroxysmal extreme pain disorder; *TrkA*, tyrosine kinase A; *TRPV*, transient receptor potential vanilloid; *TTX-R*, tetrodotoxin-resistant sodium channels; *TTX-S*, tetrodotoxin-sensitive sodium channels.

Table 6.3 Mechanisms Involved in Peripheral Neuropathic Pain: Spinal Cord Level

Structures/Receptors	Activated by	Primary Effect	Secondary Effects
Small fiber afferents to dorsal horn of spinal cord	Ischemia/voltage changes	Release of neuropeptides and EAA	Activation of DHPTN
DHPTN		Pain transduction	Central sensitization
Neurokinin-1 receptors	Neuropeptides		
NMDA receptors	EAA		Mg-inactivated/Ca-activated
AMPA	EAA		
Kainate	EAA		
Microglia	Inflammation/trauma	Pain transduction/inflammation	EAA, MAPK, prostaglandins, PIC release, ATP, nitric oxide, reactive oxygen species production

AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; *ATP*, adenosine triphosphate; *Ca*, calcium; *DHPTN*, dorsal horn pain–transmitting neurons; *EAA*, excitatory amino acids (e.g., glutamate, aspartate); *MAPK*, p38 mitogen-activated protein kinase; *Mg*, magnesium; *NMDA*, *N*-methyl-D-aspartate; *PIC*, proinflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1 β, interleukin-δ).

and DRG neurons. These hyperpolarization-activated cyclic nucleotide-gated cells are permeable to both sodium and potassium ions and may subserve a role in Aδ-mediated mechanical allodynia (Bee & Dickenson, 2007).

CALCIUM CHANNELS

Calcium channels serve an important role with respect to nerve injury and pain transmission. Calcium influx is one of the final common pathways involved in cell injury and death. There are numerous calcium channel subtypes that can be divided into low voltage, transient, or T-type and are associated with cardiac pacemaker rhythmicity and high-voltage calcium channels. The high-voltage calcium channels are further divided into subtypes L, N, P, Q, and R (Catterall, Perez-Reyes, Snutch, & Striessnig, 2005). Of these subtypes, the one most germane to pain management is the N subtype, which has been shown to mediate persistent tactile

Table 6.4 Mechanisms Involved in Peripheral Neuropathic Pain: Pain Reducers/Inhibitors

Structure	Neurotransmitter	Other Functions	Comments
PNS and CNS	Opioid peptides	Sense of well-being	β-endorphin opposes bradykinin
NRM	Opioid peptides		Receives input from periaqueductal gray matter
Periaqueductal gray matter	5-HT, norepinephrine, glycine, GABA		Multiple inputs/outputs
Caudal DRN	5-HT	Satiety/initiates sleep	Projects to spinal cord and cerebellum
Rostral DRN	5-HT	Satiety/initiates sleep	Widespread
Locus coeruleus	Norepinephrine	Arousal and reward	Associated with 5-HT
CNS	GABA, glycine	Inhibits neurotransmission	Widespread

Dopamine and acetylcholine pathways in the CNS have effects on all of these pathways.
5-HT, 5-Hydroxytryptamine or serotonin; *CNS*, central nervous system; *DRN*, dorsal raphe nucleus; *GABA*, gamma aminobutyric acid; *NRM*, nucleus raphe magnus; *PNS*, peripheral nervous system.

allodynia after nerve injury in rats (Chaplan, Pogrel, & Yaksh, 1994). These N-type calcium channels are located in presynaptic terminals and mediate catecholamine release. At presynaptic nerve terminals, calcium entry is the initial trigger mediating the release of neurotransmitters via the calcium-dependent fusion of synaptic vesicles and involves interactions with the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor complex of synaptic release proteins (Snutch, 2005). Blockage of N-type calcium channel transmission is the postulated mechanism underlying the analgesic effect of the intrathecally administered medication ziconotide (Ziconotide, 2020). Because this medication is administered intrathecally and only under specific circumstances, it is not discussed further. The gabapentinoids, gabapentin and pregabalin, exert their effects on the $\alpha_2\delta$ subunit of the Ca^{2+} channel at the N-, L-, and P/Q-type channels (Sutton, Martin, Pinnock, Lee, & Scott, 2002). This binding decreases neurotransmitter release in the CNS as a result of reduced calcium influx through the gated channels (Fudin, 2015). Sutton et al. (2002) further stated that the major effect of gabapentin and, by extension, pregabalin, is to affect N-type current. The use of these medications may reduce calcium influx into the nerve fibers, reducing the degree of axonal injury and, thus, the degree of NP. The lack of their effect on T-type calcium channels may explain why these medications are not usually associated with cardiac arrhythmias.

Induction of nociceptive nerve fiber transmission may also occur. For example, the TrkA receptor is expressed by nociceptors that bind NGF. NGF is produced by mast cells, several inflammatory cells, and endothelial cells. When the TrkA-NGF complex is formed, retrograde transport to the sensory neuron cell bodies located in the dorsal root ganglia occurs. This results in upregulation of numerous receptors and ion channels as well as the release of neuropeptides involved in pain transmission. Pappagallo and Werner cited evidence from other authors that sensory innervation of cortical and trabecular bone is mediated by this mechanism and that antibodies directed against NGF are effective in reducing pain in animal models of cancer-induced bone pain (Halvorson et al., 2005; Pappagallo & Werner, 2007; Sevcik et al., 2005).

Finally, the properties of the nociceptive fibers can be altered by inducing previously dormant receptor subtypes. The purine receptors ($P2X_3$, $P2X_{2/3}$) are activated by adenosine triphosphate, resulting in a release of neuropeptides (Pappagallo & Werner, 2007). $P2X_3$ receptors are located on peripheral sensory afferents, where their induction contributes to hyperalgesia and mechanical allodynia. Like the purine receptors, PAR-2 is activated by mast cell–derived tryptase and other proteinases that are believed to be involved in hyperalgesia. The bradykinin receptors B1 and B2 are also expressed on nociceptive neurons. The bradykinin receptor B1 is induced by tissue injury and contributes significantly to inflammatory hyperalgesia.

Regardless of the precise mechanisms involved, the nociceptive system can be viewed as an early warning system of actual or incipient tissue injury. Pain is a binary process; either tissue injury is perceived to be imminent or it is not. Pain alerts the organism to alter its behavior to minimize the amount of tissue damage, real or perceived. Failure to terminate the pain signal may result in permanent alteration of the sensory afferent system such that a chronic pain syndrome may result. Therefore, PP should be treated as soon as possible.

MODIFICATION OF SENSORY AND NOCICEPTIVE AFFERENTS

Unlike the dorsal column/lemniscal system that conducts large fiber sensory pathway information to the cortex in a relatively direct manner, nociceptive afferents can be modified at various levels within the CNS. These often occur at synapses within the spinothalamic pathways, such as the dorsal horn of the spinal cord and the brain stem, as noted in Tables 6.2 and 6.3. With incoming nociceptive volleys to the dorsal horn, neuropeptides and excitatory amino acids are released and may result in the transient depolarization and central transmission of pain by the dorsal horn pain-transmitting neurons. These pain-inducing neuropeptides include substance P, calcitonin gene–related peptide, cholecystokinin, and neurokinin A (Pappagallo & Werner,

2007). The excitatory amino acids include glutamate and aspartate. *N*-methyl-D-aspartate (NMDA) receptors may subserve a role in pain modulation as well. These receptors are normally inactivated by the presence of magnesium (Pappagallo & Werner, 2007).

However, intense or more frequent stimulation of nociceptive afferents by substance P and excitatory amino acids removes this protective "magnesium cap" such that intracellular calcium influx occurs. This calcium influx leads to a series of intracellular changes and prolonged sensitization of the pain-transmitting neurons in a phenomenon known as "wind-up" (Staud, Price, Robinson, Mauderli, & Vierck, 2004). Increased calcium influx has been implicated in both peripheral and central mechanisms of pain propagation. Counteracting this calcium influx is the presumed mechanism by which gabapentin and pregabalin produce their analgesic effects.

Wind-up may also occur through the activation of microglia, a process that can occur with peripheral nerve injury. This results in the expression of $P2X_4$ receptors on microglia in the spinal cord that leads to the release of brain-derived NGF. There is evidence that this results in the activation of NMDA receptors in the dorsal horn of the spinal cord (Ulmann et al., 2008). Ulmann et al. (2008) also reported that $P2X_4$-deficient mice lacked mechanical hyperalgesia induced by peripheral nerve injury and showed impaired brain-derived neurotrophic factor (BDNF) signaling in the spinal cord. Moreover, they noted that adenosine triphosphate stimulation did not stimulate BDNF release from $P2X_4$-deficient mice microglia in primary cultures. Another important mechanism involves the release of fractalkines, which are proteins in the chemokine family that are expressed by pain-transmitting neurons (Milligan, Sloane, & Watkins, 2008). In certain situations, fractalkines detach from neurons and activate nearby microglia (Harrison et al. 1998).

It should be recalled that pain can occur even in the absence of a peripheral nerve injury (e.g., thalamic syndrome of Dejerine-Roussy, complex regional pain syndrome type I). In these instances, pain may result from a change in the afferent traffic experienced by the CNS. Viewed from this perspective, either increased or decreased trafficking along the sensory pathways could give rise to pain perception. Restated, the CNS is constantly receiving sensory inputs, both somatic and visceral, from peripheral receptors that transmit reports back to the CNS for interpretation. Failure to transmit these signals might be interpreted as pain, as is observed in phantom limb pain. Interruption in normal transmission may also be responsible for the pain experienced contralateral to the lesion site in the thalamic syndrome of Dejerine-Roussy. Although these conditions are beyond the scope of this chapter, it is important to recognize that not all peripheral NP syndromes may be caused by alteration in nociceptive receptors or their central connections. Thus, compensating for the effects of a peripheral neuropathy with adaptive devices or physical therapy may reduce pain perception in addition to improving QOL.

Modification of sensory and nociceptive afferents may also occur in locations rostral to the dorsal horn of the spinal cord. Descending inhibitory pain pathways originate from various locations in the brain's cortical and subcortical areas. Three of the most important subcortical areas are the periaqueductal gray matter, locus ceruleus, and nucleus raphe magnus, as depicted in Figs. 6.1 and 6.2. The periaqueductal gray matter may be viewed as a hub that receives input from the cortex, thalamus, and hypothalamus. It expresses opioid receptors and stimulates the nucleus raphe magnus. The locus ceruleus inhibits the dorsal horn of the spinal cord through norepinephrine (NE)-mediated inhibitory pathways, whereas the nucleus raphe magnus inhibitory pathways project to the dorsolateral funiculus of the dorsal horn utilizing serotonin or 5-hydroxytryptamine (5-HT) and enkephalins as their inhibitory neurotransmitters. Medications that increase transmission within these pathways should have a net effect of reducing perceived pain by increasing the effects of the neurotransmitters NE, 5-HT, and, to a lesser extent, dopamine (DA). Opioids, which have similarities to endorphins and enkephalins, most likely exert their effects by increasing transmission within the descending inhibitory pain pathways. Further modification of these ascending inputs occurs in more rostral CNS regions wherein the neurotransmitter gamma aminobutyric acid (GABA) and, to a lesser extent, acetylcholine (ACh) subserve these functions. The GABA, 5-HT, and NE major pathways are shown in Fig. 6.3. There is also significant influence of DA- and ACh-mediated pathways within the CNS on these afferent and efferent tracts.

These are the mechanisms that are believed to underlie the analgesic effects of TCAs, selective serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs) such as duloxetine and venlafaxine, and opioid analgesics and their related compounds. Most of these data have been obtained

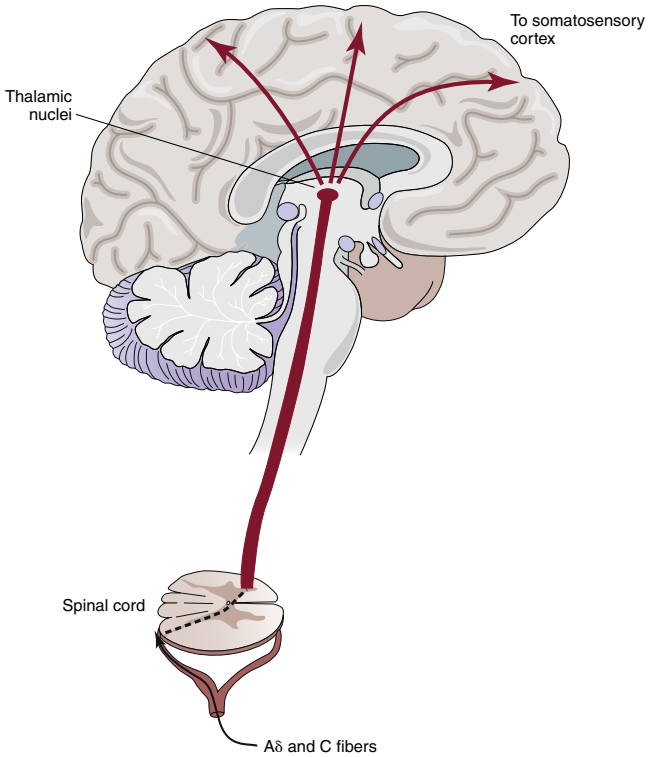


Fig. 6.1 Thinly myelinated (*Aδ*) and unmyelinated (*C*) fibers cross within the spinal cord before ascending to the thalamus and somatosensory cortex. The large, heavily myelinated fibers A([insert greek letter for beta]) that subserve vibration and position, not depicted here, cross at the cervicomedullary junction before ascending.

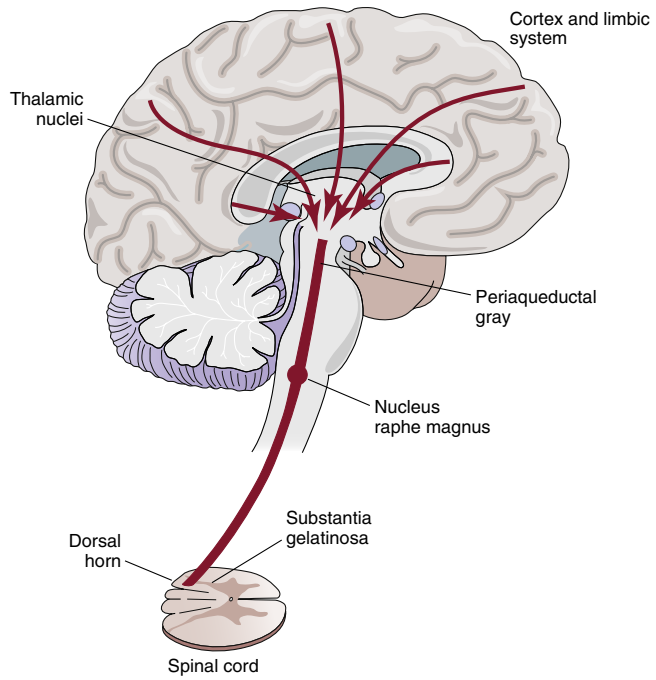


Fig. 6.2 The descending pain pathways originate in the cortex and limbic system. They exert inhibitory effects on subcortical structures and the spinal cord. Serotonin and norepinephrine are important neurotransmitters in these pathways.

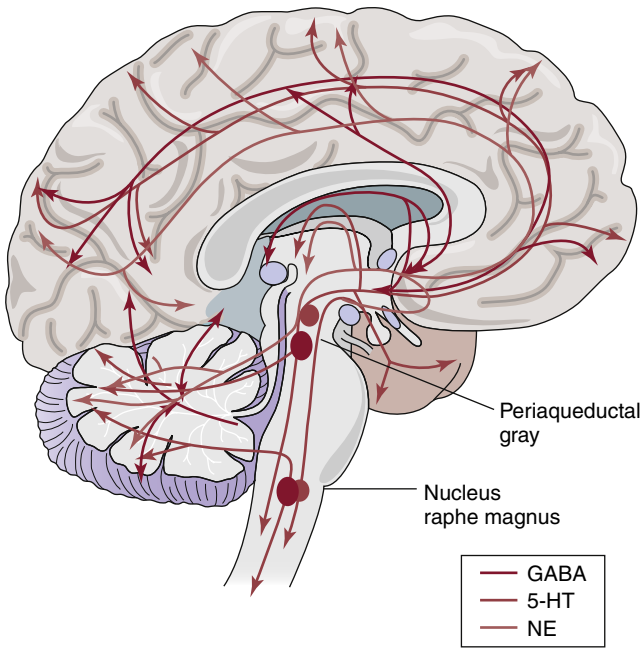


Fig. 6.3 The major pathways that use these neurotransmitters within the central nervous system. Gamma aminobutyric acid (*GABA*) is an important inhibitory neurotransmitter, with numerous projections throughout the brain. *5-HT*, Serotonin reuptake inhibitor; *NE*, norepinephrine.

in laboratory animals and have not necessarily been confirmed in humans. Nonetheless, Tables 6.5 to 6.7 summarize these agents' hypothesized mechanisms of action. Descending inhibitory pain pathways are believed to be mediated by 5-HT and NE such that increasing the availability of these neurotransmitters within this pathway should reduce pain perception (Bymaster et al., 2001). One such agent, duloxetine, is believed to have efficacy because of its relatively balanced inhibition of 5-HT and NE reuptake (Iyengar, Webster, Hemrick-Luecke, Xu, & Simmons, 2004). It has been approved by the FDA for the treatment of DPNP. Pregabalin is also approved for the same indication. TCAs are believed to have a similar mechanism of action to duloxetine (McQuay et al., 1996; Micó, Ardid, Berrocoso, & Eschalier, 2006). However, TCAs are less specific than the SNRIs because TCAs have additional actions, such as anticholinergic and histamine blockade effects. Nonetheless, inhibition of 5-HT reuptake, alone or in combination with NE reuptake inhibition, has been invoked as the mechanism underlying the clinical effect of the older and newer antidepressants (Feighner, 1999). As discussed later, TCAs and SNRIs have analgesic properties, whereas SSRIs, such as fluoxetine and sertraline, have minimal, if any, analgesic effects. With respect to the treatment of depression, a meta-analysis of 20 short-term comparative studies of five SSRIs, including citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, reported no net difference in efficacy between individual compounds, but a slower onset of action for fluoxetine (Edwards & Anderson, 1999). Thus, analgesic efficacy and antidepressant activity differ among these agents such that analgesic efficacy occurs when both NE reuptake and 5-HT reuptake are inhibited. Analogous to SSRIs, no purely selective NE reuptake inhibitor has been conclusively demonstrated to be an effective treatment for PP.

The use of traditional opioid analgesics is controversial given the recent opioid crisis. Notwithstanding, there is a significant body of literature that supports the use of opioid analgesics in NP such that a discussion is warranted. Opioid analgesics can be subdivided into four main categories: natural alkaloids derived from opium (e.g., morphine and codeine), opium derivatives (e.g., heroin), synthetic agents that resemble the morphine molecule (e.g., methadone, meperidine), and opioid antagonists, such as naloxone. The precise mechanisms by which opioid analgesics exert their effects remain to be established. One important observation is that these substances resemble two endogenous pentapeptides known as enkephalins that differ in their last amino acid. It has been hypothesized that enkephalins prevent the release of ACh, resulting in reduced nociceptive transmission. Other purported mechanisms include potentiation of the descending inhibitory pain pathways that originate from the cortex, limbic system, and periaqueductal gray matter (Ossipov, Morimura, & Porreca, 2014). However, their use is limited by the effects of physical dependence, addiction, respiratory depression, and anticholinergic side effects, such as sedation and constipation. Regardless of the precise mechanisms involved, few opioid analgesics have been shown to be effective against many different types of NP. These substances interact with one or more of the four major subtypes of opioid receptors: δ (delta), κ (kappa), μ (mu), and the nociceptin receptor (Corbett, Henderson, McKnight, & Paterson, 2006). These receptors are widely distributed throughout the CNS. The nociceptin receptor subserves anxiety, depression, appetite, and the development of tolerance to μ agonists. The δ receptors, of which there are two subtypes, mediate analgesia, antidepressant effects, and physical dependence. The κ receptors, of which there are three subtypes, mediate spinal analgesia, sedation,

Table 6.5 Level A Recommendation Medications: Tricyclic Antidepressants

Subtype	Generic Name	Mechanism of Action[a]	Number Needed to Treat (95% Confidence Interval)[b]	Additional Benefits
Secondary	Nortriptyline	NE	Similar to desipramine	
	Desipramine	NE	2.5 (1.9–3.6)	
	Amoxapine	5-HT ≈ NE/(-) DA/(-) HIS	ND	Useful in Huntington chorea
Tertiary	Amitriptyline	5-HT ≈ NE	2.1 (1.8–2.6)	
	Imipramine	5-HT ≈ NE	2.1 (1.8–2.6)	Panic disorder and generalized anxiety disorder
	Doxepin	NE/(-) HIS	ND	Used in fibromyalgia off-label
	Clomipramine	5-HT/(-) DA/some NE	ND	Useful in treating obsessive-compulsive disorder

Sources: Dworkin, R. H., O'Connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L., et al. (2010). Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings*, *85*(Suppl. 3), S3S14; Huizinga, M. M., & Peltier, A. (2007). Painful diabetic neuropathy: A management-centered review. *Clinical Diabetes*, *25*, 6–15.
[a]These mechanisms are based on preclinical data and have not been proven in humans.
[b]Based on an analysis of treatments for diabetic polyneuropathy.
5-HT, Serotonin reuptake inhibitor; *(-) DA*, dopamine antagonist; *(-) HIS*, histamine antagonist; *ND*, no data available; *NE*, norepinephrine reuptake inhibitor.

Table 6.6 Level A Recommendation Medications: Selective Serotonin and Norepinephrine Reuptake Inhibitors, Gabapentinoids, and Topical Lidocaine

Subtype	Generic Name	Mechanism of Action[a]	Number Needed to Treat (95% Confidence Interval)[b]	Additional Benefits
Selective serotonin and norepinephrine reuptake inhibitors	Duloxetine	5-HT, NE	4 (3–9)	Depression, fibromyalgia
	Venlafaxine[c]	5-HT; 5-HT/NE	5.5 (3.4–14.0)	Depression
Gabapentinoids	Gabapentin[c,d]	Ca Ch α2δ antagonist	3.9 (3.2–5.1)	PS, PHN
	Pregabalin	Ca Ch α2δ antagonist	4.2 (3.4–5.4)	PS, PHN, fibromyalgia
Topicals	Lidocaine patch[c]	Na Ch blocker	Unknown	PHN

Sources: Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., et al. (2007). Pharmacological management of neuropathic pain: Evidence-based recommendations. *Pain*, *132*, 237–251; Huizinga, M. M., & Peltier, A. (2007). Painful diabetic neuropathy: A management-centered review. *Clinical Diabetes*, *25*, 6–15.
[a]These mechanisms are based on preclinical data and have not been proven in humans.
[b]Based on an analysis of treatments in diabetic polyneuropathy.
[c]Not US Food and Drug Administration approved for the treatment of pain in any type of polyneuropathy, except for pain associated with post–herpetic neuralgia.
[d]For doses ≥2400 mg daily.
5-HT, Serotonin reuptake inhibitor; *Ca Ch α2δ antagonist*, calcium channel α2δ antagonist; *Na Ch blocker*, sodium channel blocker; *NE*, norepinephrine reuptake inhibitor; *PHN*, post–herpetic neuralgia; *PS*, adjunctive therapy for partial seizures.

miosis, and inhibition of antidiuretic hormone release. The μ receptors, of which there are also three subtypes, have the best characterized subtypes. Of these subtypes, the μ1 and μ2 receptors are the most important with respect to pain management. The μ1 receptors mediate supraspinal analgesia and physical dependence, whereas the μ2 receptors mediate respiratory depression, miosis, euphoria, reduced gastrointestinal motility, and respiratory depression. From this brief description, one can visualize the advantage of developing an agent that excited only δ receptors or a combination of μ1 and δ receptors. Several such agents have been developed. Unfortunately, pure δ agonists are not as effective in producing analgesia as μ-receptor-mediated agents (Varga et al., 2004). Furthermore, many δ agonists induce seizures at high doses, although not all δ agonists produce this effect (Jutkiewicz, Baladi, Folk, Rice, & Woods, 2006). One advantage of these δ opioid receptor agonists is that they have a novel antidepressant effect (Broom, Jutkiewicz, Rice, Traynor, & Woods, 2002). Antidepressant effects have also been noted with opioids that bind to μ and δ receptors (Zhang et al., 2006). Although opioids may have the advantages of providing pain control and some antidepressant and anti-anxiety effects, it is important to use rational polypharmacy to address the constellation of symptoms associated with PPs.

Table 6.7 Level B: Opioids and Related Compounds

Subtype	Generic Name	Mechanism of Action	Number Needed to Treat (95% Confidence Interval)
Derivative	Tramadol	μ receptor/weak 5-HT, NE	3.5 (2.4–6.4)
Opioids	See text	See text	

Sources: Célèrier, E., Laulin, J. P., Corcuff, J. B., Le Moal, M., & Simonnet, G. (2001). Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. *Journal of Neuroscience*, *21*, 4074–4080; Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., et al. (2007). Pharmacological management of neuropathic pain: Evidence-based recommendations. *Pain*, *132*, 237–251; Huizinga, M. M., & Peltier, A. (2007). Painful diabetic neuropathy: A management-centered review. *Clinical Diabetes*, *25*, 6–15; VHA Pharmacy Benefits Management Strategic Healthcare Group, and the Medical Advisory Panel, Duloxetine in painful diabetic neuropathy and fibromyalgia [article online]. (2020). Retrieved from https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp.

5-HT, 5-Serotonin reuptake inhibitor; *NE*, norepinephrine reuptake inhibitor.

Notwithstanding, opioids have numerous unwanted side effects that limit their use as first-line agents in the treatment of PP and should generally be used as second-line agents (Dworkin et al., 2010).

Lastly, the mind is contained within the brain. A person's background, experiences, and psyche have an important effect on the perception of pain and its severity. The brain's cortex, in concert with the limbic system, interprets the noxious stimuli and makes assumptions about their meaning. Neurotransmitters involved in these processes include ACh and DA. Although both are involved in the brain's "reward system," as well as in memory and cognition, DA plays a greater role than ACh in the reward system, whereas the converse is true for memory and cognition. A person's emotional state and previous experiences play a significant role in the interpretation of incoming noxious stimuli. There are some experiences that few would interpret as pleasurable, such as voluntarily striking one's contralateral thumb with a hammer driven at full force. Nonetheless, the severity of the perceived noxious stimulus will vary between individuals and even within the same individual, depending on the circumstances. For example, stubbing one's toe after a sleep-deprived night on call will likely be perceived as more noxious than stubbing one's toe during a game of beach volleyball on vacation. The inciting stimulus is the same, but the context is very different. Sunburn provides another example. Some persons are incapacitated for days after sunburn, whereas others view it as a minor inconvenience. Therefore, treating physicians should not base treatment decisions on their perception of what the patient should be experiencing, but rather based upon what the patient is reporting.

Rating scales, such as the visual analog pain rating scale and the Wong-Baker faces model, have been used to classify a particular individual's perception of pain (Huskisson, 1982; Wong, Hockenberry-Eaton, Wilson, Winkelstein, & Schwartz, 2001). These provide reliable estimates that allow for a comparison between different points in time for the same individual in therapeutic trials. There are other, more comprehensive scales, such as the McGill Pain Questionnaire and the Walid-Robinson Pain Index (WRPI) (Melzack, 1975; Walid, Hyer, Ajjan, Barth, & Robinson, 2007). The McGill Pain Questionnaire gives a more specific indication of pain qualities, whereas the WRPI provides a description of both the intensity and duration of pain, measured in months. All these rating scales have been validated, but they were not developed specifically for evaluating PP. Specifically, the WRPI was developed to measure low back pain in patients who were scheduled for spine surgery. Nonetheless, it is reasonable as a first approximation to use any of these pain rating scales when evaluating patients with a polyneuropathy so long as the same scale is used at every visit. Although a majority of existing, validated pain assessments provide a subjective measure of pain, there should be a focus on functional limitation due to pain that guides medical management. Pain can interfere with QOL by limiting activities of daily living and development of avoidance behaviors (Dahl & Lundgren, 2006). Regulatory agencies now recommend that the titration of opioid medication be based on pain interference, physical and emotional functioning, QOL, and patient-reported global rating as opposed to basing it solely on the patient's reported numeric pain value (Dworkin et al., 2005; Federation of State Medical Boards, 2013).

The authors prefer the simpler rating scales, such as the Wong-Baker faces model, because they are quick and easy to perform. Their use allows for a longitudinal and reproducible assessment of the patient's perceived pain.

EVIDENCE-BASED MEDICINE

EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM involves integrating one's individual clinical expertise with the best available external clinical evidence from systematic research (Sackett, Rosenberg, & Gray, 1996). EBM reviews the available literature, assesses its quality, and makes a recommendation to guide clinical practice.

Unfortunately, EBM has limitations because there are some interventions in which it may be impractical, unethical, or inappropriate to subject patients to double-blind, placebo-controlled trials. For example, objections have been raised to the use of "sham surgery" in which a patient would be subjected to the risks of general anesthesia but would not benefit from receiving an actual surgical procedure. Prednisone treatment of myasthenia gravis provides another example. It is generally believed that it would be unethical to subject patients with myasthenia gravis to a trial of prednisone versus placebo to document the efficacy of prednisone therapy, a treatment that is widely believed to be beneficial based on historical controls. Finally, some interventions are

Table 6.8 Evidence-Based Medicine Studies: US Preventive Services Task Force

Evidence Level	**Evidence Level**		
Level I	At least one properly designed randomized controlled trial.		
Level II-1	Well-designed controlled trials without randomization.		
Level II-2	Well-designed cohort or case-control analytic studies, preferably from more than one site.		
Level II-3	Evidence obtained from multiple time series, with or without the intervention.		
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.		
Quality of Evidence	**Summary**		
Good	Well-designed trials assessing health impact applicable to the population at large.		
Fair	Health impact assessable, but the evidence's strength has limitations.		
Poor	Unable to assess health impact let alone apply it to the population at large.		
Recommendation	**Recommendation to Provider**	**Benefit-to-Harm Ratio**	**Evidence Quality**
A	Strongly in favor	Very favorable	Good
B	In favor	Favorable	Fair or better
C	Strongly in favor	Marginal	Fair
D[a]	Against	Equal or unfavorable	Fair or better
I	No position	Indeterminate	Poor

Source: US Preventive Services Task Force. (2018). *Ratings: Grade definitions, 2000–2003 guide to clinical preventive services, third edition: Periodic updates*. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.ahrq.gov/clinic/3rduspstf/ratings.htm

[a]D recommendations include asymptomatic patients as well.

so benign that it would not be practical to conduct a trial in which expert physical therapy would be compared against novice physical therapy to demonstrate an improvement in a patient's QOL. Assistive devices and other such modifications can be initiated and later discontinued at any time with no harm done to the patient. As such, some clinical questions may never be amenable to EBM analysis. Despite its limitations, EBM represents a great leap forward in medical practice.

There are several different rating systems available, but the one most commonly used is derived from the US Preventive Services Task Force (USPSTF, 2018), as noted in Table 6.8. The American Academy of Neurology's Quality Standards' Subcommittee (AAN) modified this system, as noted in Tables 6.9 and 6.10 (Gronseth et al., 2008). These studies are ranked based on their level of evidence from I to III. The USPSTF's level I evidence reflects the "gold standard" of a well-designed randomized clinical trial (equivalent to the AAN's Class I trial). On the opposite end of the spectrum, level III evidence reflects the opinions of authorities or descriptive studies (AAN Class IV). The USPSTF then ranks the quality of the evidence based on a rating of "good," "fair," or "poor," whereas the AAN methodology rates the evidence based on specific "levels." The AAN levels are subdivided into level A (established), level B (probable), level C (possible), and level U (uncertain). Unlike the AAN system, the USPSTF's final assessment integrates these parameters to provide a level of recommendation for use in clinical practice, with grade A strongly supporting the clinical practice and grade D opposing this practice. In contrast, the AAN merely rates the quality and strength of the available evidence. Although these rating systems appear similar, an extreme example demonstrates that they are very different. Consider three unethical randomized clinical trials that assessed the use of hydrogen cyanide versus placebo for the treatment of PP wherein all the patients who received cyanide died. Both the AAN and the USPSTF would concur that three Class I trials that obtained the same results would provide compelling clinical evidence against the use of cyanide for treating PP. The USPSTF would rate the quality of this evidence as "good," as would the AAN system, level A. The USPSTF would take one additional step and issue a grade D recommendation (harmful; not recommended). Restated, an AAN level A designation should not be interpreted as indicating that the data favor using this treatment, just that the data are conclusive. In fact, the AAN system does not actually make specific recommendations. Not all level I studies will result in a USPSTF grade A recommendation. As another example, assume that several level I studies found that a medication successfully treated hypertension in all African American men older than 60 years who served on active duty in the Vietnam War. This would likely lead to a USPSTF grade B recommendation at best because it is unclear whether these results could be generalized to the entire population. Finally, lack of evidence is not equivalent to "ineffective." As such, USPSTF grade I recommendations indicate "indeterminate" rather than "ineffective." Given these differences, the reader needs to be attuned to the rating system used.

Most practitioners are unlikely to follow this method for every clinical question that arises in the course of practice. Nonetheless, all clinicians should be aware of the clinical

Table 6.9 Evidence-Based Medicine Studies: American Academy of Neurology—Classification of Evidence Rating

Classification of Evidence Rating of a Therapeutic Trial	
Class I	Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The following are required: A. Concealed allocation. B. Primary outcome clearly defined. C. Inclusion/exclusion criteria clearly defined. D. Adequate accounting for a minimum number of dropouts and crossovers to minimize bias. E. Relevant baseline characteristics presented and substantially equivalent among treatment groups or appropriate statistical adjustment.
Class II	Prospective matched group cohort study in a representative population with masked outcome that meets criteria A–E above or a randomized controlled trial that lacks one criterion of A–D.
Class III	All other controlled trials (including well-defined natural history control subjects or patients serving as their own controls) in a representative population, where outcome is assessed independently or independently derived by an objective outcome measurement; a measure unlikely to be affected by an observer's expectation or bias.
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Source: Gronseth, G., Cruccu, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K., et al. (2008). Practice parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review). *Neurology*, *71*, 1183–1190.

Table 6.10 Evidence-Based Medicine Studies: American Academy of Neurology—Level of Recommendation

Level of Recommendation	
Level A	Established as effective, ineffective, or harmful for the given condition in the specified population (requires two consistent Class I studies).[a]
Level B	Probably effective, ineffective, or harmful for the given condition in the specified population (requires at least one Class I study or two consistent Class II studies).
Level C	Possibly effective, ineffective, or harmful for the given condition in the specified population (requires at least one Class II study or two consistent Class III studies).
Level U	Inadequate or conflicting data. Treatment is unproven (studies not meeting Class I–III criteria).

Source: Gronseth, G., Cruccu, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K., et al. (2008). Practice parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review). *Neurology*, *71*, 1183–1190.

[a]In exceptional cases, one convincing Class I study may suffice for a level A recommendation under the following conditions: all Class I criteria have been met; the magnitude of the effect is large; the relative rate of improved outcome exceeds 5; and the lower limit of the confidence interval is >2.

practice guidelines generated by these methods. Patients should be offered treatments with a USPSTF A or B grade recommendation and should not be advised to have treatments or interventions with a grade D recommendation. The AAN practice parameters must be read carefully to ascertain whether the treatment under consideration is helpful or harmful because this is not explicitly stated by the evidence class. Although EBM does not specifically advise against an intervention with an USPSTF grade of C, the practitioner should inform the patient that although the intervention may be helpful, the risk-to-benefit ratio is narrow. Furthermore, USPSTF grade I interventions may or may not be helpful. In such situations, the clinician needs to explain to the patient that there are no adequate data "for or against" this treatment and that "best judgment" should be used. For the remainder of this chapter, the USPSTF system will be the one employed because it incorporates all the AAN criteria and then makes a specific recommendation.

APPROVED AND "OFF-LABEL" MEDICATION USES

Approval by the US FDA should not be equated with EBM. If a medication is approved by the FDA for a specific indication, then the agency has rendered an opinion that a medication is an effective treatment for that condition and that its benefits outweigh its risks. In general, FDA approval implies that this agency considers the medication or device to have efficacy for the approved indication as well as a favorable risk-to-benefit ratio. The FDA does not assign a grade to the level of evidence but would be unlikely to approve a medication that was not at least grade B or better for the approved indication. However, the converse is not necessarily true in that a grade A recommendation may be warranted, even when the FDA has not given formal approval to that indication. For example, aspirin was shown to reduce the risk of myocardial infarction in patients with angina pectoris long before the FDA officially recognized this indication.

According to the FDA's stated policy, "Neither the FDA nor the Federal government regulates the practice of medicine. Any approved product may be used by a licensed practitioner for uses other than those stated in the product label" (Center for Drug Evaluation and Research & US FDA, 2003). Once the medication has been approved for use, it may be prescribed

"off-label" as seen fit by any licensed practitioner with the patient's informed consent.

Unfortunately, there is a paucity of data to guide clinicians as to the optimal drug to be used in specific conditions. A recent review of NP by Dworkin et al. (2007, 2010) noted that only three broad classes of medications received a grade A recommendation for the first-line treatment of NP: antidepressants (TCAs and dual reuptake inhibitors of serotonin and NE), calcium channel $\alpha_2\delta$ ligands (gabapentin and pregabalin), and topical lidocaine. Nonetheless, this publication addressed NP in general such that radiculopathy, PHN, and other conditions were included in this analysis. The review did not restrict its purview to the treatment of PP. The FDA has approved only two medications for the specific indication of DPNP: pregabalin and duloxetine. These agents have not received FDA approval for any other PP.

Although many patients are treated "off-label" with the other medications recommended by Dworkin et al. (2010), the FDA has not approved either TCAs or gabapentin to be used as a treatment for pain associated with any type of painful peripheral neuropathy. The two FDA-approved indications for gabapentin are as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients older than 12 years with epilepsy and for the management of PHN in adults (Neurontin, 2020). A related compound, pregabalin, has been FDA approved only for use in adults as adjunctive therapy in the treatment of partial seizures and the management of PHN, DPNP, and FM (Lyrica, 2020). Duloxetine is approved in adults for the treatment of MDD, GAD, DPNP, and FM (Cymbalta, 2020). The only FDA-approved indication for the lidocaine patch is for the management of PHN in adults. Finally, although naturally occurring opioids, such as morphine, and synthetic opioids, such as tramadol, are FDA approved for the treatment of "pain," they have not been specifically FDA approved for the treatment of PP.

PREVIOUS TREATMENT RECOMMENDATIONS

In the absence of robust EBM guidance, many algorithms for the treatment of NP have been proposed (Attal et al., 2006; Dworkin et al., 2007, 2010; Moulin et al., 2007). Although these guidelines are all useful, most are based on meta-analyses and expert opinion because there are few double-blind placebo-controlled trials to provide guidance on each and every condition that results in NP. As previously discussed, the only PP that has been extensively evaluated in double-blind, multicenter, placebo-controlled trials is DPNP. Other authors have performed analyses regarding the treatment of DPNP, one of which analyzed the data to estimate the number needed to treat (NNT), the number of consecutive patients who would need to be treated for one person to report a 50% reduction in perceived pain (Huizinga & Peltier, 2007). Although this may have some utility, all analyses, including meta-analyses, are subject to numerous potential sources of bias, so their conclusions may not necessarily be accurate (Egger & Davey Smith, 1998). These biases may include such factors as not identifying negative trials because these are less likely to be published, ignoring publications in languages other than English, selection bias on the part of the reviewer, and overestimation of a drug's effect because a higher end of the dosage range was used. Even if a meta-analysis were bias-free and accurate, its findings cannot necessarily be generalized to the treatment of other painful neuropathic conditions. Therefore, there is minimal evidence guiding the treatment of pain in polyneuropathy other than DPNP. More importantly, there are few head-to-head trials wherein less expensive medications, such as TCAs, are compared with newer agents. Therefore, an integrated approach to the treatment of PP based on the available literature is in order.

There have been many publications on the treatment of DPNP, including an analysis by Huizinga and Peltier (2007), that summarized the relevant literature and made treatment recommendations. Huizinga and Peltier (2007) reported that there were no head-to-head trials that allowed for an objective comparison of one recommended agent against another. Therefore, they analyzed the available data to give a comparison based on the NNT. The mean NNT for these agents suggests that TCAs and carbamazepine (which has structure similarities to TCAs) have a better efficacy than the other medications listed. A closer evaluation notes a significant overlap in the 95% confidence intervals. As such, one cannot state with certainty that carbamazepine and TCAs are truly superior to the other agents evaluated by this study. Furthermore, this analysis of DPNP cannot be extrapolated to the treatment of all PPs. Finally, these data report what the "average" patient with this condition would likely experience and not what an individual patient would experience. In the absence of clear treatment guidelines, a practitioner should discuss all the potential treatment options with the patient so that the patient makes an informed decision.

Many physicians are tempted to combine two or more medications with different mechanisms of action, hoping that the combination will prove superior to either agent alone. Many pain management specialists combine pregabalin and duloxetine, hypothesizing that their different mechanisms of action will be additive. However, physicians should recognize that such combination therapies have not been formally evaluated in prospective, double-blind, placebo-controlled trials. Nonetheless, trials combining opioids with nonopioid agents reported that a combination was superior to placebo, that a greater degree of pain reduction was achieved, and that fewer side effects were encountered (Gilron et al., 2005; Hanna, O'Brien, & Wilson, 2008). Few, if any, level I studies compared a combination of an SNRI with a gabapentinoid against these agents individually or against a placebo. Until such evidence is forthcoming, the treating physician should attempt to treat each patient individually, taking into consideration the patient's age, comorbid conditions, and tolerance of side effects; medication cost; and evidence supporting the medication's efficacy.

GENERAL APPROACH TO THE PATIENT WITH PAINFUL NEUROPATHY

The principles of neurology are applicable to PP as well. The treating physician needs to take a detailed history, perform a physical examination, and localize the lesion in the nervous system. The patient's symptoms, the distribution of physical examination abnormalities, and the findings of

electrodiagnostic studies should narrow the range of diagnostic possibilities. Appropriate laboratory testing should then be used to identify the underlying cause.

Pain is a symptom whose presence should prompt the physician to identify and treat the underlying cause (Walid, Donahue, Darmohray, Hyer, & Robinson, 2008). Most practitioners would attempt to identify the underlying cause for a systolic blood pressure of 230 mm Hg, a pulse of 140 beats per minute, or a respiration rate of 36 breaths per minute. The same sort of due diligence needs to be paid to a person who reports significant pain. A patient who presents with new onset of "10/10" pain demands a more emergent and extensive workup than someone with a 20-year history of "2/10" pain. Even if no specific cause for the pain is identified, the physician should not assume that there is no cause and should never tell the patient that it is "all in your head." This leads to significant and often irreparable damage to the physician-patient relationship. Physicians who are uncomfortable managing "idiopathic pain" should refer these patients to a colleague who specializes in pain management.

The best possible outcomes occur when the treating physician can identify and eliminate the underlying cause of the NP process. However, the precise etiology often remains undetected despite extensive evaluations. Thus, "cures" are rarely achieved because most processes causing NP are not identified or cannot be eliminated entirely. Even when the underlying cause is identified, the underlying disease process may not be reversible. In such instances, treatments should be given that will retard or attenuate the disease process. If this is not possible, then the remaining course of action is to minimize the patient's symptoms and address any comorbid conditions. The patient should be informed that the goal is to maximize QOL and functional independence from need of assistance and pain, and minimize the effect of the disease.

When PPs are observed, there is usually some degree of small fiber dysfunction. The etiologies can be subdivided into toxic-metabolic derangements, autoimmune disorders, and traumatic injury (Portenoy, 1989; Vaillancourt & Langevin, 1999). Nervous system tissue, both central and peripheral, is particularly susceptible to toxic-metabolic derangements. Restated, "Nervous tissues malfunction when other tissues malfunction." Examples would include pancreatic insufficiency (e.g., diabetes mellitus), liver disease, thyroid disorders, and kidney dysfunction. Toxic-metabolic derangements would include diverse etiologies such as hypoxic-ischemic disorders, vitamin deficiencies, and external toxins, including alcohol and heavy metal poisoning. Table 6.1 shows the authors' recommended evaluation of a patient who presents with a PP, although these cited guidelines did not establish the highest level of evidence to warrant these recommendations, with the exception of DNA testing for suspected inherited neuropathy (England et al., 2009a, 2009b). These PP-causing conditions, their means of diagnosis, and their treatment are discussed more extensively in other chapters and will not be repeated here. Diagnostic testing should be performed only if that diagnostic test will change the patient's management.

Moreira et al. (2007) reported that patients with diabetes who have distal symmetrical diabetic polyneuropathy (DSDP) have an increased incidence of psychiatric disorders, especially anxiety and depression. In this cohort of 65 diabetic patients, anxiety disorders were present in 81.8% of those with DSDP and 60.0% of those without DSDP ($P = 0.01$). A current episode of major depression was present in 18.2% of patients with concomitant DSDP and 7.7% of those without DSDP ($P = 0.04$). Furthermore, the severity of the depressive symptoms correlated positively with the severity of DSDP symptoms ($r = 0.38$; $P = 0.006$), but not with the severity of diabetic symmetric peripheral neuropathy signs ($r = 0.07$; $P = 0.56$). The patient with PPs may have concomitant small myelinated and large fiber dysfunction as well, leading to comorbidities such as dysautonomia and gait impairment. Medications or assistive devices may improve the patient's QOL. For these reasons, the patient should be queried about any autonomic dysfunction (e.g., orthostatic hypotension). Questions regarding activities of daily living, such as ability to walk, bathe, and feed oneself, are also important. If a patient reports difficulty in these areas, then consultation with physiatry, occupational, and physical therapists is warranted.

Given the evidence that persons with PPs are at increased risk for comorbid conditions, the treating physician must screen for these disorders. Comorbid conditions amenable to treatment include major depression, anxiety, sleep disorders, and FM. There are written screening tools for all these disorders except for FM, which does require a physical examination. Although a psychiatric consultation would seem an obvious course of action, some patients are reluctant to consult a psychiatrist. Therefore, it is incumbent on the physician evaluating the patient with a PP to screen for depression. Few patients with PPs are not depressed after 6 months of constant pain. Uncomplicated, mild to moderate comorbid depression may be treated by a physician who is not a psychiatrist. Nonetheless, immediate psychiatric consultation would be indicated for patients expressing suicidal or homicidal ideation as well as for patients who do not respond to routine antidepressant therapy. Numerous screening tools are available for assessing the probability and severity of coexisting depression. Two such scales that have no restrictions on their use are the Hamilton-D and Zung depression rating scales (Depression Rating Scales, n.d.; Hamilton, 1960; Zung, 1965). Both of these scales may be completed by the patient at home before the visit or in short order when arriving for a consultation. A physician can address these issues by asking patients whether the pain condition has altered their mood in any way. This allows the patient a chance to report changes in behavior that may have been unmasked by the PP. This may change the physician's opinion regarding the choice of drug. For example, a patient with depression may respond better to treatment with an antidepressant than to agents without antidepressant properties. There is still some controversy as to whether the use of antidepressants prescribed for the treatment of unipolar depression can precipitate mania in persons who actually may have bipolar disorder (Bhagwagar, 2007). Until this issue is settled, prudence dictates that the physician counsel the patient to report any adverse symptoms with medication use, including symptoms of mania or hypomania. In such instances, referral to a psychiatrist for a definitive evaluation is recommended. The National Institute of Mental Health states that bipolar disorder has a prevalence of 2.6% of the population in the United States, whereas unipolar depression is found in 7% of men and 12% of women (Kessler,

Chiu, Demler, & Walters, 2005; Narrow, 1998; Weissman et al., 1996). These data suggest that approximately 10% of the population will have unipolar depression, which is four times as many as those with bipolar illness. One review from the United Kingdom noted that persons who were depressed were twice as likely to have cardiovascular disease as nondepressed persons (Tyrer, Lawrenson, MacRae, & Farmer, 2008). This report also noted that depressed persons were far less likely to be compliant with their medical regimen and more likely to refuse rehabilitation services. Although there is some controversy as to whether depressed persons have a worse outcome when afflicted with cardiovascular disease, it has a significant negative effect on a patient's QOL and should be treated when present.

Anxiety disorder is more prevalent than depression because it affects approximately 18% of the adult population in a given year (Kessler et al., 2005). Anxiety disorders encompass a variety of disorders, including panic disorder, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social anxiety disorder, phobias, and GAD. These entities are discussed in greater detail in general psychiatry textbooks. Patients with PPs may report these symptoms for the first time because the PP may unmask these disorders. The reason that this chapter mentions these disorders is that specific medications are effective for these conditions. For example, the TCA imipramine is prescribed for panic disorder and GAD, whereas clomipramine is the only TCA noted to be useful for treating OCD. Persons who prefer to begin using a TCA for treatment of a PP should be asked about symptoms of anxiety disorders because this information may affect the selection of the TCA. In contrast, SNRIs are effective for depression and anxiety disorders, although only duloxetine has the FDA indications for treatment of DPNP, depression, and GAD. Other agents, such as monoamine oxidase inhibitors and benzodiazepines, are also effective treatments for anxiety disorders (National Institute of Mental Health, 2018). Monoamine oxidase inhibitors and benzodiazepines have not been shown to be useful in the treatment of PP and should not be used for this indication. The treatment of PTSD remains controversial. Physicians should be aware that a patient who experienced a traumatic nerve injury may be experiencing PTSD. The patient should be questioned about the events surrounding this injury to ascertain whether PTSD might be present. Many patients, especially veterans, tend to underreport their PTSD symptoms. If PTSD cannot be excluded with confidence, then the patient should be referred to a psychiatrist specializing in PTSD.

Sleep disturbances are often reported by patients with polyneuropathies. Many patients with PPs have an inability to initiate or maintain sleep, which is a common symptom of anxiety and depression. Regardless of the underlying cause, lack of sleep usually worsens the underlying pain condition. Physicians should endeavor to improve the patient's sleep quality so that they feel rested on awakening in the morning. Although poor sleep may be a symptom of depression, other comorbid conditions may be responsible. Common causes encountered in patients include OSA and restless legs syndrome (RLS). The presence of a sleep disturbance can be assessed with the Epworth Sleepiness Scale (Epworth Sleepiness Scale, 1997). This is an eight-item questionnaire in which patients rate their "likeliness of dozing" on a scale from 0 to 3, wherein the numbers indicate no chance (0), slight chance (1), moderate chance (2), and high chance (3) of dozing. These eight situations are sitting and reading, watching television, sitting inactive in a public place, riding as a passenger in a car for 1 hour, lying down to rest in the afternoon, sitting and talking, sitting quietly after a lunch without alcohol, and being stopped by traffic in a car for a few minutes. As with the previously mentioned scales, the patient can complete this before the visit or at the time of the visit. A total score of 9 or greater indicates a high probability that a sleep disturbance is present but does not specify the cause. Additional history helps to narrow the differential diagnosis. Such questions should attempt to distinguish between OSA and RLS.

Population-based studies in North America suggest that 15%–30% of males and 10%–15% of females suffer from OSA when defined broadly as an apnea-hypopnea index greater than five events per hour of sleep. When more stringent guidelines are applied (i.e., over 15 events per hour or over five events plus symptoms), then the prevalence is approximately 15% in males and 5% in females (Peppard et al., 2013; Young et al., 2009). Both the incidence and the prevalence of this disorder are likely to increase over time as the average American's body mass index increases. Patients with adult-onset diabetes mellitus, a common cause of PP, often have an elevated body mass index and are at greater risk for symptomatic OSA. A simple screening tool, neck circumference, has been shown to be highly sensitive for detecting OSA. A neck circumference of greater than 16 inches in a woman or greater than 17 inches in a man correlates with an increased risk of OSA (Davies & Stradling, 1990). In addition, increasing neck circumference has been shown to correlate with the severity of apnea (Flemons, Remmers, Whitelaw, & Brant, 1992; Katz, Stradling, & Slutsky, 1990). Neck circumference should be assessed in all patients who report nonrefreshing sleep. Any woman with a neck circumference of greater than 16 inches (≈40 cm) or a man with a neck circumference of greater than 17 inches (≈43 cm) should be referred for a sleep study to evaluate for OSA. OSA is associated with an increased risk of hypertension and cardiovascular disease (Lanfranchi & Somers, 2001).

An incompletely understood condition, RLS results in a compulsion to move one's legs, especially during or immediately before sleep (National Institute of Neurological Disorders and Stroke, 2020). Patients who report sleep disturbances should be asked about RLS because one potentially treatable cause is anemia. RLS is often associated with chronic diseases, such as renal insufficiency, diabetes mellitus, Parkinson disease, and polyneuropathy. Treating the underlying condition often provides relief from RLS symptoms (National Institute of Neurological Disorders and Stroke, 2020). DA agonists, such as ropinirole and benzodiazepines, are effective, whereas RLS is worsened by DA antagonists and phenytoin.

FM is a chronic pain disorder that is defined by the American College of Rheumatology as widespread pain lasting at least 3 months in combination with pain at 11 or more of 18 specific tender point sites on the body (Wolfe, Smythe, & Yunus, 1990). A different definition proposed by Pope and Hudson (1991) also considers FM to be present in the absence of trigger points if at least four of the following six comorbid conditions are present: headaches, generalized

fatigue, sleep disturbance, neuropsychiatric complaints, numbness or tingling sensations, and irritable bowel symptoms. This subject was recently reviewed in detail by Arnold (2008). FM tends to respond to the same types of medications that are useful for the treatment of NP (Dworkin & Fields, 2005). Only two medications with a PP indication are also FDA approved for the treatment of FM: pregabalin and duloxetine. Although many practitioners consider FM a "dubious disease," it is unlikely that the FDA would have approved these medications for a "nonexistent" condition. Even if the treating physician does not "believe in" FM, this condition will have a significant negative effect on QOL. Given that FM is amenable to treatment, an assessment for myofascial trigger points should be part of every neuromuscular specialist's examination.

Certain medications may increase the risk of other comorbid conditions. For example, some agents, such as TCAs and pregabalin, have been associated with weight gain. As such, these agents may not be the drug of choice in a patient with adult-onset diabetes mellitus and a PP who has a high body mass index and sleep apnea. The FDA requires that all SSRIs and SNRIs display a boxed warning that the risk of suicide may be increased in persons 18 to 24 years old. As such, duloxetine may not be the drug of choice in an 18-year-old patient who reports a history of suicidal ideation. Anticonvulsant agents, such as the gabapentinoids, may not necessarily be a safer alternative because the FDA requires a warning label on all antiepileptic drugs (AEDs) because their use has been associated with increased suicidal ideation (US FDA, 2008). Additionally, gabapentinoids are newly emerging drugs of abuse and have since been rescheduled by the Drug Enforcement Administration as a Schedule V controlled substance (Peckham, Ananickal, & Sclar, 2018). This article summarized an FDA review of 199 clinical trials of 11 AEDs. The risk of suicidal behavior or thoughts was nearly doubled for patients receiving AEDs versus placebo (0.43% vs. 0.24%), leading to approximately one additional case of suicidality for every 500 patients treated with AEDs instead of placebo. However, there was no statistically significant difference in the number of actual or "completed" suicides when comparing AEDs (four cases) versus placebo (zero cases). Nonetheless, the FDA requires a warning label on all anticonvulsants, including the ones used for the treatment of NP: pregabalin, gabapentin, carbamazepine, oxcarbazepine, and phenytoin. This list also includes the benzodiazepines clonazepam and chlorazepate, which may be prescribed off-label for RLS and anxiety disorders. Furthermore, Dworkin et al. (2010) reported that there were insufficient data to give the AEDs, other than the gabapentinoids, a grade A recommendation for the treatment of NP. For these reasons, AEDs other than the gabapentinoids should not be used as first-line agents for the treatment of PP.

Iatrogenic causes of PPs need to be considered in your patient evaluation. Several chemotherapy agents (Mols, Beijers, Vreugdenhil, & van de Poll-Franse, 2014), antimicrobial agents (Snavely & Hodges, 1984), antiretroviral agents (Dalakas, 2001; Pardo, McArthur, & Griffin, 2001), and phenytoin (Mochizuki, Suyehiro, Tanizawa, Ohkubo, & Motomura, 1981) have been implicated in causing NPs/PPs. If identified as possible causative agent, it is recommended to stop that medication and provide a suitable alternative based on medical necessity.

In summary, comorbid conditions have a significant negative effect on the patient's QOL. Certain conditions, such as OSA, may increase the patient's risk of hypertension and cardiovascular diseases. Also, there is a significant overlap in the symptoms of pain, psychiatric comorbidities, and FM. Given these associations, all neuromuscular consultants should be comfortable identifying and treating these conditions. This will allow the treating physician to select an agent that will treat the NP as well as any other comorbid conditions that may be present.

"FIRST-LINE" NEUROPATHIC PAIN TREATMENTS

The available medical evidence and expert opinion support the use of the gabapentinoids, topical lidocaine, TCAs, and SNRIs as first-line agents for the treatment of the average person with NP. However, these medications differ in terms of their mechanism of action, additional benefits, side effects, and adverse effects. A summary of these data appears in Tables 6.5 to 6.7, 6.11, and 6.12. Because treatment must be individualized, the risks and benefits of each treatment should be discussed so that the patient makes an informed decision. A brief discussion of each class of medication follows. Although the important data on these medications have been summarized, all practitioners should be familiar with all the information regarding the risks and benefits for the medications that they are prescribing.

TRICYCLIC ANTIDEPRESSANTS

A significant advantage of TCAs is that they are among the least expensive medications available for the treatment of pain in polyneuropathy. It is believed that these agents act by inhibiting the reuptake of NE and 5-HT. Their proposed mechanism of action is thought to be similar to that of the SNRIs, such as duloxetine. Other authors consider these agents to have differing effects on 5-HT and NE inhibition that are reported according to "selectivity ratios" (Po, 1999). Nonetheless, TCAs have numerous side effects that may limit their clinical utility. Of the TCAs, nortriptyline may be considered to have the most NE reuptake inhibition and the least 5-HT reuptake inhibition. Amitriptyline and imipramine would be classified as "balanced," and chlomipramine would have the most 5-HT reuptake inhibition and the least NE reuptake inhibition. TCAs may also be classified as secondary or tertiary amines. In general, the tertiary amines tend to affect both NE and 5-HT reuptake inhibition, whereas the secondary amines are less "balanced" and act primarily as NE reuptake inhibitors. However, the "balanced" tertiary amines are far more likely to produce anticholinergic side effects and orthostatic hypotension than are the secondary amines. Therefore, while the tertiary amines are more likely to be effective, based on the current models of NP treatment, they are more likely to produce side effects. Dworkin et al. (2007, 2010) recommend that secondary amines be used in preference to the tertiary amines. However, younger persons who are more tolerant of side effects may benefit from the tertiary amines, especially those with difficulty initiating and maintaining sleep. Otherwise, the secondary amines should be used preferentially because they have fewer adverse effects and can be tolerated more easily in older patients.

Table 6.11 Nonnarcotic Medications and Dosing

	Medication	First Dose (mg)[a]	Increase by (mg/week)	Maximum Daily Dose (mg)	Adequate Trial Length
Tricyclic Antidepressants[b]	Nortriptyline[c]	10–25 qhs	10–25 qhs	75–150	6–8 (2 weeks at max dosage)
	Desipramine[c]	10–25 qhs	10–25 qhs	75–150	6–8 (2 weeks at max dosage)
	Amitriptyline[c]	10–25 qhs	10–25 qhs	75–150	6–8 (2 weeks at max dosage)
	Imipramine[c]	10–25 qhs	10–25 qhs	75–150	6–8 (2 weeks at max dosage)
Selective Serotonin and Norepinephrine Reuptake Inhibitors	Duloxetine [d]	20–30 qhs	20–30 qhs	60–120	4–6 weeks
	Venlafaxine	37.5 qhs to bid	37.5–75	225	4–6 weeks
Gamma Aminobutyric Acid Analogs	Gabapentin	100 qhs to bid	100–300[e]	600 tid[f]	3–8 (2 weeks at max dosage)
	Pregabalin	50–75 bid	150 mg q 3–7 days	600	4 weeks
Other	Lidocaine patch[c]	3 total q12h	NA		3–4 weeks

Sources: Célèrier, E., Laulin, J. P., Corcuff, J. B., Le Moal, M., & Simonnet, G. (2001). Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. *Journal of Neuroscience*, *21*, 4074–4080; Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., et al. (2007). Pharmacological management of neuropathic pain: Evidence-based recommendations. *Pain*, *132*, 237–251; Dworkin, R. H., O'Connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L., et al. (2010). Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings*, *85*(Suppl. 3), S3S14; Huizinga, M. M., & Peltier, A. (2007). Painful diabetic neuropathy: A management-centered review. *Clinical Diabetes*, *25*, 6–15; VHA Pharmacy Benefits Management Strategic Healthcare Group, and the Medical Advisory Panel, Duloxetine in painful diabetic neuropathy and fibromyalgia [article online]. (2020). Retrieved from https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp

[a]Starting dose and upward titration should be "lower and slower" in the elderly.
[b]Consider another agent if no response at 75 mg qhs for 2 weeks.
[c]Not US Food and Drug Administration approved for the treatment of any specific painful polyneuropathy.
[d]Duloxetine showed no significant difference between 60 mg and 120 mg for diabetic peripheral neuropathic pain.
[e]Some authors recommend a more rapid dose escalation.
[f]Some authors recommend a maximum dosage of 1200 mg po tid.
bid, two times a day; *max*, maximum; *NA*, not applicable; *qhs*, every night at bedtime; *tid*, three times a day.

Because TCAs have been in use for several decades, their side effect profile and long-term effects are well known. They are also among the least expensive medications known to be effective for the treatment of NP. However, their side effect profile limits their use. These side effects include anticholinergic symptoms, such as dry mouth, constipation, urinary retention, blurred vision, and confusion. Other significant side effects include weight gain, orthostatic hypotension, and arrhythmias. TCAs may cause unwanted side effects on the cardiac conduction system, such as lengthening of the PR interval and first-degree heart block (Burckhardt, Raeder, Muller, Imhof, & Neubauer, 1978). Patients who have first-degree heart block while using TCAs can progress to more significant degrees of heart block (Kantor, Bigger, Glassman, Macken, & Perel, 1975). Furthermore, a large, retrospective cohort analysis reported an increased risk of sudden cardiac death at doses of 100 mg daily or greater (Ray, Meredith, Thapa, Hall, & Murray, 2004). This led to a recommendation that TCAs should not be prescribed to persons with known ischemic cardiac disease. It has also become standard practice to order an electrocardiogram before initiating treatment and during TCA dose escalation in all patients older than 40 years (Dworkin et al., 2003). A second electrocardiogram is prudent when the patient will be using a dose of 100 mg daily or greater. Given the previously cited association of depression and cardiovascular disease, it may not be prudent to prescribe a TCA to anyone who is depressed and has more than one risk factor for cardiovascular disease. In such instances, duloxetine may be preferable because it is FDA approved for the treatment of unipolar depression, as maintenance therapy for unipolar depression, and as a treatment for DPNP. TCAs should be used sparingly in the elderly because they may adversely affect cognition and gait, which puts the patient at increased risk for falling (American Geriatric Society Beers Criteria® Update Expert Panel, 2019). TCAs should also be used only in persons who can tolerate their numerous side effects. The other issue with TCAs is that they have a narrow therapeutic window. Patients who are depressed sometimes attempt to commit suicide by taking an overdose of TCAs. Therefore, it is advisable to prescribe less than 1 g in total of the agent when initiating therapy. The patient should also be warned about the risks inherent in a TCA overdose.

Table 6.12 Medication/Class, Side Effects, Precautions, and Safety

Medication/Class	Common Side Effects	Relative Contraindications	Benefit-to-Risk Ratio[a]
Tricyclic antidepressants	Anticholinergic effects,[b] weight gain	Cardiac disease, suicidal ideation Depression? Cognitive impairment	Second tier[c]
Duloxetine	Nausea, headache, dry mouth	Renal or liver impairment	First tier
Pregabalin[d]	Lethargy/peripheral edema	Renal impairment	First tier
Lidocaine patch	Local irritation	Previous allergy	First tier
Tramadol[e]	Similar to opioids	History of substance abuse Cognitive impairment (initially) Suicidal ideation	Third tier
Opioids	Nausea, anticholinergic effects	Same as above	Third tier

Sources: Célèrier, E., Laulin, J. P., Corcuff, J. B., Le Moal, M., & Simonnet, G. (2001). Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. *Journal of Neuroscience*, *21*, 4074–4080; Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., et al. (2007). Pharmacological management of neuropathic pain: Evidence-based recommendations. *Pain*, *132*, 237–251; Dworkin, R. H., O'Connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L., et al. (2010). Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings*, *85*(Suppl. 3), S3S14; Huizinga, M. M., & Peltier, A. (2007). Painful diabetic neuropathy: A management-centered review. *Clinical Diabetes*, *25*, 6–15; VHA Pharmacy Benefits Management Strategic Healthcare Group, and the Medical Advisory Panel, Duloxetine in painful diabetic neuropathy and fibromyalgia [article online]. (2020). Retrieved from https://www.pbm.va.gov/PBM/clinicalguidance/drugmonographs.asp

[a]The authors' assessment of which agents are likely to provide the best level of pain relief with the fewest side effects.

[b]Anticholinergic side effects include dry mouth, dry eyes, cognitive impairment (especially in the elderly), constipation, urinary retention, and cardiac effects.

[c]Tricyclic antidepressants have a narrow therapeutic window, but their long-term side effects are better established than with tramadol or opioids.

[d]These medicines have US Food and Drug Administration approval for the treatment of pain associated with diabetic polyneuropathy. Others in their class do not have this approval and are not discussed here.

[e]This medicine inhibits serotonin reuptake and should be used cautiously in combination with tricyclic antidepressants, selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and triptans.

There are various recommended starting doses and dosing regimens for TCAs. One should use the lowest dose that maximizes the degree of pain control while minimizing side effects. In patients who report being prone to side effects, treatment should be started at 10 mg by mouth at bedtime. In this manner, the patient will likely be asleep when the medication reaches its peak plasma level such that the side effects are minimized. Otherwise, the starting dose should be initiated in the range of 10 to 25 mg at bedtime. The dose can be titrated by 10 to 25 mg every 1 to 2 weeks until an effective dose is reached. Most patients who will respond to TCAs usually require a dose of 75 mg or less. If a patient reports no response after using a TCA at 75 mg for 2 weeks, then another medication should be considered. Those who do respond can have their dose increased slowly until a maximum dose of 150 mg daily is reached. Dworkin et al. (2007) stated that the dose can be increased beyond this range if the serum level of the medication and its metabolite is less than 100 ng/mL.

In summary, TCAs have the advantage of being inexpensive, with a well-established side effect profile and over 50 years of widespread use. However, they have a narrow therapeutic window and have numerous undesirable side effects. Unless cost is an issue, the newer agents may be preferable because of their wider therapeutic window and fewer side effects.

SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs represented a significant development in the treatment of NP. Unlike TCAs, SNRIs have far fewer effects on neurotransmitters other than 5-HT and NE. SNRIs have a wider therapeutic window and are less likely to cause side effects in case of an overdose. They also have the advantage of faster onset, more rapid titration, and a wider variety of FDA-approved indications. There are two main SNRIs available on the market: venlafaxine and duloxetine. However, only duloxetine has received FDA approval to be marketed for the treatment of DPNP. The limiting side effects include nausea, dizziness, dry mouth, and erectile dysfunction. These side effects are not unique to SNRIs because they occur with SSRIs as well.

Venlafaxine tends to act more as an SSRI at the lower end of its dosage range and as an SNRI at higher doses (Dworkin et al., 2007). It also has weak DA reuptake inhibition at the higher end of the dosage range. Despite the fact that it does not have FDA approval for the treatment of pain in polyneuropathy, it does have FDA approval for the treatment of MDD, GAD, social anxiety disorder, and panic disorder in adult patients (Effexor, 2019). Because these are commonly encountered comorbid conditions, venlafaxine should remain a treatment option for patients with PP. Although duloxetine may have some advantages, venlafaxine should be considered for patients who have coexisting panic disorder or social anxiety disorder because duloxetine has not been FDA approved for these indications.

Duloxetine is a reasonable first choice for the treatment of PP if cost is not a factor. It has the advantages of once-daily dosing, a rapid titration schedule, and FDA approval for the treatment of DPNP. It is also FDA approved for the treatment of MDD and FM, two commonly encountered comorbid

conditions associated with pain as a result of polyneuropathy. It also has the advantage of causing no statistically significant weight gain. Nonetheless, it does have limitations. It has been shown to cause a slight elevation in blood glucose and blood pressure. Given that it is metabolized by both the kidney and the liver, this agent should be given cautiously to persons with hepatic or renal impairment (Cymbalta, 2020).

GABAPENTINOIDS

The two medications in this class that are commonly used for the treatment of NP are gabapentin and pregabalin. Their use in NP has become widespread because these agents are generally well tolerated, are easily titrated, have few drug interactions, and do not require laboratory monitoring. However, cost may be a limiting factor for some patients. Although the basic GABA frame is the same in both compounds, they have somewhat different structures in that the beta carbon has a different side chain. Gabapentin has five additional carbons attached to form a ring structure, whereas pregabalin has a hydrogen atom and a propyl side chain. Unlike pregabalin, gabapentin has not received FDA approval for the treatment of DPNP. Although one well-designed clinical trial showed that gabapentin had a statistically significant benefit over placebo for the treatment of pain associated with diabetic polyneuropathy, the effects were modest in that there was a 1-point reduction on an 11-point rating scale at a daily dose of 1800 mg after 2 weeks (Backonja et al., 1998). Neither longer treatment durations nor higher doses showed any significant benefit. Gabapentin's side effects include weight gain, cognitive impairment, lower extremity swelling, excess sedation, and suicidal ideation (Neurontin, 2020). Although pregabalin and gabapentin are chemically related, they have different pharmacokinetic properties (Miller & Bockbrader Chapel, 2006). Preclinical studies with pregabalin and gabapentin demonstrated similar anticonvulsant pharmacologic profiles, but pregabalin showed three- to six-fold greater potency as an anticonvulsant. Pregabalin, unlike gabapentin, exhibits linear absorption, with the observed maximum plasma drug concentration (C_{max}) and area under the plasma drug concentration–time profile increasing proportionally with dose. In contrast, the extent of gabapentin absorption decreases with increasing dose. Gabapentin absorption is saturable, leading to a nonlinear pharmacokinetic profile (Fudin, 2015). This may be one possible explanation as to why gabapentin was not more effective in higher doses in the trial previously referenced. The FDA approved pregabalin for the treatment of DPNP based on two trials. One trial of 173 patients showed that pregabalin 100 mg three times daily by mouth for 8 weeks was both safe and effective in decreasing pain associated with DPNP compared with placebo. Pregabalin also improved mood, sleep disturbance, and QOL, with minimal side effects (Rosenstock, Tuchman, LaMoreaux, & Shama, 2004). A second, 8-week-long study of 338 patients stratified by creatinine clearance to receive pregabalin at a total of 75 mg, 300 mg, or 600 mg in three divided doses showed that the two higher doses were more effective than placebo (Lesser, Sharma, LaMoreaux, & Poole, 2004). Nevertheless, a recent report indicated that pregabalin was no more effective than placebo for the treatment of painful HIV neuropathy (Simpson et al., 2010).

No statistically significant difference in efficacy between the doses of 100 mg three times daily by mouth and 200 mg three times daily by mouth was detected, whereas adverse events were more common at the higher doses. As was observed in the duloxetine studies, pain relief was noted as early as 1 week after the initiation of treatment. A more recent publication analyzed seven separate trials using pregabalin for the treatment of DPNP and noted it to be effective (Freeman, Durso-DeCruz, & Emir, 2008). Given these data, pregabalin should be preferred over gabapentin when treating PP. The most common side effects of pregabalin include dizziness, ataxia, and somnolence (Block, 2001). Pregabalin and gabapentin are controlled substances due to postmarketing surveillance identifying gabapentin misuse or abuse of these agents in conjunction with opioid abuse to enhance the CNS depressive effects of opioids (Peckham et al., 2018). Pregabalin is a Schedule V controlled substance because some patients with a history of alcohol or other substance abuse may be at increased risk for addiction to pregabalin. Despite these caveats, pregabalin may be considered a safe and effective treatment for DPNP with proper patient selection.

TOPICAL LIDOCAINE

Topical lidocaine has FDA approval for the treatment of PHN. However, Meier et al. showed that this agent could be used effectively in persons with a variety of peripheral NP conditions and allodynia, including a subgroup without PHN (Meier, Faust, Huppe, & Schmucker, 2004; Meier et al., 2003). When prescribed according to the package insert, the only side effects are the result of local skin irritation. Furthermore, the medication tends not to be absorbed systemically to any significant degree when the dose of three patches per day in a 12-hour-on/12-hour-off regimen is used or when four patches are used in an 18-hour period (Gammaitoni & Davis, 2002). The main disadvantages of this therapy were the inability to dose the medication continuously and the issue that the patch must cover the area involved. Previously, cost was a major disadvantage. However, the availability of generic alternatives and the addition of an over-the-counter lidocaine 4% patch has significantly reduced the price. For the treatment of PHN, the lidocaine patch can be cut into the shape of the affected dermatome. As a practical matter, this medication should be reserved for patients with neuropathies that have not progressed much beyond the ankles bilaterally and who do not require continuous analgesia. In addition, the use of topically applied local anesthetics (e.g., lidocaine) has been shown in multiple studies to be effective in managing symptoms when applied topically. However, more randomized controlled trials will be required to establish efficacy and safety (Casale, Symeonidou, & Bartolo, 2017).

"SECOND-LINE" NEUROPATHIC PAIN TREATMENTS

The other medications that have a grade A recommendation for the treatment of NP include the opioids and their related compounds. Opium and its derivatives have been used for the treatment of pain for millennia, although there

is some controversy regarding the use of chronic opioids for the treatment of NP. Opioid advocates promulgate these agents as effective, relatively inexpensive, and potent analgesic medications. However, the opioid crisis reinforced the concept that these agents should be used sparingly, in specific circumstances and for limited duration. While opioids have a role in the immediate postoperative period and for analgesia in terminally ill patients, they should be used sparingly, if at all, in the management of PP. Common side effects include euphoria, drowsiness, nausea, vomiting, constipation, miosis, and, in rare cases, respiratory depression.

Methadone is an analgesic with multiple mechanisms of action: opioid agonist, NMDA receptor antagonist, and serotonin and NE reuptake inhibitor. Two of the specific mechanisms of methadone that provide significant NP relief are NMDA receptor antagonism and NE reuptake inhibition. Although methadone is useful in treating multiple pain syndromes with various mechanisms of action, it is not a first-line agent for the treatment of chronic pain (Dowell, Haegerich, & Chou, 2016). It is an alternative long-acting opioid analgesic that may be useful in managing chronic pain in select patients. For patients requiring high-dose opioids that were unsuccessful in managing pain, converting to methadone is associated with improved pain relief at methadone doses as low as 10% of the calculated equianalgesic dose (Ripamonti et al., 1998). For safety, methadone should be initiated and adjusted by or in consultation with a practitioner who has the relevant knowledge and expertise. The principles used in dosing of methadone are different from other opioids because of the agent's unique pharmacokinetic and pharmacodynamic properties. Dose titration should occur after at least 5–7 days as steady-state kinetics require up to 7 days to observe its full effects. Careful considerations must be given to potential drug interactions: cytochrome P450, concurrent medications with risk of QTc prolongation, and concomitant CNS and respiratory depressants (e.g., benzodiazepines) (Bruera & Sweeney, 2002). Methadone is considered to be safe in patients with renal and/or hepatic impairment, but caution should be exercised with hypoalbuminemia due to the highly protein bound nature of methadone.

There are several methods available that use conversion ratios to initiate or titrate methadone, although no single method is considered superior. Titration should be based on patient response and not solely based on equianalgesic dosing tables. Finally, monitoring ECG for QTc interval prolongation is recommended at baseline and throughout treatment based on dosing thresholds and if certain clinical situations occur (Barbosa Neto, Arrais Garcia, & Santos Garcia, 2015; Chou et al., 2014; Krantz, Martin, Stimmel, Mehta, & Haigney, 2009).

Levorphanol is a synthetic strong opioid that is a potent NMDA receptor antagonist, mu, kappa, and delta opioid receptor agonist, as well as an inhibitor of serotonin and NE reuptake. As it bypasses hepatic first-pass metabolism, it is not subjected to numerous drug interactions (Gudin, Fudin, & Nalamachu, 2016; Reddy, Ng, Mallipeddi, & Bruera, 2018). As with methadone, its multimodal profile might prove effective for pain syndromes that are refractory to other opioid analgesics such as central pain and NP, as well as opioid-induced hyperalgesia. Notwithstanding the additional benefit of no QTc prolongation, the cost of treatment has severely limited this agent's use in clinical practice.

Tapentadol is a central-acting oral analgesic with combined opioid and noradrenergic properties, which make it potentially suitable for NP. Tapentadol was proven to be effective in relieving NP in diabetic peripheral neuropathy and in chronic low back pain. Observational studies also reported a reduction in chemotherapy-induced peripheral neuropathies (Freo, Romualdi, & Kress, 2019).

The review by Dworkin et al. (2007) makes several important points regarding opioid management. The first is that multiple trials have shown that their efficacy is comparable to that of the other medications previously discussed, but they tend to produce more side effects. Moreover, these side effects may persist throughout the duration of treatment. As such, the benefit-to-risk ratio is not as favorable. Notably, the long-term safety of long-term opioid therapy has not been evaluated systematically. There is increasing evidence that long-term opioid use may result in clinically significant alteration of both the hypothalamopituitary-adrenal and the hypothalamopituitary-gonadal axes, resulting in suppression of luteinizing hormone, follicle-stimulating hormone, testosterone, estrogen, and cortisol (Abs et al., 2000; Daniell, 2002; Finch, Roberts, Price, Hadlow, & Pullan, 2000; Lee, Ludwig, & Duerksen, 2002; Mendelson, Meyer, Ellingboe, Mirin, & McDougle, 1975; Paice, Penn, & Shott, 1996). There is also increasing evidence, both clinical and preclinical, that long-term opioid use may lead to immunosuppression (Peterson et al., 1990; Risdahl, Khanna, Peterson, & Molitor, 1998; Roy & Loh, 1996). For all of these reasons, patients with neuropathies as a result of autoimmune disorders should be counseled about this potential side effect. There is also some evidence to suggest that chronic opioid use can induce hyperalgesia (Angst & Clark, 2006; Mao, 2002). One report stated that this phenomenon can occur during the initial treatment with a high-dose opioid (Célèrier, Laulin, Corcuff, Le Moal, & Simonnet, 2001). Although this phenomenon has not been conclusively demonstrated in patients with chronic NP, its presence may make it difficult to distinguish from the phenomenon of tolerance or from an exacerbation of the underlying pain disorder. Given these potential adverse outcomes with long-term opioid use, all patients who require this treatment should be referred to pain management experts.

It is unfortunate that the terms *dependence*, *addiction*, and *tolerance* are used interchangeably by patients as well as by some health care providers. Although these entities may be interrelated, they are not identical (Nash, 2020). Dependence on a drug indicates that the body has come to rely on this agent for normal functioning such that lack of access to the drug will precipitate withdrawal symptoms. Opioid withdrawal symptoms may include sweating, tremor, vomiting, anxiety, insomnia, and muscle pain. All persons who are treated with opioids for a period will have dependence and withdrawal if they are denied access to the medication. As an example, a patient could be treated for tachycardia with a beta-blocker because the patient is unable to have a normal heart rate without that medication. That person is, in effect, dependent on the beta-blocker. If that person is admitted to a hospital without access to a beta-blocker, withdrawal symptoms, such as tachycardia, are likely to recur. However, it would be inappropriate to state that this patient was "addicted" to the beta-blocker.

Tolerance refers to the fact that escalating doses will be needed over time to achieve the same clinical effect. Some

patients even have a cross-tolerance, in which prolonged use of one opioid results in a similar effect when using other opioids. Dose escalation is to be expected when prescribing opioids for the treatment of chronic pain. Dependence and tolerance should be anticipated by both the treating provider and the patient.

Addiction is an entirely different matter. Although exposure to a substance that induces tolerance and dependence is a prerequisite, addiction is not inevitable. Addiction appears to have a biochemical basis linked to the reward system in which DA is an important neurotransmitter. This system reinforces behaviors that are pleasurable because such behaviors tend to enhance survival. This is one explanation as to why humans tend to crave calorie-dense foods. Much as chronic NP can be viewed as a protective mechanism that has gone awry, there is increasing evidence of a genetic predisposition to addictive behavior. This is believed to result from pathologic alterations in this reward system. Addiction involves physical and psychological dependence separate from the need to avoid withdrawal symptoms. Addiction almost inevitably causes physiologic, chemical, and anatomic changes in the brain, along with behavioral changes. Addiction develops after an initial exposure to the addicting substance or activity. That initial exposure must occur for addiction to develop, but the exposure does not always lead to addiction. Therefore, some children of alcoholic parents deliberately avoid alcoholic beverages. Addictions lead to repeated behavioral problems, consume a lot of time and energy, and are marked by an increasing obsession with the substance. Furthermore, the cycle of quitting the addictive behavior, going through withdrawal, and relapsing may become self-reinforcing (Greene & Chambers, 2015). However, not all addictions are illegal or self-destructive. Many people are addicted to coffee and experience withdrawal symptoms if they are denied access to it. Despite this "caffeine dependence," there is no adverse effect on their professional or personal lives. Destructive addiction occurs when there is an adverse effect on the affected person's life. Addicted individuals may be willing to risk their family, their career, or their reputation to obtain the drug. In contrast, pseudo-addiction occurs when pain is undertreated. Patients may exhibit signs of drug-seeking behavior with fixation on obtaining medications ("clock watch") that resolve once pain is adequately treated. Pseudo-addiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.

Despite these advances in the understanding of addiction, the laws that govern US society often treat addiction as a crime rather than a disease entity. This has led to a hodgepodge of regulations that vary from state to state. There is a spirited debate in the medical community as to whether physicians are reluctant to prescribe opioid medications because they fear legal prosecution or enabling an addict. There seems to be a consensus among the public that pain needs to be treated, but that addicts and those who enable them should be punished. Although there are numerous guidelines and recommendations regarding how to distinguish addicts from nonaddicts, there is no perfect test. Further, the presence of an addiction should not prevent a person from receiving treatment. Addicts with chronic pain requiring opioids need to be followed very closely by a practitioner or a group of practitioners well versed in the use of opioids for pain management and well acquainted with the local and federal laws regarding prescribing opioids. As a practical matter, this usually involves a multidisciplinary pain clinic that can coordinate written agreements, perform drug testing where indicated, and arrange for the necessary and appropriate ancillary services. Few neuromuscular practitioners have the requisite time, expertise, and support staff to ensure that these guidelines are followed. Nonetheless, clinicians should not be deterred from prescribing appropriate opioid therapy in accordance with the World Health Organization's (2020) "Pain Ladder." This is a three-step tiered approach that begins with nonopioids and escalates to opioid use. Although this approach was developed for cancer pain, the basic principles may be used in any painful condition, as noted in Table 6.11. This table incorporates evidence-based NP treatment guidelines (Célèrier et al., 2001), the use of duloxetine (VHA Pharmacy Benefits Management Strategic Healthcare Group, 2020), opioid dosing guidelines (Agency Medical Directors Group, 2010), and a comparison of opioid potency (Galvagno, Correll, & Narang, 2007). The only modification to the World Health Organization recommendation is that opioids are often required for moderate to severe acute pain. Practitioners should not withhold opioids from such patients because the goal of acute pain control is of paramount importance. Opioids may be required for the treatment of moderate to severe acute pain but should be used with caution in other situations. In the era of the opioid epidemic, one should define clear objective functional goals for pain control and medication titration.

MEDICAL MARIJUANA

Marijuana consists of dried material from the *Cannabis sativa* plant (a.k.a. Indiana Hemp) from the leaves, stems, and flower buds. Marijuana consists of more than 421 components and 60 pharmacologically active cannabinoids. Marijuana contains tetrahydrocannabinol (THC), cannabidiol (CBD), and other cannabinoids. THC is the active ingredient sought after for its psychoactive effects. The two best-described cannabinoids are THC and CBD. These substances are highly lipophilic, which leads to storage in adipose tissue, liver, muscles, and spleen and redistributes into the user's blood stream long after ingestion (Oberbarnscheidt & Miller, 2017).

Medical marijuana as defined by state laws is available in herbal form utilizing dried parts of the cannabis plant (only in some states), and essentially the same form that is sold illicitly. Medical marijuana is used in the general population for smoked consumption. Over recent decades, marijuana has become significantly more potent by cross-breeding different strains, initially 2% THC and now as much as 20%–25% per plant yield (Oberbarnscheidt & Miller, 2017).

Most literature addresses the two most common cannabinoids, THC and CBD. A systematic review and meta-analysis of 18 double-blind randomized placebo-controlled trial of cannabis and cannabinoid treatments for chronic pain reported that cannabis and cannabinoids appear to reduce pain intensity (Martin-Sanchez, Furukawa, Taylor, & Martin, 2009). Another six double-blind randomized controlled trials (n = 226) studied the use of medical cannabis in NP. All six studies reported a statistically significant benefit in terms of

pain relief (Deshpande, Mailis-Gagnon, Zoheiry, & Lakha, 2015). Another systemic review identified 28 studies (27 placebo controlled, 1 treatment controlled) of cannabis in a total of 2454 participants with chronic pain. This review included NP, cancer pain, diabetic neuropathy, FM, and HIV-associated sensory neuropathy. This meta-analysis generally reported improvements in pain measures with cannabis and cannabinoids (Whiting et al., 2015).

ANCILLARY TREATMENTS

Little EBM literature supports the utility of occupational and physical therapy for patients with PP (American Diabetes Association, 2019). Nonetheless, these allied health professionals have been of invaluable assistance in improving the QOL of patients with PP. Physical therapy, or physiotherapy, is an allied health profession that is dedicated to the development, maintenance, and restoration of maximal movement and functional ability throughout the patient's life. There are many subspecialties within physical therapy, including cardiopulmonary, geriatric, neurologic, orthopedic, and pediatric. However, most neurologic and geriatric physical therapists tend to focus on CNS disorders rather than PNS disorders. Nonetheless, these subspecialties as well as nonsubspecialty physical therapists are skilled in gait and balance assessment. As such, a physical therapy consultation should be suggested to any patient with a gait disorder. Occupational therapists focus on maximizing a person's health and well-being in the activities of daily living by modifying the environment or adapting the activity. Occupational therapists are especially skilled at evaluating tasks that involve the use of the patient's hands and hand-eye coordination. Thus, the authors recommend an occupational therapy consultation for all patients who have neurologic deficits affecting their hands, their activities of daily living, or their hand-eye coordination. Both allied health professions bring a valuable perspective to the management of a patient with PP. For these reasons, occupational therapy and physical therapy consultations are generally beneficial for all patients with polyneuropathies, painful or otherwise.

CONCLUSION

The treatment of PPs remains controversial and is an inexact science. Optimal outcomes are achieved when a physician-patient relationship based on mutual respect is established at the outset. The best outcomes occur when the underlying cause of pain is identified and removed. However, this is rarely achieved and therefore management of the condition is the norm. EBM has provided some guidelines regarding the medications that are most likely to have a beneficial outcome for the patient. The identification and treatment of all comorbid conditions will likely improve the patient's QOL. Some practitioners treating patients with PP underestimate the concomitant prevalence of suboptimal sleep, depression, FM, and OSA. While acute pain syndromes that are moderate to severe may require the use of opioid analgesics, they should generally be used when there are no viable alternatives. If opioids are employed, the goal should be to taper them as soon as practical. Thus, once adequate pain reduction has been achieved, the addition of a second, nonopioid agent, followed by a slow taper of the opioid, should be undertaken. For mild acute pain syndromes, duloxetine and pregabalin have a relatively rapid onset of action and can be initiated without adjuvant therapy in most cases. The available evidence suggests that the agent of first choice to treat PP is duloxetine in depressed patients and pregabalin in nondepressed patients. In either case, the choice of medication should be chosen by the patient after a discussion of the risks and benefits of all potential treatments. TCAs should be reserved for younger persons without cardiac risk factors who are able to tolerate their side effects and for whom cost is a factor. If an adequate trial of two medications from different classes is unsuccessful, the patient should be referred to a pain management specialist.

CONFLICT OF INTEREST STATEMENT

Daniel Menkes, MD, has previously served as a consultant for the Eli Lilly Company, manufacturer of duloxetine (Cymbalta). He has received honoraria in the past from this company for providing lectures on the diagnosis and treatment of diabetic peripheral NP and FM. He is no longer a speaker for any pharmaceutical manufacturer. He has also served as a consultant and expert witness for Neurotron Incorporated, a manufacturer of quantitative sensory testing equipment.

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7 Principles and Guidelines of Immunotherapy in Neuromuscular Disorders

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Among the variety of diseases seen by neuromuscular specialists, immune-mediated disorders generate tremendous interest. These disorders are relatively common and often respond favorably to treatment. The field has become more exciting but has also become more complicated due to the many treatments available as well due to the side effects that can arise from manipulation of the immune system. However, the timely and accurate diagnosis and management of these entities can still be a gratifying experience for both patient and physician. This chapter provides a general overview of the components and function of the immune system and discusses the use of individual therapies aimed at altering the immune response to treat these disorders. Lastly, the available evidence for the use of these drugs in the treatment of select neuromuscular disorders is summarized.

BASICS OF THE IMMUNE RESPONSE

The principal function of the immune system is the differentiation between self and non-self and resultant rejection of the latter. When infection with bacterial, viral, fungal, or parasitic organisms occurs, components of the pathogen are recognized by specialized immune cells. The first such cells to come into contact with the invading organism are macrophages and dendritic cells. These cells are able to recognize pathogens using a small number of constitutively expressed receptors called *pattern-recognition receptors*, such as the Toll-like receptors. Such receptors bind common elements of microorganisms that cause disease (e.g., endotoxin of gram-negative bacteria or lipoteichoic acid of group B *Streptococcus*) and help to provide a quick response to a threat but lack the exquisite specificity and plasticity of the adaptive immune system. The role of the innate immune response in human disease, particularly in the development of autoimmunity, is only beginning to be understood (Akira, Uematsu, & Takeuchi, 2006; Cook, Pisetsky, & Schwartz, 2004).

Adaptive immunity refers to the ability of lymphocytes to respond to a specific threat, to amplify the response to that threat, and to retain memory of the threat to quickly respond when reexposure occurs. Antigens, which are molecules that are capable of inducing an immune response, are presented to T lymphocytes via major histocompatibility complex (MHC) molecules. Class I MHC molecules present endogenous antigens, such as those present intracellularly during a viral infection. In contrast, class II MHC molecules are present on antigen-presenting cells, such as macrophages and dendritic cells, and present exogenous (i.e., extracellular) antigens to lymphocytes. In each case, recognition and response occur by binding of the antigen with the lymphocyte's T cell receptor (TCR) along with the interaction of appropriate costimulatory molecules (e.g., CD28 with CD80). The specificity of the adaptive immune response is due in large part to the vast repertoire of TCRs available. This enormous variety is generated through random rearrangement of the genes encoding for TCRs during lymphocyte development. The result is a unique TCR for each lymphocyte that binds with high affinity to a single antigen.

Once a pathogen is encountered and its antigens are presented to and recognized by a T lymphocyte, an intracellular signaling cascade is initiated that leads to an effective T cell response. The initial events in this signaling cascade consist of hydrolysis of components of the T cell's lipid bilayer to form inositol triphosphate and diacylglycerol. Diacylglycerol activates protein kinase C, and inositol triphosphate facilitates the entry of calcium into the cytosol. Calcium in turn activates numerous proteins, including calcineurin and several DNA-binding proteins. Calcineurin facilitates the release of interleukin-2 (IL-2), a powerful stimulator of T cell proliferation (discussed later), whereas DNA-binding proteins alter gene transcription. The end result of these changes is T cell proliferation and differentiation. Thus, stimulated, T cells are ready to respond to the threat.

T lymphocytes bearing the cluster of differentiation marker 8 (i.e., CD8+ lymphocytes) respond by engaging in cell-mediated cytotoxicity and act most effectively against viruses by destroying host cells that have been invaded. The response of CD4+ T lymphocytes usually involves the secretion of substances, such as cytokines, that modify the cell-mediated or humoral immune response. T helper type 1 (Th1) cells are CD4+ lymphocytes that release cytokines that strengthen the cell-mediated, cytotoxic response to an antigen. Th2 cells, in contrast, release cytokines that may be anti-inflammatory or that favor the production of antibodies by B cells.

Immunoglobulins are also produced in a large variety and contribute to the specificity of the immune system. Like the TCRs, the genes for immunoglobulin heavy and light chains undergo random genetic rearrangement during B cell development, resulting in a complement of lymphocytes that each bear a unique receptor and respond to a particular antigen. In addition, mature B lymphocytes can alter immunoglobulin production from one immunoglobulin class to another when stimulated. Immunoglobulin A (IgA) is secreted at mucosal surfaces and is most useful in repelling

pathogens in the gastrointestinal tract and respiratory tree. IgE mediates the release of cytotoxic substances from eosinophils, mast cells, and basophils and is most effective against parasitic organisms, but it also plays an important role in allergic reactions. IgM is the first subtype produced in response to a threat and is most effective at activating complement. IgG can also effectively activate complement and is able to coat, or *opsonize,* a pathogen for effective clearance by phagocytes. In addition to immunoglobulins, mature B lymphocytes are distinguished by their expression of cell markers CD19 and CD20.

Complement refers to a group of proteins that are produced in the liver and participate in humoral immune responses in association with antibodies, particularly IgM and most classes of IgG. Complement can be activated by immunoglobulin binding to an antigen or deposited through less specific mechanisms. The term *complement* refers to the ability of these proteins to supplement antibodies and phagocytes in destroying bacteria and damaged host cells. The deposition of complement on a foreign substance, allowing for its recognition by other immune components and subsequent clearance, is called *opsonization.* In addition, serum complement proteins C5b, C6, C7, C8, and C9 associate to form a cytolytic structure called the *membrane attack complex.* Some products of complement activation (e.g., C5a) may also serve as chemotactic factors, drawing immune cells to the area for a more robust response.

A key feature of the immune system is the communication between cell types, allowing for the coordination of humoral and cellular responses. This communication is mediated in large part by proteins called *cytokines* that are secreted by many different types of cells, including antigen-presenting cells and lymphocytes. The interferons and interleukins are considered cytokines, as are tumor necrosis factor (TNF) and the chemokines, or chemotactic cytokines.

Interferons were first noted to be produced in the setting of viral infection, where they effectively interfered with viral replication. Interferons, which are generated by a wide variety of cell types, are also produced in response to other microorganisms as well as neoplasms. Once interferons bind to their receptors, they initiate a broad alteration of gene expression, ultimately leading to multiple antiviral and antioncogenic actions, including apoptosis (Borden et al., 2007; Stetson & Medzhitov, 2006).

Interleukins are a large group of small polypeptide molecules that, in general, have pleiotropic effects on lymphocytes as well as many other cell types. This feature, combined with the baffling array of interactions among the different cytokines, makes the understanding of individual interleukins difficult. Still, some of these molecules have roles that are predictable enough to bear mentioning. IL-1 augments lymphocyte production of other cytokines, notably IL-2. It is also partly responsible for many of the symptoms of severe systemic illness, including fever, anorexia, myalgias, and decreased production of so-called housekeeping proteins, such as albumin. IL-2 primarily stimulates T lymphocyte proliferation. IL-10, in contrast, has a predominantly anti-inflammatory action and appears to help induce tolerance (Adkinson, 2009).

Tumor necrosis factor is a proinflammatory cytokine that was initially named for its antioncogenic actions. Its effects are similar to those of IL-1, as discussed earlier. Both TNF and IL-1 can act on endothelium to increase intercellular and vascular adhesion molecules, facilitating egress of inflammatory cells into the tissues. In addition, TNF causes the cachexia seen in some patients with cancer.

Chemokines are named for their ability to draw inflammatory cells to an area along a chemical gradient and, like interleukins, have diverse functions. Chemokines can be subdivided based on the amino acid sequence on the *N*-terminal portion of the molecule. One group has two adjacent cysteine residues (i.e., the CC family of chemokines), whereas another has two cysteine residues separated by some other amino acid (i.e., the CXC family). It is believed that CC chemokines are more effective in attracting macrophages, eosinophils, and basophils, whereas CXC chemokines attract polymorphonuclear granulocytes.

AUTOIMMUNITY

The elements of the immune system described earlier usually work together in the differentiation of self from non-self with amazing fidelity. The importance of this system in fighting infection is highlighted by the various inherited immunodeficiency states as well as by the more recent HIV/AIDS epidemic. However, when the line between self and non-self becomes blurred in autoimmune disorders, these mechanisms, which are so effective in the destruction of invading pathogens, can be unleashed on the host, with devastating consequences.

Because of the random nature of recombination of genes involved in T and B cell receptor formation, there are always some lymphocytes that have an affinity for self-antigens. Thankfully, many of these are eliminated during their development. In the bone marrow and thymus, primitive B and T lymphocytes are exposed to numerous self-proteins bound to MHC molecules. Those lymphocytes whose receptors have little or no affinity for the MHC molecule are unable to participate effectively in an appropriate immune response and are allowed to die. Lymphocytes with receptors that bind with very high affinity to the MHC molecule are likely to initiate autoimmunity and are actively targeted for destruction. Both groups undergo apoptosis, or programmed cell death. This process has been termed *clonal deletion* (Nossal, 2001).

Although many self-antigens are present in the bone marrow or thymus, not all are. Therefore, a peripheral mechanism for inducing tolerance must also be in operation. Some lymphocytes possess receptors that recognize antigens that are sequestered in immunologically privileged sites. Anatomic barriers, such as the blood-brain and blood-nerve barriers, prevent these lymphocytes from encountering their antigens under normal circumstances. Such T and B cells are said to be in a state of ignorance (Kamradt & Mitchison, 2001). If there is a breakdown of the barrier or if the antigens are released through injury or infection, then an autoimmune response may occur.

Some autoreactive lymphocytes are held in check by regulatory T cells. These unique CD4+ T cells act through membrane-bound or soluble molecules, such as cytokines, to suppress immune responses. The absence of these cells promotes the development of numerous autoimmune diseases in mice (Jonuleit & Schmitt, 2003).

Even when an autoreactive T cell encounters its antigen, activation and an immune response do not always occur. In addition to TCR binding to the protein-MHC complex, costimulatory molecules such as CD28 must bind to their respective receptors on the antigen-presenting cell if activation is to take place. If such costimulatory molecules are not present, the lymphocyte undergoes apoptosis. The presence of Fas ligand, which is constitutively expressed in some tissues, and its interaction with its receptor CD95 can also directly trigger cell death of autoreactive T lymphocytes (Kamradt & Mitchison, 2001). In addition, a proper balance of Th1 and Th2 cytokines (e.g., IL-2 and IL-10, respectively) helps to keep autoreactive lymphocytes in check.

To better explain how the cellular constituents and soluble factors of the immune system can damage the peripheral nervous system, the following is a brief review of their role in the development and maintenance of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

The initial trigger that leads to immune attack of the peripheral nerves in CIDP remains obscure, as in most autoimmune disorders. The most popular notion, for which there is some existing evidence, is molecular mimicry. Approximately one third of patients with CIDP report a preceding illness or vaccination within 6 months before the development of symptoms (McCombe, Pollard, & McCleod, 1987). In axonal forms of Guillain-Barré syndrome (GBS), certain infectious organisms, such as *Campylobacter jejuni,* are likely to cause a cross-reaction against nerve ganglioside antigens, such as GM1, and trigger the autoimmune cascade (Hughes & Cornblath, 2005). In rare cases, CIDP and malignant melanoma may coexist (Bird, Brown, Shy, & Sherer, 1996), suggesting some molecular mimicry between epitopes on melanoma cells and Schwann cells, both of which develop from the neural crest.

Regardless of the inciting event, once autoreactive T cells or immunoglobulins against nerve antigens appear, the immune system's property of biologic amplification takes over (Fig. 7.1). Circulating immunoglobulins bind to their antigens and can be recognized by patrolling monocytes that then become activated to begin phagocytosis. Once nerve antigens are digested, they are presented via MHC II molecules to T cells. T cells that recognize these antigens become activated in the presence of appropriate costimulatory molecules. Th1 cells generate IL-2, which further activates these self-reactive T cells. In addition, both T cells and phagocytes produce TNF, which increases vascular permeability and increases endothelial intercellular and vascular adhesion molecules. These substances allow for adhesion to the vascular wall and transmigration of inflammatory cells into the area. Chemokines secreted by many different cell types in the immune response also ensure that lymphocytes and macrophages are drawn to the region. Th2 cells in the area are stimulated to release interleukins, such as IL-4 and IL-6, which promote immunoglobulin production by B cells. Immunoglobulins that recognize nerve antigens not only facilitate phagocytosis but also can activate complement, resulting in membrane attack complex formation and cell lysis as well as the production of chemotactic factors (Toyka & Gold, 2003). In addition, immunoglobulins against certain myelin proteins, such as P_0, may be partially responsible for the development of conduction block seen on nerve conduction studies (Yan, Archelos, Hartung, & Pollard, 2001). A more comprehensive review of the proposed pathophysiology of CIDP is provided by Kieseier, Dalakas, and Hartung (2002).

IMMUNOTHERAPY

After a review of the components of the immune system and the problem of autoimmunity, the next topic is the available medications and treatments that can alter the immune response for those affected by autoimmune neuromuscular conditions. As with all drugs, these medications have potential side effects, some modest and some considerable. The first agents discussed are those used most frequently.

CORTICOSTEROIDS

All corticosteroids bind to the glucocorticoid receptor, which then enters the nucleus and binds to glucocorticoid-responsive elements within the chromosomal DNA. This results in alteration of the chromatin structure and subsequent up- or down-regulation of gene transcription. As expected, the consequences of this shift in gene expression are varied. Corticosteroids are known to increase apoptosis, or programmed cell death, of autoreactive T cells as well as to inhibit T cell proliferation and shift cytokine profiles (Rhen & Cidlowski, 2005).

Many corticosteroids are available, all with varying anti-inflammatory and mineralocorticoid actions. The most commonly used drug is prednisone. It is actually a prodrug and is converted by the liver to the active drug prednisolone. Although very low doses can be helpful for certain conditions, such as polymyalgia rheumatica (Salvarani, Cantini, & Hunder, 2008), most disorders require a more aggressive approach referred to as *slam and taper.* A high dose of 0.5 to 2.0 mg/kg is prescribed for daily use and after 1 month is tapered to alternate-day dosing. The dose can then be further tapered to reach the lowest dose that controls symptoms. At alternate-day or daily doses of less than 20 mg, the rate of tapering may need to be very slow, perhaps no more than 10% per month, to avoid disease recurrence or adrenal insufficiency.

Corticosteroids are also used in focal neuropathies that are of autoimmune etiology, such as Bell palsy. In this disease, the combination of corticosteroids and antiviral agents was considered beneficial. However, in two new controlled studies, the addition of antivirals was not superior to prednisolone alone. Prednisolone was given in doses of 50 mg (Sullivan et al., 2007) to 60 mg (Engström et al., 2008) daily.

Other regimens for corticosteroids have been proposed. Some experts favor a gradual introduction of steroids with a 5- to 10-mg daily dose that is increased by 5-mg increments every few days until the 0.5- to 2.0-mg/kg dose is achieved. This is primarily used for patients with myasthenia gravis in whom there is a risk of disease exacerbation by sudden, high doses of steroids. Lopate, Pestronk, and Al-Lozi (2005) suggested a unique corticosteroid regimen for patients with CIDP. They performed a retrospective study of patients with CIDP who were treated with intravenous immunoglobulin (IVIg), oral corticosteroids or cyclosporine, or intermittent

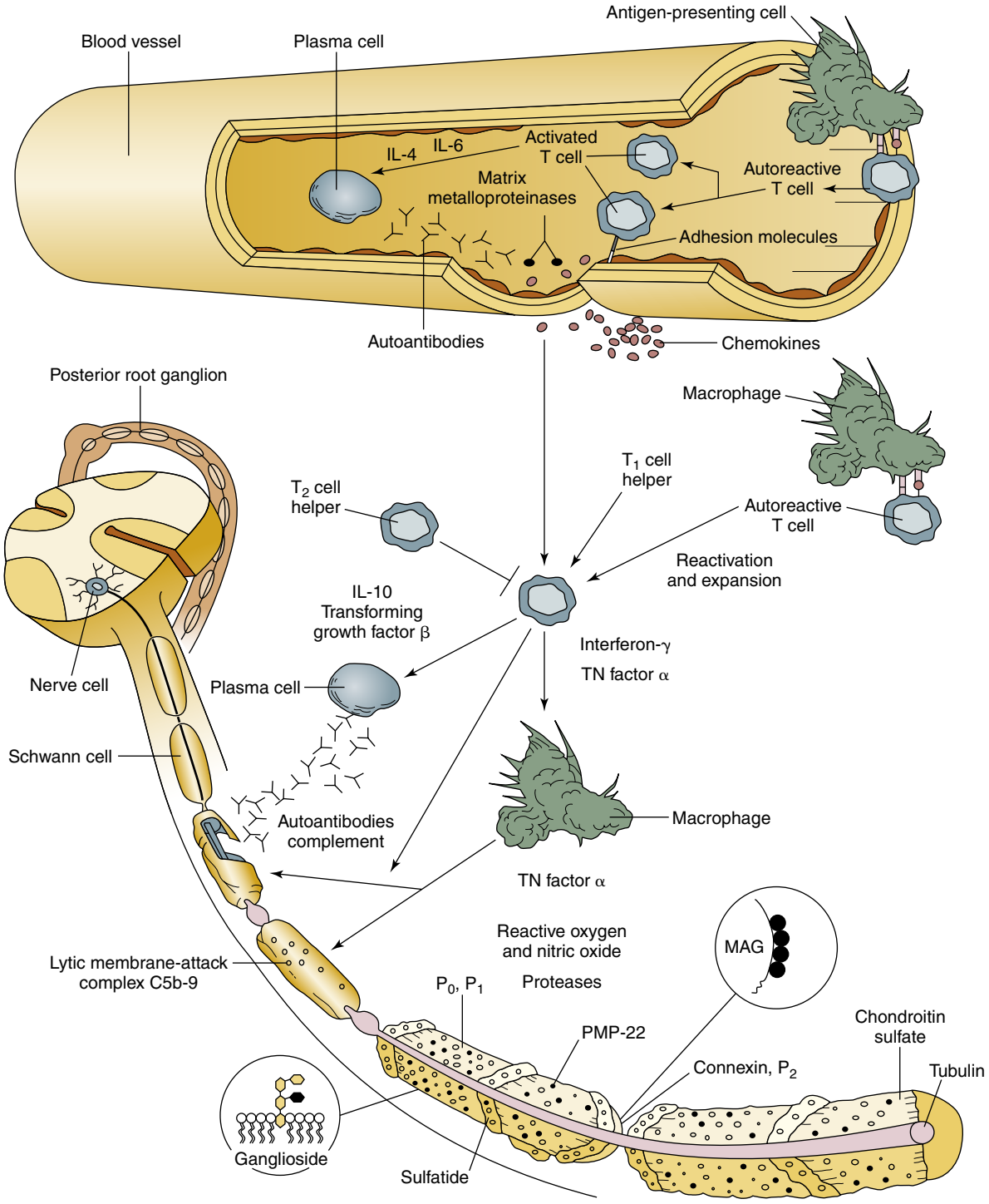


Fig. 7.1 Immunopathogenesis of chronic inflammatory demyelinating neuropathy. A schematic illustration of the basic principles of the cellular and humoral immune responses shows that autoreactive T cells recognize a specific autoantigen in the context of major histocompatibility complex class II and costimulatory molecules on the surface of antigen-presenting cells (macrophages) in the systemic immune compartment. An infection might trigger this event through molecular mimicry, a cross-reaction toward epitopes shared between the microbial agent and nerve antigens. These activated T lymphocytes can cross the blood-nerve barrier in a process involving cellular adhesion molecules, matrix metalloproteinases, and chemokines. Within the peripheral nervous system, T cells activate macrophages that enhance phagocytic activity, the production of cytokines, and the release of toxic mediators, including nitric oxide reactive oxygen intermediates, matrix metalloproteinases, and proinflammatory cytokines, including tumor necrosis factor α and interferon γ. Autoantibodies crossing the blood-nerve barrier or locally produced by plasma cells contribute to demyelination and axonal damage. Autoantibodies can mediate demyelination by antibody-dependent cellular cytotoxicity, potentially block epitopes that are functionally relevant for nerve conduction, and activate the complement system by the classic pathway, yielding proinflammatory mediators and the lytic membrane-attack complex C5b-9. Termination of the inflammatory response occurs through the induction of T cell apoptosis and the release of anti-inflammatory cytokines, including interleukin-10 and transforming growth factor β. The myelin sheath (*insets*) is composed of various proteins, such as myelin protein zero, that account for more than 50% of the total membrane protein in human peripheral nervous system myelin, myelin protein 22, myelin basic protein, myelin-associated glycoprotein, connexin 32, and gangliosides and related glycolipids. These molecules have been identified as target antigens for antibody responses with varying frequencies in patients with this disease. *IL*, Interleukin; *MAG*, myelin-associated glycoprotein; *PMP*, peripheral myelin protein; *TN*, tumor necrosis. (Modified and reprinted with permission from Koller, H., Keiseier, B. C., Jander, S., & Hartung, H. P. (2005). Chronic inflammatory demyelinating polyneuropathy. *New England Journal of Medicine, 352*, 1343-1356.)

Box 7.1 Complications of Systemic Corticosteroids

Central Nervous System

Psychosis
Mania
Depression
Insomnia
Epidural lipomatosis

Ophthalmologic

Cataracts
Glaucoma
Corneal ulceration/perforation in those with herpes simplex virus (HSV) infection

Ear/Nose/Throat

Epistaxis

Cardiovascular

Sodium and water retention
Peripheral edema
Worsening of congestive heart failure

Pulmonary

Reactivation of tuberculosis

Gastrointestinal

Gastric ulceration
Perforation (in the setting of infection)

Infectious

Increased susceptibility
Poor wound healing

Genitourinary

Decreased spermatozoa number and mobility

Endocrinologic/Musculoskeletal

Induction or worsening or diabetes mellitus
Adrenal insufficiency (on withdrawal or when stressed)
Osteoporosis
Central obesity
Avascular necrosis

Neuromuscular

Type II muscle fiber atrophy
Worsening of myasthenia gravis on initiation

intravenous methylprednisolone. They found no difference in improvement in muscle strength between groups over an average of 4.5 years of follow-up; however, weight gain and cushingoid features were much less frequent in those treated with intermittent intravenous steroids (Lopate et al., 2005). Intravenous methylprednisolone is also sometimes used in the management of myasthenia gravis in crisis. A recent study also suggested that weekly pulses of oral methylprednisolone may be effective in the treatment of CIDP (Muley, Kelkar, & Parry, 2008).

The side effects of corticosteroids are well known (Box 7.1) and often limit treatment. Acutely, most patients tolerate steroids well, but some experience insomnia or depression. Rarely, acute psychosis may occur (Hong, Cho, Kang, Chung, & Chung, 2006). Hyperglycemia and hypertension can develop quickly as well. A low-calorie, low-carbohydrate, low-sodium diet may help to lessen these problems as well as later weight gain. Gastric ulceration is also a concern, and patients may need to take proton pump inhibitors prophylactically. Late effects of steroids include the development of type II muscle fiber atrophy, glaucoma, cataracts, acne, avascular necrosis, and osteoporosis (Min & Monaco, 1991). Both calcium and vitamin D supplementation (with daily doses of 1000 mg and 800 IU, respectively) have been found to be effective in helping to prevent loss of bone mineral density in patients taking chronic glucocorticoids, and their use is strongly recommended (American College of Rheumatology Ad Hoc Committee, 2001). More active forms of vitamin D, such as calcitriol, can also be used, but patients must be monitored for the development of hypercalcemia and hypercalciuria. Several randomized clinical trials have found bisphosphonates to be effective for the prevention and treatment of glucocorticoid-induced osteoporosis (Adachi et al., 1997; Cohen et al., 1999; Reid et al., 2000; Roux et al., 1998; Saag et al., 1998). One study showed that human recombinant parathyroid hormone or teriparatide provided greater improvement in bone mineral density and fewer fractures than daily alendronate (Saag et al., 2007). Bone densitometry is recommended at the initiation of corticosteroid therapy as well as yearly thereafter (American College of Rheumatology Ad Hoc Committee, 2001).

In addition to the complications listed earlier, the development of infections while taking steroids is also feared. Patients may need to be evaluated even during the course of what appears to be a common upper respiratory illness. Patients undergoing long-term treatment with corticosteroids should be vaccinated yearly for influenza. Those taking glucocorticoids are also at risk for pneumococcal disease and should probably receive the multivalent vaccine that is available, especially if they are older than 65 years. Contrary to intuition, patients taking steroids appear to have intact immune responses to these vaccines (de Roux et al., 2006; Kapetanovic et al., 2006). Of course, these patients are susceptible to unusual infectious organisms as well. *Pneumocystis carinii,* in particular, is a concern, but effective prevention is available in the form of trimethoprim-sulfamethoxazole (Russian & Levine, 2001). Because of the many side effects of corticosteroids, other immunosuppressive drugs are often used in an attempt to lower or eliminate the steroid dosage while keeping the disease in remission.

Deflazacort is another steroid preparation that has been used in the treatment of Duchene muscular dystrophy and appears to cause less weight gain than prednisone (Bonifati et al., 2000). Deflazacort is an oxazoline derivative of prednisone and methylprednisolone. The drug has been found to be effective in rheumatoid arthritis as well as system lupus erythematosus. Deflazacort seems to produce fewer side effects (Griggs, Miller, & Greenberger, 2016; McDonald et al., 2018; Shieh et al., 2018) and may potentially be of use in managing other autoimmune diseases (Ganapati et al., 2018; Gupta et al., 2017; Loftus et al., 1991), but its higher cost remains an issue.

Vamorolone is a new dissociative steroid that has a mineralocorticoid antagonistic effect in addition to its anti-inflammatory effect. It appears to be helpful in murine

muscular dystrophy (Heier et al., 2013) and may specifically improve cardiomyopathy (Heir et al., 2019). It has also shown promise in Duchenne muscular dystrophy (Reid et al., 2000) while producing fewer side effects than traditional glucocorticoids, particularly in the way of adrenal suppression and bone turnover (Conklin et al., 2018). While still in development, vamorolone may be a promising option in the future management of autoimmune disorders as well.

INTRAVENOUS IMMUNOGLOBULIN

IVIg is a unique therapy. This blood product is prepared from a large number of donors, on average, 5000 to 10,000 for each dosage. Although the main component of IVIg is IgG, many other molecules are present. Some of these include IgA, IgM, soluble anti-TCR, and various cytokines. There is unlikely to be a single mechanism of action for IVIg, but certain ones may be important for particular diseases. Some proposed mechanisms of action include promotion of T cell apoptosis, impaired migration of T cells, restoration of the balance between pro- and anti-inflammatory cytokines, suppression of autoreactive B cells, and enhanced clearance of IgG in the circulation (Hartung, 2008). As with many other medications, the role of genetic factors in predicting responsiveness to this form of therapy is just beginning to be realized (Iijima et al., 2009).

The standard dose of IVIg is 2 g/kg. At the initiation of therapy, the dose may be divided equally over 2 to 5 days. For young patients with normal cardiovascular and renal function, infusion over 2 days may be preferred. Although there is some evidence that more rapid infusion over 2 days is superior to longer courses (Dalakas, 2004), the data from trials in GBS show no such benefit (Hughes et al., 2007). For long-term use, a dose of 1 to 2 g/kg over 1 to 2 days is given. Infusions can be repeated every 3 to 4 weeks or longer, or as the patient's symptoms dictate. Sometimes in chronic disorders, such as CIDP, 500 mg/kg weekly can be helpful.

Infusions of IVIg are well tolerated by most patients. The most common side effect is a mild headache. Rarely, a more severe headache from aseptic meningitis occurs. It is not uncommon for patients to have chills or myalgias during the initial infusion. These symptoms typically improve with acetaminophen and a slower rate of infusion. Patients may feel fatigued or mildly nauseated after treatment. Rash is not uncommon. Because of the risk of renal insufficiency as a result of acute tubular necrosis, patients should be well hydrated and electrolytes and serum creatinine should be monitored. This complication may be more common in preparations containing sucrose. Older patients and those with congestive heart failure could experience fluid overload, and more concentrated preparations may be preferred in this setting. Other serious side effects include thrombosis as a result of serum hyperviscosity. These thrombotic events include deep venous thrombosis and pulmonary embolism as well as stroke or myocardial infarction (Bertorini et al., 1996). The use of aspirin or subcutaneous or low-molecular-weight heparin should be considered in patients who are at risk for these events. In addition, a less concentrated formula may reduce this risk. Anaphylaxis is a rare complication and may occur in individuals who have anti-IgA antibodies, such as those with IgA deficiency. Because all IVIg preparations contain some level of IgA, and IgA deficiency is relatively common, IgA levels should be obtained before the administration of IVIg. If such a deficiency is identified, a preparation with a very low IgA level, such as immune globulin (Gammagard, Baxter, Westlake Village, CA), or an alternate therapy should be considered. Because IVIg is a blood product that is purified from thousands of donors, patients may be concerned about the risk of infection. They should be reassured that blood donors are screened for known transmissible infections, such as HIV and hepatitis viruses, but it is possible that currently unknown pathogens may be transmitted. Finally, some spurious laboratory test results may occur after IVIg infusion, namely, an elevated erythrocyte sedimentation rate and pseudohyponatremia (Dalakas, 2004).

Although IVIg is safe and effective for several neuromuscular disorders (Burakgazi, 2019), cost remains a major drawback to this mode of therapy. Additionally, shortages of individual preparations occur not infrequently and may limit its usage. An expert consensus on IVIg use in neuromuscular disorders has been published (Donofrio et al., 2009).

The need for intravenous access can become an issue for some patients, especially those needing treatment over several years. Subcutaneous administration of immunoglobulins via small needles and a pump may be a viable option and could reduce the cost of treatment (Lee et al., 2008). This method of administration is convenient for the patient and can be given at home and self-administered. It provides a more consistent level of IgG and has been found to be beneficial in CIDP (van Schaik et al., 2018, 2019) and autoimmune neuropathies (Harbo, Andersen, & Jakobsen, 2010; Racosta, Sposato, & Kimpinski, 2017; Uniyal, Garg, Malhotra, Kumar, & Pandey, 2018) and has been used in some other autoimmune disease (Beecher, Anderson, & Siddiqi, 2017; Berger, 2014; Cherin et al., 2016; Danieli, Pettinari, Moretti, Logullo, & Gabrielli, 2011; Gelardi, Paolini, & Danieli, 2014). The treatment is given weekly, with preparations varying in dosage. For example, Gamunex doses are 75 to 100 mg/kg weekly, whereas Hizentra is dosed at 200 to 400 mg/kg and Cuvitru is given in doses of 300 to 400 mg/kg. Infusions are administered in four sites, 10–12.5 mL per site, and can go up to 25 mL. Side effects include swelling at the sites of injection and headaches but are otherwise similar to IVIg. Overall, potential side effects are felt to be less likely, but no clear comparisons can be made at this time as this method has not been used for very long.

THERAPEUTIC PLASMA EXCHANGE

Therapeutic plasma exchange has been used primarily for patients with myasthenia gravis, GBS, and other immunological disorders (Gwathmey, Balogun, & Burns, 2014; Usmani et al., 2019). This procedure is similar to IVIg in that its effects are usually believed to be on the humoral immune system or other soluble factors, such as cytokines. As with IVIg, its effects are transient, and repeated treatments or other immunosuppressives must be used for chronic disorders.

The procedure of therapeutic plasma exchange consists of removal of whole blood from the patient followed by separation of cellular and plasma components by one of several mechanisms. The cellular components and some plasma plus a replacement solution are then returned to the patient. When a centrifugation technique is used, whole blood is spun until the components separate. The plasma

component is removed, along with immunoglobulins and other soluble large molecules. In a filtration technique, such large molecules are able to pass across the filter but the cellular elements are not. Centrifugation often uses a lower blood flow rate, and peripheral venous access may be used. Filtration devices, on the other hand, have higher flow rates and usually require central venous access. Regardless of which technique is used, a replacement solution consisting of fresh-frozen plasma, albumin, saline, or other volume expanders must be used to maintain euvolemia (Lehmann, Hartung, Hetzel, Stüve, & Kieseier, 2006). Immunoadsorption is a related technique that does not require the use of a replacement solution. The plasma component is exposed to an absorptive material of variable selectivity, and thus only certain proteins, rather than a specific volume of plasma, are removed. Absorption columns can be designed for specific disease states, such as the acetylcholine receptor antibody–selective column used in a clinical trial for the treatment of myasthenia gravis (Yeh & Chiu, 2000).

The main consideration when using therapeutic plasma exchange is venous access and the need for a central venous catheter, with its attendant risks of vascular or nerve injury, line infection, and pneumo- or hemothorax. Repeated therapy can be done using a dual lumen port-a-cath. The depletion of clotting factors during pheresis and the use of heparin if needed may predispose the patient to bleeding. Many devices use citrate as an anticoagulant, and this may lead to hypocalcemia or metabolic acidosis (Lehmann et al., 2006).

AZATHIOPRINE

Azathioprine is commonly used as a steroid-sparing agent in the treatment of neuromuscular disorders, especially myasthenia gravis. Azathioprine is a prodrug and is converted to 6-mercaptopurine by the enzyme xanthine oxidase. The active compound interferes with the formation of purines and, thus, DNA synthesis. This broad antiproliferative action suppresses clonal expansion of lymphocytes but can also lead to bone marrow suppression (Anstey & Lear, 1998).

The usual effective dosage of azathioprine is 1 to 3 mg/kg. It can be given once daily or in twice-daily divided doses, which may be better tolerated. An important consideration when initiating azathioprine treatment is the activity of thiopurine methyltransferase (TPMT). Approximately 10% of individuals are deficient in this enzyme involved in azathioprine metabolism. When such deficiency exists, azathioprine toxicity can easily occur. Deficiency of TPMT has been recognized as a major risk factor for the development of severe myelotoxicity, and many recommend assay of enzyme activity before initiating therapy (Goldsmith, Lennox, & Bhalla, 2008). The level of activity can then be used to guide drug dosing to better prevent side effects (Meggitt, Gray, & Reynolds, 2006). Patients with very low or absent TPMT activity should probably not receive azathioprine. In situations in which the TPMT assay is not available, starting at a low dose, such as 50 mg daily, is recommended, with weekly monitoring of the complete blood count (CBC) during the first 2 months.

In addition to causing myelotoxicity, azathioprine may predispose patients to infection, particularly when combined with steroids or other agents. Mild nausea and vomiting are common side effects and may be alleviated by reducing or dividing the drug dose. Pancreatitis may rarely occur. An idiosyncratic reaction that is characterized by rash, fever, nausea, vomiting, and diarrhea may develop within the first month of treatment. Some patients can become quite ill and develop hypotension, tachycardia, and oliguria. The symptoms remit with discontinuation of therapy but recur, often immediately, on rechallenge with the drug (Knowles, Gupta, Shear, & Sauder, 1995). There is some evidence that long-term use of azathioprine may increase the risk of cancer, particularly skin cancer (O'Donovan et al., 2005) and lymphoma (Silman, Petrie, Hazleman, & Evans, 1988). The overall risk appears low, but patients should be reminded to limit sun exposure and use sunscreen, especially if they are light-skinned. Liver enzyme elevations may also occur when using azathioprine but appear to be less common than with methotrexate.

Appropriate monitoring is key to preventing complications related to azathioprine therapy. CBC and liver enzymes should be assessed weekly for at least the first month, and then every 3 months thereafter. An effective dose of the drug often results in mild leukopenia. Additionally, mean corpuscular volume is often elevated when an effective dose has been reached. If the white blood cell count drops below $4000/mm^3$, the dose should be reduced, whereas leukopenia of $2500/mm^3$ or an absolute neutrophil count of less than $1000/mm^3$ should prompt discontinuation of the drug and possible consultation with a hematologist (Goldsmith et al., 2008). Periodic measurement of thiopurine metabolites can help monitor therapy and prevent toxicity (Rae, Burke, & Pinto, 2016; Zhao & Bertorini, 2018).

Azathioprine has numerous drug interactions. The most significant is the toxicity that can occur with concomitant administration of allopurinol for gout. This inhibitor of xanthine oxidase can significantly increase drug levels, and the dose of azathioprine should be reduced in these patients (Anstey & Lear, 1998). Angiotensin-converting enzyme inhibitors may also promote toxicity (Yeh & Chiu, 2000). The anticoagulant warfarin is less effective when given with azathioprine (Anstey & Lear, 1998).

Despite these cautions, azathioprine is often well tolerated. It does not have a rapid onset of action, however, and response can be delayed by up to 6 months.

METHOTREXATE

Methotrexate is sometimes used in the treatment of inflammatory myopathies and the vasculitides, as well as in some neuromuscular complications of rheumatologic disorders, such as overlap syndrome. Methotrexate, like azathioprine, inhibits DNA synthesis by interfering with purine nucleotide synthesis, but it acts through a different mechanism; methotrexate inhibits the enzyme dihydrofolate reductase. It is administered in weekly oral or parenteral doses, usually starting with 5 to 10 mg/week and increasing the amount over several weeks to reach a maximum of 25 mg/week, at a maximum of 30 mg. Doses higher than 20 mg/week can be used, but the side effects are more troublesome. Additionally, oral bioavailability is variable and is further reduced at higher doses. For this reason, some practitioners may switch to weekly intravenous or intramuscular administration if patients do not respond to oral dosing (Cannella & O'Dell, 2008) or do not tolerate the oral treatments. The doses should be adjusted in renal failure.

Methotrexate is usually well tolerated when given in small weekly doses, but several side effects merit mentioning. Complications such as oral ulcers, nausea and vomiting, myelosuppression, and flulike symptoms are at least partially related to folate deficiency and improve with supplemental folic acid (e.g., 1 mg daily). The use of folic acid does not appear to significantly reduce the effectiveness of methotrexate (Morgan et al., 1994). Liver toxicity is a recognized complication but also appears to be reduced with folic acid supplementation (van Ede et al., 2001). Screening for hepatitis and counseling patients to avoid alcohol is recommended. Pulmonary fibrosis is also a concern. A baseline chest radiograph is recommended and may be repeated yearly. Measurement of CBC and liver enzymes every 4 to 8 weeks is also recommended (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996). However, testing every 3 to 4 months is acceptable in our experience.

CYCLOPHOSPHAMIDE

Cyclophosphamide is a prototypical alkylating agent and a descendant of the more toxic nitrogen mustard. This compound is sometimes used for the treatment of steroid-resistant or -dependent cases of the inflammatory myopathies, CIDP, and myasthenia gravis. In addition, it is a valuable therapy in the management of the vasculitides. As an alkylating agent, cyclophosphamide results in abnormal cross-linkage of DNA and RNA and consequent reduction of transcription and translation. It thus inhibits the proliferation of lymphocytes. Cyclophosphamide appears to have a preferential effect on B cells (Cupps, Edgar, & Fauci, 1982; Zhu, Cupps, Whalen, & Fauci, 1987) and actively reduces their number by promoting apoptosis (Hemendinger & Bloom, 1996).

The drug is typically administered by monthly infusions at a dose of 0.5 to 1.0 g/m^2. Oral dosing is 1 to 2 mg/kg daily but is less commonly used because of increased side effects. Once it is administered, the parent drug is converted to active and inactive metabolites that are subsequently eliminated by the kidneys.

The potential complications of cyclophosphamide are well known and feared. Hemorrhagic cystitis is a classic side effect and may manifest as microscopic or gross hematuria. Mesna or 2-mercaptoethane sulfate is used to bind the metabolites of cyclophosphamide and inactivate them. It is usually administered to those receiving pulse doses of cyclophosphamide and is given before infusion as well as 4 and 8 hours after the treatment. Each dose of mesna is 60% of the dose of cyclophosphamide used (Freter & Perry, 2008; Hemendinger & Bloom, 1996). Bladder toxicity may also be minimalized by adequate hydration and frequent voiding to prevent extended contact of the bladder mucosa with the drug's active metabolites (Reingold-Keller et al., 2000). Long-term exposure to cyclophosphamide can also result in bladder cancer. This, too, may be prevented by appropriate use of mesna (Reingold-Keller et al., 2000).

Infections are a common complication of cyclophosphamide therapy. In patients treated for Wegener granulomatosis, serious infections occurred in 70% of those receiving daily oral cyclophosphamide and in 41% of those receiving pulse doses of cyclophosphamide. A major contributor to this number is the rate of infection with *P. carinii* (Guillevin et al., 1997; Stein & Taylor, 2008). Appropriate prevention with trimethoprim-sulfamethoxazole or an equivalent drug in those with sulfa allergies is recommended.

Malignancy is a concern when using cyclophosphamide. One study of patients with rheumatoid arthritis who were treated with the drug showed a four-fold increase in the overall risk of cancer (Baltus, Boersma, Hartman, & Vandenbroucke, 1983). A lifetime cumulative dose of 80 g or greater may also increase the risk of myelofibrosis. In addition to these side effects, cyclophosphamide has been associated with cardiomyopathy (Kamezaki, Fukuda, Makino, & Harada, 2005), infertility (Nicholson & Byrne, 1993), and pulmonary fibrosis (Fraiser, Kanekal, & Kehrer, 1991).

When using cyclophosphamide, the dose should be adjusted to avoid severe leukopenia below 2000 to 3000/mm^3. CBC should be obtained weekly for a month and then every 1 to 3 months.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a newer immunosuppressant that has been used most successfully—typically in combination with other drugs—for the prevention of renal transplant rejection (Behrend, Lueck, & Pichlmayr, 1997). Because of its enhanced safety profile compared with many of the medications listed earlier, it has been adopted for use in the treatment of neuromuscular disorders rather quickly. It has been used most often in the management of myasthenia gravis, but the recent results of two large randomized trials have somewhat curbed the enthusiasm for its use. Both trials found no steroid-sparing effect of mycophenolate over a period of 12 weeks (The Muscle Study Group, 2008) or 36 weeks (Sanders et al., 2008). Mycophenolate, however, seems to be effective in the treatment of myasthenia gravis but requires a longer duration of therapy, similar to azathioprine. The drug is also beneficial in other autoimmune disorders (Chaudhry, Cornblath, Griffin, O'Brien, & Drachman, 2001; Majithia & Harisdangkul, 2003; Olivo Pallo, de Souza, Miossi, & Shingo, 2018; Sanders et al., 2008).

The parent drug is metabolized in the liver to the active metabolite mycophenolic acid (MFA). The latter inhibits inositol monophosphate dehydrogenase, which is the key enzyme in the de novo pathway for purine synthesis. Although most cells of the body acquire purines from both the de novo and salvage pathways, lymphocytes only use the former (Majithia & Harisdangkul, 2003). Therefore, MMF has a selective effect on both B and T lymphocytes and less toxicity than many of the drugs mentioned previously.

The typical dosage is 2 g daily in two divided doses. Higher doses, up to 4 or 5 g daily, may be used provided severe leukopenia does not occur. Monitoring of the CBC should be done weekly for the first month of therapy, then monthly for several months. Obtaining the blood count every 3 months beyond that is reasonable. Hepatic or renal toxicity is rare and did not occur in the largest trials in patients with myasthenia gravis (The Muscle Study Group, 2008; Sanders et al., 2008). Effectiveness may be reduced with concomitant use of other medications such as acyclovir and proton pump inhibitors, which can reduce circulating drug levels.

The most common side effects are headache, paresthesias, pedal edema and abdominal cramping or diarrhea. Patients with impaired renal function are at higher risk of side effects, as are patients taking MMF along with corticosteroids

(The Muscle Study Group, 2008). Periodic measurement of MFA may be helpful in monitoring for toxicity (Magee, Ansari, & Milford, 2008; Seo & Furst, 2019; van Gelder & Hesselink, 2015). The use of a slow-release preparation may result in decrease gastrointestinal symptoms (Geon & Kaplan, 2007). A dose of 720 mg controlled-release MMF twice a day appears to have a similar effect as 1 g twice-daily regular mycophenolate, with fewer gastrointestinal side effects. Although an uncommon complication, progressive multifocal leukoencephalopathy and even central nervous system lymphoma have been reported (Vernino, Salomao, Habermann, & O'Neill, 2005).

CYCLOSPORINE

Cyclosporine is a potent T cell inhibitor that is commonly used to prevent rejection of transplanted organs. The drug interferes with calcineurin, a calcium-dependent phosphatase. This enzyme becomes activated when the TCR binds to MHC-presented antigen in the presence of appropriate costimulatory molecules. Calcineurin dephosphorylates a nuclear transcription factor that enters the nucleus and facilitates IL-2 gene transcription. Cyclosporine thus deprives T cells of a key cytokine needed for their activation and proliferation (Dalakas, 2006). Cyclosporine has been used frequently for myasthenia gravis, and there is anecdotal evidence for its use in other neuromuscular disorders.

Cyclosporine is usually administered at 3 to 5 mg/kg in divided doses. The dose can be increased, but side effects become problematic. Proper attention to drug levels and renal function are needed. Trough drug levels should be drawn 12 hours after the last dose and are optimal at 100 to 200 mg/mL. Once a benefit is seen, the dose can be reduced gradually to find the lowest effective dose. In the hands of experienced physicians, a dose of 150 mg twice daily is tolerated, with few serious side effects (Wolfe & Gross, 2004).

The presence of some of these side effects has prevented cyclosporine from gaining widespread popularity in the neurology community. The most concerning of these is renal dysfunction. This is often insidious in onset and progressive unless the dose is reduced or the drug discontinued, but acute renal insufficiency can also occur, especially with high doses of cyclosporine. The concomitant use of nonsteroidal anti-inflammatory drugs and other nephrotoxic medications is dangerous and should be avoided. Using the lowest possible dose of cyclosporine helps to prevent nephrotoxicity.

In addition to nephrotoxicity, cyclosporine use can lead to hypertension, hyperlipidemia, diabetes mellitus, hypertrichosis, gingival hyperplasia, headache, and tremor. The incidence of serious infection is increased, as expected, especially when combined with steroids or other immunosuppressants (Wolfe & Gross, 2004). Central nervous system toxicity also occurs. Although known variably as reversible posterior leukoencephalopathy or posterior reversible leukoencephalopathy syndrome, the manifestations are protean and the disorder can leave permanent deficits (Stott, Hurrell, & Anderson, 2005).

TACROLIMUS

Tacrolimus (FK506) is a macrolide drug and differs considerably in structure from cyclosporine, yet its mechanism of action is identical. There have been anecdotal reports and uncontrolled studies of its use in myasthenia gravis. Some investigators have used larger daily doses of 0.1 mg/kg with monitoring of trough levels (Ponseti et al., 2005), whereas others have used a low, fixed daily dose of 3 to 4 mg that usually does not result in detectable trough blood levels (Nagaishi, Yukitake, & Kuroda, 2008). All have reported benefit, but controlled trials are needed.

The advantage of tacrolimus is that, like cyclosporine, it appears to act quickly; some patients show improvement within a month, but the best response occurs after months of therapy (Konishi, Yoshiyama, Takamori, & Saida, 2005). In addition, tacrolimus, especially when used at a very low dosage, has fewer side effects in general than cyclosporine. Drug-induced diabetes mellitus, though, remains a concern.

RAPAMYCIN

Rapamycin, or sirolimus, is similar to cyclosporine and tacrolimus in that it inhibits IL-2 production from T cells and antigen-presenting cells; however, it does so through a unique mechanism. Rapamycin inhibits the protein known, conveniently enough, as mammalian target of rapamycin. This results in decreased translation of messenger RNA and reduced IL-2 production. Although cyclosporine has been associated with the eventual development of malignancy, especially skin cancer (Euvrard, Kanitakis, & Claudy, 2003), rapamycin appears to have antioncogenic properties (Rowinsky, 2003). Rapamycin can cause hyperlipidemia, diarrhea, thrombocytopenia, anemia, and poor wound healing (Nadiminti & Arbiser, 2005). Successful treatment of a single patient with dermatomyositis has been reported (Nadiminti & Arbiser, 2005), and there are preliminary data of a benefit in the management of inclusion body myositis (Lilleker, Bukhari, & Chinoy, 2019).

RITUXIMAB

Rituximab is one of a host of monoclonal antibodies that are changing the approach to the treatment of autoimmune disorders. Unlike IVIg, in which a multitude of antibodies having different specificities are used, these new preparations contain a highly purified antibody that works against a single target. There is great hope that these more selective therapies will result in disease control with far fewer side effects than traditional immunosuppressive medications.

Monoclonal antibodies are derived from immortalized B cells that secrete antibodies of selected specificity. The amount of foreign immunoglobulin content in these drugs varies. Chimeric monoclonal antibodies are secreted from murine-human or other hybrid cell lines. Some monoclonal antibodies are further humanized by grafting only the portion required for antigen recognition (the complementarity-determining regions) onto a human IgG molecule. The newest antibodies are fully humanized by the use of transgenic animals that carry human immunoglobulin genes. The greater the non-human content of an antibody, the greater the risk of allergic reaction in patients. However, because of the presence of anti-idiotypic antibodies in patients, the use of even fully humanized antibodies is not without this risk.

Rituximab is the monoclonal antibody best known to neuromuscular physicians. It has been used anecdotally or in uncontrolled studies in anti-MAG neuropathy (Levine & Pestronk, 1999; Pestronk et al., 2003; Renaud et al., 2003, 2006), multifocal motor neuropathy (Ruegg, Fuhr, & Steck, 2004), CIDP (Briani et al., 2004; Kilidireas, Anagnostopoulos, Karandreas, Mouselimi, & Dimopoulos, 2006; Gorson, Natarajan, Ropper, & Weinstein, 2007), other autoimmune neuropathies (Gorson et al., 2007), inflammatory myopathies (Levine, 2005; Mok, Ho, & To, 2007), myasthenia gravis (Hehir et al., 2017; Kerkeni, Marotte, & Miossec, 2008; Topakian et al., 2019; Zebardaost, Patwa, Novella, & Goldstein, 2010), and the neuropathies associated with Sjögren syndrome (Seror et al., 2007) and Waldenstrom macroglobulinemia (Dimopoulos et al., 2002).

Rituximab is a chimeric monoclonal antibody against CD20, a molecule found on the surface of developing and mature B cells. It may be expressed on plasma cells as well. The drug was initially used in the management of B cell lymphoma. A single course of rituximab is capable of depleting B cells within several weeks and maintaining depletion for months or years. IgM levels often decline after a single treatment, but IgG levels may be unaffected, presumably because of the survival of at least some plasma cells. Although the drug's effect on B cells and IgM levels is believed to play a significant role in its mechanism of action, the importance of other effects, such as the inhibition of cell migration, is still being considered (Kosmidis & Dalakas, 2010; Stubgen, 2008a).

Rituximab is given as an intravenous infusion of 375 mg/m^2 weekly for 1 month or as two infusions of 1 g every other week. Because the drug's effects are long-lasting, repeat infusions may not be needed until several months or even years have passed; however, when necessary, the cycle can be repeated after 6 months. Rituximab is believed to be most helpful in IgM-mediated diseases, such as anti-MAG neuropathy and multifocal motor neuropathy. When used for other disorders, it is theoretically advantageous to administer rituximab along with another immunosuppressant, although this likely increases the risk of infection.

Rituximab infusions are typically well tolerated, with only cough and mild hypotension being common side effects. More severe reactions, such as bronchospasm, fever, and rigors, are more common when the drug is administered to those with high B cell counts (i.e., patients with lymphoma). Progressive multifocal leukoencephalopathy has been reported in patients treated with rituximab for lymphoma, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory myopathies (Molloy & Calabrese, 2008) and other neuromuscular disorders. This disease, which is caused by reactivation of latent JC virus, is usually fatal unless the immune system can be reconstituted.

Ocrelizumab is another CD20 inhibitor that has been approved to treat multiple sclerosis (Hauser et al., 2017) and potentially may be used off-label to treat neuromuscular disorders. The drug is given in doses of 300 mg IV 2 weeks apart and then 600 mg every 6 months thereafter.

OTHER AUTOIMMUNE MONOCLONAL ANTIBODIES

Alemtuzumab is a humanized monoclonal antibody that targets CD52, a cell marker found on leukocytes and monocytes. The drug has been used in the management of leukemia and lymphoma and more recently was approved for the treatment of multiple sclerosis (Coles et al., 2012). A small series of patients with CIDP who were dependent upon IVIg have been treated with alemtuzumab, with mixed results (Marsh et al., 2010). Side effects include the expected occurrence of transfusion reactions as well as the unusual development of other autoimmune diseases such as thyroid dysfunction and idiopathic thrombocytopenic purpura (Coles et al., 2012).

Natalizumab has specificity for α4β1 integrin and inhibits adhesion and transmigration of leukocytes. The drug is approved for use in multiple sclerosis and, like rituximab, has been associated with the rare development of progressive multifocal leukoencephalopathy. No clinical trials or anecdotal reports of experience in neuromuscular disorders have been described, but these are almost certain to follow. Daclizumab is a monoclonal protein against CD25, the cell surface receptor for IL-2, that has been reported to be beneficial in ocular myositis (Garcia-Pous, Hernandez-Garfella, & Diaz-Llopis, 2007). However, there have been no reports of its use in patients with polymyositis or dermatomyositis or any other neuromuscular disorder.

COMPLEMENT INHIBITORS

Eculizumab is a humanized monoclonal antibody that binds to the C5 complement protein inhibiting its cleavage to 5A and 5B, which results in reduced chemotaxis of proinflammatory cells and inhibition of formation of the membrane attack complex formation, respectively (Howard et al., 2017). This is a novel treatment for autoimmune diseases as it blocks the complement-mediated destruction of acetylcholine receptors in myasthenia gravis and could possibly be beneficial in other autoimmune disease in which complement has a pathogenic role. Eculizumab was recently approved for the treatment of neuromyelitis optica (Pittock et al., 2019).

Eculizumab has proven effective in a double-blind controlled study in acetylcholine receptor antibody positive myasthenia gravis (Howard et al., 2017), and it has showed long-lasting efficacy (Muppidi et al., 2019). Potential complications include infection by encapsulated bacteria such as meningococcus and gonorrhea, streptococcus, haemophilus, and even fungal agents such as aspergillus. Proper vaccination is recommended, and patients should be educated about the risk of such infections. Otherwise, eculizumab appears to be rather safe, and in published trials the most common side effect compared with placebo was musculoskeletal pain (Pittock et al., 2019). The dose used is 900 mg IV weekly for 4 weeks then 1200 mg every 2 weeks thereafter. The doses can be adjusted if needed. Supplemental doses can be given in patients receiving plasma exchange. Most myasthenic patients respond well and rapidly, but there are rare nonresponders. The reasons for lack of response are not clear, but in a study of paroxysmal nocturnal hemoglobinuria, it has been reported that some genetic variants of C5 may account for a poor response to eculizumab (Nishimura et al., 2014). This suggests that it may be possible to predict which patients may not respond to this form of treatment.

Zilucoplan is a 15-amino-acid synthetic macrocyclic peptide that inhibits C5 and has also been demonstrated to be

beneficial in generalized myasthenia gravis (Howard et al., 2020). Zilucoplan is self-administered subcutaneously. Possible complications are similar to eculizumab, but because it is not a monoclonal antibody, but instead a small synthetic peptide, it may cause less immunogenicity. Zilucoplan has yet to be approved by the Food and Drug Administration.

ANTI–TUMOR NECROSIS FACTOR-α AGENTS

Tumor necrosis factor-α (TNF-α) is a potent pro-inflammatory cytokine that is likely involved in the pathogenesis of several autoimmune conditions, particularly rheumatoid arthritis and the inflammatory myopathies. Anti-TNF-α agents have been used with varied results in several neuromuscular disorders.

Infliximab is a chimeric monoclonal antibody against TNF-α. The drug has been reported to be of benefit to some patients with refractory inflammatory myopathies (Hengstman et al., 2003; Riley et al., 2008), but an open-label trial found no improvement in muscle strength (Iannone, Sciascia, Falappone, Covelli, & Lapadula, 2006). Etanercept is not a monoclonal antibody but rather a TNF-α receptor fusion protein that can bind and inactivate the cytokine. Although anecdotal reports of successful treatment of polymyositis with this agent exist (Sprott, Glatzel, & Michel, 2004), other reports document a uniform worsening of disease status during treatment (Dastmalchi et al., 2008). A pilot trial of etanercept in inclusion body myositis (IBM) found that the drug was well tolerated and a small improvement in hand grip at 1 year was noted (Barohn et al., 2006). Etanercept has also been used in a small open-label trial for the treatment of steroid-dependent myasthenia gravis. Although 5 of 11 patients improved significantly, 3 patients dropped out of the study, 1 because of a significant exacerbation of disease associated with up-regulation of TNF-α levels (Rowin, Merriggioli, Tüzün, Leurgans, & Christadoss, 2004). A series of 10 patients with CIDP treated with etanercept showed definite improvement in three cases (Chin, Sherman, Sander, Hays, & Latov, 2003).

The side effects of anti-TNF-α agents are usually mild, but several are of specific concern. Because TNF-α plays an important proinflammatory role in the immune system, the incidence of infection, particularly by intracellular organisms such as *Mycobacterium tuberculosis*, is increased. The use of these agents has also been associated with the development or clinical worsening of leukocytoclastic vasculitis, a lupus-like syndrome, and interstitial lung disease (Ramos-Casals et al., 2007). Of particular interest to neuromuscular physicians, these drugs have also been associated with a wide variety of nerve and muscle disorders, including GBS, CIDP, mononeuritis multiplex, axonal sensorimotor polyneuropathy, and inflammatory myopathies (Ramos-Casals et al., 2007; Stubgen, 2008b). Central demyelination during anti-TNF-α treatment has also been observed (Robinson, Genovese, & Moreland, 2001).

Abetacept is a fusion protein comprised of the Fc region of the immunoglobulin IgG1 fused with the extracellular domain of the cytotoxic T-lymphocyte-associated protein 4. This fusion protein prevents costimulatory signaling required for T cell activation. It has been approved for rheumatoid arthritis and has shown some promise in the management of inflammatory myopathies as well (Tjärnlund et al., 2018).

MISCELLANEOUS AGENTS

Anakinra, an IL-1 receptor antagonist, has been reported to be effective in a single patient with the antisynthetase syndrome (Furlan, Botsios, Ruffatti, Todesco, & Punzi, 2008). Interferon-β-1a has been used successfully and safely for multiple sclerosis for more than a decade. Vallat et al. explored its use for CIDP in a multicenter, open-label trial. They found that the drug was well tolerated, with no serious side effects, and only the typical asthenia and flulike symptoms. There was a significant improvement in a measure of disability and in conduction velocities, although clinical muscle strength testing was not significantly altered (Vallat et al., 2003). As such, interferon-β-1a could be considered for patients with CIDP that does not respond to other therapies. Antithymocyte globulin (ATG) is a preparation of polyclonal antihuman T lymphocyte antibodies that results in apoptosis or complement-mediated cytolysis of T cells (Dalakas, 2006). It has been used in a small open-label trial in IBM, and methotrexate was given after induction with ATG to prevent repletion of autoimmune T cells. Patients treated with this combination stabilized muscle strength or had modest gains compared with the patients who were given methotrexate alone, who all showed deterioration. Because ATG is produced in animals (e.g., horses), serum sickness is an expected complication, although it did not occur in the pilot study by Lindberg, Trysberg, Tarkowski, and Oldfors (2003).

IgG antagonists can be used in autoimmune diseases by diminishing overall IgG levels as well as inhibiting IgG recycling. They target the neonatal Fc receptor and may affect other IgG-based therapies as well. The term *neonatal* is a bit misleading as these receptors were first identified in neonatal rats but are present in adult mice and humans as well. Rozanolixizumab decreases IgG levels in healthy volunteers and appears to be beneficial in experimental models of myasthenia gravis (Kiessling et al., 2017; Liu et al., 2007). Another compound, efgartigimod, was reported as beneficial and safe in a phase II trial in generalized myasthenia gravis (Howard et al., 2019) Efgartigimod was also found beneficial and safe in the ADAPT phase 3 trial (Howard et al., 2020).

Edasalonexent is a small molecule that inhibits nuclear factor kappa B which plays a role in cell necrosis. Edasolonexent was found to be safe and beneficial in the treatment of Duchenne dystrophy in preliminary studies (Finanger et al., 2019; Monici, Aguennouz, Mazzeo, Messina, & Vita, 2003) and could become an important addition to other therapies in autoimmune disorders.

EVIDENCE-BASED MEDICINE AND TREATMENT OF AUTOIMMUNE NEUROMUSCULAR DISORDERS

Evidence-based medicine (EBM) simply refers to the incorporation of the best available clinical evidence or data when making medical decisions. The term was coined by epidemiology faculty at McMaster University in the 1990s, but the concept, although not as concisely articulated, has existed for much longer (Guyatt, 1991). EBM emphasizes empiricism in medical decision making and elevates the randomized controlled clinical trial to be the gold standard by which EBM decisions are made. That is not to say that EBM

denies the importance of other aspects of medical management, such as personal experience, patient preferences, and the recognition that all patients are unique. At its best, EBM provides a stable foundation on which to make medical decisions by recognizing what is most likely to be beneficial for a patient. At the least, it should help us avoid interventions that are likely to cause serious harm.

The application of EBM to neuromuscular disorders can be challenging. Some disorders are sufficiently rare (e.g., congenital myasthenic syndromes) that large controlled trials may never be feasible. This lack of evidence should not prohibit the use of drugs that have a reasonable mechanism of action appropriate to the pathophysiology of the condition. Other disorders are so heterogenous (e.g., myotonia congenita) that a large randomized controlled trial may obscure the benefit of an intervention in a select subpopulation of those affected. Some interventions are universally agreed to be of benefit, and a randomized, controlled trial would be unnecessary and unethical (e.g., mechanical ventilation in severe acute inflammatory demyelinating polyradiculoneuropathy).

The evidence base for interventions in autoimmune neuromuscular disorders was evaluated according to the guidelines of the American Academy of Neurology (Table 7.1). Unfortunately, most of the treatments discussed earlier, even clinically well-accepted interventions such as corticosteroids for myasthenia gravis, earned only a "U" recommendation. This does not imply that these treatments are not valuable but should spur additional and higher-quality (i.e., controlled) trials.

Table 7.1 Types of Immunotherapy

Drug	Dosage	Side Effects	Drug Monitoring	Indications	AAN Level of Evidence
Corticosteroids					
Prednisone	0.5–2 mg/kg po daily then taper	See Box 7.1	Weight, blood pressure, glucose, bone density, eye examination	CIDP Myasthenia gravis Vasculitic neuropathy Dermatomyositis Duchenne MD	C U U U A
Methylprednisolone	1 g IV q day × 3–5 days as initial treatment then 1 g IV weekly for 1 month before tapering or 500 mg po q week	See Box 7.1	As prednisone above	Discussed earlier	
IV immunoglobulin	1–2 g/kg IV over 1–5 days; may be repeated 3–6 weeks	Headaches, chills, myalgias, renal insufficiency, thrombosis, rash, anaphylaxis	Blood pressure Serum creatinine during daily infusions Pseudohyponatremia and falsely elevated sedimentation rate may be seen	AIDP CIDP Myasthenia gravis Dermatomyositis	B B B C
Therapeutic plasma exchange	500–5000 mL plasma volume per exchange × 4 exchanges	Pneumohemothorax, easy bruising or bleeding, hypotension	Blood pressure Calcium, fibrinogen	AIDP CIDP Myasthenia gravis	B C B
Inhibitors of purine synthesis					
Azathioprine	1–3 mg/kg po q day or divided bid. Initiate with a small dose (e.g., 50 mg) if TPMT assay not available Reduce dose for those on ACE inhibitors	Myelotoxicity, nausea, idiosyncratic "flulike" symptoms, pancreatitis, infections	Advise assessing TPMT activity before initiating treatment CBC weekly for 1 month then q 3 months Liver function studies Amylase, lipase if pancreatitis is suspected	Myasthenia gravis CIDP Inflammatory myopathies	C U U

Table 7.1 Types of Immunotherapy—Cont'd

Drug	Dosage	Side Effects	Drug Monitoring	Indications	AAN Level of Evidence
Methotrexate	5 mg/week to 25 mg/week po or IV/IM	Nausea Oral ulcers Hepatotoxicity Pulmonary fibrosis Infections	Screen for hepatitis, interstitial lung disease on initiation CBC and liver functions q 4–12 weeks Yearly chest X-ray Folic acid daily	Inflammatory myopathies Neuromuscular complications of rheumatologic disorders	U U
Mycophenolate mofetil	2–4 or 5 g daily, divided bid	Gastrointestinal upset, paresthesias, bone marrow suppression, liver toxicity (rare)	CBC weekly to monthly initially then trimonthly	Myasthenia gravis CIDP Myositis	B U U
Cyclophosphamide	0.5-1 g/m^2 IV q month	Myelosuppression, myelofibrosis, hemorrhagic cystitis, malignancy (especially bladder)	CBC weekly, liver function tests weekly for a month and then every 1 to 3 months, urinalysis every 1 to 3 months	Vasculitis CIDP Myasthenia gravis Inflammatory myopathies	U U U U
Calcineurin inhibitors					
Cyclosporin	3–5 mg/kg po q day divided bid	Hypertension, renal insufficiency, CNS toxicity, hirsutism	Trough drug levels weekly at first BMP weekly at first Avoid NSAIDs	Myasthenia gravis Dermatomyositis	C U
Tacrolimus	3–4 mg up to 1 mg/kg po q day divided bid	Same as discussed earlier but less common, diabetes mellitus	Trough drug levels CMP monthly	Myasthenia gravis Dermatomyositis	U U
Rapamycin	2–5 mg po q day	Hyperlipidemia	Periodic CMP	Dermatomyositis	U
Monoclononal antibodies					
Rituximab	0.375 g/m^2 IV weekly × 4 or 1 g IV q other week ×2	Infusion reactions PML (rare)	CD20 CBC, CMP Brain MRI	MMN Anti-MAG neuropathy CIDP MuSK+ MG Acetylcholine R+ myasthenia gravis	U U U A B B
Alemtuzumab	Varies	Infusion reaction Idiopathic thrombocytopenic purpura	CBC CMP	CIDP	U
Eculizumab	900 mg IV weekly × 4 then 1200 mg q 2 weeks	Infections by encapsulated bacteria such as meningococcus, etc.	Vaccination for meningococcus, etc.	Acetylcholine R+ myasthenia gravis	A
TNF-α blockers					
Infliximab	3–6 mg/kg IV periodically	Infections Inflammatory neuropathy, vasculitis	CBC, CMP monthly	Dermatomyositis Polymyositis	U
Etanercept	25 mg sq biweekly	As infliximab above	As infliximab above	Dermatomyositis Polymyositis Myasthenia gravis CIDP	U

Continued

Table 7.1 Types of Immunotherapy—Cont'd

Drug	Dosage	Side Effects	Drug Monitoring	Indications	AAN Level of Evidence
Anakinra	100 mg sq q day	Injection site reactions Diarrhea Infections Autoimmune disorders	CBC, CMP monthly	Inflammatory myopathies	U
Interferon-β-1a	30 μg IM q week	Injection site reactions Flulike symptoms Mild leucopenia, abnormal LFTs, abnormal thyroid function	CMP, TSH periodically	CIDP	U
Antithymocyte globulin	Varies	Serum sickness		Inclusion body myositis	U

ACE, Angiotensin-converting-enzyme; *AIDP,* acute inflammatory demyelinating polyneuropathy; *bid*, two times a day; *BMP*, basic metabolic panel; *CBC*, complete blood count; *CIDP*, chronic inflammatory demyelinating polyradiculoneuropathy; *CMP*, comprehensive metabolic panel; *CNS*, central nervous system; *IM*, intramuscular; *IV*, intravenous; *LFT*, liver function tests; *MAG*, myelin-associated glycoprotein; *MD*, muscular dystrophy; *MMN*, multifocal motor neuropathy; *MRI*, magnetic resonance imaging; *NSAID*, nonsteroidal anti-inflammatory drug; *PML*, progressive multifocal leukoencephalopathy; *po*, orally; *q*, every; *sq*, subcutaneous; *TPMT*, thiopurine methyltransferase; *TSH*, thyroid-stimulating hormone.

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8 Rehabilitation in Neuromuscular Disorders

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While there are no cures for so many neuromuscular disorders (NMDs), pharmacologic and other interventions are increasingly available to slow the progression of some NMDs. Rehabilitation is currently a cornerstone of comprehensive NMD management, optimizing quality of life and facilitating function and independence to the greatest extent, and for the longest duration, possible. As life expectancy increases, individually tailored rehabilitation across the trajectory of disease will become ever more important.

Rehabilitation is the process of helping a person to reach the fullest physical, psychological, social, vocational, avocational, and educational potential consistent with their physiological or anatomic impairment, environmental limitations, and desires and life plans. Realistic goals are determined by the person and those concerned with his or her care. Thus, one is working to obtain optimal function despite residual disability, even if the impairment is caused by a pathological process that cannot be reversed (Delisa, 1993).

The pathologic processes underlying NMDs are often progressive and irreversible. Comprehensive care should include rehabilitation that restores patients to a level of optimal functioning in their normal societal environments and achieves the optimal quality of life possible throughout the course of the disease. Rehabilitation includes management of musculoskeletal dysfunction, respiratory failure, dysarthria, dysphagia, pain, mood, and cognition and is attentive to the patient's environment, quality of life, and family and caregivers.

The nature of rehabilitation for individuals with NMDs can vary over time with changes in health and social supports. Thus, rehabilitation can be more challenging for these patients than for patients with static functional deficits caused by single events, such as spinal cord injury. One of the most difficult tasks for the rehabilitation team is to predict how quickly the patient's disease will progress so that the team can "stay ahead" of the disease process and can recommend interventions at appropriate times. This is most difficult with more rapidly progressing disease processes.

Rehabilitation and symptom management in NMDs may be approached in a problem-oriented manner. Rehabilitation topics addressed in this chapter include the role of exercise in patients with NMDs and management of impairments resulting in difficulties with mobility, activities of daily living (ADLs), communication, and the maintenance of oxygenation and nutrition. Musculoskeletal pain syndromes are discussed because of their direct effect on the ability to exercise, maintain mobility, and perform ADLs. Mood disorders and cognitive dysfunction are discussed because they are easily overlooked in the context of multiple rehabilitation needs and impaired communication; optimal management can allow patients to maintain social contacts, improve patient quality of life, and lessen caregiver and family stress. Palliative care is also discussed, as early initiation of palliative care provides a valuable layer of support and continuity for patients across the trajectory of illness. Palliative care collaboration provides valuable guidance for a patient's primary providers in optimizing symptom management and advance care planning. Palliative care can be provided concurrently with primary treatment and management of NMDs.

Rehabilitation needs are best addressed by interdisciplinary teams, which can consist of some or all of the following individuals: physiatrist, neurologist, psychologist, physical therapist, occupational therapist, speech therapist, recreational therapist, nutritionist, respiratory therapist, orthotist, social worker, chaplain, peer visitor, palliative care specialist, and nurse. At the center of every team are the patient and family. Studies from the Netherlands, Ireland, and Italy have shown that patients with amyotrophic lateral sclerosis (ALS) who are cared for in a multidisciplinary clinic have a better quality of life, longer survival, and fewer emergency hospitalizations and are more likely to use riluzole and noninvasive positive-pressure ventilation (NIPPV) (Chiò, Bottacchi, Buffa, Mutani, & Mora, 2006; Traynor, Alexander, Corr, Frost, & Hardiman, 2003; Van den Berg et al., 2005). They are also more likely to have the appropriate equipment and assistive devices to meet their needs. The same findings hold true for those with other NMDs.

Rehabilitation services are beneficial throughout the course of a person's life with an NMD (Turner-Stokes et al., 2007). Most NMDs are not static; as function declines, patients develop needs for new treatment interventions to improve outcomes, and additional therapy is required. Frequently, therapy is also required to maintain a certain functional status, i.e., maintenance therapy (which, since the first edition of this book, has become a Medicare-covered indication for therapy). By knowing how many therapy sessions a patient's insurance plan will allow, the rehabilitation team can thoughtfully use short bouts of therapy intermittently over time as needed, with special attention to giving patients recommendations for home use and indications for initiating new rounds of therapies. For example, a patient with early ALS may be referred to a physical therapist for help with designing an appropriate aerobic exercise and strengthening program. As increasing spasticity develops, the patient and family may return to physical therapy for a few sessions of education about stretching and range-of-motion exercises. If foot drop develops and the patient is

prescribed an ankle-foot orthosis (AFO), he or she may return for a few sessions of gait training with the new brace. As weakness increases, additional sessions of physical therapy may be necessary to teach a caregiver how to transfer the patient between surfaces effectively.

MANAGEMENT OF MUSCLE WEAKNESS

EXERCISE

Exercise is an important part of the rehabilitation process for individuals with NMDs of all severities. Early in the course of progressive disease, an exercise program can maximize strength and prolong independence. For those with disease states that respond to pharmacologic treatment (e.g., multifocal motor neuropathy), exercise can reverse acquired muscle weakness and cardiovascular deconditioning. For any patient for whom exercise is an important part of lifestyle, continuing to exercise improves mood, psychological well-being, and social engagement.

Several factors must be considered when assessing the ability of patients with NMDs to participate in and benefit from an exercise program. The specific diagnosis and rate of disease progression will affect the response to exercise. One might expect patients with neuropathic disorders to respond differently from those with myopathic disorders. In rapidly and relatively rapidly progressive diseases, slowing the rate of functional impairment is a positive outcome. In more slowly progressive diseases, a positive outcome might be actual gain of strength or aerobic exercise capacity. Response to an exercise program can be affected by patient age, baseline strength, baseline physical activity, cardiopulmonary health, and medication regimen. For example, the cardiomyopathy associated with some muscular dystrophies and the restrictive lung disease associated with both dystrophies and anterior horn cell disorders may limit aerobic capacity. Medications such as beta-blockers can limit aerobic exercise capacity. Each of these factors must be considered when designing exercise programs as well as studies to investigate the role of exercise in patients with NMDs. Generally, exercise within a patient's comfort level (no pain or prolonged postexercise soreness) is considered to be safe, without producing overuse weakness.

Four forms of exercise training are relevant to patients with NMDs: *flexibility*, *strengthening*, *aerobic*, and *balance exercises*. The general benefits of these four forms of exercise are summarized in Table 8.1.

FLEXIBILITY TRAINING

Flexibility training involves stretching and range-of-motion (ROM) exercises. Although there is little scientific literature on the role of flexibility training in patients with NMDs, it is generally accepted that this form of exercise (often in combination with orthotic use for prolonged static stretch) can help prevent the development of contractures. Contractures typically develop in the shoulder, when patients are too weak to raise their arms overhead, and also in the hips, knees, and ankles, when patients spend most of their days in wheelchairs. Contractures can place weak muscles at biomechanical disadvantage, impairing their function. In addition, it can also produce pain and interfere with positioning and the performance of ADLs. In addition to preventing contractures, ROM exercises stimulate joint and cartilage blood flow, enhancing the health and lubrication of joints in both healthy individuals and those with NMDs.

Table 8.1 Exercise Training Relevant to Patients with Neuromuscular Disorders

Type of Exercise	Description	General Benefits
Flexibility	Stretching and range of motion	Prevent contractures Prevent pain Reduce spasticity Increase joint blood flow and lubrication
Resistance	Strengthening Static (no joint movement) Isometric (constant length) Dynamic (involving joint movement) Isotonic (constant force) Isokinetic (constant velocity) Concentric (shortening contraction) Eccentric (lengthening contraction)	Reverse disuse weakness Strengthen minimally weak muscles Delay onset of impairment Muscle fiber hypertrophy Fiber-type conversion Increase protein synthesis Increase capillary density Reduce mitochondrial density Reduce lipid storage Neural adaptations
Aerobic	Low-resistance dynamic activity using large muscle groups that has a cardiopulmonary training effect	Improve functional exercise capacity Decrease psychological stress Improve quality of life Improve sleep Prevent secondary diseases Help maintain bone density Greater independence with activities of daily living in the frail elderly
Balance	Improving unipedal stance and functional reach	Reduce risk of falls

STRENGTHENING EXERCISES

Providing an appropriate exercise prescription is an important component of a rehabilitation program. Importantly, among the several forms of strengthening exercises, some may be safer than others for patients with NMDs.

Strengthening exercises can be classified as static or dynamic. Static (also called *isometric*) exercises are those performed at a constant muscle length, e.g., quadriceps setting (straight-leg raises using gravity or ankle weights to strengthen the quadriceps). Dynamic exercise involves joint movement. Dynamic muscle actions can be described as *isotonic*, *isokinetic*, *concentric*, and *eccentric*. Isotonic muscle actions supply constant force throughout a muscle movement, which rarely occurs in real-life settings. Isokinetic muscle actions are those performed at a constant velocity and require the use of specially designed exercise machines. Concentric actions are those in which the muscle shortens as it produces force, and eccentric actions are those in which the muscle lengthens as it produces force. Elbow flexion using a dumbbell (a "curl") is a concentric action of the biceps muscle; if the weight is then slowly lowered by extending the elbow, an eccentric muscle action of the biceps occurs.

Eccentric muscle actions are more efficient than concentric actions and generate more force at a given level of exertion. In healthy individuals, a heavy bout of eccentric exercise can produce a long-lasting decrease in muscle twitch tension and elevated serum creatine kinase (CK). Muscle fiber necrosis and mononuclear cell infiltration may be seen on muscle biopsy specimens for up to 20 days after such a bout of exercise. In healthy individuals, this muscle damage may serve as a stimulus for hypertrophy. However, in patients with muscle diseases affecting the cell membrane, such as the dystrophinopathies and sarcoglycanopathies, there is concern that the damage may not be reparable, and heavy exercise is generally not recommended. Both muscular and neural adaptations occur in response to strength training. Muscular adaptations take at least 6 to 8 weeks to develop. They include muscle fiber hypertrophy, conversion from type IIa to type IIx fibers, increased protein synthesis, decreased protein degradation, increased capillary density, reduced mitochondrial density, and decreased lipid storage. Neural adaptations may occur in as little as 2 weeks and account for early strength gains when a training program is initiated. Neural adaptations occur without muscle hypertrophy and may be due to increased motor unit activation and synchronization. Cross-transference is a neural adaptation in which a single limb is trained, but strength increases also occur in the contralateral untrained limb. This is an important consideration in reviewing the literature on strength training in NMDs because some studies have been designed such that a single limb is exercised, with the contralateral limb used as a control.

Studies across NMD subtypes suggest that strengthening exercise can be tolerated and has a beneficial effect.

In muscle disease (e.g., fascioscapulohumeral dystrophy [FSHD], myotonic dystrophy, hereditary muscular dystrophies), moderate-intensity strengthening exercises appear to be safe, although they do not necessarily result in dramatic strength gains in individual muscles (Voet, van der Kooi, van Engelen, & Geurts, 2019). Generally, exercise is recommended for maintaining strength and slowing disease progression (Fossmo et al., 2018).

In motor neuron disease, ALS and postpolio syndrome (PPS) are best studied. In ALS, moderate-intensity strengthening exercise is considered safe and generally recommended for its impact on function and quality of life. Although studies are limited by population heterogeneity, small sample size, and methodological differences, generally, a positive impact on function and quality of life is found, with no adverse safety events; a profound impact on survival has not been demonstrated (Clawson et al., 2018; Dal Bellow-Haas & Florence, 2013; Bello-Haas et al., 2007; Tsitkanou, Della Gatta, Foletta, & Russell, 2019). Studies of strength training in individuals with PPS have shown increased quadriceps strength without evidence of histologic muscle damage, changes in CK, or changes in motor unit physiology, suggesting neutrally mediated strength gains (Agre, Rodriquez, & Franke, 1997; Einarsson, 1991; Fillyaw et al., 1991; Spector et al. 1996).

Regarding neuromuscular junction disorders, a recent study in myasthenia gravis suggests that strengthening exercise is tolerated and may have a beneficial impact on function (Westerberg, Molin, Spörndly Nees, Widenfalk, & Punga, 2018).

In hereditary motor and sensory neuropathy, or Charcot-Marie-Tooth (CMT) neuropathy, a retrospective study showed an association between self-directed exercise strength in certain muscles, suggesting that exercise could be well tolerated in some subpopulations of individuals with CMT (Djordjevic, Fell, & Baker, 2017).

An interesting case report of heavy resistance training in a patient with a mitochondrial myopathy demonstrates a possible "gene shifting" benefit induced by exercise (Taivassalo Taivassalo, Fu, Johns, et al., 1999). When heavy resistance exercise damages the muscle, satellite cells are incorporated into the muscle as part of the repair process. In mitochondrial disorders, satellite cells contain much lower levels of mutant mitochondrial DNA than do muscle cells. By incorporating satellite cells into muscle, the proportion of mitochondria carrying mutant DNA can be reduced. In a patient with Kearns-Sayre syndrome, wild-type mitochondrial DNA in the biceps increased by 33% with an 18-day training program. Interestingly, concentric exercise appears to cause greater gene shifting than eccentric exercise.

Although most studies of strength training have focused on major muscle groups in the extremities that are important for mobility and ADLs, the impact of strength training on ventilatory muscle function is also important in patients with NMDs. A 3-month uncontrolled study of an inspiratory muscle training program in 24 adults with motor neuron disease, neuromuscular junction disorders (mainly myasthenia gravis), and myopathies demonstrated increases in forced vital capacity (FVC), maximum voluntary ventilation (MVV; a measure of ventilatory muscle endurance), and maximum inspiratory pressure (MIP) in all groups (Gross & Meiner, 1993). Interestingly, the patients with motor neuron disease were the weakest initially and made the greatest gains. Several studies have addressed the role of inspiratory muscle training in boys with Duchenne muscular dystrophy (DMD) (DiMarco et al., 1985; Smith, Coakley, & Edwards, 1988; Stern, Martin, Jones, Garrett, & Yeates, 1989; Wanke et al., 1994). One study found an increase in MIP in those with an FVC greater than 25% of predicted (Wanke et al., 1994); another study documented an increase in MVV with

no change in MIP (DiMarco et al., 1985). FVC did not improve in any of these studies, but there was no evidence of overuse weakness. Inspiratory muscle training in patients with myasthenia gravis has also improved respiratory muscle strength and endurance (Fregonezi, Resqueti, Güell, Pradas, & Casan, 2005). The clinical impact of small increases in MIP and MVV is unknown.

AEROBIC EXERCISE

Aerobic exercise refers to prolonged low-resistance dynamic activity utilizing large muscle groups; it has a cardiopulmonary training effect. The American College of Sports Medicine recommends that the minimum quantity and quality of training to maintain cardiorespiratory fitness in healthy adults is at least 30 minutes of aerobic activity at 55% to 90% of maximum heart rate (HR) or 40% to 85% of maximum oxygen uptake (Vo_2max) reserve most days of the week; activity may be accumulated in 10-minute bouts. Maximum HR can be estimated using the formula: HR = 220 – age. In healthy individuals, aerobic exercise improves functional exercise capacity, decreases psychological stress, improves quality of life, helps prevent secondary diseases (i.e., heart disease, diabetes, cancer), improves sleep, helps maintain bone density if performed in a weight-bearing manner, and produces greater independence with ADLs in the frail elderly. In general, the cardiovascular response to aerobic training in patients with NMDs appears to be the same as that in healthy adults. A study comparing the response of patients with a variety of myopathic disorders to control subjects during a cycle ergometer exercise test found that, in general, the patients had normal resting oxygen consumption and a normal oxygen cost of exercise (Carroll, Hagberg, Brooke, & Shumate, 1979). Their Vo_2max was reduced, reflecting their deconditioned status. Of the 24 patients in the study, 5 had an increased oxygen cost of exercise; their diagnoses were Becker muscular dystrophy, carnitine palmitoyl transferase deficiency, and mitochondrial myopathy.

Training studies utilizing home-based cycle ergometry have been performed in patients with FSHD, myotonic dystrophy, limb girdle muscular dystrophy (LGMD) type 2I, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy. In all of these studies, Vo_2max increased, with some self-reported improvement in strength, endurance, ability to perform ADLs, and mood (Garssen et al., 2004; Olsen, Ørngreen, & Vissing, 2005; Ørngreen, Olsen, & Vissing, 2005; Sveen, Jeppesen, Hauerslev, Krag, & Vissing, 2007). Patients with McArdle disease (myophosphorylase deficiency) have also shown a positive response to a carefully controlled walking and cycling aerobic exercise program (Maté-Muñoz et al., 2007).

Taivassalo et al. have studied adaptations to aerobic training in patients with mitochondrial myopathy. In an initial study, 10 patients with varied mitochondrial disorders (chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome, and myopathy) trained for 8 weeks on a treadmill at 60% to 80% of HR three to four times per week for 20 to 30 minutes (Taivassalo et al., 1998). Aerobic capacity and exercise duration improved by 30%. Serum lactate concentrations at rest and after exercise decreased by 30%, and magnetic resonance spectroscopy measurements of adenosine diphosphate recovery after exercise improved by 60%. In a follow-up study utilizing a similar protocol, patients with mitochondrial disorders, patients with other myopathies, and sedentary control subjects were trained (Taivassalo Taivassalo, De Stefano, Chen, et al., 1999). Aerobic capacity improved in all three groups, but the gain was greatest in the group with mitochondrial disorders. There has been some concern that endurance training might shift the proportion of mutant to wild-type mitochondrial DNA in a deleterious manner. However, studies have demonstrated an increase in the overall mitochondrial DNA content without a change in the ratio of mutant to wild-type DNA (Jeppesen et al., 2006; Taivassalo et al., 2006).

Several studies have documented aerobic training benefits in patients with PPS (Dean & Ross, 1991; Jones, Speier, Canine, Owen, & Stull, 1989; Kriz et al., 1992). These studies have utilized both cycle ergometry and treadmill training and have demonstrated increases in Vo_2max, endurance, and oxygen consumption at a given exercise intensity without any loss of strength or other adverse events.

In a study of response to aerobic exercise in individuals with ALS, the oxygen cost of exercise was increased, possibly because of spasticity. Ventilation and HR increases were proportional to those in oxygen consumption, as would be expected in healthy individuals (Sanjak et al., 1987). Interestingly, the expected increases in plasma free fatty acids, beta-hydroxybutyrate, and carnitine were blunted in patients with ALS, suggesting a possible defect in lipid metabolism.

A small study of patients with ALS and respiratory insufficiency who exercised on a treadmill while using bilevel positive airway pressure ventilation has suggested that the progression of respiratory failure may be slowed by aerobic exercise (Pinto et al., 1999).

Recently, the impact of aerobic exercise for individuals with CMT-1A and individuals with inclusion body myositis (IBM) was assessed. A 12-week exercise program utilizing recumbent exercise bicycles was found to be feasible and safe and to yield improvements in Vo_2max (Wallace et al., 2019).

BALANCE EXERCISES AND TRAINING

Balance often is impaired in patients with NMDs due to a combination of sensory neuropathy, proximal muscle weakness, and/or spasticity. In neuromuscular disease, the pattern of weakness can yield impairments in static and/or dynamic balance, with proximal weakness yielding greater impairment in static balance and distal weakness yielding greater perturbation of dynamic balance (Kaya, Alemdaroğlu, Yılmaz, Karaduman, & Topaloğlu, 2015).

Impaired balance, which may be defined as a unipedal stance time of less than 30 seconds, is a risk factor for falling among healthy older individuals (Hurvitz, Richardson, Werner, Ruhl, & Dixon, 2000). Among patients referred to a university electromyography laboratory for lower extremity complaints, an abnormal unipedal stance time (<45 seconds) had a sensitivity of 83% and specificity of 71% for predicting peripheral neuropathy (Hurvitz, Richardson, & Werner, 2001). Clinically, balance training is generally included in exercise programs for individuals with NMD. Rigorous research on the types of interventions and long-term impact on function and fall risk in this population is sparse.

Richardson, Sandman, and Vela (2001) enrolled patients with diabetic neuropathy in a 3-week exercise program designed to improve balance. The exercises included bipedal and unipedal toe raises, heel raises, and ankle inversion and

eversion exercises as well as unipedal balance challenges. Patients improved their unipedal and tandem stance time as well as their functional reach. These results suggest that balance exercises may be a promising therapy for patients with NMDs if the improvements translate into a decreased incidence of falling.

EXERCISE RECOMMENDATIONS

Existing research regarding exercise in patients with NMD is limited in scope, but some recommendations for exercise prescription can be formulated. An exercise prescription should include the form of exercise, as well as the intensity, duration, and frequency of training sessions. Research thus far has focused on the safety and efficacy of exercise with increasing attention to the impact of exercise programs on performance of ADLs, as well as mood, psychological well-being, sleep, and appetite. Even in cases where exercise has a minimal impact on physical function, it may still have an important impact on quality-of-life parameters such as those mentioned here.

Flexibility and ROM exercises are certainly safe and should be prescribed to all patients with or at risk for muscle tightness due to limited mobility or spasticity.

Strength training appears to be safe when performed with proper supervision. It can reverse disuse weakness and may improve absolute muscle strength in those with more slowly progressive NMDs or acquired NMDs that have responded to pharmacologic treatment (e.g., myasthenia gravis or dermatomyositis). Overuse weakness has not been documented with any moderate-resistance strengthening program, and moderate-resistance strength training can increase strength in muscles with an initial Medical Research Council (MRC) grade of 3/5 or better. Strength gain appears to be proportional to the initial strength of the muscle, with the strongest muscles making the greatest gains. Thus, it is logical to institute a strengthening program as early in the course of a progressive disease as possible. The goal of a resistance training program should be to maximize the strength of unaffected or minimally affected muscles to delay the onset of impairment. To ensure safety, patients should be advised to avoid high-resistance eccentric exercise. A practical recommendation is to find a weight that a patient can lift 15 to 20 times comfortably and then ask him or her to perform several sets of 10 lifts each. Patients also should be counseled to reduce their training load if they experience persistent muscle soreness or fatigue after exercise sessions.

In general, patients with NMDs have a normal cardiovascular response to aerobic training. Unless they have significant cardiac or respiratory disease, there are no apparent contraindications to aerobic exercise. The benefits of aerobic training are similar to those in healthy individuals. Patients should select a mode of exercise with minimal risk of injury from falling; for example, in patients with poor balance, a cycle ergometer may be safer than a treadmill. Balance training is a promising form of exercise for patients with a variety of NMDs. In patients with neuropathy, training has been demonstrated to improve balance, and it is hoped that this will, in turn, reduce the risk of falling.

In general, the US Department of Health and Human Services guidelines regarding intensity, duration, and frequency of exercise should be followed (US Department of Health and Human Services, 2018). The recommendation for individuals with disabilities is that they adhere to these recommendations to the greatest and safest extent possible. Barriers to clinician prescription of exercise, such as lack of confidence, lack of formal guidelines, and lack of infrastructure, must be addressed (Jones, Berry, Merali, & Bello-Haas, 2019).

ORTHOSES AND MOBILITY AIDS

Over time, individuals with NMDs may require orthoses and mobility aids to maximize function and independence. Especially for individuals with rapidly progressive disease, the rehabilitation focus may shift quickly from using exercise to optimize strength and physical fitness to utilizing assistive devices for supporting autonomy.

ORTHOSES

Orthoses are devices applied externally to the body to provide support, protection, and improved function. They support weak muscles, decrease stress on compensatory muscles, minimize fatigue, prevent deformity, and conserve energy. Orthoses can be prefabricated or individually fashioned. Orthoses are one component of a comprehensive rehabilitation program; orthosis needs must be frequently reassessed, as fit and needs change over time. To promote safety and patient/caregiver comfort, one or two physical therapy sessions can often be helpful for providing gait and transfer training to accommodate new orthoses.

SPINAL ORTHOSES

Weakness of neck extensor muscles, as can occur in inflammatory myopathies, neuromuscular junction disorders, and motor neuron diseases, can result in head drop. Head drop is associated with pain and fatigue, as well as restricted forward gaze and impaired speech, swallowing, and interpersonal communication. In severe neck extensor muscle weakness, the cervical spine can become completely flexed, resulting in substantial pain. Cervical orthoses (collars) can be utilized to mitigate head drop. Table 8.2 lists the routinely used types of cervical orthoses and their indications, including a creatively designed baseball cap orthosis (Fast & Thomas, 2008). Fig. 8.1 depicts the Headmaster collar, an example of a commonly used orthosis for the treatment of head drop.

The commonly prescribed cervical orthoses can be difficult to fit, overly restrictive, and uncomfortable. Recently, a team of designers, with input from individuals with ALS and head drop, created the Sheffield support snood, a more flexible and adjustable cervical support collar. It consists of a flexible fabric that surrounds the neck with a Velcro seal and has a vertical support element that is placed below the chin. Additional support elements can be added as needed. Emerging research suggests the Sheffield support snood provides both support and flexibility, as well as good comfort and aesthetic (Baxter et al., 2016) (Fig. 8.2). In preadolescent children with neuromuscular scoliosis, including those with spinal muscular atrophy (SMA), muscular dystrophies, and peripheral neuropathies, including the hereditary motor

Table 8.2 Cervical Orthoses/Collars

Collar Type	Examples	Indication	Benefits	Disadvantages
Soft	Foam	Mild neck extensor weakness	Comfortable Well-tolerated	Minimal limitation of neck movement
Semirigid or hard	Aspen[a] Malibu[a] Miami-J[a] Philadelphia	Moderate to severe neck weakness	Limitation of neck flexion and extension	Discomfort Skin breakdown
Open air	Headmaster Executive Canadian		Often the most acceptable balance between stability and comfort	Limited lateral support
Baseball cap (Bergsma et al., 2016)	Can be individually fabricated by a therapist	Good neck extensor strength and adequate cervical spine range of motion	Cosmesis Comfort	

[a]These collars provide increased sagittal and lateral support, as well as anterior neck access.



Fig. 8.1 Rehabmart.com, Headmaster Cervical Collar by North Coast Medical.



Fig. 8.2 Sheffield support snood. (Image reproduced with permission from Baxter, S., Reed, H., Clarke, C., Judge, S., Heron, N., Mccarthy, A., et al. (2016). Evaluating a novel cervical orthosis, the Sheffield Support Snood, in patients with amyotrophic lateral sclerosis/motor neuron disease with neck weakness. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 17*, 436-442.)

and sensory neuropathies/CMT disease, thoracolumbosacral orthoses can be used to provide support to the spinal column during growth. Molded seating supports can be used adjunctively for spine support as well. Orthosis use cannot prevent curve progression; if the curve has progressed significantly or seating positioning is compromised, surgery is typically performed at the onset of puberty in those who qualify as surgical candidates. In many individuals, surgery is performed prophylactically in anticipation of curve progression. In those who are not surgical candidates, thoracolumbosacral orthoses and wheelchair modifications addressing seating and arm height can provide stability and comfort.

UPPER EXTREMITY ORTHOSES

Upper extremity orthoses compensate for weakness, position an extremity for comfort and function, and enforce directional control in the treatment and prevention of contractures. Orthoses can be static (to prevent deformity, reduce tone), serial static (to provide stretch), static progressive (to provide stretch), dynamic (to allow restricted motion), or adaptive/functional (to compensate for absent upper extremity function).

Considerations in selecting and fitting upper extremity orthoses include cosmesis, skin protection, extremity positioning, tolerability, and individual functional goals. Tolerability includes comfort and lack of interference with desired hand functions. Grasp is most effective with the wrist in extension



Fig. 8.3 Hand splints. (A) Resting hand splint. (B) Anticlaw splint. (C) Dynamic finger extension splint. (D) Cock-up splint. (E) Opponens splint. (Reproduced with permission from Gordon, P.H., Przedborski, S., & Mitsumoto, H. (Eds.). (2006). *Amyotrophic Lateral Sclerosis.* Boca Raton, FL: CRC Press. https://doi.org/10.1201/b14133.)

and slight radial deviation. Most right-handed individuals write with the wrist slightly extended, whereas left-handed individuals write with the wrist slightly flexed. For maintenance of muscle stretch, it is desirable for joints to be held at the end range of motion for the maximal tolerated duration.

Weakness of proximal upper extremity muscles, as can be seen, for example, in FSHD, Emery-Dreifuss muscular dystrophy (EDMD), proximal myopathies, and motor neuron disorders, can result in glenohumeral joint subluxation, contractures, pain, and diminished function. Although slings cannot always prevent subluxation, they can be used for support and pain relief. Slings can be used in conjunction with appropriate seating and arm rests for individuals who use wheelchairs. Types of slings include the humeral cuff and pouch/single strap. The humeral cuff sling consists of an arm cuff on the distal humerus secured by a figure-of-eight harness. The pouch sling supports the elbow and wrist; however, because this sling holds the upper extremity in adduction, internal rotation, and elbow flexion, it may promote the development of contractures over time.

For individuals with intrinsic hand muscle weakness, wrist-hand and hand-finger orthoses can be utilized. The resting hand splint (wrist-hand orthosis) can be used during the days or at night to maintain muscle length and reduce contracture risk. This orthosis promotes wrist and metacarpophalangeal extension, along with interphalangeal flexion. An anti–claw hand splint can reduce claw-hand deformity and improve grasp by limiting metacarpophalangeal extension of digits four and five.

Individuals with finger flexor (notably IBM) or extensor weakness can use a variety of wrist-hand-finger orthoses to improve grasp and reduce contracture risk. These include the dynamic finger-extension splint for individuals with finger extensor weakness and adequate flexor strength; a volar cock-up splint for those with wrist and finger extensor weakness; and an opponens splint for those with abductor pollicis brevis, extensor pollicis longus, and extensor pollicis brevis weakness. The tenodesis orthosis (wrist-driven prehension orthosis) allows an individual with finger flexor and extensor weakness to create a three-jaw chuck handgrip using wrist extension. Fig. 8.3 depicts several of the orthoses discussed here. Functional upper extremity orthoses can afford individuals with upper extremity weakness increased independence in performing specific daily activities. These orthoses include the universal cuff to compensate for limited hand function and the balanced forearm orthosis to compensate for shoulder abduction weakness. The universal cuff is secured to the hand by an elastic strap and has a pocket that can hold utensils, hygiene tools, and writing implements. The balanced forearm orthosis (also known as a ball bearing feeder) supports the weight of the forearm and arm against gravity and utilizes ball bearings to allow for independent horizontal movement. These movements facilitate manipulation of desktop items and independent grooming and feeding. Balanced forearm orthoses can include adjustable resistance and ROM settings, as well as flexible mounting options.

Nonmotorized passive exoskeletons as well as motor-powered exoskeletons triggered by minimal muscle movement



Fig. 8.4 Boy with Duchenne muscular dystrophy testing a prototype of A-gear, while also wearing electrodiagnostic and motion detection equipment. (Image reproduced with permission from Kooren, P. N., Dunning A. G., Janssen, M. M., Lobo-Prat, J., Koopman, B. F., Paalman, M. I. et al. (2015). Design and pilot validation of A-gear: A novel wearable dynamic arm support. *Journal of Neuroengineering and Rehabilitation*, *12*, 83. https://doi.org/10.1186/s12984- 015-0072-y.)

are increasingly being refined and tested, particularly for serving the population of individuals with DMD. Dynamic arm supports with multiple joint control, such as the innovative A-gear, can be worn relatively inconspicuously and comfortably and allow the user to initiate and carry out movement in multiple planes (Kooren et al., 2015). Fig. 8.4 shows a boy with DMD wearing a prototype of A-gear. Exoskeletal technology can be utilized in both the rehabilitation training setting and in the home, with the focus in both settings generally upon facilitating functional independence for as long as possible.

Rates of use of both passive and motorized upper extremity robotics to support function remain relatively low in the DMD population, with equipment weight, aesthetic, and limitations in replicating natural movement limiting their use. Emerging attention to user assessment, new technologies such as soft (wearable) robotics and eye gaze access, and facilitation of natural mechanics for performing ADLs will hopefully improve state-of-the-art equipment and increase meaningful usability (Bergsma, Lobo-Prat, Vroom, Furlong, & Herder, 2016). A recent report described the potential for powered exoskeletal robotic technology to be triggered by surface EMG readings even in late-stage Duchenne, providing optimism that technology may be able to extend functional independence for longer than has generally been thought possible (Lobo-Prat, Janssen, Koopman, Stienen, & de Groot, 2017). Further research in this area is warranted.

LOWER EXTREMITY

LOWER EXTREMITY ORTHOSES

In NMDs, ankle dorsiflexion, knee extension, and hip flexion weakness can be quite marked. Similar to upper extremity orthoses, lower extremity orthoses are used to compensate for weakness, position an extremity for comfort and function, and enforce directional control. Orthoses should be as lightweight as possible. Cognitive status and upper body strength must be considered in order to optimize ease of use of lower extremity orthoses. The physiatrist, orthotist, and physical therapist collaborate in assessing gait and orthosis needs and in training individuals in the use of the orthoses. Often, a nurse also participates in the care of individuals using orthoses by teaching about and screening for effects on the skin.

AFOs are the most commonly prescribed lower extremity orthoses in adults with NMDs. AFOs are prescribed for individuals with ankle dorsiflexion weakness to optimize safe, efficient ambulation (promote clearing of the toe during swing phase) and prevent ankle plantar flexion contractures. When prescribed for poorly selected candidates, however, AFOs can limit both gait and function. For example, solid-ankle AFOs reduce equinus, yet in children with DMD, for example, equinus gait may be compensatory for weak quadriceps muscles. Particularly in children, impaired gait may be more functional than braced gait. Generally, AFOs can be solid or hinged, static or dynamic and can be modified to accommodate quadriceps weakness, spasticity, and desired function. Often, new or modified shoes may be required to accommodate an AFO's bulk and shape. Fig. 8.5 depicts examples of commonly used AFOs.

Solid (nonhinged) AFOs include the solid-ankle, semi-solid-ankle, and posterior leaf spring (PLS) AFOs. The standard solid-ankle AFO is made of thermoplastic material and provides maximal static stability in all planes of ankle-foot movement. This AFO encapsulates the posterior calf, with the proximal border 1 to 2 inches below the fibular head. Anterior and posterior trimlines are at the midlines of the malleoli. Because it is a static AFO, it does not allow for any ankle movement in the sagittal plane. This restriction of movement can limit sit-to-stand transfers and stair climbing. As needed, an AFO can be set in a few degrees of plantar flexion to help prevent buckling at the knee or a few degrees of dorsiflexion to limit hyperextension at the knee. If the AFO is set in dorsiflexion, an individual must have sufficient quadriceps control to compensate for rapid knee flexion during the loading phase of gait. Semi-solid-ankle AFOs have trimlines posterior to the malleoli, and although they do not provide as complete ankle support as solid-ankle AFOs, semi-solid-ankle AFOs may be better tolerated than solid-ankle AFOs when used bilaterally.

The PLS AFO is a dynamic AFO, allowing for some flexibility of the anatomic ankle joint in the sagittal plane. The PLS AFO has trimlines posterior to the malleoli and has a narrow posterior calf component. It allows for tibial advancement over the forefoot during the stance phase of gait and for adequate clearance of the foot during the swing phase. However, it does not provide complete ankle stability in other planes of motion or provide firm equinus support. The PLS AFO is indicated for individuals with mild ankle dorsiflexion weakness but limited tone. Hypertonicity and spasticity can diminish the functionality of the PLS AFO by overcoming its flexibility.

Floor-reaction AFOs are solid-ankle AFOs that incorporate pretibial shells that limit tibial advancement during the stance phase of gait, thus reinforcing knee extension and overall gait stability. These AFOs are indicated when quadriceps strength is ≤3+/5 on the MRC scale and knee range of motion is good. Floor-reaction AFOs are not indicated for individuals with structural knee abnormalities. Individuals with poor postural control may need to use canes or other assistive devices along with the floor-reaction AFOs.

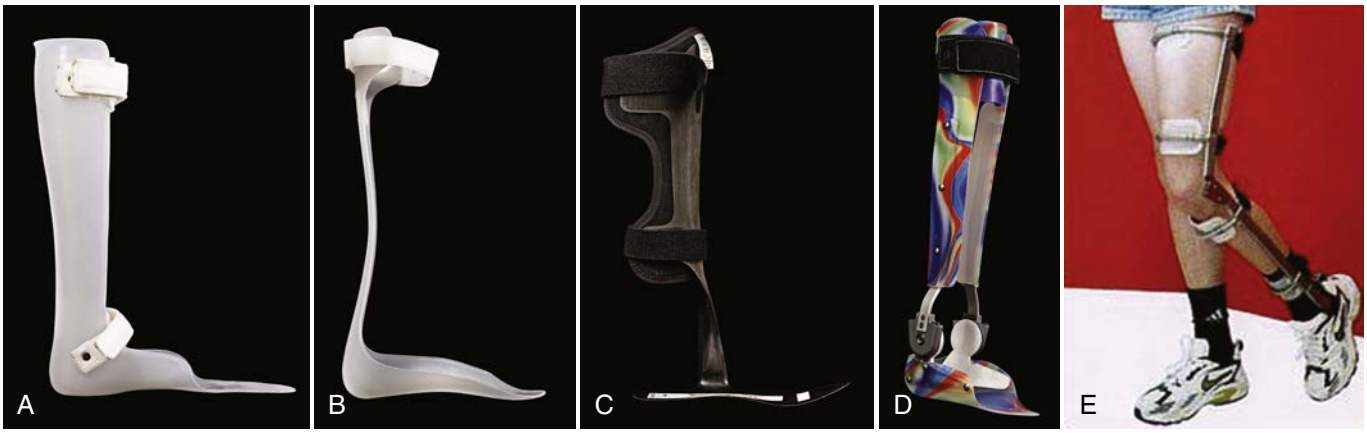


Fig. 8.5 Lower extremity orthoses. (A) Solid-ankle ankle-foot orthosis (AFO). (B) Standard posterior leaf spring orthosis. (C) Floor-reaction AFO. (D) Hinged AFO with anterior shell. (E) Stance control knee-ankle-foot orthosis. (A–D, Courtesy of Mitch Weiss, www.mitchweiss.com; E, with permission from Becker Orthopedic, www.beckerortho.com.)

As compared with solid AFOs, hinged (or articulating) AFOs allow for easier sit-to-stand transfers and stair climbing. The articulation across the ankle allows for improved anterior displacement of the tibia over the foot during the stance phase of gait. Hinged AFOs tend to be most appropriate for individuals with mild ankle dorsiflexion weakness and fairly preserved quadriceps strength. A 90-degree plantar flexion stop can be added to a hinged AFO to limit ankle plantar flexion in the setting of increased tone. A disadvantage of the hinged AFO is slightly increased weight and greater bulk around the ankle, making it more difficult to find shoes to accommodate it. Adductor spasticity and bilateral hinged AFO use can result in the medial aspects of the orthosis componentry catching, leading to falls.

In individuals with progressive quadriceps weakness, such as those with IBM, even a floor-reaction AFO may provide insufficient support over time. The stance-control knee-ankle-foot orthosis (KAFO) can lock and unlock without user manipulation, thus optimizing gait mechanics. The weight of this orthosis and the training required for its use may prohibit individuals with excessive weakness, fatigue, or cognitive impairment from successfully utilizing the device. Older KAFO designs include those with ratchet locks, drop locks, ball locks (for individuals with poor hand control), and dial locks (adjustable for knee flexion contractures). These older designs are often used by patients with a history of polio and by some boys with DMD but are not practical for those with most other NMDs. They are relatively heavy and require walking with a locked knee, which is not possible in the setting of significant proximal weakness.

Antispasticity features that can be incorporated into AFOs and KAFOs include full foot plates, metatarsal head supports, built-up medial longitudinal arches, plantar flexion stops, and peroneal ridges.

If upper body strength allows, AFO and KAFO use can be accompanied by the use of crutches, canes, and walkers as needed for support and balance.

LOWER EXTREMITY ROBOTICS

In the NMD population, lower extremity robotics tend to be used somewhat experimentally, and for gait training more so than for daily home use. This is due in large part to cost and cumbersome nature of use (existing robotics are bulky and limited substantially in use by proximal and upper extremity weakness).

Exoskeletal supported treadmill training, historically utilized in nondegenerative conditions such as spinal cord injury, stroke, and cerebral palsy, has recently been tested in individuals with proximal weakness and gait impairment resulting from LGMD. The repetitive ambulation training seems to be both feasible and to have a positive effect on ambulation endurance (Sczesny-Kaiser et al., 2017). While there are limited data in this area, a recent case report suggests that the combination of conventional rehabilitation therapy and overground exoskeletal supported gait training may have a beneficial impact on gait parameters in myotonic dystrophy type 1 (Portaro et al., 2019).

CANES, CRUTCHES, AND WALKERS

Canes, crutches, and walkers can be used with or without orthoses to normalize gait pattern, reduce energy expenditure, and enhance balance, safety, and mobility. These aids can be considered extensions of the upper limbs; therefore, the maintenance of upper limb strength and range of motion can prolong their use. Device selection is based on strength, tone, and range of motion in the trunk and upper and lower extremities; degree of body weight support needed; degree of fatigue present; rate of disease progression; individual desires and goals; and insurance coverage/affordability. Training by a physical therapist on any aid prescribed is recommended.

In general, canes provide the least support for gait stability and can be recommended for individuals with mild lower extremity weakness or balance impairments. Canes can be wooden or aluminum, solid or adjustable height, with one or four points of contact with the ground, and with narrow or wide bases. Grips on handles can be enlarged to accommodate handgrip weakness. A cane should be held in the arm opposite the weakest side and should be fitted for 20 degrees of elbow flexion. One should lead with the stronger limb on flat ground. One should also lead with the stronger limb for ascending stairs and with the weaker limb for

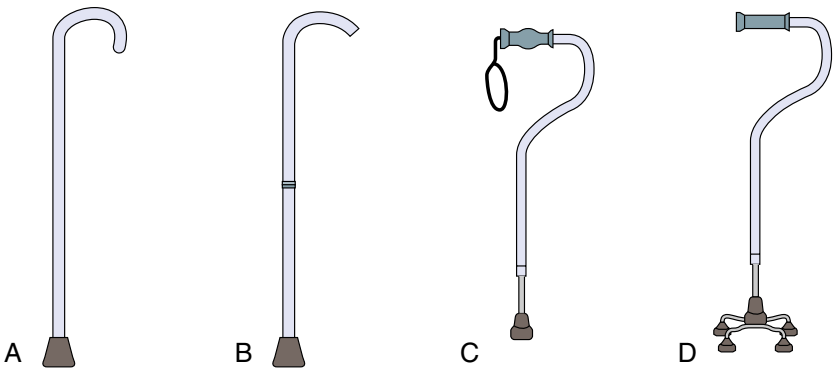


Fig. 8.6 Canes. (A) Standard wooden cane. (B) Adjustable aluminum cane. (C) Adjustable aluminum cane with offset handle. (D) Four-point quad cane. (Reproduced with permission from *Amyotrophic lateral sclerosis*. (2006) Taylor & Francis.)

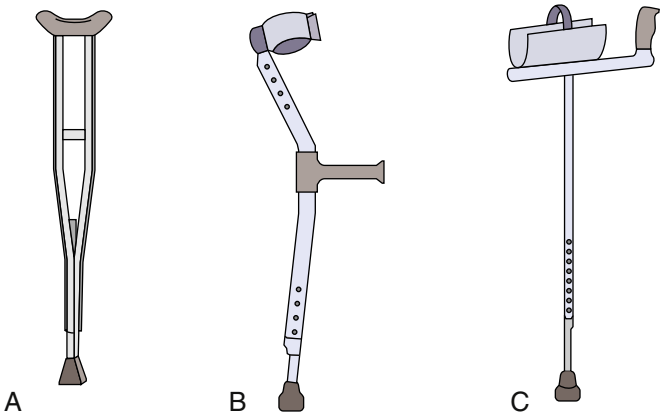


Fig. 8.7 Crutches. (A) Axillary crutch. (B) Lofstrand or Canadian crutch. (C) Platform crutch. (Reproduced with permission from Gordon, P.H., Przedborski, S., & Mitsumoto, H. (Eds.). (2006). *Amyotrophic Lateral Sclerosis.* Boca Raton, FL: CRC Press. https://doi.org/10.1201/b14133.)

descending stairs. Quad canes, which provide four points of contact with the ground, can be of standard or wide base and provide additional stability as compared with standard canes. Different types of canes are shown in Fig. 8.6.

Crutches provide support from the axilla to the floor. They are indicated for individuals with lower extremity weakness but preserved upper extremity and trunk strength. Lofstrand crutches are typically recommended over standard axillary crutches because they provide a forearm cuff that can free hands for use during standing. Platform forearm orthoses are useful for individuals with elbow flexion contractures or severe hand weakness. Crutch tips and handgrips must be routinely evaluated to ensure integrity and safety. Three types of crutches are depicted in Fig. 8.7.

Walkers provide greater support for ambulation than canes and crutches. Options for walkers include folding, wheeled, and with brakes. Seating surfaces, baskets, and trays can also be added. When brakes are selected, push-down brakes (engage when body weight is placed over the walker) are preferable to squeeze brakes for individuals with hand weakness. A lightweight wheeled walker with a seat and handbrakes is commonly used by people with ALS early in disease course. Given the rapidity of disease progression, however, once an individual begins to use a walker, anticipatory planning for fall prevention and response, as well as future wheelchair use, should be initiated. Three walkers are depicted in Fig. 8.8.



Fig. 8.8 Walkers. (A) Standard walker. (B) Wheeled walker. (C) Specialized walker. (Reproduced with permission from *Amyotrophic lateral sclerosis*. (2006). Taylor & Francis.)

SEATED MOBILITY OPTIONS

When independent or assisted ambulation is not feasible, seated mobility options can be used to maximize functional independence. These include power scooters, manual wheelchairs, and power wheelchairs. Power scooters should be recommended with caution for individuals with NMDs. Power scooters require good upper extremity and trunk strength, cannot be modified for disease progression, and when covered by insurance, can preclude insurance coverage of power wheelchairs within a several-year time period. Individuals with IBM tend be the largest subset of individuals with NMD who use power scooters.

A manual wheelchair can be used when an individual cannot ambulate long distances independently. Frequently, individuals with NMDs will not be able to self-propel a manual wheelchair due to easy fatigability and the need to conserve energy. For ease of transport, wheelchairs prescribed should be lightweight (<36 pounds) or ultra-lightweight (<30 pounds) and with folding frames rather than rigid frames. Of note, a standard manual wheelchair, such as that used in hospitals, should not be prescribed because it is heavier than these chairs and comes in a more restricted set of seat width, seat depth, and back height options. Standing capability for a manual wheelchair, which can provide weight-bearing and pressure relief, confers limited stability and flexibility for wheelchair modifications and is not typically prescribed for individuals with NMDs. Particularly for individuals with rapidly progressive diseases, such as ALS, a manual wheelchair should be rented or borrowed through organizations such as the Amyotrophic Lateral Sclerosis Association or Muscular Dystrophy Association, because most insurance companies will reimburse for only one wheelchair purchase over the course of several years. Insurance coverage for an eventual power wheelchair should be the priority.

Power-assist wheelchairs provide powered assistance to manually controlled use. They are heavier than manual wheelchairs and do not provide the flexibility of modifications available for fully powered wheelchairs. For these reasons, as well as the considerations described earlier, power-assist wheelchairs are typically not recommended for individuals with progressive NMDs.

When manual wheelchair use is no longer feasible due to weakness or the need for the use of ventilator or other equipment, full-power wheelchairs are used. The transition from manual to power wheelchair use can be psychologically, physically, and logistically challenging. These challenges include psychological adjustment to disease progression, the need to modify previously used methods for performing ADLs and transfers, the need to modify home and work environments, and the need to modify vehicles and typical means of transportation.

Power wheelchairs are divided into three classifications by the Centers for Medicare and Medicaid Services (2019). Class A wheelchairs are the conventional nonprogrammable power wheelchairs with basic seating. Class B wheelchairs can be modified based on an individual's needs in the realms of speed, acceleration, and braking. Class C wheelchairs, the most durable and modifiable, allow for seating, pressure relief, and ventilator modifications. Class C wheelchairs allow for the most flexibility and accommodation for long-term needs.

Specialty wheelchair and seating clinics, often coordinated by physical therapists, can provide expert recommendations to a rehabilitation team regarding optimal individualized wheelchair systems. Seat width, depth, and height, as well as back height and leg rest length, are based generally on the height and size of the user. Componentry for head and neck support (e.g., head rests), trunk support (e.g., lateral supports), seating/cushioning (e.g., molded cushioning to accommodate orthopedic abnormalities), pain and pressure relief (e.g., tilt-in-space or recline functionalities), upper and lower extremity support, and seatbelts can be individualized based on patient needs. Flexibility for adding items such as trays, ventilators, and communication or other equipment must also be specified.

Final factors that must be specified are type of drive and user-wheelchair interfaces. Wheelchairs can be front-, mid-, or rear-wheel drive. Front-wheel drive chairs navigate bumps and curb cuts well but do not track straight consistently. Mid-wheel drive chairs have the smallest turning radius and can negotiate some outdoor terrain. Rear-wheel drive chairs have the most consistent straight tracking but have a large turning radius and are most appropriate for patients who are heavy outdoor users. Many factors go into drive selection. Because most homes were not built to accommodate wheelchairs with large turning radii, mid-wheel drive chairs are often utilized to facilitate use in the home.

The user-wheelchair interface refers to the means by which a user controls their wheelchair. Interfaces include the joystick, sip-and-puff mechanism, head array switch, voice control, and eye gaze control. Joystick selection includes several features: proportional versus switched control, mounting site (joysticks can be operated by nearly any body part), and shape. The sensitivity of the input device must be programmed to match the user's capabilities. The sip-and-puff mechanism is particularly useful for individuals with SMA, who retain strong respiratory systems while losing significant extremity strength. Eye gaze control can be valuable for individuals with advanced ALS. Importantly, eye gaze control requires substantial training time and cognitive capacity. These factors need to be anticipated in advance.

Integrated controls are also available—for these, a single input device, such as a joystick, can be toggled between controlling the wheelchair and controlling other electronic devices in the home.

Wheelchair features can be designed to accommodate weakness, spasticity, contractures, and anticipated medical and functional needs. Allowing an individual to personalize a wheelchair through choice of a esthetic design features such as color is also recommended.

The process of obtaining a power wheelchair through insurance requires multiple steps, including detailed physician documentation of need. It is recommended that a prescriber review each patient's insurance company requirements prior to initiating a wheelchair prescription. Typically, in order for a patient to qualify for a powered mobility device, the prescribing physician must document why a manual device is insufficient, that the device is required for home-based mobility-related ADLs (insurance does not cover mobility devices for activities out of the home, including medical appointments; the mobility device must be required to facilitate the performance of typical ADLs in their typical location, e.g., bathing in a bathroom), that the individual receiving the wheelchair has expressed willingness to use it, and that the individual has the cognitive capacity and supports to be able to use it (Karol & Elerson, 2007). It can easily take 4–6 months from the time of prescription for an individual to receive a power wheelchair.

ORTHOSES AND MOBILITY DEVICES IN PEDIATRICS

The landscape of orthotics and mobility devices for children with NMDs can be somewhat different from that for adults. Orthotic options more often include KAFOs, hip-knee-ankle-foot orthoses, and reciprocating gait orthoses. In adults, other considerations, including rapidity of disease course, energy cost of using complicated, heavy orthoses, and psychological barriers, often restrict the range of orthoses used.

Upright environmental exploration promotes cognitive, motor, and social development in children and is encouraged to the greatest extent possible. Standing frames, caster carts, and reverse walkers can be used to support standing and normalize interactions with peers and others. For example, the reverse walker has a posterior horizontal bar and the user's arms are placed on the siderails. In this way, there is no barrier between the user and an individual or object in front of them.

Adaptive strollers are often used for toddlers and children who require positioning support. These can appear very similar to typical strollers, although they have built-in supports and straps. They can be substantially more expensive than typical strollers. As compared with wheelchairs, they are less visually identifiable as specialized equipment and can be easier to transport. Insurance companies vary in their coverage of adaptive strollers.

Adaptive car seats and boosters are also available, with variable insurance coverage.

Wheelchair design features for children include flexibility for accommodating growth, capability for incorporating



Fig. 8.9 (A) Adaptive stroller (Kimba Buggy). (B) Pediatric wheelchair. (A, (Courtesy of Otto Bock Mobility Solutions GmbH - Kimba Buggy.); B, reproduced with permission from Permobil.)

educational technologies, and capability for facilitating interactions with peers. Wheelchairs must also be manageable and transportable by families. A common feature unique as compared with wheelchairs for adults is a seat that can lower to the floor to allow for face-to-face play with peers.

Fig. 8.9 shows an adaptive stroller and a pediatric wheelchair.

ASSISTIVE DEVICES FOR ACTIVITIES OF DAILY LIVING

Basic ADLs include self-care tasks such as eating and feeding, grooming and bathing, dressing and undressing, toileting, and initiating functional mobility. Engaging in sexual activity is often considered an ADL as well. Instrumental ADLs (IADLs) are activities that support daily life and tend to be more complex than ADLs. Individuals can often remain independent in their homes with assistance with IADLs. IADLs include housework, meal preparation, caring for children and pets, shopping, driving, managing finances, managing medications, and participating in safety and emergency procedures.

Several types of modifications can facilitate independence with ADLs and IADLs. A task can be modified, the tools needed to complete the task can be modified, or the environments in which the task is performed can be modified. Most often, a combination of these modifications is required. Assistive devices for self-feeding and manipulating food; for grooming, bathing, and toileting; and for dressing and undressing can be found in Tables 8.3 to 8.5. To optimize their use, these devices must be appropriately placed near the individual using them and should be used when the individual is appropriately awake and attentive. Occupational therapists can provide additional recommendations as well as assistance with creating appropriate individualized aids. Individuals and families can also share creative adaptations that can, in turn, be shared with others.

ASSISTIVE DEVICES FOR FUNCTIONAL MOBILITY

Assisted ambulation and wheelchair mobility permit substantial independence for individuals with NMDs.

Table 8.3 Assistive Devices for Self-Feeding and Manipulating Food

Device	Use
Universal cuff	To hold utensils; compensate for intrinsic hand weakness
Balanced forearm orthosis	To bring food to mouth; compensate for upper extremity weakness
Built-up utensil and cup handles, rocker knives, swivel utensils, weighted utensils and cups, extended straws, straw holders	To manipulate utensils, cups, straws; compensate for intrinsic hand weakness
Scoop dishes, plate guards, food bumpers	To manipulate food, reduce spilling
Spork	To allow for multiple functions with one utensil
Nonslip matting, bowls and plates with suction bottoms	To prevent slipping
Sippy cups, cut-out cups, spouted cups, modified shapes for bottles	To consume liquids; compensate for upper extremity weakness and oromotor dysfunction

Daily functional mobility also includes bed mobility, transfers, and long-distance transportation. Bed mobility—getting into and out of bed and repositioning while in bed—can be facilitated by overhead trapezes, step stools, and powered hospital beds. Transfers—transitioning between surfaces—can be facilitated by using ability-appropriate techniques as taught by a rehabilitation team, use of a slide board, and use of wheelchair features such as adjustable seat height. Long-distance transportation can be facilitated by driving modifications such as hand controls and built-up knobs and handles, as well as transportation modifications such as wheelchair tie-down systems, power lifts and ramps, and custom car seats for children.

Table 8.4 Assistive Devices for Grooming, Bathing, and Toileting

Device	Use
Shower benches, bathtub seats, shower commode chairs, grab bars,[a] raised toilet seats	To accommodate weakness, conserve energy, promote safe transfers
Handheld shower heads, long-handled sponges, bath mitts, electric toothbrushes and shavers, long-handled combs, strap-fitted hairbrushes, swiveling back scrubbers, clamp-on adjustable mirrors, nail brushes with suction cup bases	To accommodate weakness and diminished range of motion, promote complete hygiene
Shoulder-mounted shampoo rinse trays	To facilitate hair-washing from a wheelchair over a sink
Toenail clippers with long handles	To accommodate spine flexion weakness

[a]It is important to educate patients and families that grab bars must be specifically and appropriately installed; typical towel racks are insufficient to support body weight.

Table 8.5 Assistive Devices for Dressing and Undressing

Device	Use
Mechanical button loopers, modified button and snap hooks, modified zipper pulls and hooks, hook-and-loop clothing closures, elastic shoelaces	To compensate for intrinsic hand weakness and impaired dexterity
Long-handled sock and shoe horns	To reduce the need for lumbar flexion for donning and doffing socks
Dressing sticks with mechanical graspers	To compensate for upper extremity weakness and allow an individual to pull the side of a sweater or shirt across the front of the body

Public transportation systems are required by law to accommodate individuals with mobility and other impairments; often, these public transportation systems will provide access to existing buses and trains, as well as specialized paratransport systems. To enroll in the latter, patients require a physician's documentation of justification. On-demand car services are increasingly providing accessible transport vehicles and drivers trained to accommodate riders with special needs as well.

ASSISTIVE DEVICES FOR ENVIRONMENTAL CONTROL AND COMMUNICATION

Environmental controls and communication aids allow individuals to manipulate their surroundings and interact with others. Generally, inputs for environmental control and communication systems include switches, remote controls, and computers. As mainstream technology becomes increasingly voice-activated, so too are adaptive devices able to be voice-activated. For example, individuals with NMDs and substantial physical limitation are able to use off-the-shelf voice-activated technology in their homes for operating appliances and communicating with others. For individuals with NMDs who are anarthric or dysarthric but can use their hands, simple text-to-voice smartphone technology available to the general public has been invaluable in facilitating communication.

Physical environmental controls include key extenders to provide larger key grip surface areas, doorknob adapters that convert doorknobs to lever mechanisms, electric door openers, and lamp switch extenders.

Call bells that connect to caregivers or emergency response systems can be accessed in a variety of ways, ranging from voice activation to hand control to respiratory (sip and puff) control. Telecommunication or texting devices that allow rapid written communication are particularly important for individuals with bulbar-predominant disorders that limit voiced communication. All equipment should be carefully selected and tested and should be evaluated frequently for ease of use. A caregiver should ensure that the call bell is placed within reach and/or is accessible before leaving an individual on their own for any amount of time.

ASSISTIVE DEVICES FOR COMMUNITY PARTICIPATION

Additional equipment can be prescribed or created to optimize participation in the classroom, work environment, and leisure and athletic activities. Devices prescribed and created to meet individual needs are as numerous as the number of individuals who use them. Individual needs and desires can be optimized via evaluation by a rehabilitation team that includes a physical therapist, occupational therapist, recreational therapist, technology specialist, educational specialist, and physiatrist. Often, individuals and families create their own solutions to daily ADL and IADL challenges, and professional care teams can learn important tricks and tips from them that can be shared with other patients and families.

ENVIRONMENTAL EVALUATIONS AND MODIFICATIONS

Physical and occupational therapists can provide home evaluations and make recommendations for improved accessibility and safety. Home modifications and renovations typically are not reimbursable by Medicare or most private insurance companies but may be covered by Medicaid in some instances. The range of possible home modifications is vast; basic adaptations to accommodate wheelchair use are discussed here.

To access a home, portable ramps, vertical platform lifts, or permanent ramps can be installed. A ramp cannot exceed 1 foot of height per 12 feet of length. Doorframe widths of

32 inches will allow most wheelchairs and walkers to clear. If a wheelchair must enter a door from an angle, a doorframe width of 36 inches is usually required. Doors to small rooms can be made more accessible by reversing them to swing open instead of inward, replacing them with folding doors, or removing them entirely. Offset hinges can increase doorway width by 2 inches. These modifications can allow for sufficient space for room entry and maneuvering within the room. A minimum of 60 inches for a wheelchair turning radius and 30 to 36 inches to approach a surface for transfer is recommended as well. Door handles, light switches, soap dishes, and other reachable items should be between 30 and 36 inches from the floor to allow for accessibility from a seated position.

Home modifications for hygiene and toileting include eliminating rims from shower stalls and creating a space for commode use outside of bathrooms if there is inadequate bathroom space. Kitchen modifications include removing cabinets from under sinks to accommodate wheelchairs. Staircases can be fit with custom-made chair glides and stair lifts, but their use may be limited by cost, home infrastructure, and limited space to allow for transfers at the tops and bottoms of the staircases. Often, individuals who have upper floor bedrooms transform lower floor rooms, such as dens, into bedrooms. When possible, partners should consider sleeping in the same room as the individual with NMD, in order to maintain typical relationship interaction to the greatest extent possible.

SCHOOL AND WORKPLACE MODIFICATIONS

The Americans with Disabilities Act and the Individuals with Disabilities Education Act require modifications for the school and workplace, as well as other community venues, to accommodate individual needs that can be generated by NMDs. A key role for physicians and other clinicians involved in the care of individuals with NMDs is to educate patients about their rights and to advocate for patients through communication with schools and workplaces. Clinicians can also point individuals with NMDs and their caregivers to local and national support and advocacy organizations. These organizations can provide additional information and recommendations for communicating with schools and workplaces regarding obtaining appropriate accommodations.

ORTHOPEDIC CONSIDERATIONS

Skeletal deformities most commonly encountered in the context of NMDs include scoliosis, joint contractures, and abnormalities of the feet. Despite conservative efforts at the prevention of these deformities, surgical orthopedic intervention is often required. The goals of both rehabilitation and orthopedic intervention include optimizing functional independence, comfort, pulmonary function, and personal hygiene.

NEUROMUSCULAR SCOLIOSIS

Neuromuscular scoliosis—sagittal deformity of the spine in individuals with neuropathic or myopathic disease—is particularly common in rapidly progressive NMDs that begin in childhood. Although the precise mechanisms generating scoliosis have not been fully elucidated, muscle strength imbalances, immobility, and possibly dominant handedness likely contribute. In DMD, the development of scoliosis seems to co-occur with the onset of wheelchair use, but no causal relationship between wheelchair use and curve progression has been established. Both scoliosis and the onset of wheelchair use occur during the pubertal growth spurt, around ages 13 to 15 years.

Scoliosis, particularly with curves greater than 40 degrees, creates significant difficulty with seating and positioning, use of the upper extremities, and comfort, and it can also cause respiratory compromise (Karol & Elerson, 2007).

Bracing does not prevent curve progression in neuromuscular scoliosis. Seating modification, optimizing muscle strength and use, and patient and family education have similarly not been shown to affect the progression of scoliosis (Hsu, 1983). Surgical spine fusion with instrumentation and early postoperative mobilization are the treatment of choice for individuals with progressive neuromuscular scoliosis. Surgery seems to improve sitting balance and function, as well as ease of care. A recent Cochrane review suggests that there are insufficient rigorous data on the impact of surgery on respiratory function, quality of life, functional status, and life expectancy (Cheuk, Wong, Wraige, Baxter, & Cole, 2015).

JOINT CONTRACTURES

Joint contractures—limitations in full range of motion of joints—are a major consequence of immobility, diminished weight bearing, and muscle imbalance in NMDs. In particular, increased wheelchair use is associated with flexion contractures at the hip, knee, ankle, and elbow, especially in muscles with less than antigravity strength (McDonald, 1998). Because contractures can limit mobility, positioning, hygiene, and comfort, prevention of contractures remains a key component of rehabilitation management.

The cornerstone of contracture prevention is the use of physical modalities. These include daily upright weight bearing with uniform weight distribution, active and passive stretching, and the use of bracing and splinting to promote muscle stretch. For those who cannot perform active stretching of multi-joint muscle groups, passive (performed by another person) stretching is especially important, because typical daily positions do not place key muscles—the gastrocnemius, hamstring, rectus femoris, tensor fascia lata, and iliopsoas muscles—at maximal stretch. Heat and ultrasound may augment the effects of stretching and positioning (Hornyak & Pangilinan, 2007). Individuals with sensory impairment who are using contracture prevention programs must be monitored for fractures and skin breakdown.

An individually tailored contracture prevention program should be initiated as early as possible. The program can be developed by a physical or occupational therapist and can be taught to family members or other caregivers to perform on at least a daily basis. In addition, the program should focus on muscle groups particularly affected in a given condition. For example, a program for an individual with DMD might include the gastrocnemius, soleus, hamstring muscles, the iliotibial band, and the wrist flexors. In EDMD, elbow flexors must be addressed early. In SMA type 2, the

hip, knee, and wrist must be addressed. Importantly, a multimodality approach is key. For example, in a recent study examining 128 boys with DMD taking deflazacort, stretching alone (>5 minutes, >3 times a week) did not seem to prevent contractures (Choi, Chun, Kim, & Shin, 2018). Of note, the stretching regimens were not standardized. The combination of stretching and orthotic use for contracture prevention was not addressed. Further research is warranted in this area. Particularly in individuals who use wheelchairs as a primary means of mobility, contractures may develop despite stretching, positioning, and splinting. Surgical intervention for fixed deformities can promote ease of positioning, prolong capacity for upright weight bearing, and, in some cases, prolong duration of braced ambulation. Because loss of ambulation is associated with weakness more than with contractures, however, surgical intervention for contractures will typically not permit resumption of independent ambulation that was previously lost.

ABNORMALITIES OF THE FEET

Bony and soft-tissue abnormalities of the feet, including cavus (high-arched) feet, equinus (excess plantar flexion), and hammer toes (fixed flexion of the proximal interphalangeal joints of the small toes with hyperextension of the metatarsophalangeal and distal interphalangeal joints), are associated with peripheral neuropathies and weakness of the intrinsic foot muscles, as in CMT disease. These deformities can result in pain, calluses, skin breakdown, gait instability, and ankle instability. Stretching, orthoses, and serial casting in children may delay progression to fixed deformities. However, surgical intervention is often required to promote stability. Shoe modifications such as a widened toebox can improve comfort and protect skin.

Chapter 9 provides further detail on these and other related topics.

RESPIRATORY FAILURE

Progressive respiratory failure impairs quality of life and limits life expectancy in many NMDs, including the anterior horn cell diseases (ALS, PPS, SMA), severe forms of neuropathy (acute inflammatory demyelinating polyneuropathy), neuromuscular junction disorders, and several forms of muscular dystrophies and myopathies. The rehabilitation team must be aware of the patient's respiratory status because it will affect the ability to participate in exercise programs and rehabilitation therapies. Some physiatrists have specialized expertise in pulmonary rehabilitation and the management of patients with restrictive lung disease. In particular, they are skilled in the management of patients using noninvasive ventilatory techniques and equipment, including NIPPV, the pneumobelt, and negative pressure devices such as a cuirass or poncho ventilator. The insufflator-exsufflator (Cough Assist) and manually assisted coughing are indicated to help clear secretions in patients with expiratory muscle weakness. Respiratory monitoring, respiratory therapy services, and care by a pulmonologist are integral to the rehabilitation program for many patients with NMDs.

A recent study evaluated sleep quality in adults with DMD; while hypoventilation can contribute to poor sleep quality, it is not the only contributing factor—if respiratory etiologies are not found, further investigation of subjective poor sleep quality (e.g., for pain, fatigue, anxiety) is warranted (Crescimanno et al., 2020). Among individuals with DMD using noninvasive ventilation, respiratory insufficiency and sleep quality were independent predictors of poor quality of life (Crescimanno, Greco, D'Alia, Messina, & Marrone, 2019).

Patient preferences for use of noninvasive and invasive ventilatory support must be elicited early and through thoughtful advance care planning. Sufficient time for discussion during patient visits is crucial to providing thoughtful goal-concordant care. Preferences may change over time and should be queried at regular intervals by patients' regular clinicians.

Pulmonary assessment, monitoring, management, and rehabilitation are discussed in greater detail in Chapter 2.

DYSARTHRIA

Dysarthria is a motor speech disorder resulting in impaired articulation and speech intelligibility. It interferes with verbal communication when receptive language and other means of communication may be fully intact and can diminish social interaction and quality of life. In NMDs, dysarthria can result from dysfunction of upper motor neurons, lower motor neurons, both upper and lower motor neurons, the neuromuscular junction, and/or muscle itself. The rehabilitation team focuses on maximizing independent communication with attention to the type of dysarthria present, the rate of progression, and patient and family goals.

IDENTIFICATION

In upper motor neuron (also called *spastic* or *pseudobulbar*) dysarthria, speech can be slurred, strained, and harsh, with slowness of movements and occasional bursts of loudness and unanticipated stops. There can be associated brisk gag and jaw reflexes, and notable absence of tongue atrophy and fasciculations. In contrast, lower motor neuron (also called *flaccid* or *bulbar*) dysarthria features a weak voice and associated wasting and weakness of tongue, palatal, and facial muscles; diminished reflexes; and nasal phonation. Dysarthria resulting from neuromuscular junction or muscle pathology typically presents with lower motor neuron features. In motor neuron disease with lower motor neuron features, fasciculations of the tongue can also be seen. In mixed dysarthria, the degrees of flaccidity and spasticity in any single individual can vary (Tomik & Guiloff, 2008).

DYSARTHRIA IN MOTOR NEURON DISEASES

Motor neuron diseases often feature dysarthria of the upper and/or lower motor neuron varieties (Traynor et al., 2000). Dysarthria in ALS, for example, is of the mixed type, typically with prominent lower motor neuron features. Early signs of this pattern of dysarthria include slow speech rate, altered voice quality, difficulty singing, difficulty enunciating, and diminished intelligibility, resulting in decreased communication effectiveness. Speech may also sound hoarse and hypophonic, related to vocal cord and respiratory muscle weakness.

The cornerstone of rehabilitation management in progressive dysarthria is the utilization of verbal and nonverbal strategies to optimize communication throughout the course of disease progression. Speech-language pathology, neurology, physiatry, and, occasionally, otolaryngology assessments can yield comprehensive rehabilitation management strategies with these goals in mind. Of note, aggressive speech therapy per se typically does not have lasting long-term benefits in motor neuron diseases and may worsen speech impairment by causing fatigue.

In mild dysarthria, the rehabilitation team focuses on training patients and social contacts in compensatory techniques to prolong verbal communication. These can include slowing speech rate, using alternative words, spelling, repeating and overarticulating consonants, speaking face to face, using monosyllabic speech, and conserving energy by minimizing environmental noise and the distance between the patient and listeners. Importantly, developing personalized communication strategies between patient and listener can also prolong effective communication; these can include shared strategies for understanding gestures, facial expressions, and eye contact, as well as a system for confirming understanding.

Palatal lifts and palatal augmentation prostheses can be utilized to address hypernasality/hypophonia and consonant articulation, respectively, although little data exist regarding their efficacy. A retrospective review of the use of lifts and prostheses suggests that patients experience improved ease of speaking with their use (Esposito, Mitsumoto, & Shanks, 2000).

As dysarthria progresses, the rehabilitation team can provide augmentative and alternative communication systems. Higher-technology devices are not necessarily better for patients; device recommendations must consider patient and caregiver physical capability, education level, cognitive functional status, socioeconomic means, and general preferences. Optimally, training begins before acute need for the technology. Equipment can often be rented or acquired from charitable organizations. See Table 8.6 for a listing of augmentative communication devices.

Asynchronous communication, including the use of e-mail, texting, and online social networks, can promote maintenance of social contacts without hindrance by slowness of speech/impaired direct in-person communication and should also be encouraged as appropriate.

Finally, brain-computer interfaces (BCIs) are an active area of current study with much promise for use in severe dysarthria/anarthria that prevents verbal communication and co-occurs with severe motor impairment preventing other means of communication. BCIs output information from the brain directly to a computer. The use of both noninvasive (scalp recordings of electroencephalographic [EEG] changes) and invasive (direct recordings from the motor cortex) devices is being investigated in ALS and other conditions resulting in severe dysarthria/anarthria (Hochberg, 2008; Nijboer et al., 2008).

A recent study demonstrated the feasibility of EEG-based BCI use in the home by individuals with ALS. Patients and caregivers described that benefits exceeded burden, and nearly all participants who completed BCI training elected to keep the equipment after the study period (Wolpaw et al., 2018). Fig. 8.10 depicts the BCI utilized in this study.

Assessment and training by occupational and adaptive technology specialists can provide technology users with individually designed accessible communication systems, mounting systems, and switches. Importantly, any technologies selected should be flexible to accommodate changes in user capabilities over time.

Table 8.6 Common Augmentative Devices to Enhance Communication

Type of Technology	Examples
Low	Communication boards, with manual writing Letter/word/picture boards, with eye gaze selection Alarm systems, such as buzzers, with accessible triggers
Higher	Portable voice amplifiers Voice record/playback devices (a patient can record phrases while still intelligible and play them back when no longer able to produce them physiologically) Computerized voice synthesizers on personal computers or dedicated devices (selection of information can be manual, by eye gaze, or by infrared signal) Word prediction technology for spelling words Specialized telephone equipment: hands-free, voice-free, or both

DYSARTHRIA IN NEUROMUSCULAR JUNCTION DISORDERS

Neuromuscular junction disorders, including myasthenia gravis and the Lambert-Eaton myasthenic syndrome (LEMS), can also produce dysarthria, typically with lower motor neuron–type features and a nasal tone. In myasthenia gravis, impairment severity can fluctuate over the course of the day and with medications that alter neuromuscular junction transmission. Bulbar symptoms are presenting symptoms in 15% of individuals with myasthenia gravis and approximately 5% of individuals with LEMS. The latter statistic may be higher in practice, because the recognition of bulbar symptoms as part of LEMS is beginning to emerge (Burns, Russell, LaChance, & Jones, 2003; Wirtz et al., 2002).

Treatment of the underlying disorders produces resolution or improvement of dysarthria. A study of intravenous immunoglobulin in the treatment of LEMS specifically addressed bulbar function by measuring drinking times before and after therapy; there was improvement in this outcome measure after treatment (Bain et al., 1996).

When dysarthria persists despite attempts at disease treatment, rehabilitation management can be employed to optimize speech quality and communication. The rehabilitation program includes patient and family education, speech therapy, and adaptive equipment as needed. Patients and families should be educated about symptoms and triggers, medication compliance, and energy conservation. Speech therapists can offer training in the control of speech rate, articulation, and interpersonal communication strategies. Augmentative communication devices and environmental modifications can also be employed. Finally, there may be

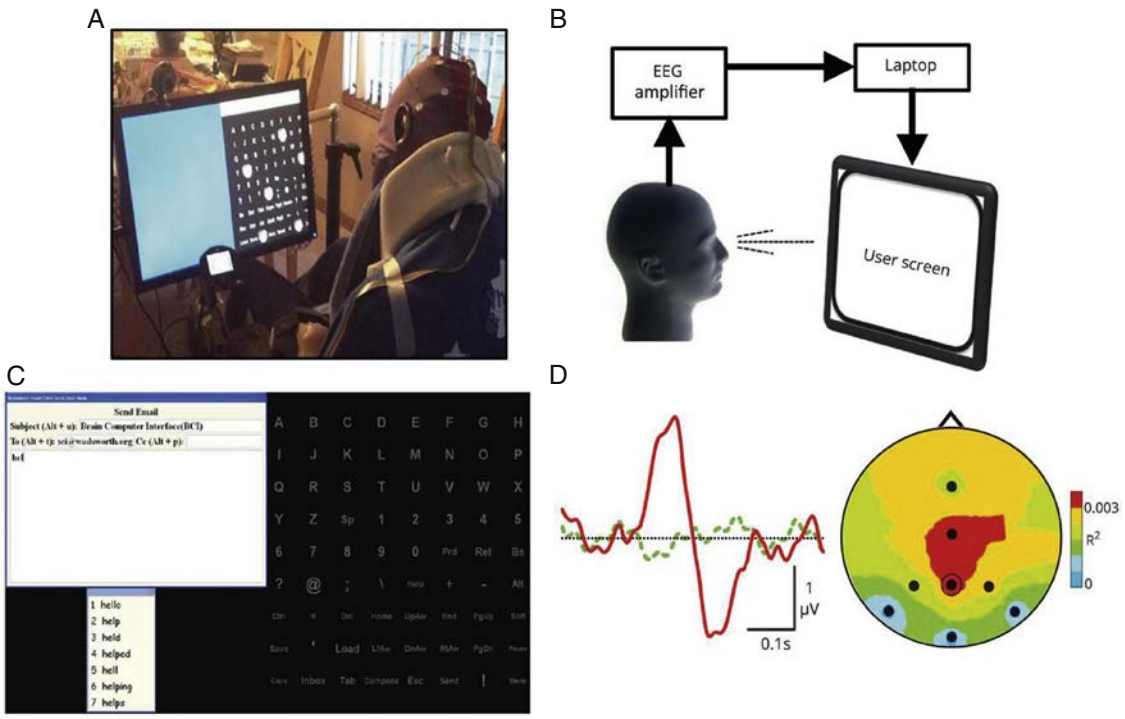


Fig. 8.10 (A) A home user operating the brain-computer interface (BCI). (B) The EEG amplifier amplifies and digitizes the 8 EEG channels. The laptop computer analyzes the EEG, controls the user screen, and stores all data. (C) BCI operation illustrated with the e-mail application. The 72-item matrix of possible selections (i.e., letters, numbers, functions) is equivalent to a full keyboard. To make a selection, the user pays attention to the desired item as groups of items flash in rapid succession. The e-mail message appears at the top left. A predictive speller option (Word Q3; Mayer-Johnson) is at the bottom left (e.g., after spelling "hel," the user can complete the word "hello" simply by selecting the numeral 1). (D) BCI detection of the user's selection. (Left) The user's average EEG response at location Pz to the flash of a group of items that includes the desired item (solid red) differs from the average response to the flash of a group that does not include it (dashed green). The BCI detects this difference and selects the desired item. (Right) Topographic distribution (238 milliseconds after flash; nose at top) of the difference between the 2 responses (measured as R2). The EEG recording sites are indicated (Pz is circled). The difference between the responses has a typical posterior-central focus. (Reproduced with permission from Wolpaw, J. R., Bedlack, R. S., Reda, D. J., Ringer, R. J., Banks, P. G., Vaughan, T. M., et al. (2018). Independent home use of a brain-computer interface by people with amyotrophic lateral sclerosis. *Neurology, 91*, e258-e267.)

a role for respiratory muscle and breathing training in enhancing intelligibility of speech in the setting of dysarthria in neuromuscular junction disorders. Such training has shown positive effects on respiratory muscle strength and endurance (Fregonezi et al., 2005); in turn, improved breath support may enhance speech volume and intelligibility.

DYSARTHRIA IN MYOPATHIES/MUSCULAR DYSTROPHIES/PERIPHERAL NEUROPATHIES

Myopathic (congenital myopathies, mitochondrial myopathies), muscular dystrophic (myotonic dystrophy, oculopharyngeal muscular dystrophy), and peripheral neuropathic (including the hereditary peroneal muscular atrophy syndromes) conditions can also feature lower motor neuron–type or flaccid dysarthria. The general management approach to these conditions is similar to that outlined earlier: optimizing native verbal communication as long as feasible and facilitating continued communication via augmentative and alternative technologies, with early training.

In notable distinction to many other NMDs, however, in which activity can worsen speech production, the opposite is true in myotonic dystrophy. In myotonic dystrophy, both muscle weakness and myotonia contribute to impaired articulation, and speaking loudly may provoke myotonia. Warm-up exercises with prolonged sound production may improve repetition rate and fluency of speech and decrease the myotonic component of dysarthria without producing fatigue (de Swart, van Engelen, van de Kerkhof, & Maassen, 2004). This suggests that more aggressive speech therapy with practice exercises may be of benefit in the treatment of dysarthria in myotonic dystrophy, whereas there remains insufficient evidence of beneficial effects of aggressive speech therapy in the dysarthria of most other NMDs (Knuijt et al., 2011).

DYSPHAGIA

Oropharyngeal dysphagia, resulting from weakness and discoordination of facial, oral, and pharyngeal musculature, is common in many NMDs. Dysphagia can result in aspiration of oral contents, leading to pulmonary infection, social embarrassment, inadequate oral intake, malnutrition, and weight loss. In fact, many patients with myotonic dystrophy, for example, report dysphagia as the most disabling symptom of their disease (Rönnblom, Forsberg, & Danielsson, 1996).

IDENTIFICATION

Indicators of dysphagia include changes in the quality of speech (wet-sounding voice), drooling and leaking of liquids from the mouth, coughing, nasal regurgitation, and choking while eating. Patients may also develop pneumonia after an episode of choking, multiple episodes of pneumonia over

the course of one year, and increasingly prolonged eating time. Unintentional weight loss, dehydration, and malnutrition may develop over time as well.

Patients and family members should be educated early about the signs and dangers of dysphagia. At the first sign of dysphagia, evaluation by a speech-language specialist and, in some cases, a dietitian will allow prompt diagnosis and intervention.

COMPENSATORY STRATEGIES AND INTERVENTIONS

When oropharyngeal dysphagia is identified, the rehabilitation team can design a program of interventions and compensatory strategies to facilitate safe oral intake to the greatest extent possible. These include positional, behavioral, and dietary modifications. Positional changes include posterior head tilt with swallow initiation, chin tuck, and head turning to the side of greater weakness if there is asymmetry. Behavioral interventions include scheduling meals during times of maximal arousal and minimal distraction. Dietary changes include altering food consistency (e.g., thickening liquids) and increasing the caloric density of foods. Finally, in cases in which dysphagia is exacerbated by preoral challenges (i.e., weakness in the extremities limiting ability to bring food and fluid to the mouth), balanced forearm orthoses, universal cuffs, and modified utensils can be used.

If oral intake remains inadequate despite conservative interventions, gastrostomy tubes can be used for supplemental nutrition, weight stabilizations, and possible prolongation of survival. The use of gastrostomy tubes has not been shown to reduce the risk of aspiration. The American Academy of Neurology recommends the placement of gastrostomy tubes for individuals with ALS while they can still tolerate oral intake and before the FVC falls below 50% of predicted because morbidity and mortality associated with the procedure are lower when individuals do not have severe respiratory insufficiency (Miller et al., 2009). However, more recent studies have demonstrated that feeding tubes can be safely placed in individuals with lower FVCs if bilevel positive airway pressure assistance is used during the procedure or if radiologic insertion techniques are used (Rosenfeld & Ellis, 2008; Thornton et al., 2002).

Additional surgical management in select cases of oropharyngeal dysphagia related to impaired relaxation of the cricopharyngeus muscle in neuromuscular disease—particularly IBM—includes botulinum toxin injection, physical dilatation of the muscle, and cricopharyngeal myotomy (Jaradeh, 2006; Oh, Brumfield, Hoskin, Kasperbauer, & Basford, 2008; Urtizberea, 2004).

As with complex decisions regarding interventions for respiratory failure, thoughtful advance care planning regarding management and interventions for dysphagia is also warranted.

Chapter 4 provides further detail on these and other related topics.

PAIN

Among individuals with NMDs, pain is a common experience and can contribute substantially to decreased health-related quality of life. Pain can be acute, chronic, or a combination of both.

With the exception of some peripheral neuropathic syndromes, pain is not typically a feature of the primary NMD itself, but rather is secondary to the impact of the disease on the musculoskeletal system. Of a sample of 811 patients with a range of NMDs, 83% reported ongoing pain, most commonly in the back (Abresch, Carter, Jensen, & Kilmer, 2002). In PPS, shoulder pain is also quite common (Stoelb et al., 2008).

Pain can arise from weakness, abnormal posture and gait, immobility, loss of range of motion, contractures, spasticity, and cramps, as well as from joint instability, nerve impingement from muscle atrophy, improper positioning, lack of frequent repositioning, skin ulceration, and overuse injury. Pain can also arise from common non-NMD etiologies. In individuals with NMDs, pain can be potentiated by deconditioning, depression, and comorbid health conditions. It is associated with increased fatigue, diminished coping ability, and altered sleep patterns (Abresch et al., 2002). Pain can limit participation in daily activities and social interactions and can be a source of anxiety for family members and caregivers (Jensen et al., 2008; Mah, Thannhauser, McNeil, & Dewey, 2008). Pain in individuals with NMDs has also been shown to persist for many years (Pizzimenti, Aragona, Onesti, & Inghilleri, 2013), including in an uncontrolled state at end of life (Chiò, Mora, & Luria, 2017; Ganzini, Johnston, & Silveira, 2002). These statistics suggest that current practices in pain assessment and management are insufficient.

ASSESSMENT OF PAIN

The assessment of physical pain must begin with open-ended questions and sensitivity to the contributions of biologic, psychological, and social factors to both the experience of and description of pain. Recently, through surveys and structured interviews of patients with physical disability from nonneuromuscular causes who use adapted mobility equipment, a set of common pain descriptors in sensory, affective, and temporal dimensions was created. These descriptors may be helpful prompts for patients with NMDs who need assistance in describing their pain and can be used over time to assess the efficacy of treatments. Pain sensation descriptors include aching, jumping, sore, cool/cold, numbing, shooting, cramping, pulling, throbbing, heavy/dull, radiating, tight, hot/burning, sharp/stabbing, and tingling. Pain affect descriptors include tiring/exhausting, nagging/bothersome, frustrating, emotional/psychological, and worrisome/afraid. Temporal descriptors include steady/constant, momentary/brief, and comes and goes (Dudgeon et al., 2005). In NMDs, additional descriptors of discomfort include soreness, fatigue, and local discomfort from prolonged positioning or equipment. Increased rates of impaired glucose tolerance in patients with myotonic dystrophy may predispose individuals with that condition to peripheral neuropathies and the typical symptoms associated with them.

The Functional Independence Measure self-report instrument has been validated for use in patients with NMDs and chronic pain and can be used to assess an individual's perception of independence in the settings of neuromuscular disease and pain (Jensen, Abresch, & Carter, 2005).

PREVENTION OF PAIN

In rapidly progressive NMDs, weakness and immobility cannot be prevented. However, musculoskeletal pain complications

from weakness and immobility can often be prevented. Prevention includes optimizing cardiopulmonary fitness to maintain stable pain threshold and mood, stretching to preserve range of motion, and using appropriately fitted equipment to optimize positioning and skin care. Frequent assisted weight shifts are necessary for individuals who cannot perform weight shifts on their own—both for prevention of musculoskeletal pain and pain from skin ulceration. The nature and role of exercise were described earlier in this chapter.

Prophylaxis may also exist for fractures related to disuse osteoporosis. Among individuals with DMD attending a sample of neuromuscular clinics, 21% were reported to have experienced a fracture, with a peak age of 8 to 11 years at the time of fracture. Upper limb fractures were most common in individuals using KAFOs, and lower limb fractures were most common in individuals with independent mobility or wheelchair use. Fracture prevalence did not appear to be affected by steroid use. McDonald et al. (2002) were unable to ascertain whether this number is significantly different from fracture prevalence in an average pediatric population, but they do note that fracture site and peak age do differ from those of children without DMD. In children with DMD and fractures, early aggressive mobilization after the fracture may decrease limitations in ambulation, which in turn may reduce pain and contractures.

Low bone mass has been reported in individuals with DMD, and alendronate may prevent loss of bone mass in DMD. Further study is required to delineate the impact of preserved bone mass on fracture rate (Hawker et al., 2005). In adults with limited mobility, screening bone density scans can be used to identify diminished bone mass, and primary care physicians or endocrinologists can assist in determining appropriate candidates for treatments including bisphosphonates.

MANAGEMENT OF PAIN

Despite the best efforts at prevention, musculoskeletal pain syndromes do develop in individuals with NMDs. Pain and pain interference with daily life activities and social satisfaction can cause significant disability and diminished quality of life.

A rehabilitation team, including a physiatrist, physical therapist, occupational therapist, adaptive technology specialist, psychologist, and primary caregivers, is well suited to provide comprehensive pain management.

Back pain resulting from weakness and immobility, often associated with the use of adaptive mobility equipment, is common in individuals with NMDs. In a recent retrospective survey, 66% of individuals with myotonic dystrophy and 74% of individuals with FSHD reported pain in the back—the most frequently cited region of pain in those conditions (Jensen, Abresch, Carter, & McDonald, 2005). Back pain can be minimized by wheelchair seating that includes lumbar support, firm compressible cushions (gel), and foam wedges for proper positioning. Weight shifting/pressure relief, required as frequently as every 15 minutes for as long a duration as possible, can reduce pressure on the bony structures of the lower back and the skin over the ischial spines. Patients must be taught to perform appropriate weight shifts. If a patient cannot perform weight shifts independently, a power tilt-in-space wheelchair control can provide pressure relief and skin protection. Sleeping surfaces must also be optimized for pressure relief.

Neck pain resulting from neck weakness and head drop occurs in a range of NMDs, including ALS, myasthenia gravis, and the inflammatory myopathies. Cervical orthoses, as well as wheelchair head supports and reclining capabilities, can mitigate neck pain. ROM exercises can prevent pain associated with the development of contractures.

Shoulder pain from subluxation, adhesive capsulitis, and complex regional pain syndrome can be a consequence of loss of range of motion associated with weakness and immobility. Shoulder pain can also arise from, or be complicated by, fractures, calcification, and musculotendinous damage. Prevention of these painful conditions includes maintenance of range of motion, optimization of positioning, and prompt treatment of comorbid pain-generating conditions. A figure-of-eight humeral cuff sling can minimize pain in those with shoulder subluxation when forced to have the arm in a dependent position, such as during ambulation.

Spinal deformities, including scoliosis and kyphosis, are common in muscular dystrophies and SMA. Hyperlordosis, with or without scoliosis, is seen in many forms of muscular dystrophy as well. Bony spinal can result in pain due to both altered positioning and secondary limitations in movement and ambulation. Pain resulting from these deformities can be minimized with proper seating and positioning.

In a recent study of adolescents with SMA, DMD, or Becker muscular dystrophy, 69% reported pain in the past 3 months, particularly in the neck/back and legs, and exacerbated by sitting, too much activity, and "being lifted or transferred' (Lager & Kroksmark, 2015). A comprehensive pain management program should include a pain diary that can help guide daily activity. Caregivers should also be reminded about the importance of providing patient-guided transfers in order to optimize comfort (and autonomy). In NMDs with upper motor neuron features, spasticity can both directly cause pain and indirectly result in pain due to limitation of extremity movement or trauma from uncontrolled movement. A recent Cochrane Neuromuscular Disease Group topic review revealed only one randomized controlled trial in the treatment of spasticity in ALS; evaluation of this study revealed insufficient data to determine the impact of moderate-intensity endurance exercises for the trunk and limbs (Ashworth, Satkunam, & Deforge, 2012). No studies on other spasticity management modalities met review criteria. However, treatments used successfully in practice to manage spasticity in individuals with NMDs include oral medications, sustained muscle stretching, positional splinting (with good skin care), modalities including heat and cold, botulinum toxin injections, nerve blocks, and intrathecal baclofen pumps. In motor neuron disease with a combination of upper and lower motor neuron signs, caution must be taken that spasticity treatment does not diminish function and comfort by excessively exacerbating weakness. With respect to medications, one must be cautious with dantrolene because it can cause excessive weakness by acting directly on muscle. Finally, cramping is a common symptom in many NMDs. Recently, evidence-based treatments for reducing cramping in some of the NMDs have emerged—namely, mexiletine for reducing cramps in ALS (Oskarsson et al., 2018) and botulinum toxin injections for decreasing cramps in diabetic neuropathy (Restivo et al., 2018).

ADDITIONAL PAIN MANAGEMENT STRATEGIES

No single treatment has been shown to provide lasting relief of pain in NMDs. Patients inquiring about chiropractic treatments should be counseled that individuals with weakness of

the cervical or trunk musculature should avoid high-velocity spine manipulation because they are at increased risk for neurologic or bony injury. Additional research is warranted in the use of complementary and alternative medicine approaches for pain control in NMDs.

Some pain relief can be obtained from oral medications, which include scheduled acetaminophen with or without nonsteroidal anti-inflammatories, tricyclic antidepressants, sodium channel–blocking anticonvulsants, antiepileptics (especially if there is a neuropathic component to pain), opioids (morphine can also relieve air hunger), hydroxyzine (synergistic with opioids), dextromethorphan, and cannabinoids (can also promote saliva reduction, appetite stimulation, sleep induction, and bronchodilation). Muscle atrophy can limit the effectiveness of intramuscular injections, and excessive diaphoresis can limit the effectiveness of transdermal medications. Patient-controlled analgesia can be limited by an individual's capacity to control the unit, so it is a less recommended option for individuals with more advanced NMDs. Medications should be titrated to patient comfort, and risks and benefits discussed thoroughly with patients before initiation.

More invasive interventions, including steroid injections to treat joint discomfort and manipulation under anesthesia to treat adhesive capsulitis, are available for selected patients. Manipulation under anesthesia should be attempted with great caution, because it can be associated with both anesthesia-related risks and significant joint damage.

When adhesive capsulitis and contractures develop, consideration of goals of care is important. For example, an individual with adhesive capsulitis with rapidly progressive NMD might prefer to be treated with conservative pain control rather than manipulation under anesthesia.

MOOD DISORDERS

Psychological challenges for individuals with NMDs include grief, fear, and repeated need to confront new episodes of functional decline and associated changes in lifestyle and relationships. Although features of depressed mood and anxiety often manifest, these are not necessarily correlated with the degree of neuromuscular impairment. Symptoms of depression, such as fatigue, inanition, limited social interactions, decreased enjoyment of daily activities, and even tearfulness, may overlap with features of an individual's primary NMD. It is therefore important to routinely screen for symptoms of depression in individuals with NMDs and elicit information from caregivers and families regarding changes in patients' behaviors and moods. Recent studies of depressed mood in ALS suggest that hopelessness and concerns about end of life are not uncommon.

Pseudobulbar affect and its management are discussed in Chapter 11.

Family, social, religious, spiritual, and formal support networks can provide sources of hope and forums for both sharing feelings and acquiring strategies to address them. Consistent support by health care professionals of both the patient and caregivers can also mitigate fears and promote acceptance of one's disease and life changes.

A variety of standard pharmacologic interventions to treat depression can be trialed in patients with neuromuscular disease. Frequently, these agents can simultaneously address primary disease symptoms. For example, agents with anticholinergic properties can both improve mood and treat sialorrhea and non–respiratory-based insomnia. See Chapter 11 for a more detailed discussion of sialorrhea/pseudohypersalivation and insomnia.

A psychiatrist or clinical psychologist can provide cognitive behavioral and other interventions that facilitate coping and engagement in pleasurable activities. A spiritual advisor can also assist patients in drawing on personal sources of strength.

As with symptoms of depression, symptoms of anxiety can also overlap with features of primary NMDs. For example, breathlessness can occur with acute episodes of anxiety or result from respiratory failure, which simultaneously incites feelings of anxiety. After addressing medical causes of anxiety to the greatest extent possible, anxiety itself can be addressed with social, pharmacologic, and counseling interventions. Pharmacologic management includes benzodiazepines and buspirone. Benzodiazepines must be used with caution, because they can exacerbate respiratory depression and fatigue. They should not be used in individuals with severe respiratory insufficiency or with myasthenic syndromes. Buspirone does not suppress respiration, but it may take several weeks before anxiolysis is achieved; it should be avoided in individuals with myasthenia.

COGNITIVE DYSFUNCTION

Cognitive dysfunction is a clinically important feature in many NMDs, distinct from motor, mood, and behavioral changes associated with the disorders. Cognitive dysfunction has implications for decision making, interactions with family and caregivers, and interactions with professional care providers. For the professional care team, cognitive dysfunction also affects the design of individualized rehabilitation programs and clinical trials. Particularly as rehabilitation technology options become more complex, providers must carefully select appropriate candidates for their use. It is important to educate patients and families about the possible cognitive changes associated with their neuromuscular conditions and for family members and care providers to monitor for and address cognitive changes over time. Lack of familiarity with cognitive manifestations of these conditions may prevent providers from discussing them upfront with patients and from recommending early educational and technological interventions.

QUALITY OF LIFE

Research generally shows that the degree of physical impairment does not directly correlate with satisfaction with life circumstances among individuals with NMDs. Rather, decision-making capability, social interactions, setting of care provision, spirituality, feelings of hope, the nature of coping strategies, and amelioration of manageable disease-related conditions may more directly affect overall life satisfaction (Bach, Campagnolo, & Hoeman, 1991; Bromberg, 2008; Jacques et al., 2019; Nätterlund & Ahlström, 2001; Padua et al., 2002; Pangalila et al., 2015; Robbins, Simmons, Bremer, Walsh, & Fischer, 2001). Both primary caregivers and professional care providers tend to underestimate

patients' experienced quality of life. Therefore, the rehabilitation team—in fact, the entire care provision team—must be well educated about and comfortable discussing features of disease processes and their implications for daily life and relationships, setting realistic expectations, and offering management options. If a patient makes extreme or uncharacteristic requests regarding their life or care, care providers must ensure that all efforts have been made to optimize quality of life before attributing the requests to nonmodifiable disease-related distress.

MEASUREMENT

Efforts are underway to develop an instrument for measuring quality of life among people with NMDs (Dany et al., 2017). In any assessment of quality of life, the patient's voice should be paramount. For example, in the oft-studied realm of the role of mechanical ventilation in NMD, it has been shown that most patients with ALS who opt for mechanical ventilation would choose the same option again if given the choice, whereas only half of their care providers would choose that option for themselves (Moss et al., 1993).

ROLE OF THE PROFESSIONAL CARE TEAM

Throughout the course of an NMD, the clinical care team is uniquely poised to positively affect patient quality of life. Opportunities to affect quality of life for both patient and family/caregivers are at the time of diagnosis (framing expectations and long-term vision of comfort and support), throughout the course of the disease (addressing disease manifestations that diminish health-related quality of life), near and at death (facilitating education and appropriate services, respecting patient autonomy), and after death (providing continued support for family and other caregivers). The first three of these opportunities are discussed here; the lattermost is discussed in the next section, entitled "Roles of the Caregiver and Family."

At all stages of disease progression, identifying and addressing patient and family psychological needs are important parts of optimizing quality of life. For example, while quality of life is frequently rated relatively high by individuals with ALS on questionnaires and in research studies, this can obscure the very real psychological impact of the diagnosis and disease trajectory on patients and families (Burns, Graham, Rose, & Simmons, 2012). It is important that care for the caregiver be provided simultaneously with care for the patient, because caregiver quality of life can significantly affect patient quality of life.

From the very beginning of the course of a disease, the care team can frame patient expectations and long-term visions of comfort and support, thereby influencing the quality-of-life experience around receiving the diagnosis and planning for the future. The American Academy of Neurology ALS Practice Parameter guidelines recommend that the physician deliver the diagnosis in person, discuss implications at that time, respect patient wishes regarding the ways information is transmitted (e.g., to patient versus via family members), provide materials about support and advocacy organizations, and provide documentation that summarizes the discussion (Miller et al., 2009). Annual conversations for advance care planning, including end-of-life preferences, are part of the American Academy of Neurology Quality Measures (Miller et al., 2013).

Throughout the course of the disease, the professional care team can educate patients and caregivers so that they can make informed treatment decisions and establish meaningful, appropriate short- and long-term goals. The professional care team can also foster open, reliable relationships with patients and families, another component of support for quality of life. It is important for care providers to discuss sexual activity with patients and partners. Although ability and interest in sexual activity can be affected by mobility impairments and pain, individuals can maintain fulfilling sex lives and intimate personal relationships. The care team must also treat disease manifestations that diminish health-related quality of life. Such conditions include dysarthria, dysphagia, respiratory failure, spasticity, sialorrhea, thickened secretions, pain, mood changes, cognitive decline, and weakness/fatigue-related decreases in capacity to perform ADLs. Advice regarding exercise regimens, as described earlier in this chapter, can promote physical activity, which can be followed by increases in overall psychological well-being.

Near and at death, consideration of quality of death is an important component of the consideration of quality of life. Maintaining individual choice about circumstances and location of death, comfort as death nears, and respect for personal autonomy are important components of comprehensive quality-of-life care. Death in the home with comfort and dignity is the preferred option for many patients. Hospice services for patients with NMDs, as discussed in the section of this chapter entitled "Palliative Care and Hospice," tend to be underused yet have the potential to substantially increase quality of life and death. A large academic center multidisciplinary ALS clinic reported that when a palliative care specialist was integrated into the clinic, 14.8% of patients were referred to palliative care over the course of a year. In 91% of cases, referral was for advance care planning support, including discussion of goals of care and decision making about tracheostomy or feeding tube (Brizzi, Paganoni, Zehm, De Marchi, & Berry, 2019).

Despite best efforts by professional and family care providers, not all individuals with NMDs maintain stable or positive experiences of satisfaction and meaning in their lives over time. Reasons for this are many, including loss of decision-making capacity, requirement for care provision outside of the home, loss of ability to communicate and perform other personally valued functions, and incomplete response shifts (incomplete reorganization of internal values and standards, which allow individuals to derive equal pleasure from life activities performed in new, modified ways).

Notable differences in perceived quality of life are present across cultures as well, affecting major patient and family decisions, including preferences for mechanical ventilation and, in some countries, euthanasia. Cultural perspectives must be discussed with patients and families and taken into account in consideration of individual circumstances.

ROLES OF THE CAREGIVER AND FAMILY

Primary caregivers for adults with NMDs are typically spouses and, for children with NMDs, parents. The roles of these

primary caregivers extend beyond direct provision of medical care and physical accommodations. Caregivers hold responsibilities for emotional care, financial support, decision making, and advocacy.

The caregiver is also challenged to adapt to major life changes, manage anxieties about uncertainties for the future, cope with losses, find ways to find joy amid sadness and anxiety, and maintain personal health and hygiene. In multimember families, care for an individual with NMD can divert attention from other family members; this is a particularly difficult challenge. Family functioning predicts adjustment to these challenges better than degree of disability or illness in the individual requiring care.

Williams and Donnelly (Williams, Donnelly, Holmlund, & Battaglia, 2008) describe a range of caregiver and family needs throughout the course of a loved one's illness. After initial adjustment to a diagnosis, caregivers state needs such as "I have a need to not fight with him/her because I feel guilty"; "I have a need to accommodate the intrusion of medical helpers into my family"; "I have to be careful that I don't say too much or express too many negative feelings because then my loved one gets too depressed." Some state, "I need reassurance from professionals (e.g., hospice) that I am caring for my husband in the best possible way"; "I need not to be alone when my loved one dies"; and "I have a need to have people be aware of my loved one's physical needs, especially in the hospital, when he can't speak and I can't be with him."

Financial expenses for care of an individual with an NMD, especially if mechanical ventilation is required, can exceed hundreds of thousands of dollars per year. In-home care for a patient who uses mechanical ventilation can be less expensive than care in a skilled nursing facility, and this fact often needs to be actively presented to insurance companies when service coverage is being determined. A skilled case manager or social worker, along with medical clinicians, can assist in this process.

Costs of care can be defrayed somewhat by hiring private aides instead of hiring through agencies, selecting modifiable durable medical equipment, renting or borrowing equipment from charitable organizations, and using hospice services when appropriate. The federal Family and Medical Leave Act allows primary caregivers time off from work to care for loved ones, but this leave is unpaid.

Unfortunately, the challenges that beset caregivers and families—even the most committed, well-connected, and financially capable ones—can result in adverse outcomes for those caregivers and families. Social isolation demands on time and financial resources, limitations on personal and family opportunities, and constant readjustment of routines and expectations can lead caregivers to feel burdened. In turn, feeling burdened leads to increased stress, guilt, anxiety, and depression.

Addressing caregiver burden is part of comprehensive rehabilitation care for individuals with NMDs. Increased home care services, support groups, and counseling interventions can reduce stress. Caregivers and families should be encouraged to draw on sources of strength, including spiritual and cultural community groups. Professional care providers can also mitigate stress through validation of caregiver concerns, reassurance of the positive impact of their care, reinforcement of the importance of their own self-care, and acknowledgment of caregiver and family as experts in the care of their loved one. Importantly, professional care providers can elicit, address, and allay sources of guilt in caregivers and family members as well.

Despite the many challenges in providing care for a loved one with an NMD, caregivers and family members can derive great satisfaction and life enrichment in caring for their loved ones. In a qualitative study of parents' experiences caring for children with NMDs requiring mechanical ventilation, one parent encapsulated a common sentiment, that the child's "lifeline is us." Similarly, the parents' lifeline is the child. The mutual dependence between parents and child defined each of their lives. These families would choose mechanical ventilation if given the chance to make the decision again (Mah et al., 2008).

For caregivers, families, and clinicians, appropriate closure at the end of a patient's life can set the stage for healthy grieving and recovery. Hospice services for families can smooth this transition and are described in more detail in the next section. Both clinicians and families can find additional closure and support when clinicians attend funeral and memorial services.

PALLIATIVE CARE AND HOSPICE

Many patients with life-limiting NMDs can benefit from palliative care and, eventually, hospice services.

Palliative care, in many ways like that of rehabilitation care, is a patient- and family-centered model of care focused on optimizing comfort and quality of life. It can be initiated at any time, from the time of diagnosis through bereavement. Early initiation of palliative care is favored and is increasingly identified as a quality benchmark for optimal clinical care (Tolchin, 2020; Turner-Stokes et al., 2007). Early initiation of palliative care can be especially valuable for individuals who may rapidly lose the cognitive capacity to make decisions (e.g., frontotemporal dementia in ALS).The palliative care skillset includes physical, psychosocial, and existential symptom management and advanced communication skills for advance care planning, conflict resolution, decision-making support, and ethics guidance.

Palliative care is commonly provided in two forms: primary palliative care and specialist palliative care. Neurologists and physiatrists can provide primary palliative care through expert symptom management and thoughtful communication with patients, families, and care teams. When palliative care needs exceed these providers' skillsets, the providers can engage the collaboration of specialist palliative care providers. Fellowship-trained palliative care specialists have expertise in advanced management of physical, psychosocial, and spiritual distress and in addressing complex family dynamics and advance care planning needs. They can also educate patients and families about hospice and facilitate referrals as appropriate.

In this way, specialist palliative care involvement provides an extra layer of support for patients and families, as well as the rehabilitation team.

Hospice is a set of specialized intensive end-of-life services. In the United States, individuals with a life expectancy of 6 months or less and the desire to limit invasive intervention can be eligible for hospice services. Hospice

services are provided by an interdisciplinary team of physicians, nurses, social workers, and chaplains. The team can also include physical or occupational therapists and volunteers who provide social support. Hospice clinicians provide symptom management, psychosocial and spiritual support, anticipation and management of end-of-life symptoms, and bereavement support. Hospice also provides basic supplies, 24-hour phone access to clinicians, and a set of easy-to-access medications for the home. Hospice can be provided in the home, a hospital, or other facility, with attention toward supporting death in the patient's preferred location.

Individuals with progressive life-limiting illnesses, such as ALS, DMD, or myotonic muscular dystrophy, can often benefit from earlier hospice referrals than they receive in practice. Early hospice referrals can be limited by clinician lack of awareness and difficulty prognosticating remaining length of life. Individuals with NMDs can qualify for hospice services even when prognosis is difficult to specify—some individuals with NMDs receive hospice services for several years. Although documentation of a life expectancy of 6 months or less is required for hospice eligibility, additional criteria for hospice services for individuals with ALS and, by extrapolation, other NMDs are as follows: there must be an overall rapid progression of disease within the past 12 months and the patient and family must desire no further aggressive treatment or cardiopulmonary resuscitation. One of the following typically must also be present: increased respiratory distress, severely impaired nutrition, or life-threatening complications.

A clinician must discuss several topics with patients and families when he or she suspects that hospice services might be of benefit. First, a primary provider can remain involved in patient care while the patient receives hospice services. Second, hospice can have the connotation of hopelessness, imminent death, and the relinquishing of control and treatment. Clinicians must educate families about the reasons for their recommendations of hospice (e.g., grief counseling, provision of medical supplies) and the continued hope and care that will be maintained. Third, clinicians can explain that although the hospice enrollment requires a life expectancy of 6 months or less, the prognosis is not definite. It may be difficult for patients and families to accept hospice services after a single conversation with a clinician, and the conversation may need to be held over the course of several visits and/or phone calls. Also of importance for clinicians to note is that while hospice does clinical provider visits, hospice agencies typically do NOT provide home health aides or expensive equipment. Equipment such as wheelchairs and bilevel positive airway pressure ventilators may need to be procured prior to the initiation of hospice services. Hospice agencies vary in their ability to manage feeding tubes and ventilatory equipment and to include medications such as riluzole in their care plans.

Some home care programs offer home palliative care and/or bridge-to-hospice programs so that patients can develop relationships with a direct care staff that will continue to care for them during the hospice care period.

The provision of end-of-life care is eased by the early assignment of a durable power of attorney and a set of frequently updated advance directives. Long-term planning should be a part of comprehensive care from the time of diagnosis throughout the course of illness, because goals, wishes, and family dynamics change over time.

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9 Orthopedic Surgery in Neuromuscular Disorders

William C. Warner Jr., MD

Neuromuscular disorders (NMDs) in children include conditions that affect the spinal cord, peripheral nerves, neuromuscular junction, and muscles. Orthopedic treatment of children with NMD has been aimed at preventing worsening of deformities and providing stability to the skeletal system to improve the quality of life for these children. Patients with severe NMDs have listed their priorities as the ability to communicate with others, the ability to perform many of the activities of daily living, mobility, and ambulation (Bleck, 1979). The role of the orthopedic surgeon in achieving these goals includes prescribing orthoses for lower extremity control to facilitate transfer to and from wheelchairs, preventing or correcting joint contractures, and maintaining appropriate standing and sitting posture. Treatment must be individualized for each patient according to the particular disorder, the severity of involvement, and the ambulation status of the patient.

Fractures are common in children with NMDs because of disuse osteoporosis, steroid treatment, and frequent falls (Larson & Henderson, 2000). Fracture treatment with splinting, cast-bracing, or surgery emphasizes a quick return to walking if the patient is ambulatory. Spinal bracing may be necessary to assist with sitting balance, a knee-ankle-foot orthosis can provide stability for patients with proximal muscle weakness, and an ankle-foot orthosis (AFO) can help position the ankle and foot plantigrade to help prevent progressive deformities. Most children with NMD will eventually require the use of a wheelchair, and these chairs must be carefully contoured to accommodate the spinal deformities and pelvic obliquity that usually are present.

MUSCULAR DYSTROPHY

The muscular dystrophies are a group of hereditary disorders of skeletal muscle that produce progressive muscle degeneration and associated weakness. The disorders differ in the distribution and severity of muscle weakness, the age of onset, the rate of progression, and the pattern of inheritance (Fig. 9.1).

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy, a sex-linked recessive inherited trait, occurs in males and in females with Turner syndrome; carriers are female. It is reported to occur in 1 in 3500 live births (Emery, 1991; Shapiro & Specht, 1993a; Sussman, 2002). There is a family history in 70% of patients, and the condition occurs as a spontaneous mutation in approximately 30% of patients (Hoffman et al., 1996). In contrast, Becker muscular dystrophy, the second most common form, occurs in 1 in 30,000 live male births; other types of muscular dystrophy are rare. Children with Duchenne muscular dystrophy usually reach early motor milestones at appropriate times, but independent ambulation may be delayed; many are initially toe-walkers. The disease will usually become evident between ages 3 and 6 years. The ability to ambulate typically is lost by about age 10 years; however, with treatment with steroids ambulation can continue into the late teenage years.

Clinical features include large, firm calf muscles; the tendency to toe-walk; a widely based, lordotic stance; a waddling Trendelenburg gait; and a positive Gowers test indicative of proximal muscle weakness (Fig. 9.2). The diagnosis usually is obvious by the time the child is 5 or 6 years old. Diagnosis is confirmed by a dramatically elevated level of creatine kinase (50 to 100 times normal) and DNA analysis of blood samples (Pasternak, Wong, & Elson, 1995; Sussman, 2002). Muscle biopsy demonstrates variations in fiber size in internal nuclei, split fibers, degenerating or regenerating fibers, and fibrofatty tissue deposition. Dystrophin testing of the muscle biopsy will confirm the type of muscular dystrophy.

ORTHOPEDIC PHYSICAL EXAMINATION

The degree of muscular weakness depends on the age of the patient and the type of dystrophy. Because the proximal musculature weakens before the distal muscles, examination of the lower extremities demonstrates an early weakness of gluteal muscle strength. The weakness in the proximal muscles of the lower extremity can be demonstrated by a decrease in the ability to rise from the floor without assistance of the upper extremities (Gowers sign). The calf pseudohypertrophy is caused by infiltration of the muscle by fat and fibrosis, giving the calves the feel of hard rubber (Fig. 9.3). The extrinsic muscles of the foot and ankle retain their strength longer than the proximal muscles of the hip and knee. The posterior tibial muscle retains its strength for the longest time. This pattern of weakness causes an equinovarus deformity of the foot. Weakness of the shoulder girdle musculature can be demonstrated by the Meryon sign, which is elicited by lifting the child with one arm encircling the child's chest. Most children contract the muscles about the shoulder to increase shoulder stability and facilitate lifting. In children with muscular dystrophy, however, the arms abduct because of the severe shoulder abductor muscle weakness, until they eventually

slide through the examiner's arms unless the chest is tightly encircled. Later in the disease process, the Thomas test demonstrates hip flexion contracture, and the Ober test demonstrates an abduction contracture of the hip.

ORTHOPEDIC TREATMENT

The major goal of early treatment is to maintain functional ambulation as long as possible. Between ages 8 and 14 years (with a median of 10 years), children with Duchenne muscular dystrophy typically have a sensation of locking of the joints. Contractures of the lower extremity may require early treatment to prolong the child's ability to ambulate, if even for 1 to 2 years. This requires prevention or retardation of the development of contractures of the lower extremity, which would eventually prohibit ambulation. It is easier to keep patients walking than to induce them to resume walking once they have stopped. When children with Duchenne muscular dystrophy stop walking, they also become more susceptible to the development of scoliosis and severe contractures of the lower extremities. Scoliosis will develop in nearly all children with Duchenne muscular dystrophy, usually when they require aided mobility or shortly after becoming wheelchair bound. The use of steroids has been shown to decrease the occurrence of scoliosis in these patients (Archer, Gardner, Roper, Chikermane, & Tatman, 2016; Connolly, Kim, & Bridwell, 2013; Lebel, Corston, McAdam, Biggar, & Alman, 2013; Wong et al., 2017).

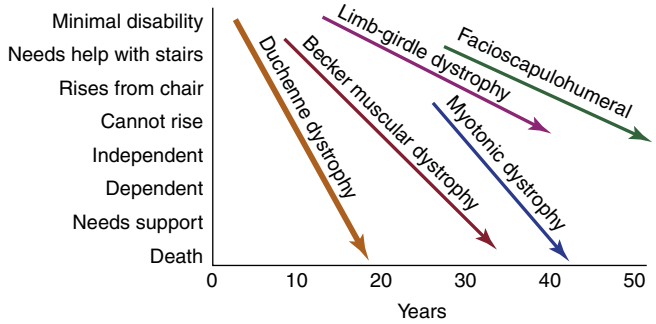


Fig. 9.1 Natural history of muscular dystrophies. The *arrows* show the average clinical course with level of disability and age. (Adapted from Staheli, L. T. (2001). *Practice of pediatric orthopedics* (p. 338). Philadelphia: Lippincott Williams & Wilkins.)

BONE HEALTH—OSTEOPOROSIS AND FRACTURE MANAGEMENT

Because of disuse- and steroid-induced osteoporosis and frequent falls, fractures are common in children with neuromuscular disease (James et al., 2015). Patients with Duchene muscular dystrophy who are on glucocorticoid therapy often develop osteoporosis (McMillan, 2019). Studies have shown a significant decrease in bone mineral density on dual-energy x-ray absorptiometry scans in boys with Duchenne muscular dystrophy, with 44% sustaining fractures. One study found that 33% of patients with Duchenne or Becker muscular dystrophy had sustained at least one fracture; full-time wheelchair use was a significant risk factor for fracture (James et al., 2015). Up to 30% of Duchene muscular dystrophy patients develop symptomatic vertebral fractures (McMillan, 2019). Most fractures are nondisplaced metaphyseal fractures that heal rapidly. Minimally displaced metaphyseal fractures of the lower limbs should be splinted so that walking can be resumed quickly. If braces are being used, they can be enlarged to accommodate the fractured limb and allow progressive weight bearing. Displaced diaphyseal fractures often require surgical stabilization to allow mobilization during fracture healing. McAdam et al. reported fat embolism syndrome following minor trauma in five Duchenne muscular dystrophy patients, four of whom died (McAdam, 2012). Medical treatment of disuse and steroid induced osteopenia may decrease the frequency of fractures in this patient population. An algorithm for osteoporosis monitoring, diagnosis, and treatment of patients with Duchenne muscular dystrophy has been developed (Fig. 9.4) (McAdam, Rastogi, Macleod, & Douglas Biggar, 2012).

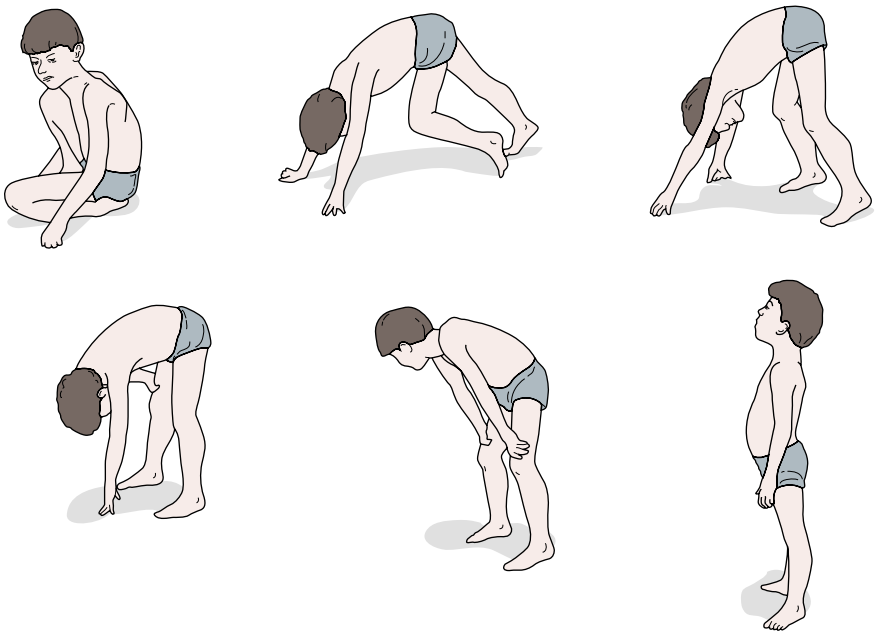


Fig. 9.2 Gowers sign. Child must use hands to rise from a sitting position. (From Warner, W. C, Jr. (2008). Neuromuscular disorders. In: S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed., p. 1505). Philadelphia: Elsevier.)



Fig. 9.3 Pseudohypertrophy of the calf in a patient with muscular dystrophy. (From Warner, W. C., Jr. (2008). Neuromuscular disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed., p. 1505). Philadelphia: Elsevier.)

Correction of Lower Extremity Contractures

Three approaches have been used for surgical correction of lower extremity contractures:

1. Ambulatory approach. The goal of surgery during the ambulatory period is to correct any contractures in the lower extremity while the patient is still ambulatory. Early aggressive surgery may be indicated for the first appearance of contractures in the lower extremities; a plateau in muscle strength, usually around age 5 to 6 years; and difficulty maintaining an upright posture with the feet together. Some surgeons suggest that surgery should be performed before deterioration of the Gowers maneuver time or time to rise from the floor (Forst & Forst, 1999; Goertzen, Baltzer, & Voit, 1995; Rideau et al., 1995; Ward, Hadjiyannakis, McMillan, Noritz, & Weber, 2018); others have recommended surgery later in the ambulatory phase, just before the cessation of ambulation (Manzur et al., 1992; Smith, Green, Cole, Robison, & Fenichel, 1993).
2. Rehabilitative approach. Surgery is done after the patient has lost the ability to walk but with the intention that walking will resume (Vignos, Wagner, Kaplan, & Spencer, 1983). Surgery during this stage usually only allows for minimal ambulation with braces.
3. Palliative approach. The palliative approach treats only contractures that interfere with shoe wear and comfortable positioning in a wheelchair.

A comparison of ambulation and foot position in three groups of patients with Duchenne muscular dystrophy (those who had surgery to maintain ambulation, those who had

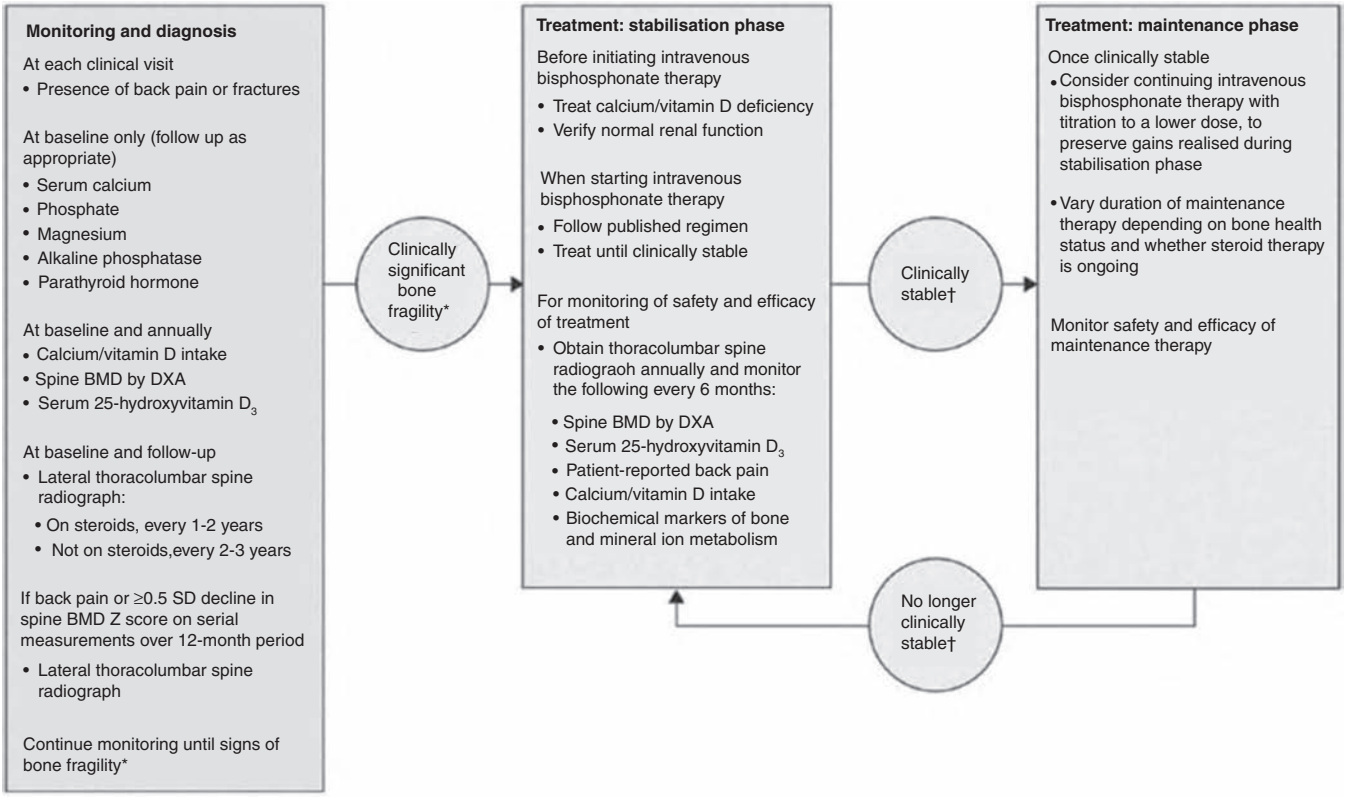


Fig. 9.4 Osteoporosis monitoring, diagnosis, and treatment algorithm for patients with Duchenne muscular dystrophy. *Signs of clinically significant bone fragility are low-trauma fractures of long bones or vertebra. †Clinical stability refers to the absence of nonvertebral fractures, stable healed vertebral fractures, absence of new VFs in previously normal vertebral bodies, absence of bone and back pain, and a BMD score appropriate for height or >2 SDs. *BMD*, Bone mineral density; *DXA*, dual-energy X-ray absorptiometry. (From Birnkrant, D. J., Bushby, K., Bann, C. M., Alman, B. A., Apkon, S. D., Blackwell, A., et al. (2018). Diagnosis and management of Duchenne muscular dystrophy, part 2: Respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurology, 17*, 353.)

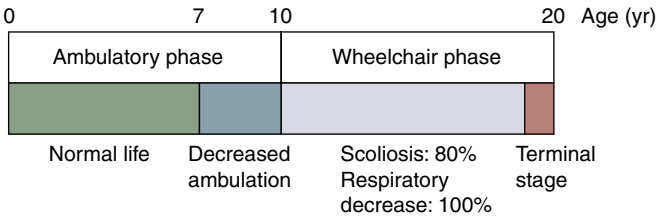


Fig. 9.5 Natural course of Duchenne muscular dystrophy: age-related stages. Correction of contractures generally is done during the ambulatory phase. (From Rideau, Y., Duport, C., Delaubier, A., Renardel-Irani, A., & Bach, J. R. (1995). Early treatment to preserve quality of locomotion for children with Duchenne muscular dystrophy. *Seminars in Neurology, 15*, 9-17.)

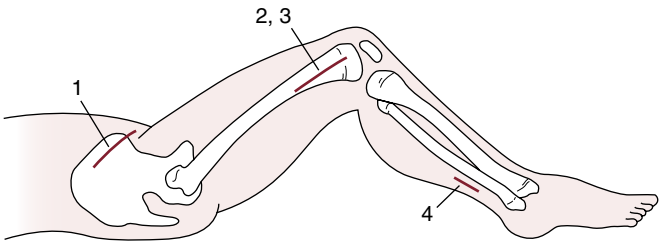


Fig. 9.6 Tenotomy sites for release of hip flexors (*1*), tensor fasciae latae and fascia lata (*2, 3*), and Achilles tendon (*4*). (Redrawn from Siegel, I. M. (1980). Maintenance of ambulation in Duchenne muscular dystrophy: The role of the orthopaedic surgeon. *Clinical Pediatrics, 19*, 383-388.)

surgery to correct and maintain foot position, and those who had no surgery) found that the mean age at cessation of ambulation for those who had surgery was 11.2 years, compared to 10.3 years in those who did not have surgery (Scher & Mubarak, 2002). Foot position was neutral in 94% of those who had surgery, and none had toe flexion deformities; 96% of those who had surgery reported being able to wear any type of shoes, compared to only 60% of those who had no surgery. In contrast, another study of full-time wheelchair users with Duchenne muscular dystrophy found no significant differences between patients who did and did not have foot surgery with respect to shoe wear, hypersensitivity, or cosmesis (Leitch et al., 2005). Hindfoot motion was significantly better but equinus contracture was significantly worse in those who had not had surgery.

Currently the most common approach is to correct contractures just before the patient has a significant decline in ambulation and before the patient has to use a wheelchair (i.e., the ambulatory approach) (Fig. 9.5) (Apkon et al., 2018). This is only after a thorough discussion with the family and patient about the goals of surgery.

Mild equinus contractures of the feet can help force the knee into extension, which in turn helps prevent the knee buckling caused by severe weakness of the quadriceps. Stretching exercises and nightly bracing can be used to prevent the contractures from becoming severe. Flexion and abduction contractures of the hip, however, impede ambulation and should be minimized. Exercises to stretch the hip muscles and lower extremity braces worn at night to prevent the child's sleeping in a frog position are helpful initially. If surgery is indicated, the foot and hip contractures can be released simultaneously, usually through small incisions. Ambulation should be resumed immediately after surgery if possible. Polypropylene braces are preferred to long-term casting. Prolonged immobilization must be avoided to prevent or limit the progressive muscle weakness caused by disuse.

Percutaneous Release of Hip Flexion and Abduction Contractures and Achilles Tendon Contractures

A small (no. 15) blade is inserted percutaneously just medial and distal to the anterior superior iliac spine (Fig. 9.6) to release first the sartorius muscle, then the tensor fasciae femoris muscle, taking care to avoid the neurovascular structures of the anterior thigh. Then, through another small incision approximately 3 to 4 cm proximal to the upper pole of the patella, the fascia lata is released, as is the deeper lateral intermuscular septum. The Achilles tendon is released through a small posterolateral incision.

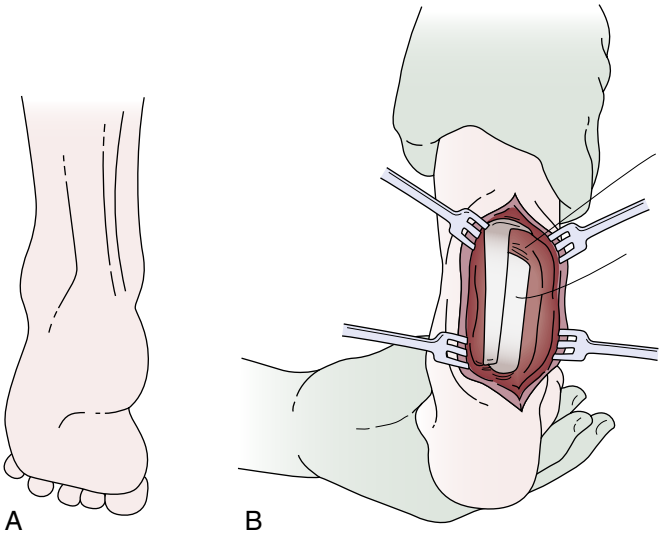


Fig. 9.7 Sliding lengthening of the Achilles tendon. (A) Posteromedial incision. (B) Two cuts are made through one half of the tendon in opposite directions. Rotation of the fibers must be followed accurately. Placing the foot in dorsiflexion causes the tendon fibers to separate. (Redrawn from Green, N. E. (1995). Cerebral palsy. In S. T. Canale, J. H. Beaty (Eds.), *Operative pediatric orthopaedics* (2nd ed.). St. Louis, MO: Mosby.)

Open Lengthening of the Achilles Tendon

A posteromedial incision (Fig. 9.7A) is used to expose the Achilles tendon from its insertion to approximately 10 cm proximally, preserving the tendon sheath. The posteromedial two thirds of the tendon is divided near its insertion. With moderate dorsiflexion force applied to the foot, the medial two thirds of the tendon is divided approximately 5 to 8 cm proximal to the site of the distal division. The foot is then dorsiflexed so that the tendon lengthens to the desired length (Fig. 9.7B). The tendon can be sutured in a side-to-side fashion with absorbable suture. The tendon sheath and subcutaneous tissues are carefully closed to prevent adherence of the tendon to the overlying skin, and a short-leg cast is applied with the ankle in maximal dorsiflexion.

Transfer of Posterior Tibial Tendon to Dorsum of Foot

In patients with marked overpull of the posterior tibial muscle, a posterior tibial tendon transfer of the posterior tibial tendon to the dorsum of the foot (Fig. 9.8), combined with other tenotomies or tendon lengthening, has been found

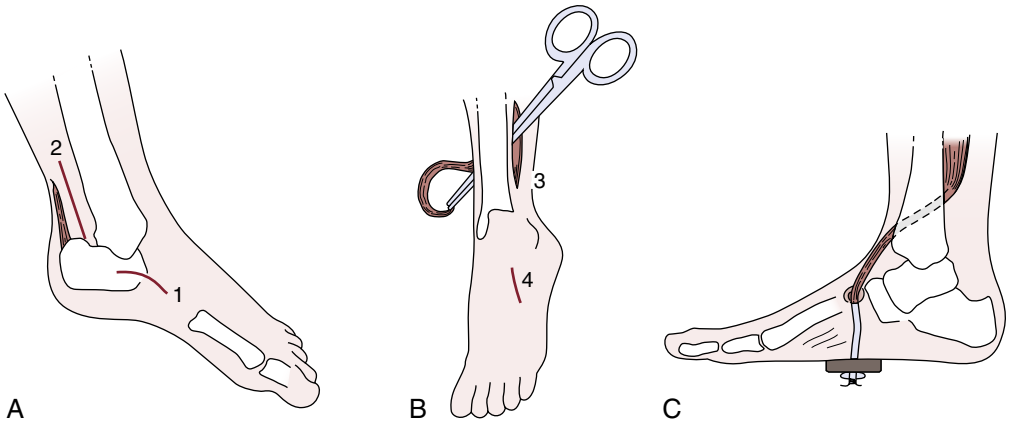


Fig. 9.8 Posterior tibial tendon transfer. (A) First (*1*) and second (*2*) incisions. (B) Third (*3*) and fourth (*4*) incisions and clamp placement for pulling posterior tibial tendon from posterior to anterior compartment of the leg. (C) Position of the transplanted tendon and suture tied over a felt pad and button the plantar aspect of the foot. (From Greene, W. B. (1992). Transfer versus lengthening of the posterior tibial tendon in Duchenne's muscular dystrophy. *Foot & Ankle, 13*, 526-531.)

to give better results than posterior tibial tendon lengthening alone. Although transfer of the posterior tibial tendon is technically more demanding and has a higher perioperative complication rate, most patients retain the plantigrade posture of their feet, even after walking ceases. Despite the more extensive surgical procedure, early ambulation of the patient usually is not impeded.

Transfer of Posterior Tibial Tendon to Dorsum of Base of Second Metatarsal

Transfer of the posterior tibial tendon to the dorsum of the base of the second metatarsal rather than the dorsum of the foot has as a cited advantage the more distal placement of the posterior tibial tendon, which increases the lever arm in dorsiflexion of the ankle. This technique also allows easier plantar flexion and dorsiflexion balancing of the ankle at the time of surgery. Lengthening of the posterior tibial tendon is required to have sufficient length for the tendon to be transferred to the second metatarsal with this technique.

Equinus contractures can be corrected by either a percutaneous or open Achilles tendon lengthening. If an open procedure is needed because of severe contractures, lengthening or release of the posterior tibial, flexor digitorum, and flexor hallicus longus tendons also may be needed. Once these lengthening procedures or releases are done, the child will need an AFO to continue to stand or ambulate.

Correction of Spinal Deformities

Approximately 75% to 90% of boys with Duchenne muscular dystrophy develop scoliosis (Sussman, 2002; Forst & Forst, 1999). The age of onset of scoliosis is generally about the same as the age at which they lose the ability to walk, between 10 and 14 years (Karol, 2007). A significant association has been shown between prolonged ambulation and a reduced risk of scoliosis development (Kinali et al., 2006), and the use of steroids has been shown to slow the progression of scoliosis and delay the need for surgery (Alman, Raza, & Biggar, 2004). Before steroids were used in Duchenne patients, scoliosis developed in more than 90%; since steroid use began, the rate has fallen to only 10% to 20%. A review of the Nationwide Inpatient Sample from 2001 to 2012 demonstrated a significant decrease in the rate of scoliosis surgery in patients with Duchenne muscular dystrophy. Lebel et al. (2013) reported that only 20% of their patients receiving steroids required spinal fusion, but 90% of patients not receiving steroids did.

Weakness in the trunk and paraspinal muscles leads to collapse of the developing spine into what is usually a long C-shaped curve with the apex in the thoracolumbar region. Over time, the curve progresses and involves the entire thoracic and lumbar spine, resulting in pelvic obliquity (Fig. 9.9). This scoliosis does not respond to nonoperative treatment such as bracing and adaptive seating, and it is almost inevitably progressive, often increasing by 8 to 12 degrees per year (Colbert & Craig, 1987). Surgery generally is recommended when the scoliotic curve measures 20 to 30 degrees (Heller, Wirtz, Siebert, & Forst, 2001; Mubarak, Morin, & Leach, 1993a; Sussman, 1984), although some recommend spinal fusion at the onset of the deformity in patients who use a wheelchair full-time even when the curve is less than 20 degrees (Galasko, Delaney, & Morris, 1992; Shapiro & Specht, 1993a; Smith, Koreska, & Moseley, 1989). A delay in surgery allows the curve to progress further and pulmonary and cardiac function to worsen, adding to the risks of spinal surgery in these patients.

The patient's pulmonary function probably is more important than the size of the curve in decision making. Ideally, vital capacity should be 40% to 50% of normal. Patients who have a forced vital capacity of less than 35% are at high risk for pulmonary complications, whereas those with a forced vital capacity of greater than 50% are likely to have few postoperative pulmonary problems and usually can be weaned from the ventilator the night of surgery or the day after (Jenkins, Bohn, Edmonds, Levison, & Barker, 1982; Miller, Moseley, Koreska, & Levison, 1988). A few small studies have indicated that spinal surgery can be safely done on patients with a vital capacity of less than 30% (Gill et al., 2006; Harper, Ambler, & Edge, 2004; Marsh, Edge, & Lehovsky, 2003).

The goals of spinal surgery in patients with Duchenne muscular dystrophy are to obtain and maintain sitting balance and to correct pelvic obliquity so that the patient is able to use a wheelchair for the remainder of his life. The effect of spinal fusion on pulmonary function remains a matter of debate, with some studies finding no effect on the rate of pulmonary decline (Karol, 2007; Kennedy et al., 1995; Miller et al., 1988, 1991; Velasco, Colin, Zurakowski, Darras, & Shapiro, 2007) and others finding reduced rates of decline (Chua et al., 2016; Galasko et al., 1992; Jenkins et al., 1982; Sawnani et al., 2019). Most authors agree that pulmonary function does not improve after surgical fusion of scoliosis (Kennedy et al., 1995; Miller et al., 1991, 1998); however,

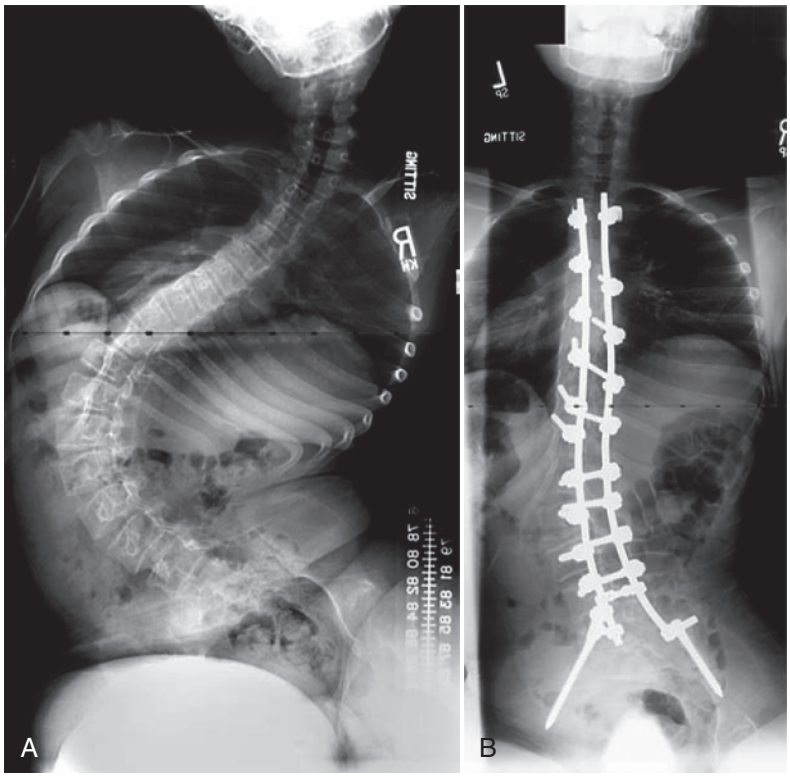


Fig. 9.9 (A) Spinal deformity in a 13-year-old boy with Duchenne muscular dystrophy; his forced vital capacity was 34%. (B) After posterior spinal fusion with pedicle screw construct and iliac screws for pelvic fixation. (From Karol, L. A. (2007). Scoliosis in patients with Duchenne muscular dystrophy. *Journal of Bone and Joint Surgery. American Volume, 89*, 159.)

patients who have had spinal stabilization do have a substantially enhanced quality of life compared with patients who have not (Bridwell, Baldus, Iffrig, Lenke, & Blanke, 1999; Granata et al., 1996). Suggested benefits of spinal fusion in patients with Duchenne muscular dystrophy include preservation of sitting balance, prevention of back pain, improvement in spinal decompensation, freeing the arms of the necessity of trunk support, improvement in body image, and possible slowing of the deterioration of pulmonary function (Miller et al., 1988).

Segmental spinal instrumentation is recommended in patients with Duchenne muscular dystrophy because of the neuromuscular etiology and because the bone is relatively osteopenic due to nonambulation and chronic steroid use. Instrumentation with sublaminar wires and cross-link rods (Fig. 9.10) or a unit rod or segmental instrumentation with pedicle screws (Fig. 9.11) has been a useful technique for these patients. In patients with smaller curves and fixed pelvic obliquity, the fusion and instrumentation can end at L5. If fixed pelvic obliquity is more than 15 degrees, fusion to the pelvis with iliac screws, Galveston technique (Fig. 9.12), or S-rod pelvic fixation is recommended. The fusion should extend to the upper thoracic spine, to T2 or T3. The sagittal contours of the spine, especially lumbar lordosis, should be maintained for sitting balance and pressure distribution.

Because of the pulmonary compromise in these patients, rapid postoperative mobilization is important. We generally use no orthoses after surgery.

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy has a later onset and slower rate of muscle deterioration than Duchenne muscular dystrophy (Herring & Tachdjian, 2008). Orthopedic treatment of patients with Becker muscular dystrophy depends on the severity of the disease. In patients with large amounts of functional dystrophin, orthopedic procedures frequently are not needed until after childhood, and in patients with more severe forms of the disease, treatment considerations are the same as for patients with Duchenne muscular dystrophy. Contractures of the foot and overpull of the posterior tibial muscle can be treated effectively with Achilles tendon lengthening and posterior tibial tendon transfers with good long-term results. Patients rarely need soft-tissue releases around the hips. Because scoliosis is not as common in patients with Becker muscular dystrophy as in those with Duchenne muscular dystrophy, guidelines for surgical correction of the scoliosis are not clearly defined and treatment must be individualized for each patient.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

During the first few years of life, patients with Emery-Dreifuss muscular dystrophy have muscle weakness, an awkward gait, and a tendency for toe-walking. The full syndrome, usually occurring in the teens, is characterized by fixed equinus deformities of the ankles, flexion contractures of the elbows, extension contracture of the neck, and tightness of the lumbar paravertebral muscles (Emery, 1989; Goncu, Guzel, & Guler-Uysal, 2003). It is important to recognize Emery-Dreifuss muscular dystrophy because of the associated cardiac abnormalities that usually are asymptomatic but can lead to sudden cardiac death (Bialer, McDaniel, & Kelly, 1991; Muntoni, 2004; Rakovec, Zidar, Sinkovec, Zupan, & Brecelj, 1995).

Orthopedic treatment of patients with Emery-Dreifuss muscular dystrophy involves release of the heel cord contractures and other muscles around the foot, usually by Achilles tendon

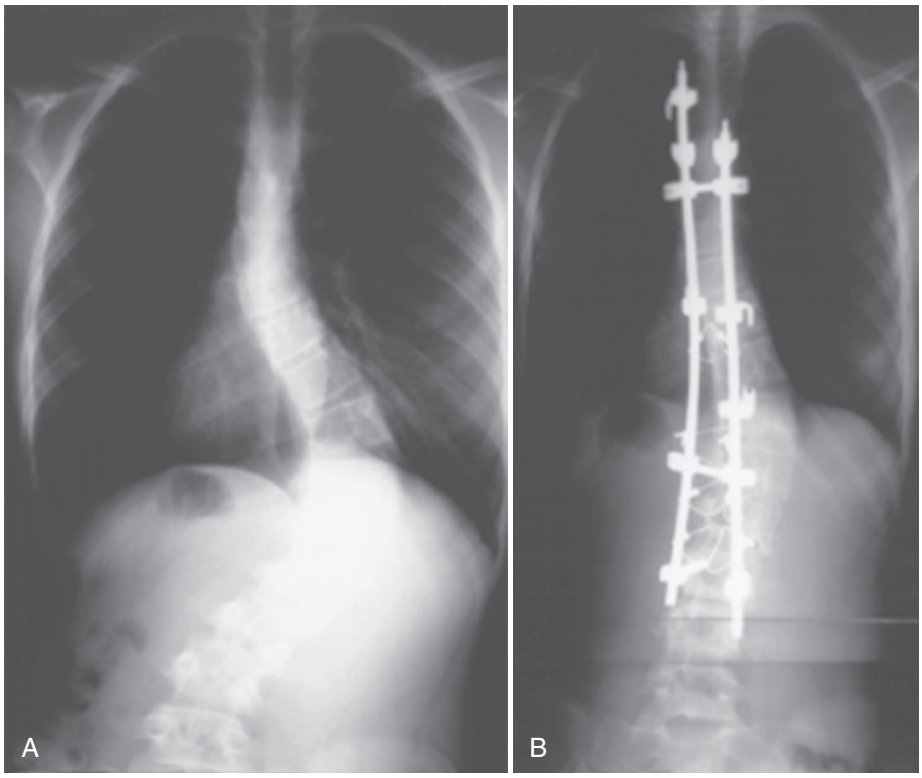


Fig. 9.10 (A) Thoracolumbar curve of 77 degrees. (B) After correction with hooks and sublaminar cables, the curve is 22 degrees. (From Freeman, B. L., III. (2008). Scoliosis and kyphosis. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)

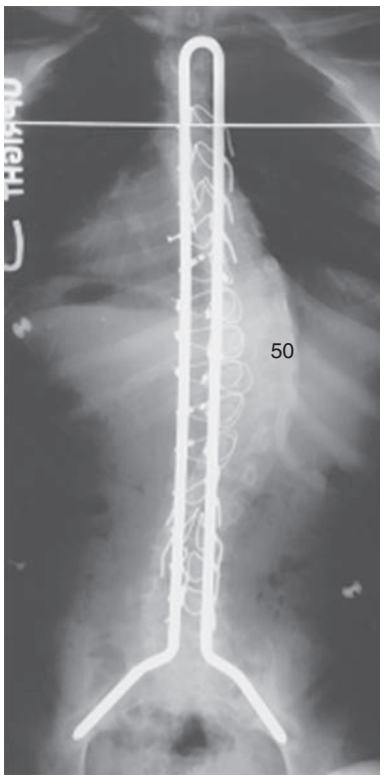


Fig. 9.11 Unit rod for neuromuscular scoliosis. Single, continuous ¼-inch stainless steel rod has a U bend at the top and bullet-shaped ends for insertion into the pelvis. (From Freeman, B. L., III. (2008). Scoliosis and kyphosis. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)



Fig. 9.12 Stabilization of the pelvis with the Galveston technique. Segment of rod is driven into each ilium. (From Freeman, B. L., III. (2008). Scoliosis and kyphosis. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)

lengthening and posterior ankle capsulotomy (Shapiro & Specht, 1991). Anterior transfer of the posterior tibial tendon also may be needed. Elbow flexion contractures usually do not exceed 35 degrees, but contractures of 90 degrees have been reported; these contractures generally do not require surgical release (Shapiro & Specht, 1991). Full flexion and normal pronation and supination are maintained. Contractures around the neck and back should be treated conservatively with range-of-motion exercises, although full range of motion should not be expected. Scoliosis may occur in patients with this form of muscular dystrophy, but progression is less frequent and less severe than in those with Duchenne muscular dystrophy, and spinal fusion is infrequently necessary.

LIMB-GIRDLE DYSTROPHY

The clinical characteristics of limb-girdle dystrophy sometimes are indistinguishable from those of Becker and Duchenne muscular dystrophy, but normal dystrophin is noted on laboratory studies (Guglieri & Bushby, 2008; Pogue et al., 2001; Straub & Bushby, 2008). Limb-girdle dystrophy usually occurs in the first to fourth decades of life (Yamanouchi, Arikawa, Arahata, Ozawa, & Nonaka, 1995). There are two major forms: the more common pelvic girdle type and a scapulohumeral type (Letournel, Fardeau, Lytle, Serrault, & Gosselin, 1990). Initial muscle weakness involves the pelvic or shoulder girdle (Fig. 9.13). Lower extremity weakness usually involves the gluteus maximus, the iliopsoas, and the quadriceps muscles. Upper extremity weakness may involve the trapezius, the serratus anterior, the rhomboids, the latissimus dorsi, and the pectoralis major muscles. Some weakness also may develop in the prime movers of the fingers and wrists. Orthopedic surgery is seldom required for patients with limb-girdle dystrophy. Stabilization of the scapula to the ribs may be required for winging of the scapula; rarely muscle transfers around the wrist may be needed.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

The onset of facioscapulohumeral muscular dystrophy (FSHD) may be in early childhood, in which case the disease runs a rapid, progressive course, confining most children to a wheelchair by age 8 or 9 years; alternatively, onset may occur in patients aged 15 to 35 years, in which case the disease progresses more slowly.

The most striking clinical manifestation is facial weakness with an inability to whistle, purse the lips, wrinkle the brow, or blow out the cheeks (Fig. 9.14). The greatest functional impairments are the inability to abduct and flex the arms at the glenohumeral joints and winging of the scapula, both caused by progressive weakness of the muscles that fix the scapula to the thoracic wall, while the muscles that abduct the glenohumeral joint remain strong. As the disease progresses, weakness of the lower extremities, especially in the peroneal and the anterior tibial muscles, results in a foot drop that requires the use of an AFO. Sometimes the quadriceps muscle is involved, requiring expansion of the orthosis to a knee-ankle-foot orthosis. Scoliosis is rare, although increased lumbar lordosis is common.

The inability to functionally flex and abduct the shoulder is usually treated by stabilization of the scapula with scapulothoracic arthrodesis (Letournel et al., 1990). Scapulothoracic fusion with strut grafts or with plates and screws provides a satisfactory fusion of the medial border of the scapula to the posterior thoracic ribs; however, it is associated with significant complications, including pneumothorax, pleural effusion, atelectasis, and pseudarthrosis (Berne, Laude, Laporte, Fardeau, & Saillant, 2003; Krishnan et al., 2005). A

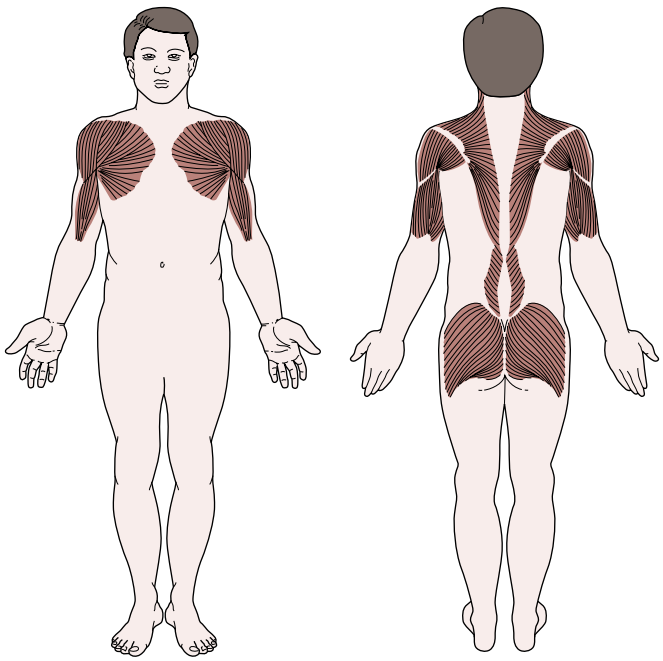


Fig. 9.13 Pattern of weakness in limb-girdle muscular dystrophy. (From Warner, W. C., Jr. (2008). Neuromuscular disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)

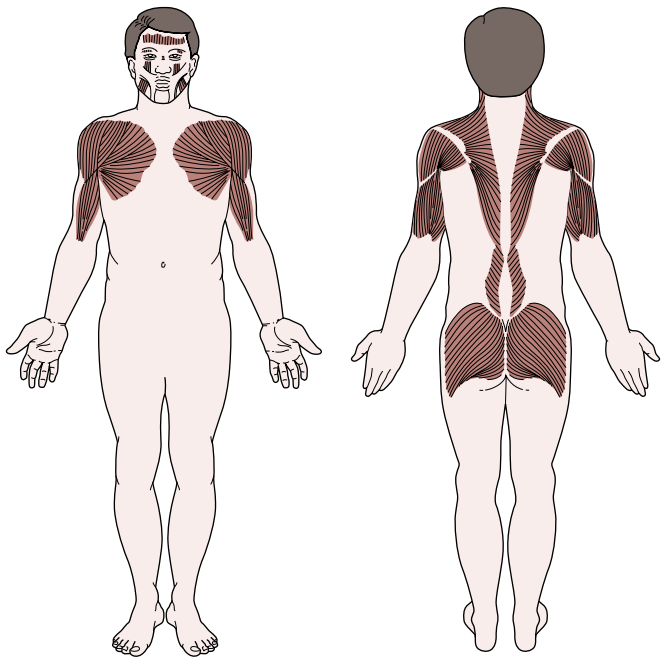


Fig. 9.14 Pattern of weakness of facioscapulohumeral muscular dystrophy. (From Warner, W. C., Jr. (2008). Neuromuscular disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)

loss of pulses and motor and sensory function also has been reported after scapulothoracic arthrodesis (Mackenzie, Riddle, Earley, & Sawatzky, 2003). The pulses and neurologic function returned when the scapula was repositioned to relieve compression of the neurovascular structures. A simplified technique (Fig. 9.15A) has produced good results after scapulocostal fusion in patients with FSHD (Jakab & Gledhill, 1993) (Fig. 9.15B and C).

An early-onset form of FSHD has been described in which weakness is rapidly progressive and the lower extremities also are affected (Klinge et al., 2006; Korf, Bresnan, Shapiro, Sotrel, & Abroms, 1985; Shapiro & Specht, 1993b). Patients become wheelchair bound by the second decade of life. Facial weakness is seen in infancy; this is followed by sensorineural hearing loss at an average age of 5 years. A progressive lumbar hyperlordosis develops and is almost pathognomonic for infantile FSHD. The hyperlordosis leads to fixed hip flexion contractures. Treatment consists of accommodation of the lordosis in the wheelchair. Spinal bracing has not been successful. Spinal fusion may be indicated to assist with sitting balance. Scapulothoracic fusion is not indicated in these patients because of the advanced weakness associated with this form of FSHD.

CONGENITAL MUSCULAR DYSTROPHIES AND CONGENITAL MYOPATHIES

Congenital muscular dystrophies are defined by the histologic appearance of the muscle biopsy rather than by specific clinical or molecular criteria (Cardamone, Darras, & Ryan, 2003; Sewry et al., 1996). Weakness and contractures at birth can cause hip dislocation, clubfeet, or other deformities. Respiratory weakness and difficulty with feeding and swallowing are common. The clinical appearance is one of dysmorphism, with kyphoscoliosis, chest deformities, a long face, and a high palate. Muscle tissue gradually is replaced with fibrous tissue, and contractures could become severe. Treatment is aimed at keeping the patient ambulatory and preventing contractures by exercises and orthotic splinting. Equinus and varus deformities of the feet may require releases if they interfere with ambulation. Congenital dislocation of the hip and clubfoot are treated conventionally, but recurrence is frequent.

MYOTONIC DYSTROPHY

Myotonic dystrophy is characterized by an inability of the muscles to relax after contraction. It is progressive and usually is present at birth, although it may develop in childhood. In addition to the inability of the muscles to relax, muscle weakness causes the most functional impairment. Other defects include hyperostosis of the skull, frontal and temporal baldness, gonadal atrophy, dysphasia, dysarthria, electrocardiographic abnormalities, and mental retardation (Groh et al., 2008; Schara & Schoser, 2006). The characteristic clinical appearance is a tent-shaped mouth, facial diplegia, and dull expression. About half of the children with myotonic dystrophy have clubfoot, and hip dysplasia

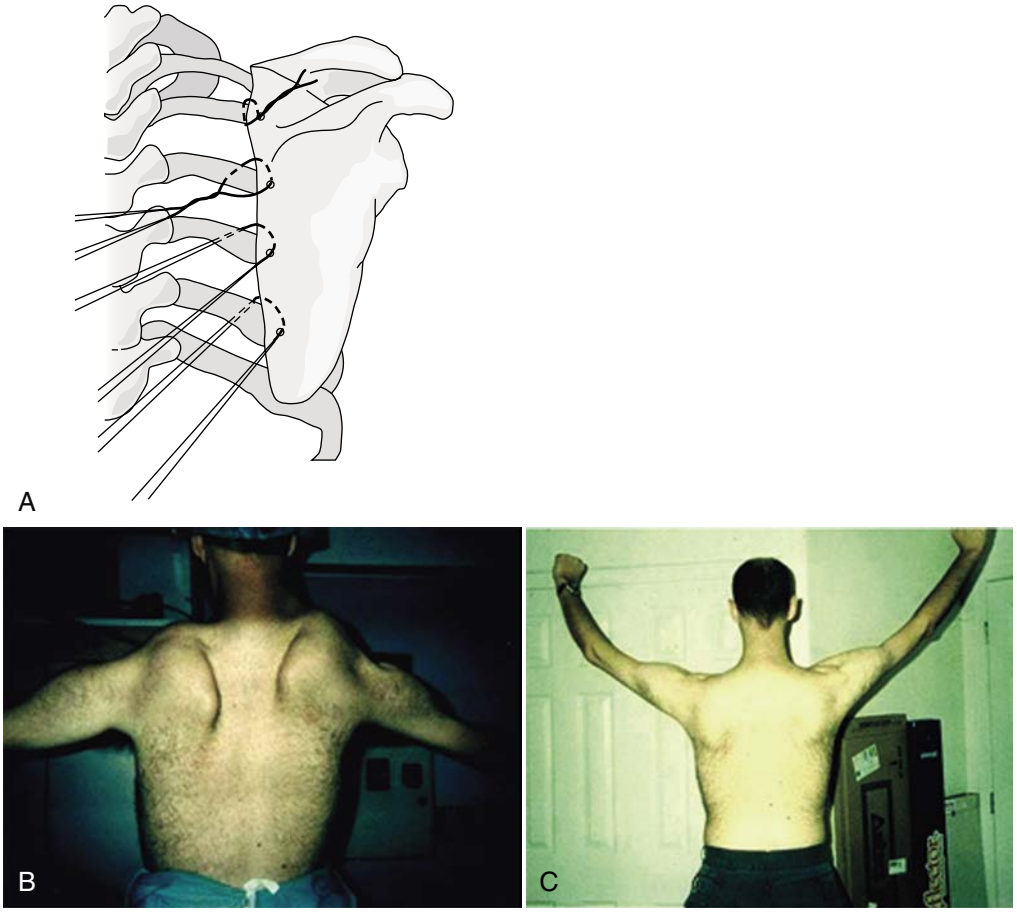


Fig. 9.15 (A) Technique for scapulocostal fusion in patients with facioscapulohumeral muscular dystrophy. (B) Winging of the scapula in a patient with facioscapulohumeral dystrophy. (C) After scapulocostal fusion. (A, From Jakab, E., & Gledhill, R. B. (1993). Simplified technique for scapulocostal fusion in facioscapulohumeral dystrophy. *Journal of Pediatric Orthopedics, 13*, 750.)

and scoliosis may exist (Schara & Schoser, 2006; Ricker, 1999). The hip dysplasia is treated conventionally but, because of capsular laxity, may not respond as readily as in other children. Serial casting can correct equinovarus deformity early on, but recurrence is likely and extensile release usually is required; triple arthrodesis may be required at skeletal maturity because of recurrence despite extensile releases. In patients with marked clubfoot deformity, extensive posteromedial release may not be sufficient to correct the deformity, and a talectomy may be needed. An AFO, which frequently is needed for weakness in dorsiflexion, usually can maintain postoperative correction. In some adolescent patients, scoliosis develops and should be treated with the same principles as for the treatment of idiopathic scoliosis (Themistocleous et al., 2005). The high incidence of cardiac abnormalities and decreased pulmonary function will increase the risk of surgery and may prohibit surgery in these patients.

HEREDITARY MOTOR AND SENSORY NEUROPATHIES

Hereditary motor and sensory neuropathies (HMSNs) are a large group of inherited neuropathic disorders. The most common disorder among these neuropathies is Charcot-Marie-Tooth disease (CMT).

CHARCOT-MARIE-TOOTH DISEASE (PERONEAL MUSCULAR ATROPHY)

CMT is an inherited degenerative disorder of the peripheral nervous system that causes muscle atrophy and loss of proprioception. It usually is an autosomal dominant trait but can be X-linked recessive or autosomal recessive. The incidence of the various forms of CMT ranges from 20 per 100,000 to 1 per 2500 (Bassam, 2014; Holmberg, 1993; Mendell, 1998). Over 90 genes have been identified to be associated with CMT. Muscle atrophy is steadily progressive in most patients with the autosomal dominant form; less often, the disease arrests completely or manifests intermittently. The recessive forms have an early onset (first or second decade) and are more rapidly progressive. Initial complaints usually are general weakness of the foot and an unsteady gait. Foot problems include pain under the metatarsal heads, claw toes, foot fatigue, and difficulty in wearing regular shoes. Distal loss of proprioception and spinal ataxia are common. CMT should be suspected in patients with claw toes, high arches, thin legs, poor balance, and an unsteady gait. In addition to physical examination and family history, electromyograms showing an increased amplitude in duration of response and slow nerve conduction velocity typically confirm the diagnosis in the demyelinating types, but DNA testing also may be necessary.

Advances in molecular biology have improved the ability to confirm the diagnosis of CMT disease and to differentiate between variants of the condition. The use of molecular biology may allow orthopedic surgeons to make more specific treatment recommendations for patients with the variants of CMT disease. For example, patients with the most common form, CMT1A, which is due to a duplication of the PMP22 gene, rarely require the use of a wheelchair, while patients with the CMT2A type caused by abnormalities in the MFN2 gene usually become non-ambulatory in their 20s.

CAVOVARUS FOOT DEFORMITY

The most common neuromuscular cause of cavovarus foot deformity in both adults and children is CMT (Alexander & Johnson, 1989; Guyton, 2006; Schwend & Drennan, 2003). This is a complex deformity of the forefoot and hindfoot. Surgery often is required to stabilize the foot. A study of over 2700 patients with CMT found that 71% of patients had foot deformities, with pes cavus and hammer toes the most common. Thirty percent of patients had some form of operative treatment to their feet at a median age of 15 years, and 33% had surgery more than once, highlighting the need for long-term postoperative follow-up (Laurá et al., 2018).

Although muscle imbalance is known to cause the cavovarus deformity, theories explaining which muscles are involved and how the imbalances produce the rigid cavovarus deformity do not completely account for the clinical deformity. The most widely accepted explanation for the neuropathic cavovarus deformity of CMT is that it is caused by a combination of intrinsic and extrinsic muscle weakness, beginning with weakness of the intrinsic foot muscles and the anterior tibial muscle, with normal strength in the posterior tibial and peroneus longus muscles (Beals & Nickisch, 2008; Berciano & Combarros, 2003; Mann & Missirian, 1988; Sabir & Lyttle, 1983; Tynan, Klenerman, Helliwell, Edwards, & Hayward, 1992). The triceps surae also is weak and may be contracted. The forefoot is pulled into equinus relative to the hindfoot, and the first ray becomes plantar-flexed. The long toe extensors attempt to assist the weak anterior tibial tendon in dorsiflexion but contribute to metatarsal plantar flexion. As the long toe extensors try to dorsiflex the foot, the toes are extended at the metatarsophalangeal joints (Fig. 9.16). This extension or clawing of the toes forces the heads of the metatarsals into a plantar-flexed position and increases the cavus deformity. The forefoot also is forced into a pronated position, with mild adduction of the metatarsals. Initially, the foot is supple and plantigrade with weight-bearing, but as the forefoot becomes more rigidly



Fig. 9.16 Clawing of left toe in a patient with Charcot-Marie-Tooth disease.

pronated, the hindfoot will assume a varus position (Fig. 9.17). Weight-bearing becomes a "tripod" mechanism, with weight borne on the heel and the first and fifth metatarsal head (Nagai et al., 2006) (Fig. 9.18).

Clinical and Radiographic Evaluation

Although CMT is the most common neurologic cause of cavus foot deformity, it is essential to confirm the diagnosis. In one study, nearly 80% of pediatric patients with bilateral cavus foot deformities were diagnosed with CMT; among those with a family history, 91% had CMT (Beals & Manoli, 1996). Many adult patients with cavus feet have no clear etiology for the deformity. Other possible neurologic causes for the cavus foot should be considered (Box 9.1).



Fig. 9.17 Varus position of hindfoot in a patient with Charcot-Marie-Tooth disease.

Physical Examination

Physical examination should include observation of the patient standing and walking to evaluate the degree of difficulty with balance and to assess for other associated deformities of the spine or hips. Patients often seek treatment because of frequent ankle sprains as a result of the cavovarus foot and underlying muscle weakness. In a patient with a cavus foot, the "peek-a-boo" sign is obvious when the foot is viewed from the front. Normally, the heel is hidden behind the foot, but with a cavus foot, its medial side is readily visible (Beals & Manoli, 1996) (Fig. 9.19). The plantar fascia feels like a tight band in the sole of the foot as the forefoot is dorsiflexed. Calluses often are present on the soles of the feet, usually along the lateral border of the foot, especially in the area of the base of the fifth metatarsal.

Motor examination should focus on the relative balance of the agonist-antagonist pairs that generate the foot deformities. Active dorsiflexion against resistance can evaluate the anterior tibial muscle and help detect the use of the extensor hallucis longus as an accessory dorsiflexor, resulting in a claw toe deformity of the hallux. Resisted eversion of the foot directly tests the peroneus brevis, and the longus can be partially isolated by asking the patient to depress the first ray. A handheld dynamometry unit has been reported to provide reliable and objective measures of muscle strength in CMT patients (Burns, Redmond, Ouvrier, & Crosbie, 2005).

The rigidity of the deformity also must be determined because this indicates to what degree tendon transfers or bony procedures can be used for correction. The Coleman block test (Fig. 9.20) is used to help determine the rigidity of the hindfoot varus (Coleman & Chesnut, 1997). The patient stands on a block of wood with the heel and lateral forefoot supported by the block, allowing the plantar-flexed first ray to drop. If dropping the first ray over the edge of the block allows the hindfoot to correct to a valgus position,

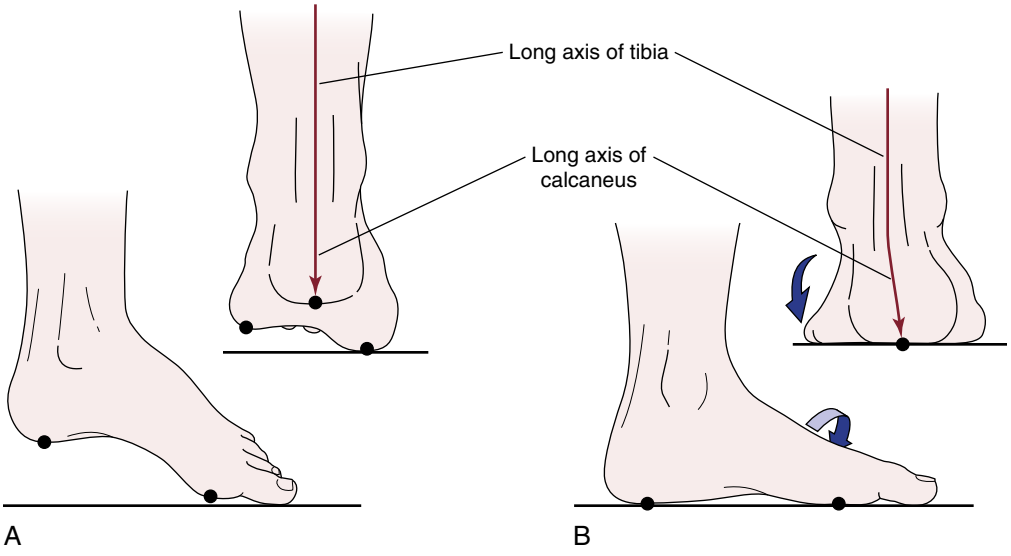


Fig. 9.18 (A) Posterior and lateral views of a cavus foot in a non-weight-bearing position. The long axes of the tibia and the calcaneus are parallel and the first metatarsal is pronated. *Dots* indicate the three major weight-bearing plantar areas (heel and first and fifth metatarsals). (B) Posterior and lateral views of a cavus foot in weight-bearing position. The long axes of the tibia and the calcaneus are not parallel. With weight-bearing, a rigid equinus forefoot deformity forces the flexible hindfoot into varus, producing the tripod effect. (Adapted from Paulos, L., Coleman, S. S., & Samuelson, K. M. (1980). Pes cavovarus: Review of a surgical approach using selective soft-tissue procedures. *Journal of Bone and Joint Surgery. American Volume, 62*, 942-953.)

Box 9.1 Potential Neurologic Causes of Cavus Foot Deformity Other Than Charcot-Marie-Tooth Disease

Infectious

Poliomyelitis

Degenerative

Friedreich ataxia
Hereditary cerebellar ataxia
Roussy-Lévy syndrome
Spinal muscular atrophy

Structural

Spinal cord tumor
Syringomyelia
Diastematomyelia
Spinal dysraphism

Central

Cerebral palsy

From Guyton, G. P. (2006). Current concepts review: Orthopaedic aspects of Charcot-Marie-Tooth disease. *Foot & Ankle International*, *27*, 1003-1010.



Fig. 9.19 Peek-a-boo sign in a cavus foot. When viewed from the front, the heel is normally hidden behind the foot *(left),* but with a cavus foot the medial side of the heel is readily visible *(right).* (From Raikin, S. M., Slenker, N., & Ratigan, B. (2008). The association of a varus hindfoot and fracture of the fifth metatarsal metaphyseal-diaphyseal junction. The Jones fracture. *American Journal of Sports Medicine, 36*, 1367-1373.)

the hindfoot is flexible; if correction of the varus does not occur, the hindfoot is rigid. The hindfoot also can be examined for flexibility with the patient lying prone with the knee flexed.

Careful examination of the peripheral and central nervous systems is required, including electromyography and nerve conduction velocity studies. In demyelinating forms



Fig. 9.20 Coleman block test. A wooden block is placed under the hindfoot and lateral forefoot, with the first metatarsal head off the block. With a flexible deformity, the hindfoot everts into valgus when the plantar-flexed first metatarsal is not bearing weight. With a fixed deformity, the heel position does not change.

of CMT, electrophysiologic testing reveals slowing of the motor nerve conduction velocities due to loss of myelin. The hip and spine should be closely examined; hip dysplasia has been reported in 6% to 8% of children with CMT and scoliosis in as many as a third of children and half of adults with CMT (Chan, Gowen, & Kumar, 2006; Horacek, Mazanec, Morris, & Kobesova, 2007; Karol & Elerson, 2007; McGann & Gurd, 2002; Walker et al., 1994).

Radiographic Examination

Standard anteroposterior, lateral, and oblique radiographs are the most useful methods for evaluating the foot; however, to determine any significant relationships between the bones, it is essential that the anteroposterior and lateral views be made with the foot in a weight-bearing or simulated weight-bearing position. Anteroposterior views document the degree of forefoot adduction. The degree of cavus can be estimated on the lateral view by determining the talus-first metatarsal (Meary) angle, the angle between the long axis of the first metatarsal and long axis of the talus; the normal angle is 0 degrees; in the cavus foot, it usually measures greater than 5 degrees (Alexander & Johnson, 1989). Other measurements include the Hibbs angle, defined as the angle between a line drawn along the longitudinal axis of the calcaneus and one drawn down the shaft of the first metatarsal (normally less than 45 degrees, often near 90 degrees in the cavus foot), and the calcaneal pitch angle, which differentiates between calcaneocavus (more than 30 degrees) and forefoot cavus (less than 30 degrees) (Shapiro & Specht, 1993b) (Fig. 9.21).

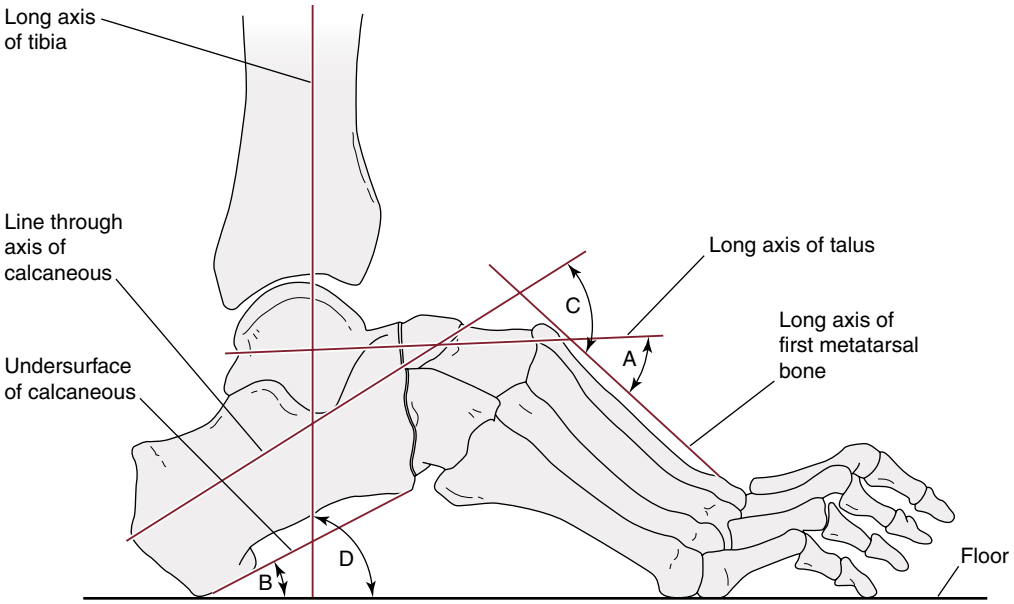


Fig. 9.21 Radiographic angles for evaluating lateral weight-bearing radiographs of the cavovarus foot. *A*, Meary angle. *B*, Calcaneal pitch angle. *C*, Hibbs angle. *D*, Weight-bearing tibioplantar angle. (Adapted from Alexander, I. J., & Johnson, K. A. (1989). Assessment and management of pes cavus in Charcot-Marie-Tooth disease. *Clinical Orthopaedics and Related Research,* 246, 273-281.)

Radiographs using the Coleman block test demonstrate the correction of the varus deformity if the hindfoot is flexible. Equinus can be measured by the lateral tibial calcaneal angle. If this angle exceeds 30 degrees, the ankle is dorsiflexed, and the tendency for patients to walk on their toes is specifically not due to ankle equinus. Cross-sectional imaging modalities have little role in the evaluation of CMT. Magnetic resonance imaging will show fatty infiltration in the peroneus brevis or anterior tibialis muscle, but muscle function is better determined clinically.

Orthopedic Treatment

Treatment is determined by the age of the patient and the severity of the deformity.

Nonoperative Treatment. Nonoperative treatment of the cavovarus foot generally has been unsuccessful, although a brace may help manage symptoms of drop foot and ankle instability (Guyton, 2006). In active patients with mild lateral ankle ligament laxity, a simple figure-of-eight Velcro-strap ankle brace often is sufficient (Guyton, 2006; Refshauge, Raymond, Nicholson, & van den Dolder, 2006). For more severe foot drop, a posterior spring-leaf AFO provides dorsiflexion assistance and is lightweight and easy to transfer between shoes. A custom-molded leather boot brace or a conventional double-metal upright shoe-based AFO may be needed for more support, especially in obese patients. However, poor compliance with brace-wear has been found in patients with severe bilateral foot drop caused by CMT (Vinci & Gargiulo, 2008). Reasons given for discarding the AFO were that it highlighted patients' disabilities, was not essential for limited daily walking, and was uncomfortable.

Some studies have suggested that neurotrophin-3 (NT-3) may augment nerve regeneration in animal models of CMT, and a small clinical study (eight patients) showed possible minor benefits, but currently, there is no clear evidence that NT-3 is an effective treatment for CMT (Young, De Jonghe, Stögbauer, & Butterfass-Bahloul, 2008). Small trials of exercise, creatine monohydrate, and purified bovine brain gangliosides have been done, but none showed significant benefit. Identification of the genes causing CMT may allow the development of feasible gene therapy options.

Operative Treatment of Foot Deformities. Surgical procedures are of three types: soft tissue (plantar fascia release, tendon release, or tendon transfer), osteotomy (metatarsal, midfoot, calcaneal), and joint-stabilizing (triple arthrodesis). The goals of operative treatment are correction of the deformity and rebalancing of the deforming muscle forces.

Experience in the treatment of foot deformities in CMT has demonstrated that early, aggressive treatment when the hindfoot is flexible and early soft-tissue releases can delay the need for more extensive reconstructive procedures. Even in a young patient with a fixed hindfoot deformity, limited soft-tissue release combined with osteotomies of the first metatarsal, midfoot, or calcaneus can provide a satisfactory functional outcome without the loss of hindfoot and midfoot joint motion that occurs with triple arthrodesis.

Initial treatment of a flexible cavus foot consists of plantar fascia release or plantar fascia and medial soft-tissue release (Fig. 9.22). This can be combined with appropriate tendon transfers to rebalance the foot.

Flexible claw toe deformity usually is corrected without additional surgery when the midfoot deformity is corrected. For clawing in a young child without severe weakness of the anterior tibial muscle, the extensor hallicus longus tendon can be transferred to the first metatarsal neck with tenodesis or fusion of the interphalangeal joint of the great toe (Fig. 9.23). This converts the extensor hallicus longus into an active dorsiflexor of the plantar-flexed first metatarsal. For adolescents or children with severe weakness of the anterior tibial muscle, the second through fifth long toe extensors can be transferred to the middle cuneiform, with fusion or tenodesis of the interphalangeal joint. For severe deformity, the posterior tibial tendon can be transferred anteriorly to the middle cuneiform instead of the long toe extensors. Anterior transfer of the posterior tibial tendon removes a deforming force and allows the posterior tibial muscle to assist with ankle dorsiflexion. The peroneus longus functions as a plantar flexor of the first metatarsal. Transfer of this muscle

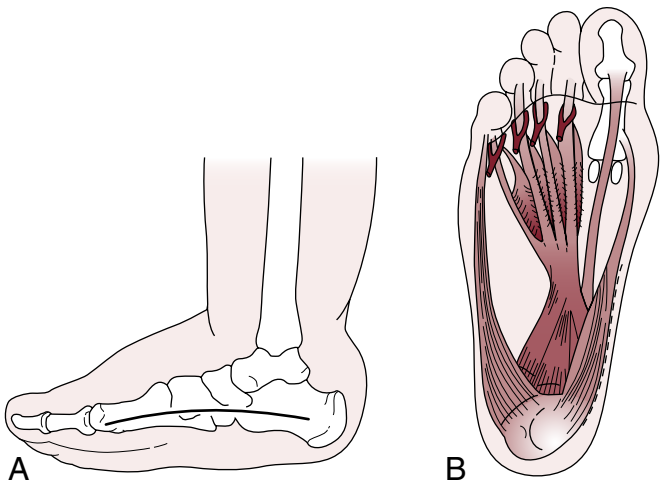


Fig. 9.22 Plantar-medial release for cavovarus deformity. (A) Incision. (B) Release of musculotendinous mass. (Redrawn from Coleman, S. S. (1983). *Complex foot deformities in children.* Philadelphia: Lea & Febiger.)

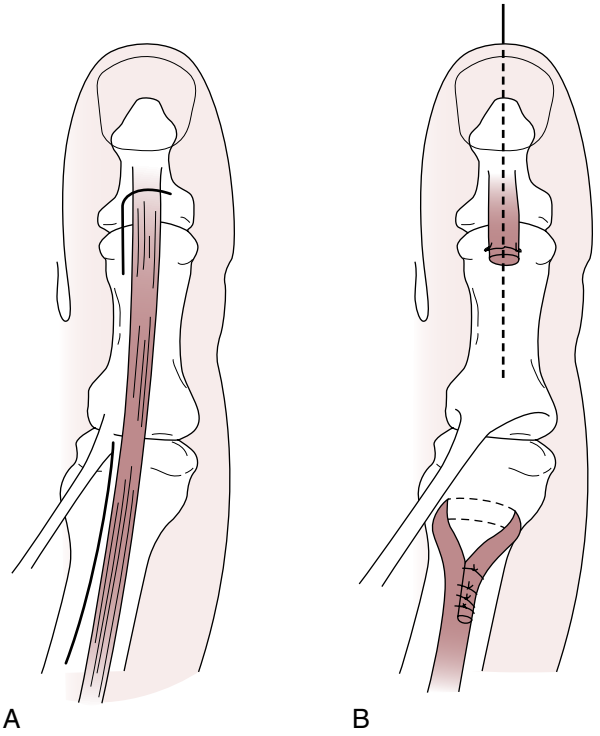


Fig. 9.23 Transfer of extensor hallucis longus tendon for claw toe deformity (Jones procedure). (A) Incisions. (B) Completed transfer. (From Warner, W. C. (2008). Neuromuscular disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed., p. 1518). Philadelphia: Elsevier.)

to the peroneous brevis changes its function from plantar flexion of the first metatarsal to eversion of the forefoot.

Children younger than age 8 years with supple hindfeet usually respond to plantar releases and appropriate tendon transfers. A more extensive plantar-medial release and osteotomy of the first metatarsal can be used for rigid forefoot deformity. In children younger than age 12 years with rigid hindfoot deformities, radical plantar-medial release, first metatarsal dorsiflexion osteotomy or midfoot osteotomy, and a calcaneal osteotomy usually correct the deformity. For a fixed hindfoot varus deformity with a prominent calcaneus, a lateral closing wedge osteotomy may be preferred to shorten the heel. If the heel is not prominent, a sliding calcaneal osteotomy gives satisfactory results.

Many patients with CMT do not require triple arthrodesis; soft-tissue procedures and osteotomies are sufficient in skeletally immature feet and those with less severe deformity. Appropriate wedge resections correct both the hindfoot varus and midfoot component of the cavus deformity; soft-tissue release and muscle balancing are required for the forefoot deformity. Some authors recommend restoring hindfoot stability with a triple arthrodesis and transferring the posterior tibial tendon anteriorly to eliminate the need for a postoperative drop-foot brace. Because of early degenerative changes in the ankle, forefoot, and midfoot, triple arthrodesis generally is considered a salvage procedure for patients in whom other procedures were unsuccessful or in patients with untreated severe fixed deformities (Fig. 9.24); however, some surgeons prefer triple arthrodesis to midfoot osteotomy because of a more reliable correction of the deformity and the possibility of arthritic changes caused by an osteotomy that crosses multiple joints (Mann & Hsu, 1992; Wetmore & Drennan, 1989; Wukich & Bowen, 1989).

Surgical procedures usually are staged (Olney, 2000) (Fig. 9.25). The initial procedure is a radical plantar or plantar-medial release, with a dorsal closing wedge osteotomy of the first metatarsal base if necessary. Achilles tendon lengthening usually is not needed because ankle equinus usually is not present. If Achilles tendon lengthening is needed for ankle equinus, it should not be done as part of the initial procedure because the force used to dorsiflex the forefoot would not allow for adequate correction of the equinus deformity. If the hindfoot is flexible and a posterior release is not necessary, posterior tibial tendon transfer can be done as part of the initial procedure for severe anterior tibial weakness.

HIP DYSPLASIA

Hip dysplasia has been reported in approximately 6% to 8% of patients with CMT (Chan et al., 2006; Fuller & DeLuca, 1995; Kumar, Marks, Bowen, & MacEwen, 1985; McGann & Gurd, 2002; Walker et al., 1994). Dysplasia is more likely to occur in HMSN type I than in HMSN type II. The treating physician should be aware of this association. If hip dysplasia is present, it should be corrected. The periacetabular osteotomy has been reported to successfully correct the hip dysplasia, but complications were more frequent with CMT dysplasia than with developmental dysplasia (Novais, Kim, Carry, & Millis, 2016) (Fig. 9.26).

SPINAL DEFORMITIES

Scoliosis is uncommon in association with CMT, usually reported to occur in approximately 10% of patients (Karol & Elerson, 2007), although Walker et al. (1994) reported frequencies of 37% in children and 50% in adults. In a review of 175 patients with HMSN, Horacek et al. (2007) found spinal deformity in 26%. The curve usually is mild to moderate and often does not require any treatment. In patients with CMT, Hensinger and MacEwen (1976) reported associated kyphosis in half their patients with scoliosis. They reported that nonoperative treatment with a brace was well tolerated and successfully controlled the curve in many patients.

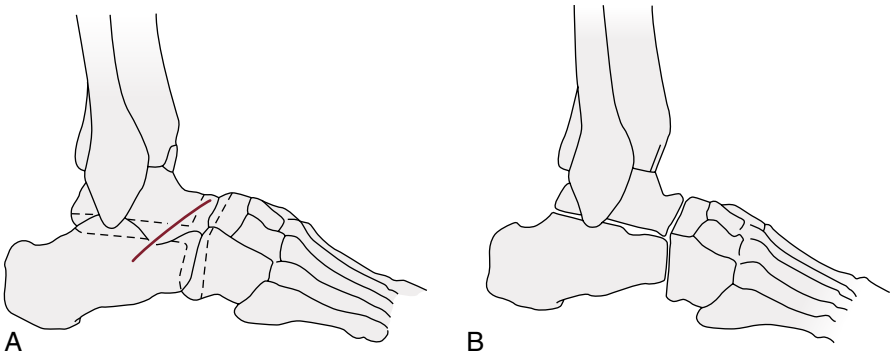


Fig. 9.24 Triple arthrodesis. (A) Oblique incision to expose subtalar, talonavicular, and calcaneocuboid joints. (B) Cartilage and cortical bone are removed from all joint surfaces; appropriate bony wedges are removed if necessary for deformity correction. (From Warner, W. C. (2008). Paralytic disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed., p. 1412). Philadelphia: Elsevier.)

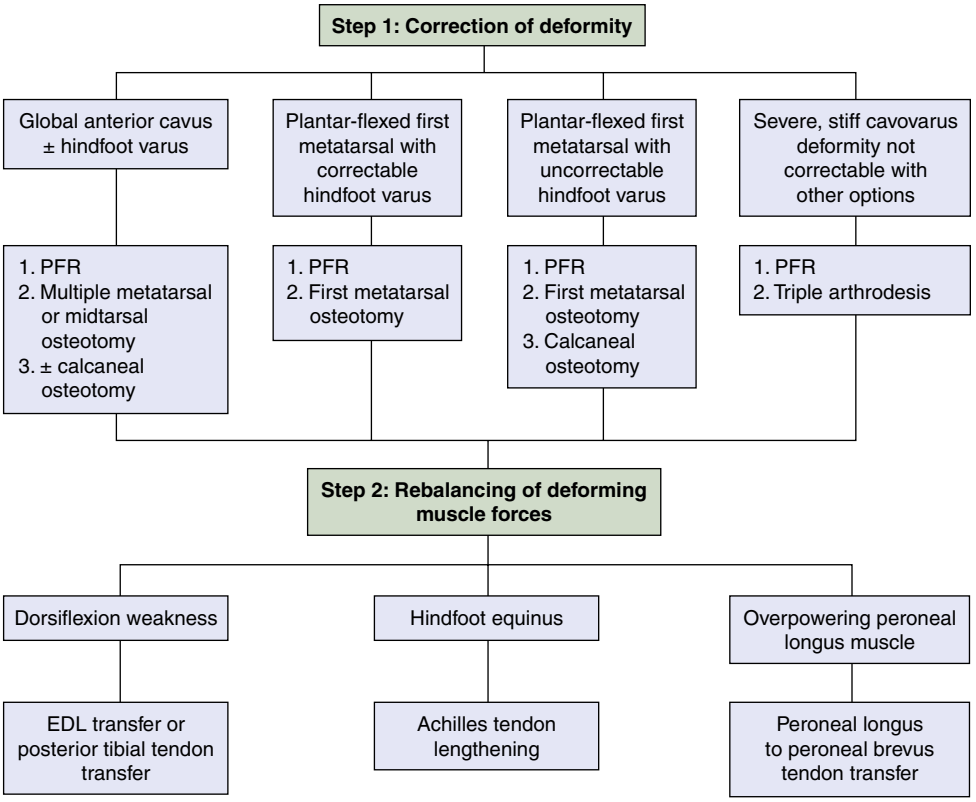


Fig. 9.25 Treatment algorithm for correction of cavovalgus foot in pediatric patients with Charcot-Marie-Tooth disease. *EDL,* Extensor digitorum longus; *PFR*, plantar fascia release. (From Olney, B. (2000). Treatment of the cavus foot. Deformity in the pediatric patient with Charcot-Marie-Tooth disease. *Foot & Ankle Clinics, 5*, 305-315.)

Generally, spinal deformities in children with CMT can be managed by the same techniques used for idiopathic scoliosis. Because of the demyelinization of the peripheral nerves and degeneration of the dorsal root ganglion and dorsal column of the spinal cord, somatosensory-evoked potentials may be absent.

CHARCOT-MARIE-TOOTH VARIANTS

Roussy-Lévy syndrome (hereditary areflexic dystaxia) is an autosomal dominant disease with the clinical characteristics of classic CMT plus a static tremor in the hands. The disease usually begins in infancy, but symptoms may not show until adolescence. It is characterized by severe alterations in nerve conduction and sensory dysfunction (Berciano & Combarros, 2003).

Dejerine-Sottas syndrome (familial interstitial hypertrophic neuritis) usually is an autosomal recessive disease but may show an autosomal dominant inheritance with variable penetrance. The disease usually begins in infancy but may not appear until adolescence. Along with the classic pes cavus deformity, marked sensory loss occurs in all four extremities, and patients also may have clubfoot or kyphoscoliosis (Berciano & Combarros, 2003; Jani-Acsadi, Krajewski, & Shy, 2008; Payerson, 2004).

Refsum disease is an autosomal recessive disorder beginning in childhood or puberty in which the spinal fluid protein is increased. The gene responsible for Refsum disease is on chromosome 10. The condition is caused by a defect in phytanoyl-CoA hydroxylase, which is responsible for the degradation of phytanic acid. It is accompanied by retinitis pigmentosa and is characterized by a hypertrophic neuropathy with ataxia and areflexia. Distal sensory and motor loss occurs in the hands and feet. The course is unpredictable, with repeated reactivations and remissions, but the prognosis is poor (Wills, Manning, & Reilly, 2001).

Neuronal-type CMT is an autosomal dominant disease with a usually late onset (middle age or later). The small

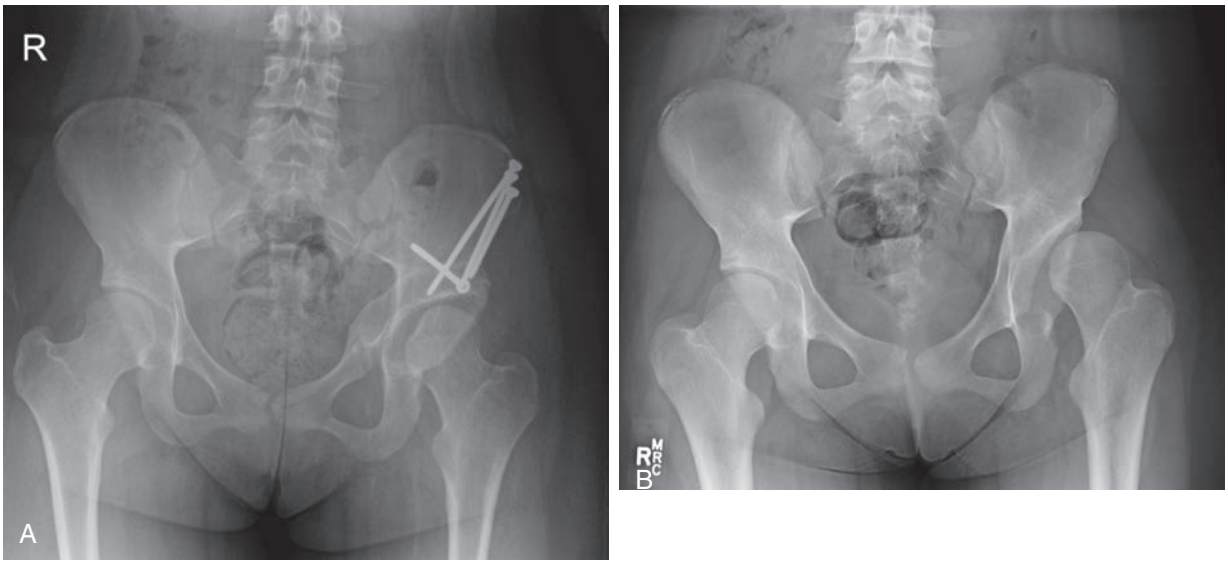


Fig. 9.26 Correction of hip dysplasia (A) with Bernese periacetabublar osteotomy (B).

muscles of the hands are not as weak as in other forms of the disease, but the ankle muscles and plantar muscles of the feet are much weaker and more atrophic.

FRIEDREICH ATAXIA

Friedreich ataxia is an autosomal recessive condition characterized by spinocerebellar degeneration. The prevalence of Friedreich ataxia is approximately 1 in 50,000 (Pandolfo, 2008). An ataxic gait usually is the presenting symptom, with onset routinely between ages 7 and 15 years. The diagnosis is suggested by the clinical triad of ataxia, areflexia, and a positive Babinski reflex (Wood, 1998). Definitive diagnosis can be made with DNA testing. The disease is progressive, and almost all patients are wheelchair bound by the first or second decade of life. Patients typically demonstrate progressive dysarthria or weakness, decreased vibratory sense in the lower extremities, cardiomyopathy, pes cavus, and scoliosis. Knee jerk and ankle jerk reflexes are lost quite early. Patients usually die in the fourth or fifth decade of life as a result of progressive cardiomyopathy, pneumonia, or aspiration.

The primary concern of the orthopedist is the correction of foot and spinal deformities (Fig. 9.27). In patients with Friedreich ataxia, the plantar reflex sometimes is so great that when standing is attempted, the feet and toes immediately plantar-flex and the posterior tibial tendon pulls the forefoot into equinovarus. If general anesthesia is contraindicated because of myocardial involvement or other medical conditions, tenotomies of the Achilles tendon, the posterior tibial tendon at the ankle, and the toe flexors at the plantar side of the metatarsophalangeal joints can be done with the patient under local anesthesia. Surgery should be delayed in patients who are able to walk and who have deformities that are either supple or can be controlled in braces; however, the cavovarus deformities tend to worsen and become rigid. In patients with rigid cavovarus deformity, primary triple arthrodesis provides a solid base of support with a fixed plantigrade foot. Because most patients become wheelchair bound, later development of ankle and midfoot degenerative changes seldom is clinically significant. Posterior tibial tenotomy, lengthening, or transfer should be combined with triple arthrodesis. Bracing is routinely required after surgery (Delatycki et al., 2005).

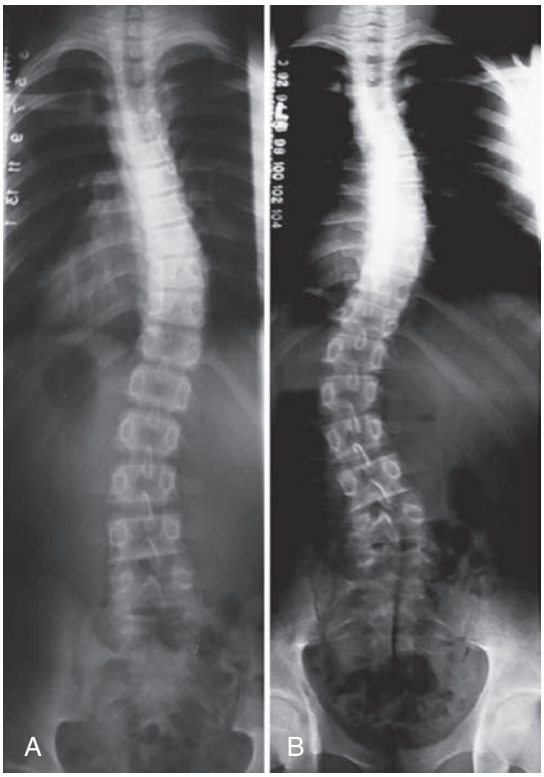


Fig. 9.27 Scoliosis in a patient with Friedreich ataxia. (A) At age 14, she had a 26-degree thoracic curve and a 25-degree lumbar curve; brace treatment was begun. (B) At age 16.5 years, after 1 year of bracing and 1 year of follow-up, the residual thoracic curve is 30 degrees and the lumbar curve is 39 degrees. (From Milbrandt, T. A., Kunes, J. R., & Karol, L. A. (2008). Friedreich's ataxia and scoliosis: The experience at two institutions. *Journal of Pediatric Orthopedics, 28*, 236.)

Scoliosis is frequent in patients with Friedreich ataxia, occurring in 60% to 100% (Cady & Bobechko, 1984; Milbrandt, Kunes, & Karol, 2008; Shapiro & Specht, 1993b). Curve patterns are variable and may or may not resemble idiopathic curves (Labelle, Tohmé, Duhaime, & Allard, 1986; Milbrandt et al., 2008). Stabilization of the spine should be performed when the curve is greater than 40 to 50 degrees and the patient is no longer ambulatory. A single-stage posterior arthrodesis with segmental instrumentation is the treatment of choice. The fusion should extend from the upper thoracic spine to the lower region of the lumbar spine, as in patients with Duchenne muscular dystrophy.

SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is an inherited degenerative disease of the anterior horn cells of the spinal cord that occurs in 1 in 20,000 births (Han & McDonald, 2008; Lunn & Wang, 2008; Oskoui & Kaufmann, 2008). It is generally transmitted by an autosomal recessive gene, but other hereditary patterns have been described. SMA has been classified into five types. SMA 0 occurs before birth and is fatal within 2 weeks. In SMA I, severe generalized weakness manifests in patients younger than age 6 months, and terminal respiratory failure occurs early. SMA II occurs during the middle of the first year and, after initial progression of weakness, may remain static for long periods. SMA III develops later, with gradual onset of weakness and a slowly progressive course (Hensinger & MacEwen, 1976; Kumar et al., 1985; Novais et al., 2016). SMA IV is a rare adult form.

Orthopedic treatment generally is required for hip and spine problems (Granata, Cervellati, Ballestrazzi, Corbascio, & Merlini, 1993; Riddick, Winter, & Lutter, 1982; Sporer & Smith, 2003; Thompson & Larsen, 1990; Zenios, Sampath, Cole, Khan, & Galasko, 2005). Children with SMA I are markedly hypotonic and generally succumb to the disease early in life. In these patients, orthopedic reconstruction is not warranted; however, patients with SMA I may develop fractures that heal quickly with appropriate splinting. Many children with infantile SMA II (Werdnig-Hoffmann disease) are never able to walk even with braces, but most patients with the juvenile form (SMA III, Kugelberg-Welander disease) are able to walk for many years. Gentle passive range-of-motion exercises and positioning instructions can be beneficial initially. Surgical release of contractures rarely is required. Because of the absence of movement and weight-bearing, coxa valga deformity of the hip is frequent, and unilateral or bilateral hip subluxation may occur (Fig. 9.28). Because many of these children are sitters, a stable and comfortable sitting position is essential. Traditionally, proximal femoral varus derotational osteotomy has been used in nonambulatory patients to produce a more stable sitting base. Efforts to maintain the reduction of the hips for good sitting balance may prevent pain and pelvic obliquity. However, Sporer and Smith (2003) recommended observation instead of surgical intervention because of the small number of patients who had symptoms or seating problems in their series.

Recent advances in the medical management of SMA include the use of a compound known as nusinersen, which was released in 2016 by the Food and Drug Administration. It is an antisense oligonucleotide administered intrathecally that modifies the splicing of SMN2 and increases the number of full-length protein molecules. It has been shown to improve motor function and motor milestone development in all types of SMA, with younger and asymptomatic patients, those who have not yet developed joint contractures or scoliosis, having better outcomes. Efforts are ongoing to improve drug delivery either by implantable pumps or by orally administered medications (Goodkey, Aslesh, Maruyama, & Yokota, 2018; Mercuri et al., 2018; Strauss et al., 2018). A newly developed gene therapy, onasemnogene abeparvovec-xioi (Zolgensma, Novartis), has been approved by the U.S. FDA to treat all SMA types in children up to age 2, in whom Zolgensma is administered as a one-time infusion into the vein.



Fig. 9.28 Coxa valga deformity and subluxation in a 12-year-old child with spinal muscular atrophy. (From Warner, W. C., Jr. (2008). Neuromuscular disorders. In S. T. Canale & J. H. Beaty (Eds.), *Campbell's operative orthopaedics* (11th ed.). Philadelphia: Elsevier.)

Among children with SMA who survive childhood, scoliosis becomes the greatest threat during adolescence. Scoliosis is seen in nearly 100% of children with type II SMA and in children with type III SMA who become nonambulatory. It usually is progressive and severe and can limit daily function and cause cardiopulmonary problems. Bracing may be indicated during the growing years to slow curve progression, but spinal stabilization is ultimately required in almost all adolescent patients. Several authors have emphasized the importance of early surgery before the curve becomes severe and rigid. The treatment of choice is a long posterior fusion, using segmental instrumentation. This fusion and instrumentation usually should extend to the pelvis in nonambulatory patients to prevent pelvic obliquity.

For most older patients, long posterior spinal fusion (PSF) to the pelvis is the treatment of choice. A 10-year follow-up of 11 patients with SMA who had PSF showed that PSF resulted in significant curve correction and an improvement in the rate of decline of forced vital capacity from 5.3% per year preoperatively to 1.3% per year postoperatively. During PSF, it is important to leave a midline "window" centrally in the fusion mass, typically at L3–L4, to allow access for intrathecal injection or port placement for the administration of nusinersen (Strauss et al., 2018).

Intraoperative and postoperative complications are frequent in these patients, and thorough preoperative evaluation is mandatory.

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10 Perioperative Management of Patients With Neuromuscular Disorders

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INTRODUCTION

Patients with neuromuscular disorders (NMDs) are at increased risk for complications during or immediately after surgery; they share a common risk of respiratory failure, atelectasis, and pneumonia and may have longer hospital stays and increased risks of morbidity, as compared with those without neuromuscular diseases (Bardorf, Sproule, & Kaufmann, 2010; Blatter & Finder, 2013).

Hypoventilation can occur due to respiratory muscle weakness. Increased chest wall compliance in younger patients can contribute to atelectasis. Upper airway obstruction is common, due to pharyngeal and laryngeal muscle weakness/discoordination. Macroglossia, as in the case of Duchenne muscular dystrophy (DMD) or Pompe disease, can complicate intubation and contribute to airway obstruction.

Aspiration is a significant risk for these patients. Oropharyngeal weakness and incoordination, as well as failure to protect the airway opening, can lead to aspiration, which can be compounded by abdominal muscle weakness with an ineffective cough.

The patient's characteristics may vary with localization of the primary lesion (Lee, 2012), and those with upper motor lesions are more likely to be associated with chest wall immotility and increased tone, whereas lower motor neuron lesions are more likely to be associated with chest wall mobility and flaccid paralysis.

CHARACTERISTICS OF PHYSIOLOGIC ABNORMALITIES

Those with NMDs typically have inspiratory and expiratory muscle weakness, but all aspects of the respiratory physiology could be altered. Early, children could have excessive chest wall compliance. Some have chest wall deformity (Papastamelos, Panitch, & Allen, 1996), such as pectus excavatum. Development of scoliosis can lead to decreased chest wall compliance (Estenne, Heilporn, Delhez, Yernault, & De Troyer, 1983), as can intercostal muscle fibrosis (commonly seen in DMD).

Respiratory control is also altered in many patients, particularly in those with mitochondrial myopathy (Barohn, Clanton, Sahenk, & Mendell, 1990).

With chronic carbon dioxide retention, the characteristic hypercarbic ventilatory response can be diminished. Without hypoventilation, however, even patients with significant weakness do not necessarily develop a blunted respiratory drive (Bégin, Mathieu, Almirall, & Grassino, 1997). Chronic respiratory acidosis from hypoventilation is offset by a compensatory metabolic alkalosis which in turn blunts respiratory drive. Sleep disordered breathing is common (Ragette, Mellies, Schwake, Voit, & Teschler, 2002).

Recognition of impaired cough is also key to the prevention of respiratory complications in neuromuscular diseases. Each phase of cough can be affected by weakness (Gozal, 2000). The inspiratory phase of cough is affected by diaphragm weakness. Glottic closure is limited by bulbar dysfunction, and the expiratory phase of cough is restricted from both thoracic and abdominal muscle weakness.

PREOPERATIVE MANAGEMENT

Prior to surgery, a patient with significant neuromuscular weakness should undergo pulmonary assessment. The simplest pulmonary test is a pulse oximetry, and if this reveals SpO_2 under 95%, measurement of carbon dioxide in the blood or end-tidal (or transcutaneous) CO_2 should be obtained (Birnkrant et al., 2007). When conducting blood gas measurement, sampling from the arterial circulation is preferable as it permits A-a gradient calculation, but capillary gas measurement can be reliable, especially in younger patients. Hypoxemia in the presence of normal carbon dioxide levels, particularly in those individuals with neurocognitive disabilities, is strongly suggestive of ventilation-perfusion mismatch, and suggests chronic aspiration or atelectasis.

Pulmonary function testing (spirometry, plethysmography, and measurement of CO_2) should be performed in patients capable of participation. The risks and complications of pediatric neuromuscular diseases have best been described in DMD. Forced vital capacity (FVC) has predictive value in DMD and can be used to assess risk for respiratory complications. DMD patients with an FVC under 50% of predicted are at increased risk of respiratory complications when undergoing a procedure, and those with an FVC of under 30% are at higher risk (Birnkrant et al., 2007). Vital capacity can also be shown to predict daytime ventilation in patients with DMD. Toussaint, Steens, and Soudon (2007) noticed that vital capacity below 680 mL was very sensitive to threshold for detection of daytime hypercapnia.

In patients with NMDs with the risk of hypoventilation as assessed by FVC, the clinician should consider perioperative training with noninvasive positive pressure ventilation (NPPV). Perioperative training can increase the likelihood of successful postoperative NPPV use (Bach, Ishikawa, & Kim, 1997; Birnkrant, Ferguson, Martin, & Gordon, 2006). Patients with an ineffective cough, history of recurrent pneumonia, and loss of expiratory muscle strength, as measured by maximum expiratory pressure (MEP; i.e., below 60 cm of H_2O) (Miske, Hickey, Kolb, Weiner, & Panitch, 2004), should receive preoperative training with a mechanical insufflation-exsufflation device (Birnkrant et al., 2007).

CARDIOVASCULAR ASSESSMENT

Cardiovascular involvement occurs in different neuromuscular diseases, particularly DMD, and some limb-girdle dystrophies and may have dilated cardiomyopathy, and dysrhythmias and surgery could predispose to heart failure (Schmidt, Burmeister, Lilje, Wappler, & Bischoff, 2003). Preoperative cardiology consultation with echocardiography and electrocardiogram is especially important in patients with DMD. Treatments with angiotensin-converting enzyme inhibitors, beta-blockers, and even corticosteroids can be beneficial. Cardiovascular dysfunction (particularly dysrhythmia) is also common in myotonic dystrophy (DM) and accounts for 20% of deaths in these patients.

NUTRITIONAL ASSESSMENT

Malnutrition adversely affects respiratory muscle strength (Hart et al., 2004). It is reasonable to suggest that a cachectic patient with these disorders is not an appropriate candidate for surgery, particularly elective surgery.

Malnutrition puts the patient at risk of perioperative loss of skin integrity due to pressure ulceration, and patients may need a feeding tube prior to consideration for surgery such as spinal fusion.

Another cause of low weight is chronic respiratory failure, and patients with respiratory failure lose weight either due to insufficient intake with chronic dyspnea or due to increased energy expenditure with increased work of breathing (Allen et al., 2003; Birnkrant et al., 2007; Laaban, 2000). Malnutrition in some patients with neuromuscular diseases may be an indication for implementation of NPPV (Birnkrant et al., 2007) and consideration for gastrostomy placement.

ADVANCE DIRECTIVES

Many neuromuscular diseases are progressive and fatal, and goals of care should be discussed in detail, and advance directive status should be well documented (Birnkrant, Pope, & Eiben, 1999).

INTRAOPERATIVE MANAGEMENT

Major surgery in patients with neuromuscular diseases involving general anesthesia requires a well-trained team (Birnkrant et al., 2006), including an anesthesiologist that should, particularly in these disorders, have experience with these patients, and the respiratory therapist should have experience in pediatrics and NPPV and airway clearance techniques. An intensive care unit (ICU) should be readily accessible to manage a potentially prolonged postoperative course (Birnkrant et al., 2007). Sedation should be performed by an anesthesiologist and full monitoring (American Academy of Pediatrics, American Academy of Pediatric Dentistry, Work Group on Sedation, Coté, & Wilson, 2006; Birnkrant et al., 1999). In addition to pulse oximetry and cardiac monitoring, the ability to measure carbon dioxide levels and end-tidal transcutaenous CO_2 is advised.

RESPIRATORY SUPPORT DURING INDUCTION MAINTENANCE AND RECOVERY

Intubation in these patients can be affected by abnormalities of the airway, for example, those with Duchenne's dystrophy who have an enlarged tongue. Neck and shoulder rigidity can also limit the extension of necks. Jaw ankylosis is also common in DMD, which can make intubation difficult. A protocol for respiratory support should be followed.

Anesthesiologists should consider interoperative noninvasive ventilation depending on the procedure (Boitano, Jordan, & Benditt, 2001; Pope, Birnkrant, Martin, & Repucci, 1997), and neuromuscular patients with chronic respiratory insufficiency may benefit with additional ventilation support during induction and recovery.

Manual positive pressure breaths can be delivered via resuscitation bags if there is a prolonged period of recovery, and the patient may require full noninvasive respiratory support from a conventional ventilator (Harper, Ambler, & Edge, 2004; Niranjan & Bach, 1998), depending on the degree of baseline respiratory compromise as measured by FVC, for example. It is reasonable to expect that patients will need to be extubated directly to NPPV, commonly via full face mask (Bach & Sabharwal, 2005; Lumbierres et al., 2007).

POSTOPERATIVE MANAGEMENT

Patients with respiratory insufficiency, including those who use NPPV at baseline, are more likely to require extubation to NPPV (Bach & Sabharwal, 2005; Pope et al., 1997). NPPV can be weaned postoperatively to baseline levels, as tolerated (Gill et al., 2006). Return to baseline support often takes much longer than the immediate recovery from anesthesia (Almenrader & Patel, 2006). This is particularly seen in patients with DM.

Surgeries that affect chest wall shape and have significant postoperative pain such as spinal fusion may be beneficial with support above baseline (Bach & Sabharwal, 2005). In addition, narcotic pain medication affects respiration and cough. NPPV can help to avoid the need to prolong intubation or tracheostomy in high-risk patients (Bach & Sabharwal, 2005).

If the patient uses NPPV at home, it is reasonable to attempt to use this on interphase in the hospital as well (Bach & Sabharwal, 2005; Birnkrant et al., 2006). If a patient is extubated to NPPV, it is advisable to perform it in the ICU (Lumbierres et al., 2007).

It is advisable to assess levels of carbon dioxide in the blood or with end-tidal or transcutaneous CO_2 measurement prior to initiating increasing levels of oxygen supplementation.

Neuromuscular patients with respiratory insufficiency are at high risk of hypercapnia (Benditt, 2009; Marsh, Edge, & Lehovsky, 2003; Smith, Edwards, & Calverley, 1989). The optimal management of hypercapnia is respiratory support rather than supplemental oxygen, which can suppress respiratory drive and lead to respiratory failure.

An escalating oxygen requirement in patients with neuromuscular diseases can also suggest other etiologies. Atelectasis is common in postoperative patients (Panitch, 2006; Schmidt-Nowara & Altman, 1984). Aggressive treatment of atelectasis includes use of mechanical insufflation/exsufflation. Aspiration can increase with hypoxemia (Klinger, Lehmann-Horn, & Jurkat-Rott, 2005) and necessitates assistive cough therapy.

Sedating analgesics may have an additive effect on baseline respiratory insufficiency in patients with neuromuscular disease, but adequate pain management is essential (Brambrink & Kirsch, 2007; Tiffreau, Viet, & Thévenon, 2006), even if sedating analgesia necessitates prolonged intubation or NPPV use. It is worth considering other measurements such as nerve blockade that can reduce need for analgesia (Brambrink & Kirsch, 2007).

ASSISTIVE COUGH AND AIRWAY CLEARANCE

Many patients with neuromuscular disease have an ineffective cough. Inadequate cough strength can be indicated by low peak cough flow or peak flow on spirometry and diminished MEP on pulmonary function testing (Chatwin et al., 2003; Szeinberg et al., 1988).

Patients with impaired cough should have access to a mechanical insufflation and exsufflation device. This form of augmented airway clearance provides cycles of positive pressure followed by negative pressure. Patients and families need to be introduced to the idea of mechanical insufflation-exsufflation prior to surgery.

Cough assistive technology is also used when surgical pain limits effective postoperative cough, and it is generally well tolerated even in patients who have undergone thoracic and abdominal surgeries.

Impaired mucociliary clearance should be considered in some neuromuscular patients. In one study, 66% of patients with chronic pulmonary aspiration were found to have bronchiectasis (Piccione, McPhail, Fenchel, Brody, & Boesch, 2012). For these patients, chest physiotherapy is helpful, such as use of a high-frequency chest wall compression vest device if the procedure allows this therapy. Newer airway clearance therapies to augment mucociliary clearance include intrapulmonary percussive ventilation (IPV®, Percussionaire) and the MetaNeb® (HillRom) system (a high-frequency airway oscillation and positive expiratory pressure device used in hospitalized patients who cannot tolerate chest wall compression therapy).

There are some studies that suggest benefit with the use of chest wall vest therapy in the mechanically complex patient, but its use may be limited by operative considerations in cases of abdominal or thoracic surgery (Plioplys, Lewis, & Kasnicka, 2002).

CARDIOVASCULAR MANAGEMENT

An expert panel in the American Academy of Pediatrics has recommended perioperative cardiac evaluation in patients with DMD (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2005), and this recommendation is valuable in the preoperative evaluation of all patients with significant weakness.

Neuromuscular patients with normal perioperative ECG and echocardiogram are still at risk of cardiac complications during surgery (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2005). Thorough evaluation should be considered and precautionary observation as management.

Cardiovascular complications are well-established complications in myopathies. Fluid shifts associated with surgery can increase the likelihood of heart failure (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2005). Judicious management of fluid balance in these patients is essential.

NUTRITIONAL MANAGEMENT

Patients with NMDs are often at risk of gastrointestinal dismotility (Barohn, Levine, Olson, & Mendell, 1988). Following surgery, patients often are immobile and take opioid analgesics, further limiting motility, so establishing a bowel regimen is necessary. Poor nutrition aggravates baseline respiratory insufficiency (Iannaccone, Owens, Scot, & Teitell, 2003). Postoperative consideration of enteral feeding tubes or parenteral nutrition can help with these complications.

In the following sections, we will discuss specific issues related to particular NMDs.

PERIOPERATIVE MANAGEMENT IN SPECIFIC NEUROMUSCULAR DISORDERS

MOTOR NEURON DISEASES

Adults with motor neuron diseases, particularly amyotrophic lateral sclerosis (ALS), may undergo percutaneous endoscopic gastrostomy (PEG) tube placement and tracheostomy for management of the disorder. They also may undergo general surgical procedures common in those in late adulthood, and these should be performed under careful monitoring.

Dysphagia is a common symptom in patients with ALS, usually developing at about the same time as respiratory insufficiency; for this reason, pulmonary function should be assessed and oxygen saturation carefully monitored during PEG tube placement (Albert, Murphy, Del Bene, & Rowland, 1999; Kasarskis & Neville, 1996; Mazzini et al., 1995), which requires sedation. The procedure is recommended to be done early and in patients whose vital capacity is more than 50% of predicted (Miller et al., 1999), although there are insufficient data to suggest a specific timing (Miller et al., 2009). The use of noninvasive ventilation in those who are at risk and do not have a tracheotomy appears safe and reduces complications (Boitano et al., 2001). PEG tube placement does not prevent aspiration pneumonia, but it does improve the patient's quality of life and nutritional state. In our center, we perform the procedure in the inpatient setting, followed by at least 24 hours of intravenous (IV) fluids until bowel sounds are present and tube feeding can be started.

Tracheostomy should be discussed early, including its complications, and performed in patients who do not tolerate noninvasive respiratory assistance or have inadequate

ventilation. The procedure helps to reduce dead space and improves suctioning. Tracheostomy should be done in the hospital setting after proper discussion with the patient and family concerning long-term care and complications, which include infections, excessive bleeding, and mucus plugs. Patients should be observed for at least 24 hours after the initiation of respiratory assistance (Bertorini, 2004) (see also Chapters 2, 12, and 13).

SPINAL MUSCULAR ATROPHY

Patients with type 1 spinal muscular atrophy (SMA) develop respiratory failure early, and tracheostomy and PEG tube placement are done in those whose parents opt for aggressive management. These procedures and their complications should be discussed as soon as the diagnosis is made. These patients have difficulty swallowing and have an increased risk of complications (Grünebaum, Nutman, & Nitzn, 1981), and aspiration and nutritional failure are very common. It is reasonable to consider parenteral gastrostomy tube and fundoplication prior to major surgeries such as spinal fusion (Durkin, Schroth, Helin, & Shaaban, 2008; Wang et al., 2007). If necessary, a laporoscopic approach should be considered (Durkin et al., 2008; Yuan, Wang, Trela, & Albanese, 2007).

Patients with types 2 and 3 SMA may develop respiratory failure later, but tracheostomy and PEG tube placement should be discussed early and performed as soon as they appear necessary (Ragette et al., 2002). This approach has been shown to prolong survival (Samaha et al., 1994).

Scoliosis surgery is done in patients with types 2 and 3 SMA, but those with type 1 SMA usually die before the procedure is necessary. The surgery should be performed before the curvature has become severe. Those with vital capacity below 35% usually have a poorer prognosis and might require permanent tracheotomy (Lyager, Steffensen, & Juhl, 1995). Surgical risks are increased for those with frequent respiratory infections (Merlini et al., 1989). Other orthopedic procedures that may be required by patients with SMA, such as correction of hip deformities, are discussed in Chapters 9 and 13. These procedures require careful preoperative and postoperative monitoring and management with respiratory therapy, including the use of incentive spirometry, with monitoring of pulse oximetry and arterial blood gases when necessary. Prompt mobilization is recommended.

FRIEDREICH ATAXIA

Individuals with Friedreich ataxia may undergo surgery to correct the orthopedic deformities that accompany the disease, such as surgical correction of foot abnormalities to improve ambulation (Hensinger & MacEwen, 1976). Scoliosis may cause respiratory complications, and scoliosis surgery is the most important invasive procedure performed in this disorder. It is usually done on individuals who are wheelchair bound, have vital capacities at least 40% of normal, and have a curvature of more than 60% of normal (Labelle, Tohmé, Duhaime, & Allard, 1986).

Perioperative care of those with Friedreich ataxia is further complicated by diabetes mellitus and hypertrophic cardiomyopathy that frequently accompany the neuromuscular symptoms. Thus, preoperative care of these patients requires not only oximetry but also cardiac assessment and monitoring as well as frequent electrolyte and glucose measurements. Other, more generalized complications are not uncommon in this population; these include aspiration pneumonia and pulmonary embolism (Delatycki et al., 2005).

PERIPHERAL NEUROPATHIES

Patients with peripheral neuropathy, particularly those with Charcot-Marie-Tooth disease, might need orthopedic surgery for foot deformities (Alexander & Johnson, 1989), but they usually do not require special monitoring. Spinal deformities are rare, but they occur in some with the early childhood forms, and these should be managed similarly to those in patients with Friedreich ataxia, although careful cardiac monitoring is not necessary. Those with more severe forms, such as Dejerine-Sottas syndrome, might require a tracheostomy and even PEG tube placement.

Individuals with severe acute neuropathies, such as Guillain-Barré syndrome, may require tracheostomy and PEG tube placement, but these procedures usually are done when the patient is intubated and in the ICU. Nonetheless, these patients require proper cardiac monitoring because of the possibility of dysautonomia and cardiac arrhythmias.

MYASTHENIA GRAVIS

Myasthenia gravis is a disease in which respiratory failure could occur during surgical procedures requiring deep sedation or general anesthesia. Special care should be taken to avoid the use of paralyzing agents or drugs that might aggravate the disease and cause a myasthenic crisis (see Chapter 19). Adequate electrolyte balance must be maintained to prevent hypokalemia, which can worsen weakness (Bégin et al., 1997).

Those receiving corticosteroids should take their daily dosage either orally or parentally, with a booster dose of 100 mg of Solu-Cortef (Pfizer, New York) IV the day of surgery and another the following day.

Thymectomy may be done, particularly in younger patients with generalized myasthenia gravis (Seybold, Howard, Duane, Payne, & Harrison, 1971). The procedure has definitively been proven to be beneficial in a controlled study (Wolfe et al., 2016), providing long-term benefit (Wolfe et al., 2019), and it is considered the standard of care (Olanow, Wechsler, Sirotkin-Roses, Stajich, & Roses, 1987). Although there is substantial variation in the actual procedure performed, the surgery of choice is total or complete thymectomy (Jaretzki et al., 1988). Robotic surgery could be considered, particularly in high-risk cases. Those with anti-MuSK-positive myasthenia gravis do not seem to respond to thymectomy, and it is not recommended in these patients at this time (Sanders, El-Salem, Massey, McConville, & Vincent, 2003).

Thymectomy in children may also be beneficial because it was reported to induce remissions of the disease in uncontrolled trials (Sarnat, McGarry, & Lewis, 1977; Seybold, 1998). There is lingering concern, however, that removal of the thymus organ at a young age may lead to lasting, and potentially harmful, alterations of T-cell populations (Brearley et al., 1987; Halnon et al., 2005; Mendell, Warmolts, &

Bass, 1977). Thus, the decision to choose the procedure in children should be made on an individual basis.

Thymectomy has low incidences of morbidity and mortality, and it should be done early in generalized myasthenia (Masaoka & Monden, 1994). Some clinicians recommend that thymectomy be done before the initiation of corticosteroid therapy (Machens, Emskötter, Busch, & Izbicki, 1998), but most patients are already receiving steroids when they undergo thymectomy. The chance of infection is not higher than in those receiving immunotherapy, but the risk is increased in those with severe disease (Machens et al., 1998).

Severe myasthenia gravis should first be stabilized with corticosteroids and, if necessary, plasmapheresis (d'Empaire, Hoaglin, Perlo, & Pontoppidan, 1985; Spence, Morin, & Katz, 1984) or immunoglobulin G infusions before thymectomy using standard protocols. Both procedures appear to produce similar benefits (Jensen & Bril, 2008). Either procedure should be done about 2 weeks before thymectomy if pulmonary function is adequate.

After surgery, patients should be extubated promptly and monitored with pulse oximetry and, if necessary, measurements of arterial blood gases in the ICU setting for 24 to 48 hours.

The common practice of withholding anticholinesterase drugs for 48 hours after surgery is of questionable value. We administer the oral medication or its parenteral equivalent starting with half of the preoperative dosage 12 hours after the procedure, increasing to the full dose over 2 days. This method is in agreement with the findings of a large study of complications of 324 thymectomies in which the incidence of complications was higher in patients requiring prolonged intubation, apparently from withholding medications (Kas et al., 2001). Tracheostomy is performed only in patients who require prolonged intubation and respiratory assistance.

MUSCULAR DYSTROPHIES

Patients with myopathies, particularly muscular dystrophies and congenital myopathies, might undergo a series of surgeries during their lifetime. The risks and benefits should be carefully assessed, and the procedure should be done under careful pulmonary and cardiac monitoring.

Scoliosis surgery is performed in patients with myopathies who have Cobb angles between 30% and 50%. There are no absolute pulmonary function contraindications to scoliosis repair, and good outcomes have been reported in patients with severe weakness (Apkon et al., 2018). Tendon releases should be done with minimal anesthesia, and patients should be carefully observed and promptly extubated.

Those with Emery-Dreifuss, Duchenne (DMD), and limb-girdle dystrophies that affect the heart (i.e., LGMD2I) must be carefully monitored during surgery for cardiac arrhythmias (see Chapter 3) and for electrolyte disturbance, which require immediate treatment. An expert panel of the American Academy of Pediatrics recommended preoperative cardiac evaluation in patients with DMD (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2005), and this recommendation should be considered for all cases of myopathies.

Tracheostomy and, rarely, gastrostomy are necessary in patients with late stages of the disorders, and the use of noninvasive ventilation helps to prevent complications (Pope et al., 1997).

Patients with muscular dystrophy who undergo any surgical procedure should be evaluated closely by a medical team that includes a neuromuscular specialist, anesthesiologist, pulmonologist, and cardiologist, and the procedure should be done with monitoring for cardiac arrhythmias and with oximetry.

A unique and important complication to be avoided is the development of malignant hyperthermia (MH) or rather MH-like syndrome (MHLS) or hyperkalemia-induced rhabdomyolysis (Larach, Rosenberg, Gronert, & Allen, 1997; Nathan, Ganesh, Godinez, Nicolson, & Greeley, 2005). Although DMD patients who develop this syndrome do not have the calcium channel mutations or all the features of MH syndrome (MHS), the presentation and management are otherwise similar to those in other patients (Hayes, Veyckemans, & Bissonnette, 2008). Drugs that can precipitate MH should be avoided, and dantrolene should be available to be used when necessary.

It also should be pointed out that patients with Becker muscular dystrophy and limb-girdle muscular dystrophies with cardiomyopathy might undergo cardiac transplantation, particularly those in whom the weakness is not severe, and proper measures should be taken perioperatively and postoperatively (Komanapalli et al., 2006) to prevent complications such as electrolyte disturbances and MHLS.

MYOTONIC DYSTROPHY

DM is discussed separately because these patients may develop multiple medical problems that require surgical intervention, which can be associated with complications (Harper & Rudel, 1994). Respiratory dysfunction can occur not only in patients with DM type 1 (Souayah, Tick Chong, Dreyer, Cros, & Schmahmann, 2007) but also in those with DM type 2. The risk of complications can be increased in these patients because of diabetes, respiratory failure, and cardiomyopathy.

Patients with DM have increased sensitivity to anesthetics (Dundee, 1951; Kilburn, Eagan, Sieker, & Heyman, 1959; Mathieu et al., 1997) and muscle relaxants (Aldridge, 1985) and could develop cardiac conduction delays, diabetes, as well as respiratory insufficiency caused by muscle weakness (Mathieu et al., 1997; Souayah et al., 2007) and poor respiratory drive, which could result in alveolar hypoventilation (Kilburn et al., 1959). Exacerbation of myotonia occurs with lower body temperatures when depolarizing relaxants are used (Aldridge, 1985; Dundee, 1951). MH also has been reported in these patients (Harper & Rudel, 1994).

It is recommended that general anesthesia be avoided when possible; surgical procedures should be done with monitoring for cardiac arrhythmia and for MH. Postoperatively, those with DM should receive proper early physical therapy and incentive respirometry. Noninvasive ventilation temporarily after surgical procedures is useful. A unique complication of DM is intestinal pseudo-obstruction or megacolon, which could be managed with a rectal tube placement.

Surgical guidelines for the preoperative and perioperative management of these patients are listed in Box 10.1. The details can be found in the DM website (Myotonic Dystrophy Foundation, n.d.).

Box 10.1 Preoperative and Postoperative Care and Complications of Anesthesia in Myotonic Dystrophy

Preoperative Evaluation, Care

Perform electrocardiogram (ECG)
Perform pulmonary function testing (including supine and upright forced vital capacity) and arterial blood gas measurement
Obtain chest radiograph
Encourage incentive respirometry

Intraoperative Monitoring

Monitor ECGs
Measure arterial blood pressure
Use a peripheral nerve stimulator to monitor blockage of peripheral muscle
Monitor temperature
Warm the mattress
Warm intravenous fluids
Maintain humidification of anesthetic gases

Postoperative Care

Retain endotracheal tube in place and ventilate if necessary in an intensive care unit
Monitor oxygen saturation and P_{CO_2} for at least 24 hours postoperatively to avoid overlooking delayed-onset apnea
Use controlled-flow oxygen therapy with close monitoring of ventilation in patients relying on hypoxic drive due to chronic respiratory insufficiency
Provide early physiotherapy
Monitor ECG
Keep patient warm
Monitor swallowing closely to check for signs of aspiration
Treat all infections vigorously
Encourage incentive respirometry
Administer subcutaneous heparin if intubation is prolonged

Anesthetic Agents

When possible, use local or regional anesthesia, such as an epidural block
Avoid succinylcholine and other depolarizing muscle relaxants
Avoid or use only minimal dose of thiopental; for muscle relaxation, use short-acting agents (e.g., atracurium or vecuronium)
Avoid or use only minimal doses of opiates or other analgesics to avoid respiratory depression
When possible, avoid general anesthesia; if necessary, use combination of nitrous oxide/oxygen mixture with an agent such as 0.8% enflurane or 1.0% isoflurane; also consider propofol
Use anticholinesterases (e.g., neostigmine) with care; may be preferable to ventilate the patient until residual curarization wears off

Modified from Moxley, R. T., III. (1992). Myotonic muscular dystrophy. In L. P. Rowland, S. DiMauro (Eds.), *Handbook of clinical neurology. Myopathies* (2nd ed., pp. 209–244). Amsterdam: Elsevier Science, with permission.

CHANNELOPATHIES

Channelopathies, particularly myotonia congenita, do not require surgery for management, but patients with these conditions might undergo procedures similar to those done in the general population. Complications include MH and exacerbation of myotonia from the use of agents such as succinylcholine (Russell & Hirsch, 1994; Schwartz, Rockoff, & Koka, 1984). Hypokalemia might exacerbate myotonia and cause arrhythmias and weakness, particularly in those with hypokalemic paralysis, whereas hyperkalemia causes weakness in those with hyperkalemic periodic paralysis and could also cause arrhythmias. For this reason, proper electrolyte balance and maintenance of potassium levels around 4 μg/L are advised. Patients should be monitored for at least 24 hours after surgery.

Propofol is recommended for anesthesia in patients with channelopathies; this drug acts by enhancing gamma-aminobutyric acid-mediated sympathetic inhibition and might block sodium influx through the channels in the heart and brain. Propofol stabilizes membranes, decreasing their excitability (England, 2001; Haeseler et al., 2001).

MALIGNANT HYPERTHERMIA SYNDROME

MHS, a condition described initially by Denborough and Lovell in 1960 (Denborough & Lovell, 1960), is characterized by severe muscle rigidity, fever, cardiac arrhythmia, and rhabdomyolysis. MH occurs particularly with exposure to general anesthetics such as halothane and depolarizing muscle relaxants. Other manifestations include acidosis, hypermetabolism, fever, hyperkalemia, cardiac arrhythmias, and initial hypocalcemia due to intracellular calcium accumulation.

The syndrome has an incidence of 1 in 15,000 children and 1 in 50,000 adults (Bertorini, 2002; Gronert, 1994; Jurkat-Rott, McCarthy, & Lehmann-Horn, 2000). It is an autosomal dominant inherited disorder more frequently associated with mutations of the ryanodine calcium channel gene, which is allelic to central core disease (Quane et al., 1993). It has also been reported in patients with dihydropyridine voltage-gated calcium channel disorders (Kim et al., 2013; Monnier, Procaccio, Stieglitz, & Lunardi, 1997). Both channels are involved in muscle calcium release, and attacks of MH are caused by excessive release of calcium by the sarcoplasmic reticulum (SR) under certain conditions (Finsterer, 2002).

The genetic mutations associated with MHS appear to be lower than the threshold for calcium release by the SR altering excitation-contraction coupling and manifesting as massive muscle necrosis, similar to what occurs in porcine stress syndrome (Finsterer, 2002).

During attacks, the increased intracellular calcium causes muscle contractures that lead to increased oxygen consumption, glycogenolysis, and depletion of high-energy phosphate compounds with elevation of body temperature. There also is a limitation of calcium reuptake by the SR for muscle relaxation, increasing muscle contractures, which further increases intramuscular calcium accumulation and necrosis (Fig. 10.1). This results in leakage of phosphate and potassium into the bloodstream, which could cause cardiac arrhythmias. Serum uric and lactic acids, creatine kinase (CK), and myoglobin are increased, which could cause renal failure (Bertorini, 2002; Gronert, 1994).

Several mutations of the SR calcium receptor genes are associated with MHS (Finsterer, 2002; Iles et al., 1994; Kim et al., 2013; Manning et al., 1998; Monnier et al., 1997; Quane et al., 1993). MHS or MHLS also has been reported in a variety of muscle diseases, including channelopathies, muscular dystrophies, and congenital myopathies such as central core

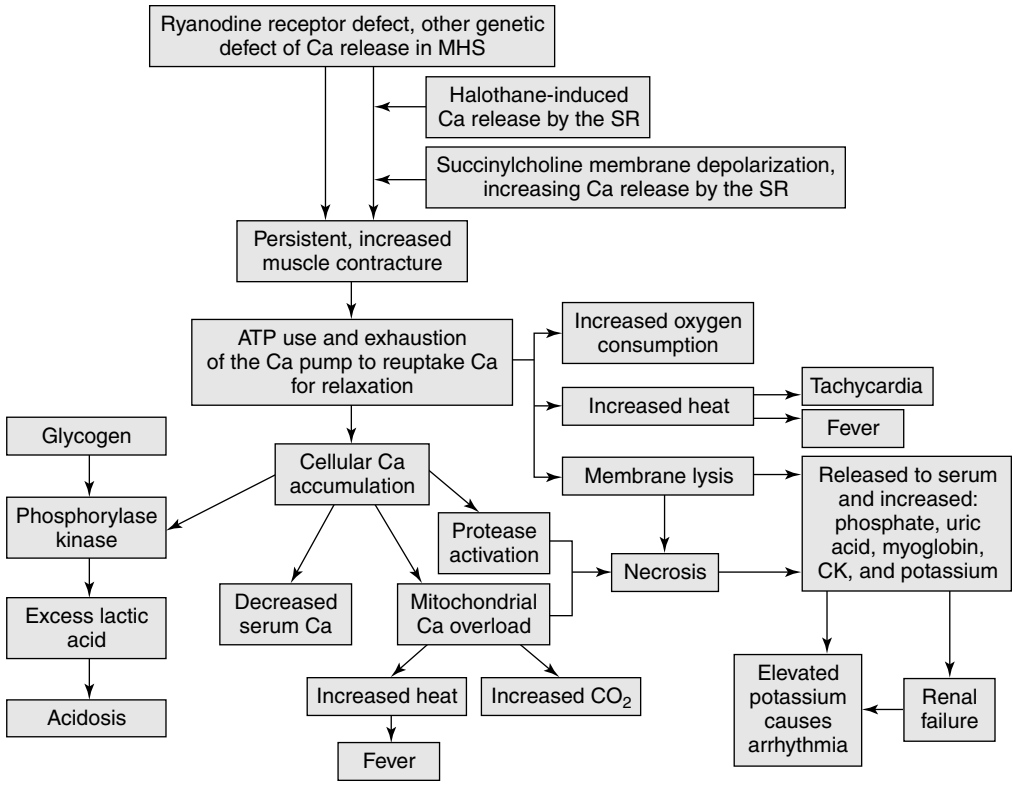


Fig. 10.1 Possible mechanisms of clinical and laboratory abnormalities in malignant hyperthermia syndrome. *ATP*, Adenosine 5′-triphosphate; *Ca*, calcium; *CK*, creatine kinase; CO_2, carbon dioxide; *MHS*, malignant hyperthermia syndrome; *SR*, sarcoplasmic reticulum. (Modified from Bertorini, T. E. (1997). Myoglobinuria, malignant hyperthermia, neuroleptic malignant syndrome and serotonin syndrome. *Neurologic Clinics, 15*, 658.)

Box 10.2 Individuals at Risk for Malignant Hyperthermia or Malignant Hyperthermia-Like Syndrome

Family history of malignant hyperthermia
King-Denborough syndrome
Evans myopathy
Central core disease
Multicore diseases
Muscular dystrophy (dystrophinopathy, myotonic dystrophy)
Periodic paralysis
Myotonia congenita
Carnitine palmitoyltransferase deficiency
Phosphorylase deficiency; possibly other glycogen storage myopathies
Brody's disease
Idiopathic hyperCKemia

Box 10.3 Medications and Their Relationship to Malignant Hyperthermia

Triggering Agents
Inhalation Anesthetics
Halothane
Enflurane
Isoflurane
Desflurane
Sevoflurane
Depolarizing Blockers
Succinylcholine
Decamethonium
Controversial Agents
Calcium, potassium salts
Ketamine
Catecholamines
Phenothiazines, monoamine oxidase inhibitors
Safe Agents
Nitrous oxide
Barbiturates
Local anesthetics
Narcotics
Nondepolarizing neuromuscular relaxants
Antibiotics
Propranolol
Propofol
Benzodiazepines

Modified from Kauss, J., & Rocko, M. A. (1994). Malignant hyperthermia. *Pediatric Clinics of the North America*, *41*, 133.

and mini-core disease (Gronert, 1994). Central core disease and mini-core disease are caused by mutations of the genes for calcium receptors that are associated with MHS (Loke & MacLennan, 1998; McCarthy et al., 1990; Quane et al., 1993). A list of conditions in which MH or MHLS has been observed is given in Box 10.2. It also should be mentioned that, although halothane and depolarizing skeletal muscle relaxants are the drugs most often implicated in triggering the disorder, several other medications have been reported to induce attacks of MHS in subjects at risk (Box 10.3).

Box 10.4 Clinical Events and Laboratory Findings during Malignant Hyperthermia

Clinical Events

Unexplained, sudden increase in end-tidal CO_2
Unexplained tachycardia, tachypnea, labile blood pressure, or arrhythmias
Masseter muscle rigidity or generalized muscle rigidity
Unanticipated respiratory or metabolic acidosis
Increasing patient temperature
Cola-colored urine (myoglobinuria)
Mottled, cyanotic, hot skin; sweating; decreased SpO_2

Laboratory Findings

Arterial blood gases; $Paco_2$ ≥60 mm Hg, base excess more negative than -8 mEq/L, pH <7.25
Potassium ion >6 mEq/L
Creatine kinase >10,000 IU/L after anesthetic without succinylcholine
Serum myoglobin >170 µg/L

Modified from Karlet, M. C. (1998). Malignant hyperthermia: Considerations for ambulatory surgery. *Journal of Perianesthesia Nursing, 13*, 306, with permission.

Box 10.5 Recommended Steps in Managing Patients with Suspected Malignant Hyperthermia

Discontinue the anesthetic and deliver 100% oxygen.
Administer dantrolene IV, 2 to 3 mg/kg every 5 minutes for a total of 10 mg/kg.
Get help; consult the malignant hyperthermia hotline for guidance. * * www.mhous.org, United States and Canada: 1-800-644-9737, other countries: 209-417-3722.
Administer sodium bicarbonate and ice in IV saline infusion, avoiding Ringer lactate.
Cover the stomach, bladder, and rectum with iced saline and use cooling blankets while closely monitoring body temperature.
Treat arrhythmias by reducing hyperkalemia with antiarrhythmic drugs but not calcium channel blockers.
Monitor end-tidal CO_2 and blood gases; increase end-tidal CO_2.
Treat hyperkalemia with hyperventilation, bicarbonate, glucose, and insulin; in life-threatening cases, use calcium chloride.
Ensure urine output is greater than 2 mL/kg/hour by hydration, or by use of mannitol, furosemide, or both diuretics.
Treat unexpected cardiac arrests in children by treating hyperkalemia first.
Monitor blood gases, potassium, and calcium and check for the presence of myoglobulin in urine in the recovery room or intensive care unit (ICU) for a minimum of 24 hours. Monitor coagulation parameters; correct if necessary.
Administer dantrolene IV 1 mg/kg every 6 hours for 24 to 48 hours or up to 10 mg/kg/day followed by oral dantrolene for another day.
Observe patient in the ICU for at least 36 hours.
Refer the patient and family to a malignant hyperthermia testing center; provide genetic counseling
Obtain information from www.mhaus.org.
www.mhreg.org.
http://www.emhg.org1.

Modified from Malignant Hyperthermia Association of the United States (MHAUS). (1995). *Emergency therapy for malignant hyperthermia.* New York: Malignant Hyperthermia Association of the United States. Updated in 2018.

The diagnosis is based on the clinical presentation and should be suspected early in those who develop masseter contractures and then generalized muscle rigidity with a rapid rise in body temperature, tachycardia, acidosis, and hypermetabolism (Bertorini, 2002; Gronert, 1994).

Anesthesiologists should suspect MHS in patients who have early excessive masseter contractions and elevations of the end-tidal CO_2 during the induction of anesthesia, or if there are signs of acidosis with elevated body temperature and tachycardia (Box 10.4).

Recognition of individuals at risk before surgery is important. In patients considered to be at risk for MHS, particularly those with a strong family history, a muscle contracture test is recommended (Fletcher, Rosenberg, & Aggarwal, 1999; Heiman-Patterson, Rosenberg, Fletcher, & Tahmoush, 1988; Larach, 1989; The European Malignant Hyperpyrexia Group, 1984), but is not universally available. DNA testing is of only limited usefulness because patients who do not have known mutations that are associated with MHS might still develop the syndrome (Gronert, 1994; Kim et al., 2013; Lee, McGlinch, McGlinch, & Capacchione, 2017; Quane et al., 1993; Rosenberg, Davis, James, Pollock, & Stowell, 2007).

Patients with myopathies and those with unexplained elevated serum CK should undergo surgery with proper monitoring and should be considered as being at risk for this syndrome and undergo proper education. Attacks of MH could also be triggered by stress, heat, and vigorous exercises (Lee et al., 2017).

TREATMENT AND MANAGEMENT

The treatment of MHS consists of correction of fluid and electrolyte imbalances, reduction of temperature, and especially the use of dantrolene, a muscle relaxant that decreases calcium release by the SR and thus inhibits muscle contractions. Preoperative use of dantrolene is recommended in patients at risk. Box 10.5 gives a detailed list of steps in the management of MHS, including proper dosing of dantrolene. Anesthetics that can contribute to an attack should be avoided in those at risk (Bertorini, 2002; Gronert, 1994; Litman, 2019; Rosenberg, Pollock, Schiemann, Bulger, & Stowell, 2015). Operating rooms and emergency departments should be instructed and prepared (Normandin & Benotti, 2019). The Malignant Hyperthermia Association of the United States provides guidelines with restrictions and wallet cards.

COMPLICATIONS OF MAJOR SURGERY AND ORGAN TRANSPLANTATION

Patients undergoing major surgery may manifest a variety of neurologic complications. Some could develop weakness or sensory symptoms from nerve or plexus injuries due to

stretching or compression. Others may experience prolonged weakness and difficulty weaning from the ventilator due to neuromuscular blockade. For some patients, recovery from surgery could be difficult and the neuromuscular complications of critical illness and prolonged hospitalization could become a concern. In addition to peripheral complications, certain subjects are at risk of central nervous system (CNS) injury (e.g., in the form of ischemia), particularly when undergoing cardiovascular procedures.

Those undergoing organ transplantation face additional risks from immunosuppression, including infections such as toxoplasmosis, herpes zoster, tuberculosis, and others (Mohammadi, Salarzaei, & Parooie, 2019; Wijdicks, 2001). The medications used for immunosuppression could cause other complications, as discussed in Chapter 7. Particularly, calcineurin inhibitors produce neurotoxicity, inducing tremors, posterior reversible leukoencephalopathy, seizures, mental status changes, paralysis, and speech abnormalities (Pless & Zivkovic, 2002; Walker & Brochstein, 1988). This section discusses some of the more common neuromuscular complications seen in association with surgery and transplantation.

CARDIOTHORACIC SURGERY AND TRANSPLANTATION

Most neurological complications of cardiac surgery and transplantation affect the CNS (Rush, Yip, & Meschia, 2008; Sila, 1989). Cardiac surgery also might result in brachial plexopathies from retraction of the sternum, which causes weakness in muscles innervated by the lower trunk, with pain (Dajczman, Gordon, Kreisman, & Wolkove, 1991; Lederman et al., 1982; Vahl, Carl, Müller-Vahl, & Struck, 1991; Wilbourn, 2007) and numbness that should be differentiated from ulnar compression, which can also occur in this setting (Watson, Merchant, & Brown, 1992).

Another common presentation seen in those undergoing cardiovascular surgery is foot drop due to peroneal palsy. Recurrent laryngeal or phrenic nerve lesions causing hoarseness and difficulty breathing can also be seen, and phrenic nerve injury with resultant diaphragmatic paralysis may occur, likely in those undergoing coronary revascularization with mobilization of the right internal mammary artery for bypass (Deng, Byth, & Paterson, 2004). Catheterization procedures and pump placements could damage adjacent nerves in the limb (e.g., femoral or median nerves).

Mobilization or resection of a whole lung as in a transplantation procedure also carries a risk of nerve injury. Severe gastroesophageal reflux or even gastroparesis may result from damage to the vagus nerve (Young, Hadjiliadis, Davis, & Palmer, 2003). Diaphragmatic paralysis and resultant ventilatory weakness could also develop from phrenic nerve injury (Ferdinande et al., 2004; Maziak, Maurer, & Kesten, 1996; Schweickert, Gruener, & Garrity, 2008; Sheridan et al., 1995). Patients might also develop generalized weakness secondary to poor oxidative metabolism of muscle fibers (Zivkovic & Linden, 2008).

EVALUATION AND DIAGNOSIS

A detailed neurologic examination should define if the weakness is generalized or focal, if it affects the upper motor neuron or lower motor neuron, and, in the latter, if this is caused by peripheral nerve or brachial plexus injuries. The evaluation should include the sniff test, nerve conduction studies, and needle electromyography (EMG) (Zivkovic & Linden, 2008). Phrenic nerve studies and fluoroscopy are helpful for the diagnosis of phrenic neuropathy. Laryngoscopy is necessary in patients with recurrent laryngeal nerve paralysis.

Those with gastroparesis and gastroesophageal reflux disease require a proper gastrointestinal evaluation and esophageal motility studies and proper management; those with generalized weakness should have adequate electrolyte and CK measurements in addition to the electrophysiologic studies.

TREATMENT AND MANAGEMENT

Measures to avoid complications include proper padding to avoid compressions, prompt mobilization, and physical therapy. Patients who develop phrenic nerve paralysis and dyspnea should be maintained in the upright position and receive intermittent noninvasive ventilation.

Patients with vagal nerve dysfunction with gastroparesis and gastroesophageal reflux disease may require metoclopramide and pump inhibitors as well as maintenance of the upright position.

The treatment of focal nerve paralysis is discussed in Chapter 17.

ABDOMINAL SURGERY AND TRANSPLANTATION

Abdominal surgery is associated with complications of anesthesia (Bronster et al., 2000; Campellone, Lacomis, Kramer, Van Cott, & Giuliani, 1998; Kutcher, 2008; Nonthasoot, Sirichindakul, Nivatvongs, & Sangsubhan, 2006; Weissenborn et al., 2003; Zivkovic & Linden, 2008) and also with nerve compression or stretching from retractors. The lumbosacral plexus and lateral femoral cutaneous nerve may be injured, and compression may cause peroneal palsy (Nonthasoot et al., 2006).

Intestinal surgery, particularly small-bowel resection, may cause malabsorption, with deficiencies of various vitamins manifesting as peripheral neuropathy or generalized weakness (Campellone et al., 1998). Encephalopathy may be seen in those undergoing liver transplantation.

In contrast to the encephalopathy commonly seen in liver failure, spastic paraparesis from so-called *hepatic myelopathy* is rare. Spinal cord compression from a structural lesion (e.g., hematoma or tumor) should be excluded radiographically. Orthotopic liver transplantation has been reported to improve the condition (Kutcher, 2008; Weissenborn et al., 2003). The postoperative complications of liver transplantation have improved significantly, particularly with control of infections (Adam et al., 2012). The lack of sufficient number of liver transplants makes waiting a problem, and for this reason, new methods of management should be considered for the future, such as regenerative medicine and bioengineering methods (Bizzaro, Russo, & Burra, 2019). Another cause of myelopathy is spinal cord infarction, which is usually due to occlusion of the spinal artery of Adamkiewicz. This is a particular concern during procedures that involve cross-clamping of the aorta, such as surgical repair of an abdominal aortic aneurysm.

Steatorrhea from any cause may result in deficiencies of fat-soluble vitamins. Vitamin E deficiency might manifest with

ataxia and peripheral neuropathy, whereas vitamin D deficiency could cause generalized weakness, and vitamin A deficiency could cause visual disturbances. Most vitamin B deficiencies are associated with peripheral neuropathies, but thiamine deficiency often presents with Wernicke encephalopathy.

EVALUATION AND DIAGNOSIS

Clinical evaluation is important, and this should be followed by EMG studies and measurement of electrolytes and serum CK.

Patients with generalized weakness require periodic measurements of electrolytes and vitamin levels.

TREATMENT AND MANAGEMENT

Avoidance of retractor injuries and the use of padding are very important. Patients require proper vitamin supplementation using periodic measurements of vitamins and nutrients, complete blood counts, and chemistry profiles. Pyridoxine and erythrocyte transketolase levels should be measured in those with symptomatic peripheral neuropathy; if reduced, replacement therapy should be initiated.

Ambulation, physical therapy, and respiratory assistance should be used when necessary.

COMPLICATIONS OF BARIATRIC SURGERY

Approximately 4.6% of patients who have bariatric surgery for weight reduction develop neurologic complications (Abarbanel, Berginer, Osimani, Solomon, & Charuzi, 1987), including encephalopathy (Salas-Salvadó et al., 2000), vision loss (Banerji & Hurwitz, 1971), ataxia, and neuromuscular manifestations such as radiculopathy, polyneuropathy, and myeloneuropathy (Pories, 2008; Koffman & Daboul, 2008; Thaisetthawatkul, Collazo-Clavell, Sarr, Norell, & Dyck, 2004). Nerve entrapments such as carpal tunnel syndrome, ulnar neuropathy (Koffman & Daboul, 2008), meralgia paresthetica (Macgregor & Thoburn, 1999), and radiculoplexopathy also can be seen (Thaisetthawatkul et al., 2004). Rarely, patients develop a myopathy, and rhabdomyolysis can occur (de Oliveira et al., 2008). In spite of this, bariatric surgery is relatively safe even in older patients, producing not only weight reduction but also remission of diabetes (Petrick et al., 2019). Some complications occur during the procedure, such as retractor-induced nerve damage or compression such as peroneal palsy. Most other complications, however, are caused by malnourishment with deficiency of various micronutrients and vitamins (Thaisetthawatkul et al., 2004). Occasionally, a peripheral neuropathy is related to an autoimmune disorder (Koffman & Daboul, 2008; Thaisetthawatkul et al., 2004). A sensory neuropathy can be caused by copper (Kumar, 2006), pyridoxine, thiamine, and vitamin B_{12} deficiencies (MacLean, Rhode, & Shizgal, 1983; Schilling, Gohdes, & Hardie, 1984).

DIAGNOSIS AND EVALUATION

The evaluation includes obtaining measurements of electrolytes and serum CK immediately after surgery to document and prevent the development of severe rhabdomyolysis. Patients should then have measurements taken of nutrients and vitamin levels. The use of other tests depends on the clinical manifestations; for example, those with sensorimotor neuropathy or entrapment neuropathy should have electrophysiologic testing. The polyneuropathy in patients who have bariatric surgery is usually sensory or sensorimotor, and the electrodiagnosis documents the presence of axonal degeneration with some features of demyelination (Thaisetthawatkul et al., 2004). In those with prominent demyelination, an autoimmune etiology should be considered, especially if there is no evidence of vitamin deficiency or response to vitamin supplementation (Bertorini, 2008).

Some patients may develop an acute paralysis similar to Guillain-Barré syndrome and should be properly diagnosed and treated. Although a nutritional polyneuropathy could present in this way, severe hypokalemia also should be considered (Banerji & Hurwitz, 1971).

Myeloneuropathy manifests as long-tract findings presenting as combined degeneration, an ataxic neuropathy caused by vitamin B_{12} or copper deficiency, particularly in patients receiving zinc supplementation (Kumar, 2006). Neuroimaging to exclude a structural cause should be done, and somatosensory evoked potentials may also be useful.

TREATMENT AND MANAGEMENT

Nerve compression during surgery should be prevented with adequate padding and avoidance of improper retraction and nerve stretching. After surgery, early mobilization and physical therapy are recommended.

Patients should be treated with good nourishment and vitamin supplementation. Clinical laboratory evaluation should be performed every 6 months or more frequently if necessary, and this should include a complete blood count, chemistry profile, and measurements of iron, zinc, magnesium and selenium, vitamin B_{12}, and folate levels. In symptomatic patients, measurement of vitamin B_{12}, vitamin A, pyridoxine, copper, thiamine, zinc, and erythrocyte transketolase levels should be obtained.

Vitamin supplementation should include oral vitamin B_{12} in doses of 100 mcg and folate daily by mouth (MacLean et al., 1983; Schilling et al., 1984). In patients with low levels of vitamin B_{12} who are symptomatic, parenteral administration of 1000 μg a week for 1 month and then 1000 μg monthly is needed. Thiamine deficiency is treated with IV administration of 50 to 100 mg of thiamine daily for up to 14 days, followed by 100 mg orally daily. Patients with frequent vomiting should receive vitamin C and calcium with vitamin D in doses of 1600 mg/day. Vitamin D deficiency should be treated with weekly vitamin D_2 in dosages of 50,000 units orally and multivitamin preparations (MacLean et al., 1983).

Those with copper deficiency should discontinue zinc supplementation and receive copper in dosages of 6 mg/day orally for 1 week, then 4 mg for an additional week, and then 2 mg permanently (Kumar, 2006), as discussed in Chapter 21.

Patients with severe demyelinating neuropathy and evidence of an autoimmune etiology should be treated with immunotherapy (Bertorini, 2008).

Physical therapy and rehabilitation followed by an exercise program are very important in the care of these patients.

NEUROMUSCULAR DISORDERS ACQUIRED IN THE INTENSIVE CARE UNIT

Neuromuscular disorders acquired in the ICU are broadly categorized as critical illness polyneuropathy (CIP), critical

illness myopathy (CIM), and prolonged neuromuscular junction blockade. After pulmonary and cardiac causes have been eliminated, an underlying neuromuscular condition should be suspected in patients in the ICU after surgery or for other causes who have limb weakness and difficulty weaning off the ventilator, who have sepsis or multiorgan failure, or who received neuromuscular blocking agents and steroids.

Singly or in combination, CIP and CIM are characterized by flaccid limbs and respiratory muscle weakness. These syndromes occur in critically ill patients during prolonged ICU hospitalization undergoing mechanical ventilation because of their critical illness or its treatment. Usually the weakness with, or less commonly without, failure to wean from the ventilator appears when the underlying critical illness improves, unmasking the NMD.

The diagnosis frequently is challenging, and a preexisting NMD should be excluded. Electrodiagnostic studies are helpful to establish the diagnosis, despite the difficulty of performing such studies in the ICU environment.

HISTORICAL NOTE

In 1961, Mertens described *coma-polyneuropathies* in patients with severe metabolic crises and circulatory shock (Mertens, 1961). Bolton and colleagues described patients in the ICU with severe limb weakness and difficulty weaning off the ventilator due to severe primary distal axonal motor sensory neuropathy (Bolton, Brown, & Sibbald, 1983; Bolton, Gilbert, Hahn, & Sibbald, 1984). In 1987, Zochodne and colleagues coined the term *critical illness neuropathy* to describe this event since it occurs in ICU patients with sepsis and multiple organ failure (Zochodne et al., 1987). The clinical, electrophysiological, and pathological features have subsequently been detailed (Zifko, Zipko, & Bolton, 1998).

In 1972, Karpati and colleagues described corticosteroid-induced myopathy, characterized by thick filament myopathy in animal models after hind-limb nerve transection (Karpati, Carpenter, & Eisen, 1972). In 1977, MacFarlane and colleagues described acute quadriplegic myopathy in a young asthmatic patient who received high-dose corticosteroids (MacFarlane & Rosenthal, 1977). Various other names for the primary myopathic disease in patients with critical illness were used in the 1990s; however, the term *critical illness myopathy*, coined by Latronico and colleagues in 1996, is now widely used (Latronico et al., 1996).

CRITICAL ILLNESS POLYNEUROPATHY

As the length of time spent in the ICU increases, CIP occurs as a complication of sepsis and multiorgan failure. Despite improvements in medical and surgical care, the mortality rate in critically ill patients remains high—30% to 50% (Dellinger et al., 2004). Sepsis, trauma, and burns can evoke a severe systemic response known as *systemic inflammatory response syndrome* (SIRS). As many as 70% of patients with SIRS and multiorgan dysfunction, common in the ICU, may develop clinical, electrophysiologic, or histopathologic evidence of peripheral nerve dysfunction (Bolton, Young, & Zochodne, 1993). In SIRS, cellular and proinflammatory humoral responses are activated and interact with adhesion molecules to cause endothelial damage, local tissue edema, and subsequent disturbances of microcirculation. These disturbances may impair the delivery of oxygen and glucose to the peripheral and CNSs, causing septic encephalopathy and CIP (Bolton, 1995; Young et al., 1990).

Critical illness polyneuropathy ranges from mild to severe and is usually recognized when a preexisting encephalopathy associated with sepsis resolves. The severity of the neuropathy increases with time in the ICU, hyperglycemia, and hypoalbuminemia. This symmetric neuropathy is a sensorimotor axonal type that causes limb weakness, and difficulty weaning from the ventilator is common and may be the first recognized manifestation. Tendon reflexes are attenuated or lost. Distal sensation is impaired, but this is difficult to assess in intubated ICU patients. Muscle atrophy in the distal muscles is common. Facial weakness is rare, and extraocular muscle movements are spared. Neuropathic pain is not characteristic of CIP, and autonomic dysfunction is uncommon. CIP may resemble axonal Guillain-Barré syndrome on the basis of clinical examination alone and may be difficult to differentiate from myopathic or neuromuscular junction disorders. CIP has been reported in children, but is less common than in adults (Dimachkie, Austin, Slopis, & Vriesendorp, 1995). With the COVID-19 pandemic, there appears to be an increasing number of critical illness neuropathy and myopathy, and there are already reported cases of Guillain-Barré syndrome (Ahmad & Rathore, 2020).

EVALUATION AND DIAGNOSIS

Patient charts should be meticulously reviewed for documentation of sepsis and multiorgan failure. The use of IV corticosteroids, neuromuscular blocking agents, and drugs such as aminoglycosides or magnesium increases the incidence of CIP. The presence of significant facial or extraocular muscle weakness suggests prolonged neuromuscular junction blockade.

Nerve conduction studies typically show low amplitude of motor and sensory action potentials, with low normal or mildly slow conduction velocities, indicative of motor and sensory axonal loss. Compound muscle action potential (CMAP) amplitude decline predates clinical symptoms, whereas sensory nerve action potential (SNAP) decline occurs later. Because of the difficulty of performing nerve conduction studies in the ICU environment and the presence of tissue edema, sensory conduction studies can be difficult. Needle EMG examination reveals predominant distal denervation and decreased recruitment of the motor unit action potentials (MUAPs). However, voluntary muscle activation polyphasic MUAPs might be seen consistent with acute denervation, as well as many patients having variable combination features of both CIP and CIM disorders. Peripheral nerve versus direct muscle stimulation and measures of the CMAP amplitude and duration may help identify CIP from CIM (Khan, Harrison, Rich, & Moss, 2006). Needle EMG of the diaphragm helps to establish the diagnosis in patients who have difficulty weaning from the ventilator. Repetitive motor nerve studies are unremarkable unless there is persistent pharmacologic neuromuscular blockade. Laboratory testing and cerebrospinal fluid (CSF) studies usually are normal. Nerve biopsy is rarely indicated and shows varied degrees of primary axonal degeneration and lack of inflammatory cellular infiltrates or segmental demyelination. Likewise, muscle biopsy is not

required, but demonstrates neuropathic changes and may also reveal the coexistence of myopathic changes (de Letter et al., 2001; Dimachkie et al., 1995).

The differential diagnosis should include other axonal neuropathies, such as axonal Guillain-Barré syndrome, coexisting neuropathy, transient weakness secondary to prolonged neuromuscular junction blockade, and weakness secondary to CIM. Facial weakness, elevated CSF protein, and associated autonomic dysfunction are characteristic of Guillain-Barré syndrome, whereas an elevated serum CK level is more consistent with CIM. However, CIP may occur independently or in association with CIM.

TREATMENT AND MANAGEMENT

Aside from the general principles of management, there are no known specific therapies for CIP. Early treatment of sepsis with appropriate antibiotics and avoidance of SIRS are critical. Adequate nutritional intake, correction of underlying metabolic abnormalities, maintenance of circulation, oxygenation, and management of airways and ventilator weaning are essential. Prophylaxis for deep venous thrombosis, physical therapy, rehabilitation, and basic care of paralyzed patients are warranted. Early physical therapy and occupational therapy as soon as the patient is hemodynamically stable resulted in better functional outcomes at hospital discharge, shorter duration of delirium, and ventilator-free days in critically ill patients (Schweickert et al., 2009). Range-of-motion exercises and bracing are helpful to prevent contractures and disuse muscle atrophy; however, as patients improve, rehabilitation and assistive devices for ambulation may be required. Percutaneous neuromuscular electrical stimulation may preserve muscle mass and enhance the strength and endurance capacity of critically ill patients, but definite evidence of the efficacy in CIP and CIM muscle weakness is still lacking (Poulsen et al., 2011).

Treatment of CIP with IV immunoglobulins (IVIgs) in a small group of patients produced no improvement (Wijdicks & Fulgham, 1994). However, a retrospective study of 33 patients showed that early treatment of sepsis or SIRS with IVIg may prevent the development of CIP (Mohr, Englisch, Roth, Burchardi, & Zielmann, 1997). Monoclonal and polyclonal antibodies against bacterial endotoxins, tumor necrosis factor-alpha, interleukin-1 receptor antagonists, and the oxygen radical scavenger *N*-acetylcysteine have been unsuccessful (Dhainaut et al., 1994; Spies et al., 1994). In one study, intensive insulin therapy in critically ill patients reduced the incidence of CIP, as well as the morbidity and mortality of critical illness (Mesotten, Swinnen, Vanderhoydonc, Wouters, & Van den Berghe, 2004). More recent and future directions include the role of electrophysiological measurements as an early predictor, basic research to determine various medications that redispose to, and abnormalities of gene transcription for earlier diagnosis and therapeutic targets for CIP and CIM.

The mortality rate from sepsis and multiorgan failure in the ICU is high (30% to 50%). Recovery from CIP depends on the disease severity. Those with mild CIP usually recover within a matter of weeks, whereas recovery from severe CIP may take months. Recovery may not occur in patients with profound weakness, and nearly 22% may have severe residual deficits after 1 year (Litman, 2019). Clinical and electrodiagnostic evidence of neuropathy may remain up to 5 years after the critical illness recovery (Fletcher et al., 2003).

CRITICAL ILLNESS MYOPATHY

CIM is a rapidly evolving myopathy that affects critically ill patients; it can occur independent of or in association with CIP, for which it is sometimes named critical illness myopathy and neuropathy (Latronico et al., 2007). Various names have been used to describe this entity, including acute quadriplegic myopathy, critical care myopathy, necrotizing myopathy of intensive care, thick filament myopathy, and others; however, the term *critical illness myopathy* is now widely accepted.

CIM usually afflicts patients exposed to high doses of IV corticosteroids, often in combination with nondepolarizing neuromuscular junction blocking agents. It occurs in patients with asthma treated with high-dose IV corticosteroids and in 7% of organ transplant patients (Douglass et al., 1992; Lacomis, Giuliani, Van Cott, & Kramer, 1996; Perea et al., 2001). CIM also has been associated with propofol administration, high IV doses of corticosteroids in patients with myasthenia gravis, and rarely in patients with sepsis and multi-organ failure who were not exposed to corticosteroids (Hanson et al., 1997; Deconinck, Van Parijs, Beckers-Bleukx, & Van den Bergh, 1998; Panegyres, Squier, Mills, & Newsom-Davis, 1993).

The main clinical feature of CIM is diffuse flaccid muscle weakness that occurs after the onset of critical illness. This usually is symmetric and proximal more than distal, although in some patients the weakness is more prominent distally and rarely asymptomatic or upper extremity predominant. In most patients, all limb muscles, neck flexors, facial muscles, and diaphragm are involved. Respiratory failure is common, with subsequent difficulty weaning from mechanical ventilation. Tendon reflexes are often depressed but can be preserved or increased in some patients with concurrent encephalopathy. Variable muscle atrophy is common. Sensory perception usually is normal, when tested, in cooperative patients. Extraocular muscle weakness is rare in CIM and usually suggests prolonged neuromuscular junction blockade (Lacomis, 2011; Vattemi et al., 2003).

The pathogenesis of CIM is uncertain, although a number of triggering factors are recognized. Exposure to both corticosteroids and neuromuscular blocking agents suggests a potential pathogenic role; however, CIM also has been reported in patients who were not exposed to either of these classes of agents (Deconinck et al., 1998). It appears that IV corticosteroids, in conjunction with neuromuscular blocking agents, critical illness, protracted immobility, and a high-stress catabolic state, trigger a proteolytic and apoptic mechanism that leads to myofibril atrophy, network disruption, and varying degrees of necrosis (Danon & Carpenter, 1991; Di Giovanni et al., 2004; Hirano et al., 1992; Lacomis et al., 1996; Showalter & Engel, 1997). Animal models showed abnormalities in ion channels and inexcitability of myofibers due to increased sodium channel inactivation at their resting potential (Rich & Pinter, 2001). Likewise, electrophysiologic studies in CIM demonstrated muscle membrane inexcitability to direct electrical stimulus, whereas denervated muscle maintained normal excitability (Rich, Bird, Raps, McCluskey, & Teener, 1997).

EVALUATION AND DIAGNOSIS

Electrodiagnostic studies often show reduced CMAP amplitudes, normal nerve conduction velocities, and absence of

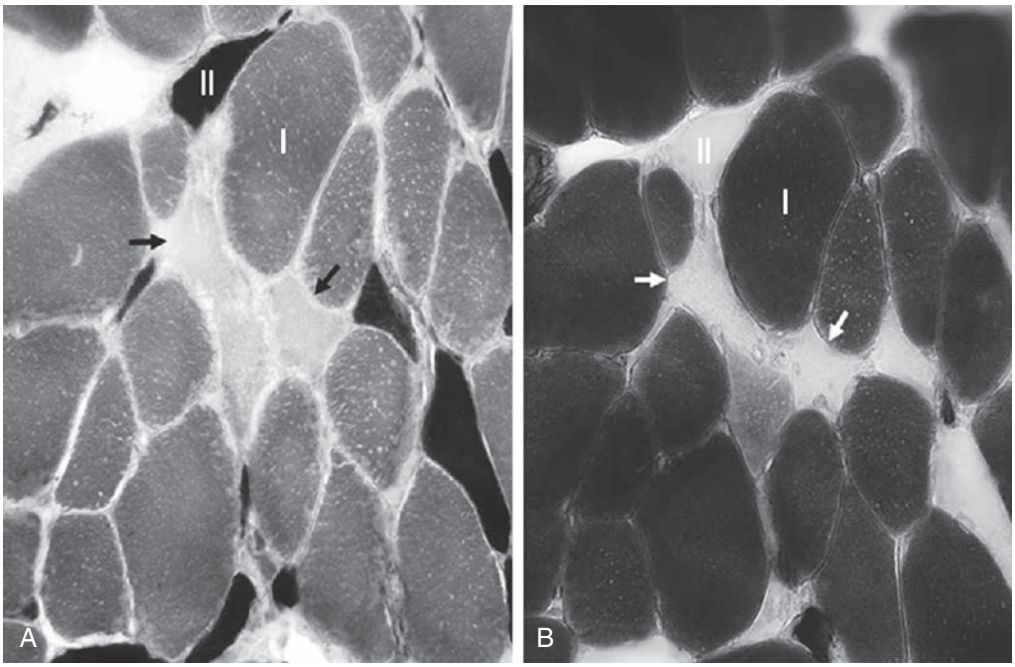


Fig. 10.2 (A) Muscle biopsy from a patient with critical illness myopathy stained with ATPase at pH 9.4. Notice the very pale fibers from loss of myosin *(arrows)*. (B) They also appear pale in the acid pH (4.3) *(arrows).* Magnification in both A and B is ×400.

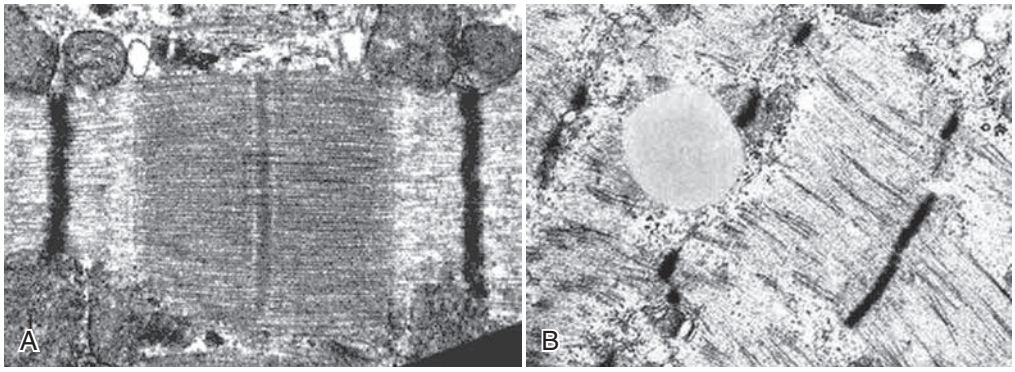


Fig. 10.3 (A) Normal biopsy specimen. (B) Electron microscopy on the biopsy of the same patient as in Figure 10.2. There is a loss of the thick filaments, while thin filaments and Z lines are preserved. Magnification in both A and B is ×79,920.

CMAP amplitude changes on repetitive nerve stimulation. SNAP usually are normal, but may show mild abnormalities suggestive of concurrent neuropathy. Needle EMG examination reveals abnormal spontaneous activity, which indicates underlying muscle fiber necrosis and membrane irritability. Myopathic MUAPs are sparse initially, but prominent later in the course of the disease (Zochodne, Ramsay, Saly, Shelley, & Moffatt, 1994).

Muscle biopsy shows myofiber atrophy, especially of type II fibers, and varied degrees of myofiber necrosis, degeneration, and regeneration. Selective loss of thick filament myosin is a characteristic finding in CIM, manifesting as a disrupted or patchy loss of myofiber visible with ATPase staining and best confirmed by immunohistochemical stains and electron microscopy (Zivkovic & Linden, 2008) (Figs. 10.2 and 10.3). Widespread myofiber necrosis is seen in a more severe entity, known as *acute necrotizing myopathy of intensive care* (Maziak et al., 1996). Selective loss of thick filaments in human muscle is not specific to CIM and has been reported in other disorders, such as dermatomyositis, thrombocytopenic purpura, congenital myopathy, and myopathy associated with human immunodeficiency virus infection (Fernández-Lorente et al., 2010; Guarneri, Bertolini, & Latronico, 2008; Hanson et al., 1997; Simpson & Bender, 1988). Laboratory studies in CIM show elevation of serum CK during the first 2 weeks, which can be missed if neuromuscular evaluation is delayed once medical complications obscure the weakness (Box 10.6).

TREATMENT AND MANAGEMENT

Although there are considerable data on disease mechanism, there is no specific treatment for CIM. Avoidance of high-dose IV corticosteroids and cautious use of neuromuscular blocking agents, or limiting the duration of their use, reduce the risk of CIM occurrence. Treating the underlying illness, infection, and associated metabolic disorders should be initiated vigorously, along with adequate nutrition. Prophylaxis with subcutaneous heparin or enoxaparin (Lovenox) and pneumatic stockings are warranted to prevent deep venous thrombosis. Physical therapy and nursing care of paralyzed patients are necessary to prevent decubitus ulcers and joint contractures or superimposed disuse muscle atrophy. Monitoring of respiratory functions, mechanical ventilation, and early tracheostomy are indicated in patients with respiratory failure. In patients with an established or suspected diagnosis of CIM, corticosteroids and paralytic agents should be tapered off. Serial CK measurements during high-dose

Box 10.6 Clinical and Diagnostic Features of Critical Illness Neuropathy and Critical Illness Myopathy

Critical Illness Neuropathy	*Critical Illness Myopathy*
Clinical Features	**Clinical Features**
Critically ill patient	Critically ill, receive IV corticosteroids
Mild to severe limb weakness distal > proximal	Proximal > distal muscle weakness
Distal sensory deficit	Sensory perception is usually normal
Tendon reflexes attenuated or lost	Tendon reflexes are preserved
Facial weakness rare	Facial and neck muscle weakness
EOM spared	EOM spared
Respiratory failure is common	Respiratory failure is common
Diagnostic Features	**Diagnostic Features**
Normal serum CK level	Elevated serum CK during first 2 weeks
Reduced CMAP & SNAP amplitude	Reduced CMAP and normal SNAP
Low normal or mildly reduced NCV	Normal NCV
Denervation signs & decreased recruitment	Needle EMG abnormal spontaneous
Polyphasic MUAP might be seen	Activity, prominent myopathic MUAP
Muscle biopsy; neuropathic changes	Muscle biopsy; myofiber necrosis
Nerve biopsy; axonal degeneration	Degeneration, regeneration, and lack of inflammatory cellular infiltrates loss of thick filament myosin

CK, Creatine kinase; *CMAP*, compound muscle action potential; *EMG*, electromyography; *EOM*, extraocular movement; *MUAP*, motor unit action potential; *NCV*, nerve conduction velocity; *SNAP*, sensory nerve action potential.

IV corticosteroid and paralytic agent administration in the ICU may allow an early diagnosis of CIM. In patients with rhabdomyolysis, IV hydration with alkaline diuresis is recommended to avoid renal failure. A rehabilitation program is highly recommended as patients improve. Patients at risk for CIM and CIP could be monitored by serial peroneal (fibular) moor nerve conduction study (Latronico et al., 2007).

In general, most patients with CIM who survive their critical illness recover fully within 2 to 3 months; however, CIM prolongs ICU hospitalization and is associated with high medical costs (Guarneri et al., 2008). Patients with more severe muscle necrosis may have a worse prognosis. Prospective studies that assess effective innovative and physiotherapy are necessary to identify specific treatment for CIM.

PROLONGED NEUROMUSCULAR JUNCTION BLOCKADE

Neuromuscular blocking agents used to facilitate mechanical ventilation may cause a transient prolonged weakness. This usually occurs in patients with renal or liver failure treated with high doses of pancuronium or vecuronium (Barohn et al., 1994; Campellone et al., 1998; Gooch, 1995; Gorson & Ropper, 1996; Segredo et al., 1992; Vanderheyden, Reynolds, Gerold, & Emanuele, 1992).

Neuromuscular blocking agents are metabolized by the liver and cleared by the kidneys; thus, the effect of these agents may last for several days or up to a week or two after their use has been discontinued. Concurrent use of corticosteroids and aminoglycosides may contribute to neuromuscular junction failure. Female gender, acidosis, and hypermagnesemia are risk factors (Gooch, Moore, & Ryser, 1993).

Like other ICU neuromuscular syndromes, prolonged neuromuscular junction blockade causes generalized flaccid muscle weakness; however, facial and extraocular muscle weakness and areflexia are characteristic of this syndrome. Sensory disturbances usually are absent or minimal.

Some patients may have associated CIM, especially those who received concomitant corticosteroids in high doses; these patients may have variably elevated serum CK and myopathic features on needle EMG and muscle biopsy likely owing to a combination due to neuromuscular blocking agent functional denervation and the steroid effect on muscle (Gooch et al., 1993).

EVALUATION AND DIAGNOSIS

Electrophysiologic studies demonstrate a decreased CMAP amplitude and area, which in some cases are further reduced during repetitive nerve stimulation. Both presynaptic and postsynaptic defects in neuromuscular transmission have been suggested; abnormal responses to low and high stimulation rates have been described. Spontaneous activity and myopathic MUAP may be seen on needle EMG examination in those with severe prolonged neuromuscular blockade. Motor and sensory nerve conduction velocities and SNAP amplitude are normal (Gooch et al., 1993).

TREATMENT AND MANAGEMENT

Prevention of prolonged neuromuscular junction blockade by minimizing the use of paralytic agents or the use of a bolus instead of continuous administration is recommended. Administration of neostigmine may temporarily improve weakness. Hemodialysis is not an effective therapy and only partially reduces the paralytic agent's metabolites. Hyperglycemia has a detrimental effect on nerve and muscle function, and glycemic control is warranted. In general, prolonged neuromuscular junction blockade is a self-limited syndrome that usually persists for a few days or a week until the paralytic agent metabolites are excreted. Patients who have persistent weakness lasting for more than 2 to 3 weeks are likely to have coexisting CIM or CIP (Gorson & Ropper, 1996).

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Molecular and Genetic Therapies

11

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Genetic testing and development of genetically based therapies for hereditary neuromuscular disorders (NMD) have undergone an explosive growth over the last decade leading to widespread use of genetic testing in clinical practice and availability of novel genetically based therapies for disorders such as Duchenne muscular dystrophy (DMD, discussed in Chapter 20), spinal muscular atrophy (SMA; discussed in Chapter 13), and peripheral neuropathy associated with hereditary transthyretin amyloidosis (hATTR-PN; previously also known as transthyretin familial amyloid polyneuropathy [TTR-FAP]) (Adams et al., 2018; Benson et al., 2018; Finkel et al., 2017; Mendell et al., 2016, 2017). Newly approved treatments have changed the clinical course and long-term prognosis for patients with these disorders but have also raised new clinical challenges. As the field of genetic testing and treatments continues to evolve, improved methods for genetic diagnoses and development of new therapeutic modalities for genetic disorders are to be expected, with all the attendant issues of choice and duration of therapies, necessary supportive care, costs, etc. In this chapter, we provide an overview of the approaches to genetic testing and genetic treatments in NMD.

PREVALENCE OF HEREDITARY NMD

The prevalence of hereditary NMD varies depending on geography and ethnic background. Although rare, they are among the most common single gene disorders (Benarroch, Bonne, Rivier, & Hamroun, 2019). As of March 2020, 587 genes were implicated in NMD (Benarroch et al., 2019). Available data on the worldwide prevalence of these disorders are limited because most epidemiologic studies report prevalence in Caucasian, especially western European and North American populations. In a population-based study of patients with genetic muscle disease in Northern England, Norwood and colleagues found that the combined prevalence of genetic disorders of muscle was 37/100,000, representing approximately 76% of 1105 studied cases. The myotonic dystrophies types 1 and 2 (DM1 and DM2; discussed in Chapter 20) were the most common, with a point prevalence of 10.6/100,000. Dystrophinopathies (DMD and Becker muscular dystrophy [BMD]) constituted the next most common group (23%, 8.5/100,000), followed by facioscapulohumeral dystrophy (FSHD) (11%, 3.9/100,000). SMA accounted for 5% (1.9/100,000). The limb-girdle muscular dystrophies (LGMDs; also discussed in Chapter 20) were seen in only 6% of their clinic population, with a combined prevalence of 2.3/100,000 (Norwood et al., 2009). Other rarer disorders included congenital muscular dystrophies, congenital myopathies, Emery-Dreifuss muscular dystrophy, and oculopharyngeal muscular dystrophy (Norwood et al., 2009).

DMD and BMD affect 1 in 3500 and 1 in 18,500 live born males, respectively (Emery, 1991). SMA is the most common inherited motor neuron disorder in children, and carrier frequency is estimated at 1/52 to 1/100 with an incidence of 1 per 10,000 births (Verhaart et al., 2017). The annual incidence of amyotrophic lateral sclerosis (ALS; discussed in Chapter 12) is about 2–3/100,000, with a prevalence of 5/100,000, and varies with the case definition used. Although most ALS is sporadic, approximately 5%–10% is familial (fALS) (Johnston et al., 2006; Kurland & Mulder, 1955a, 1955b).

The prevalence of hereditary neuropathies is estimated at 1:2500 (Eggermann et al., 2018). Charcot-Marie Tooth disease type 1 (CMT-1; discussed in Chapter 14) is the most common form and constitutes approximately 55% of all hereditary neuropathies, with a prevalence of 1/1214 in the general population (Braathen, 2012; Eggermann et al., 2018; Fridman et al., 2015). This is followed by CMT-2 (14%) and CMT-X (7%). Hereditary sensory autonomic neuropathy is rare, accounting for approximately 3% of all hereditary neuropathies (Eggermann et al., 2018; Fridman et al., 2015). There is some ethnic predilection to these disorders, e.g., autosomal recessive CMT-4D (HMSN-Lom) in Gypsies from Lom in Bulgaria, Slovenia, Spain, Italy, Hungary, and Serbia (Dacković et al., 2008). In a database review study, the global prevalence of hATTR-PN was estimated at 10,186 (range, 5,526–38,468) (Schmidt et al., 2018).

OVERVIEW OF GENETICS

STRUCTURE OF THE GENOME

The genetic "code" is composed of deoxyribonucleic acid, a double helix with two complementary strands. Each strand is composed of a chain of nucleotides, the basic structural unit of DNA. A nucleotide is made up of a phosphate group, a sugar (deoxyribose), and an organic base. The bases are of four types: two pyrimidines: cytosine (C) and thymine (T), and two purines: adenine (A) and guanine (G). The double helix is formed by hydrogen bond pairing of the

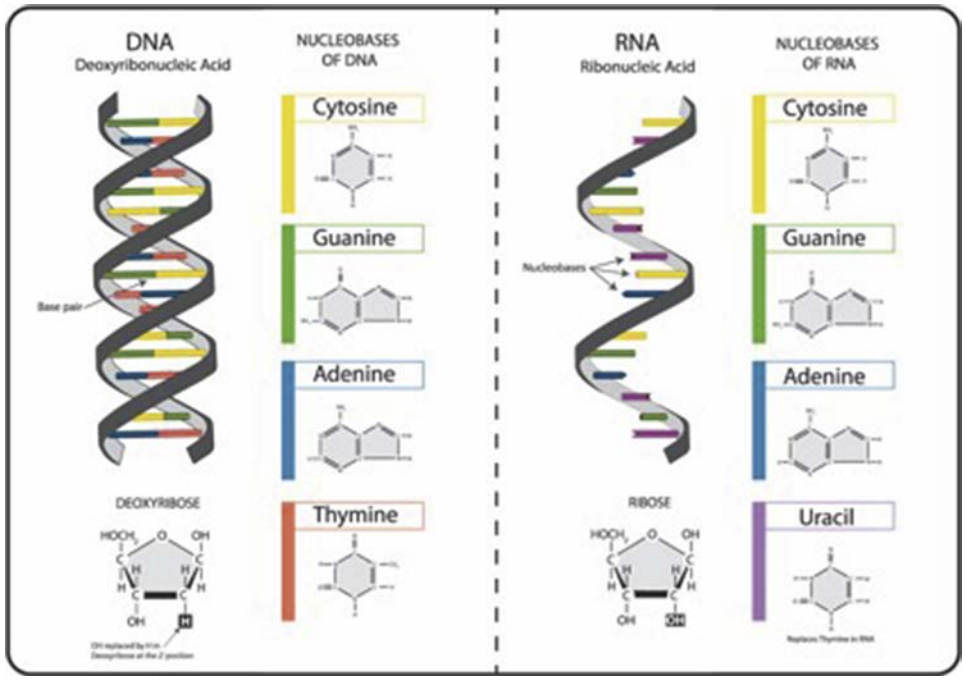


Fig. 11.1 Structure of nucleic acids. The nucleic acids, DNA and RNA, are made up of chains of nucleotides. Each nucleotide contains a phosphate base, a sugar (deoxyribose in DNA, ribose in RNA), and an organic base. There are four organic bases: adenine and guanine (purines) and thymine/uracil and cytosine (pyrimidines). DNA is a double helix, where adenine pairs with thymine and guanine with cytosine of the complementary strand by hydrogen bonds (Watson-Crick base pairing). RNA is single stranded and the base uracil replaces thymine. (From Goyal, N., & Narayanaswami, P. (2018). Making sense of antisense oligonucleotides. *Muscle & Nerve, 57*, 356–370, Figure 1, with permission from Wiley.)

nucleotide bases of two DNA strands in an orderly manner, where A pairs with T of the complementary strand, and G with C (Watson-Crick base pairing). DNA is packed into chromosomes around histone proteins (Fig. 11.1). The human genome consists of the full set of DNA included in the 23 pairs of chromosomes (one set inherited from each parent). Genes are the basic physical and functional units of the genome, composed of sequences of nucleotides that code for distinct proteins (Knoers & Monnens, 2006). The human genome contains 19,000 to 20,000 genes (Ezkurdia et al., 2014). An exon is the portion of the gene that is translated into protein. In each exon, a sequence of three nucleotide bases (the triplet codon) codes for one amino acid; the sequence of triplet codons determines the amino acid sequence of the protein. The unexpressed portions of a gene in between exons are termed "introns." "Exome" refers to the sequence of all exons of all protein coding genes. Although comprising only 1%–2% of the genome, the exome carries an estimated 85% of mutations that cause single gene disorders (Majewski, Schwartzentruber, Lalonde, Montpetit, & Jabado, 2011).

INHERITANCE PATTERNS

Mendelian disorders, named after Gregor Mendel, are disorders caused by single gene mutations (monogenic). They can be due to a change in a single base pair of a nucleotide coding for a protein (point mutations, substitutions), the loss (deletion) or gain (duplication) of a single or multiple base pairs. Many genetic NMDs fall under this category. An allele refers to an alternate form of a gene present at the same location on a chromosome. In the human genome, there are two alleles for each gene, one on each chromosome (Genetic Alliance, The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009). Genetic disorders may also be caused by variations in the number or structure of a chromosome. Aneuploidy refers to a missing (e.g., Turners syndrome, loss of an X chromosome) or an extra (e.g., trisomy 21) chromosome. Structural chromosomal variations include deletions, duplications, insertions, inversions, or translocations of a segment of a chromosome. Multifactorial diseases such as diabetes mellitus are caused by an interaction among genetic, environmental, and behavioral factors (Genetic Alliance, The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009).

The basic modes of inheritance for monogenic disorders are autosomal dominant (AD), autosomal recessive (AR), X-linked dominant, X-linked recessive (XL-R), and mitochondrial. AD disorders manifest when a mutation is present in one copy of the gene (heterozygous mutations). They tend to occur in every generation, although phenotypic variation and "mild" phenotypes result in the appearance of "skipped" generations (incomplete penetrance). The affected individual has an affected parent of either sex. AR disorders occur when mutations are present in both copies of the gene (homozygous mutations, with both parents unaffected, each carrying one copy of the mutated gene). X-linked disorders can be inherited either dominantly or in a recessive manner. Since males have only one X chromosome, either a dominant or recessive mutation will result in manifest disease. In females, recessive X-chromosome mutations require two copies for manifest disease and one copy results in carrier state (Genetic Alliance, The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009). Female carriers of XL-R mutations can have mild symptoms (manifest carriers). Other, more complex inheritance patterns such as compound heterozygosity (two different mutated alleles at a particular gene locus) and double heterozygosity (two different mutated alleles at two separate genetic loci) are also described. Mutations can occur spontaneously (de novo) in the absence of a family history (Genetic Alliance, The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009).

Trinucleotide repeats are sets of three nucleotides present in succession in varying copy numbers in the genome. Trinucleotide repeat expansions, where the number of triplets is greater than normal, underlie several neurologic disorders and NMD (e.g., DM1, with an unstable CTG trinucleotide repeat in the 3' untranslated region of the dystrophia myotonica protein kinase gene on chromosome 19q) (McMurray, 2010). In FSHD type 1 (FSHD1), a contraction of the D4Z4 region on the Double Homeobox (DUX4) gene on chromosome 4 results in hypomethylation of the D4Z4 region and aberrant expression of DUX4 (Greco, Goossens, van Engelen, & van der Maarel, 2020).

Although the diagnosis of an inherited NMD is relatively simple in the presence of a classical phenotype and a family history, the diagnosis can be challenging when there is an overlap in the phenotype of more than one distinct disorder, as in LGMD. Diagnosis is also not straightforward in apparently sporadic cases, where the mode of inheritance may be any pattern, or due to a de novo dominant mutation.

GENETIC TESTING IN NMDS

Genetic testing plays an important role in the diagnosis, prognosis, and management of inherited NMD (Kassardjian et al., 2016). It may be used for diagnostic evaluation of a symptomatic individual, as a tool for screening of nonaffected family members, carrier testing for individuals with a family history or ethnic predisposition to a recessive disorder, for prenatal diagnostic testing in situations with an increased risk of having a baby with a genetic/chromosomal disorder, or for newborn screening (Genetic Alliance, The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009; Kassardjian et al., 2016; Narayanaswami, Carter, David, Weiss, & Amato, 2015). Establishing a diagnosis of a genetic disorder provides closure to patients and families, avoids repeated and potentially invasive testing such as muscle biopsy in search of a treatable condition, avoids therapeutic trials of immunosuppressant or other treatments with their attendant adverse effects and costs, provides strategies for screening of cardiorespiratory and other extramuscular complications, informs long-term prognosis, and facilitates genetic counseling for pregnancy and family planning. Genetic testing is a prerequisite for participation in therapeutic trials (Kassardjian et al., 2016; Narayanaswami et al., 2015). Use of genetic testing should be guided by clinical features, signs and symptoms, possible pattern of inheritance if a family history is available, and at times, results of histopathologic testing such as muscle biopsy. However, the place of muscle biopsy is likely changing in the algorithm of the evaluation of genetic NMD, as discussed later (Narayanaswami et al., 2015). The specimen for genetic testing may include blood, saliva, or histopathologic material (muscle or nerve biopsy specimens, other tissues).

METHODS OF GENETIC TESTING (Table 11.1)

A mutation is defined as a permanent change in the nucleotide sequence, whereas a polymorphism is defined as a

Table 11.1 Methods of Genetic Testing

Method	Type of Mutation	Advantages	Disadvantages
Sanger sequencing	Point mutations	Traditional approach, based on clinical features	Misses large deletions/duplications and repeat expansions Slow, expensive
Southern blot	Duplications, deletions in exons	Inexpensive	Limited clinical utility
Fluorescent in situ hybridization	Chromosomal deletions, duplications, and translocations	Useful for large chromosomal level abnormalities	Limited clinical utility
Single-nucleotide polymorphism array and oligonucleotide array	Copy number variants (CNVs), small deletions and duplications, and uniparental disomy		Will not detect point mutations
Comparative genomic hybridization array	CNVs at the chromosomal level (ploidy) and deletions or duplications of large chromosome areas	Detects submicroscopic chromosomal alterations	Limited clinical utility
Multiplex ligand-dependent probe amplification	Large deletions or duplications that may be missed by gene sequencing		Does not detect small mutations, inversions, translocations, and CNVs
Targeted whole exome sequencing	Multiple genes of interest sequenced	Sensitive	Repeat expansions not detected, variants of uncertain significance (VUS), expensive
Whole exome sequencing (WES)	All exons of all protein coding genes sequenced	Sensitive, higher diagnostic yield than Sanger sequencing	Expensive, VUS, secondary findings
Whole genome sequencing	Entire genome, including exons, introns and regulatory elements sequenced	Data of additive yield over WES not yet available	Expensive, VUS, secondary findings

variant with a frequency above 1%. These terms are often incorrectly assumed to imply they are disease causing and benign, respectively. Hence, the term "variant" has been recommended to replace both terms (Richards et al., 2015). In this review, we use these terms interchangeably. Variants have further been classified into five groups, based on their relevance to Mendelian disorders: (i) pathogenic, (ii) likely pathogenic, (iii) uncertain significance, (iv) likely benign, and (v) benign (Richards et al., 2015).

In 1977, Sanger described a DNA sequencing technique (Sanger, Nicklen, & Coulson, 1977) that was used to sequence the human genome in the Human Genome Project (McPherson et al., 2001). Briefly, the process involves incubating strands of the DNA sequence to be identified with radiolabeled primers (short single stranded nucleic acids that initiate DNA synthesis). In addition, DNA polymerase (an enzyme that synthesizes a strand of DNA complementary to the original strand), deoxynucleotide triphosphates (dNTPs; the building blocks of the complementary DNA strand), and dideoxynucleotide triphosphates (ddNTPs; which prevent addition of dNTPs by DNA polymerase and thus terminate DNA strand synthesis) are incorporated. There are four sets of sequencing reactions, each with a different ddNTP, carrying one of the four bases A, T, G, or C. In each sequence, as the reaction proceeds, synthesis of the complementary DNA strand is interrupted by a ddNTP and complementary DNA strands of different lengths are thus formed. These strands from each of the four reactions are separated by size using polyacrylamide gel electrophoresis. An autoradiograph of the DNA bands thus separated is used to read the corresponding DNA sequence off the gel, and the complementary sequence is then determined, providing the DNA sequence of the original strand (Valencia, Pervaiz, Husami, Qian, & Zhang, 2013). Traditional genetic testing for NMD was based on gene-by-gene sequential testing, driven by clinical hypotheses and knowledge of the most common mutations for specific disorders. However, Sanger sequencing requires a large amount of the DNA template and is time consuming and expensive. It also lacks sensitivity for large deletions/duplications and for repeat expansions (Volk & Kubisch, 2017).

Southern blotting detects deletions or duplications of one or more exons of the gene. DNA is digested by restriction enzymes that recognize a specific site. The fragments are sorted by size by agarose gel electrophoresis and transferred to a nylon or nitrocellulose membrane. Single-stranded DNA probes that are labeled with radioactive tracers are then added to the membrane. The probe hybridizes (associates) with the complementary fragment of interest. The labeled probes are detected by autoradiography (Knoers & Monnens, 2006; Sertic, 2004).

Fluorescent in situ hybridization (FISH) locates the position of specific DNA sequences on chromosomes and is useful for the analysis of chromosome deletions, duplications, and translocations using a probe that is targeted to the sequence of interest. Short sequences of single-stranded DNA (probes) are tagged with fluorescent markers to detect chromosomal DNA that has a complementary sequence. Locus-specific probes bind to complementary areas of a chromosome, such as a gene, or a repetitive sequence such as a centromere or telomere to detect abnormal duplication of a gene or chromosome (Huber, von Voithenberg, & Kaigala, 2018.)

Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variation and are composed of sequence differences at single nucleotide or base pair sites. They occur frequently in normal individuals. SNPs have been implicated as disease modifiers in several neuromuscular diseases, including DMD, SMA, ALS, and LGMD (Lamar & McNally, 2014). Copy number variants (CNVs) are changes in the number of copies of specific segments of DNA, either deletions or duplications. A CNV is defined as a DNA segment that is 1 kb or larger and presents in variable copy numbers in comparison to a reference genome (Feuk, Carson, & Scherer, 2006). Although found in normal individuals, they also contribute to diseases such as Alzheimer disease and Parkinson disease (Rovelet-Lecrux et al., 2006; Singleton et al., 2003). Oligonucleotides are short synthetic sequences of approximately 13–25 nucleotides (Dias & Stein, 2002). DNA microarrays are slides that have multiple microscopic spots in defined positions, with each spot containing a known DNA sequence or gene. They are also referred to as gene chips or DNA chips (Govindarajan, Duraiyan, Kaliyappan, & Palanisamy, 2012).

SNP microarray analysis (DNA probes that target SNPs) and oligonucleotide microarray analysis (short sequence probes of single-stranded DNA or ribonucleic acid [RNA] that hybridize to target complementary nucleic acid sequences) detect CNVs, small deletions, and duplications and uniparental disomy but not point mutations (Levy & Burnside, 2019; Lucito et al., 2003; Vento & Schmidt, 2012). In contrast to comparative genomic hybridization (CGH) arrays, SNP arrays measure the absolute fluorescence probe intensities of the patient sample compared to the intensities of multiple normal control samples that are individually run, normalized, and combined to create a reference (Levy & Burnside, 2019).

CGH array is based on in situ hybridization of normal metaphase chromosome spreads with a test set and a reference set of whole genomic DNA that are differentially labeled using fluorescent markers, usually red and green. The two labeled sets are denatured into single-stranded DNA, mixed in a 1:1 ratio and hybridized in situ to normal metaphase chromosome spreads. The labeled DNA binds to target sequences in the metaphase spread in a concentration-dependent manner. CGH detects chromosomal imbalances: CNVs at the chromosomal level (changes in the number of chromosomes, ploidy) and deletions or duplications of large chromosome areas (extra or missing chromosomal material) (Bryndorf et al., 1995). For instance, in a deletion of chromosome 17p, there will be greater fluorescent labeling of the reference color than test color, and vice versa in the case of 17p duplication. Unlike FISH, which is based on the examination of a single target and requires prior knowledge of the region being tested, CGH can be used to quickly scan an entire genome for imbalances. Array CGH uses microarrays rather than metaphases. Since DNA probes are much smaller than metaphase chromosomes, array CGH has a higher resolution (i.e., ability to detect smaller changes). The resolution depends on the probe size and the genomic distance between two probes, since CNVs in the segment between two probes cannot be detected. This technique is equivalent to thousands of FISH assays and can detect submicroscopic chromosomal alterations.

Multiplex ligand-dependent probe amplification (MLPA) is useful in identifying large deletions or duplications that may be missed by gene sequencing. MLPA can analyze up to 50 DNA sequences in a single reaction and detect CNVs and small intragenic rearrangements. In MLPA, which is a multiplex polymerase chain reaction (PCR)-based assay, multiple probes that are specific for the exon of interest are used to evaluate the number of copies of the DNA sequence (Stuppia, Antonucci, Palka, & Gatta, 2012). MLPA does not detect small mutations, inversions, translocations, and CNVs.

Conventional genetic testing for monogenic disorders involves several sequential steps including genome-wide linkage to identify mutations that cosegregate within affected individuals, positional cloning, and, finally, targeted candidate gene sequencing. Linkage is the tendency for genes and their resulting traits to be inherited together because of their proximity on the same chromosome. Linkage analysis estimates the distance between two genetic loci. The statistical probability of two genetic loci being close enough to be inherited together is the logarithm of the odds (LOD) score. A LOD score of 3 or greater generally assumes that the loci are linked. In screening affected and unaffected family members, linkage analysis identifies disease causing mutations by testing for a locus that cosegregates with a known genetic marker in affected but not in unaffected members (Ott, Wang, & Leal, 2015; Pulst, 1999). Positional cloning then locates the position of the disease-associated gene along the chromosome (Puliti, Caridi, Ravazzolo, & Ghiggeri, 2007). Targeted sequencing of the identified candidate genes is then performed. In AR disorders, autozygosity mapping, which identifies regions of the genome that are homozygous in affected individuals but not in unaffected family members, is followed by gene sequencing to identify the causal mutation (Lander & Botstein, 1987; Vahidnezhad, Youssefian, Jazayeri, & Uitto, 2018). However, these techniques require several affected family members and are therefore not useful in rare disorders when only a few cases are available or in sporadic cases due to de novo mutations. Additional limits of these approaches include phenotypic heterogeneity (different phenotypes with a mutation in the same gene, e.g., mutations in the dysferlin gene causing both LGMD and Miyoshi myopathy) (Nguyen et al., 2005), locus or genotypic heterogeneity (similar clinical presentations due to mutations in different genes, e.g., mutations in both anoctamin and dysferlin genes causing LGMD and Miyoshi myopathy phenotypes), clinical patterns merging over time, and incomplete penetrance (Rabbani, Mahdieh, Hosomichi, Nakaoka, & Inoue, 2012). Once the genetic mutation for a given disease is identified and reported in the literature, testing for common mutations becomes commercially available. However, as the number of genetic NMDs expands and genetic heterogeneity is increasingly recognized, single gene approaches are no longer efficient, and "reflex" panels sequentially testing for common mutations followed by less common ones are often performed.

In 2004, next generation sequencing (NGS) methods, also termed "massively parallel sequencing," using high-throughput platforms were introduced, making it possible to sequence several thousands of pieces of DNA simultaneously. NGS platforms can complete genome sequencing within a few weeks at a fraction of the cost of Sanger sequencing. Whole genome sequencing (WGS), as the name implies, analyzes the entire genome, including coding and noncoding regions. NGS techniques can also be used for whole exome sequencing (WES) (Warr et al., 2015). WES refers to sequencing of all exons of protein coding genes and may include exon-flanking intronic sequences to a varying extent (Botstein & Risch, 2003). WES is often sufficient to identify the genes underlying Mendelian disorders and reduces the time and costs associated with WGS (Warr et al., 2015). Targeted WES is used to sequence a panel of genes that are relevant to a specific disease group.

In NGS, genomic DNA is extracted and broken down into short segments of about 350 bp. Adaptors, or priming sequences of DNA, are added to the ends of these fragments. The segments are then mixed with probes that are complementary to all known exons in the genome, which are consequently captured. The remaining DNA is washed away, leaving behind the enriched exome sequences for amplification followed by massive parallel sequencing of the enriched, amplified library. Fluorescent nucleotides are added during sequencing, resulting in their incorporation into strands of DNA. The incorporation of each fluorescent nucleotide into a sequence is detected using laser activation. Millions of short sequence reads are mapped to a reference genome, and variants within the genome are identified (Bamshad et al., 2011; Keogh & Chinnery, 2013). These variants are then filtered by various techniques. The first step is to cross-reference the variants against publicly available databases of exomes from unaffected individuals and thus exclude nonpathogenic variations. An example of such a reference databases is ClinVar (ClinVar, n.d.; Landrum et al., 2014). The remaining variations are then filtered in several ways: the mode of inheritance, segregation within affected family members, etc. (Bamshad et al., 2011). Because there are normal ethnic and racial variations in the genome, population-specific databases are being developed (Higasa et al., 2016; Wall, Stawiski, Ratan, & Kim, 2019; Ahmed et al., 2019).

Strategies for genetic testing depend upon the pretest probability of a diagnosis based on clinical features, family history, extramuscular manifestations such as cardiopulmonary involvement, etc. Sequencing of a single gene of interest or sequencing of selective exons of a gene is efficient if the pretest probability of a disease is high and the majority of pathogenic mutations are due to deletions or duplications. Approximately 5% of Mendelian disorders are attributable to gene deletions or duplications (Armour, Barton, Cockburn, & Taylor, 2002). For example, in DMD, the large size of the dystrophin gene lends itself to a relatively high spontaneous mutation rate. The most common mutations are large (>1 exon) deletions (≈68%), large duplications (≈11%), followed by small deletions, insertions, and point mutations (≈20%) (Beroud et al., 2007; Bladen et al., 2015). The first step in genetic testing of suspected dystrophinopathy is usually deletion/duplication analysis because of its ease and cost-efficiency, followed by sequence analysis of DMD coding regions and then whole-exome testing (Bello & Pegoraro, 2016). If a repeat expansion disorder is suspected, PCR-based methods and Southern blotting are the standard methods of diagnosis.

More frequently, clinical assessment narrows the differential diagnosis to a group of disorders rather than providing a single diagnosis. In this situation, Sanger sequencing of

multiple individual genes is neither time nor cost effective, and the diagnostic strategy has rapidly moved toward targeted WES or WES. Targeted WES is now more easily available commercially. Panels of genes relevant to the disease group, e.g., "hereditary demyelinating neuropathy panel," "neuromuscular panel," etc., sequence the exons of several genes associated with those disorders effectively, efficiently, and cost-effectively. However, the usefulness of these panels depends on the number of genes tested. As more genes are discovered, panels have to be updated. The additive yield of WES in muscular dystrophies ranges from about 30% to 70% and averages at approximately 40%. In this group, WES may pick up unsuspected, treatable disorders such as acid maltase deficiency (Pompe disease) (Ankala et al., 2015; Börklü-Yücel et al., 2020; Dai et al., 2015; Fichna et al., 2018; Ghaoui et al., 2015; Ghosh & Zhou, 2012; Harris et al., 2017; Kuhn et al., 2016; Nallamilli et al., 2018; Reddy et al., 2017; Savarese et al., 2016; Seong et al., 2016). A diagnostic yield of up to 75% is described in populations with a high rate of consanguinity (Fattahi et al., 2017; Monies et al., 2016). In a study of pediatric NMD, both targeted WES with a neuromuscular disease panel and WES were more efficient (diagnostic yield 42%–75% and 79%, respectively) compared to conventional algorithmic diagnosis (muscle biopsy with immunohistochemistry [IHC] and Western blot, followed by candidate gene sequencing) and significantly reduced the cost per diagnosis from US$16,495 to US$3,706 for the neuromuscular disease panel and US$5,646 for WES (Schofield et al., 2017).

The most common inherited peripheral neuropathy, CMT1A, is associated with duplication of the 17p PMP22 gene in over 70% of patients. Over 80% of cases are diagnosed by traditional methods (Rudnik-Schoneborn et al., 2016; Saporta et al., 2011). Along with PMP-22 duplication, variants in the genes encoding gap junction 1 (GJB1), mitofuscin 2 (MFX2), and myelin protein-0 (MPZ) causing CMT-X, CMT-2A, and CMI-1B, respectively, account for >90% of genetically diagnosed neuropathies (Fridman et al., 2015; Murphy et al., 2012; Rossor, Tomaselli, & Reilly, 2016; Saporta et al., 2011). Despite this, only 60% of clinically diagnosed CMT patients receive a genetic diagnosis (Fridman et al., 2015; Murphy et al., 2012; Rossor, Polke, Houlden, & Reilly, 2013). With targeted WES, a diagnostic yield ranging from 19% to 53% has been reported, including detection of known variants and descriptions of novel variants (Choi et al., 2012; Drew et al., 2015; Gonzaga-Jauregui et al., 2015; Hartley et al., 2018; Klein et al., 2014; Schabhuttl et al., 2014). In axonal neuropathies with or without family history, the yield is much lower, approximately 2% without a family history and 7% with family history of neuropathy (Lee, Dankwa, Edmundson, Cornblath, & Scherer, 2019). The yield depends upon the panel used, and custom panels may have to be created based on the clinical pattern. Other factors determining the yield include the number of genes in the panel and how exhaustive public reference databases are. The use of "trios," in which the affected individual and their parents undergo WES, can be useful, when available, to segregate the variant between affected and unaffected members and to identify de novo mutations in AD disorders. An increase in diagnostic rate from 40% for single WES to 60% for trio WES has been reported (Ghaoui et al., 2015).

The chromosome 9 open reading frame 72 (C9orf72) hexanucleotide repeat expansion is the most frequent gene associated with ALS, present in approximately 39%–50% of fALS and 7% of sALS (Ghasemi & Brown, 2018; Majounie et al., 2012). This mutation, along with mutations in cytosolic copper-zinc superoxide dismutase (SOD1; 20%–25% of fALS) (Ghasemi & Brown, 2018; Andersen, 2006), transactive response DNA binding protein 43 (TARDP/TDP-43, 5%) (Ghasemi & Brown, 2018; Lattante, Rouleau, & Kabashi, 2013), and fused-in-sarcoma gene mutations (FUS; 5%) (Deng, Gao, & Jankovic, 2014; Ghasemi & Brown, 2018), accounts for 60%–90% of all fALS and 10% of apparent sALS. There is variation in clinical practice regarding genetic testing in ALS; Sanger sequencing of individual genes is commercially available (Vajda et al., 2017). Recommendations are available regarding genetic testing of patients and presymptomatic genetic testing of family members (Andersen et al., 2012; Benatar et al., 2016). Depending on the availability and cost, testing for C9orf72 repeat expansions may be offered to all patients with ALS of European descent with or without family history and in sALS with early onset (<50 years) because of the frequency of the mutation in this population, because of the clinical and counseling implications of the results, and because therapies for C9orf72 ALS are in the pipeline. In early-onset sALS or fALS with negative C9orf72 testing, targeted WES is the next step (Roggenbuck, Quick, & Kolb, 2017).

It is important to understand the limitations of targeted WES. Incomplete enrichment or "coverage" of the sequences of interest is one such limitation. Coverage may be defined as depth, or the average number of reads that align to, or "cover," known reference bases, or, more simply, how many times the base or mutation has been "read" by the sequencer. Uneven capture of nucleotide sequences can result in some exons with low coverage or in reads of DNA outside of the exome, that is, "off-target" reads. Low coverage (<5 reads per base) may result in a sequencing error being falsely interpreted as a mutation, or a true mutation being missed (Teer & Mullikin, 2010). Minor misalignment of the sequenced DNA to the reference genome may cause small base substitutions or insertions/deletions to be missed, or suggest new mutations (Bamshad et al., 2011). Disease-causing mutations in noncoding parts of the genome such as introns, regulatory components (promoters and enhancers), and splice sites will not be detected (Majewski et al., 2011). Approximately 15% of Mendelian disorders are attributed to such mutations (Keogh & Chinnery, 2013). Importantly, repeat disorders are generally not detected by exome sequencing. In the neuromuscular context, these include the more common adult muscular dystrophies, DM1, DM2, and FSHD. Cross-referencing using reference databases may omit pathogenic mutations because carriers who have not yet expressed the disease or have no symptoms due to reduced penetrance may be present in the reference panels (Bamshad et al., 2011; Singleton, 2011). The underrepresentation of Latin American, African, and Asian populations in reference databases compared to European populations limits the generalizability of these databases (Landry, Ali, Williams, Rehm, & Bonham, 2018; Popejoy & Fullerton, 2016). WES is not optimal to detect CNVs, although newer platforms have had some success in this regard (Chen et al., 2017; Shen, Szankasi, Durtschi, Kelley, & Xu, 2019; Valipakka et al., 2017). Finally, a major

challenge with WES is the detection of variants of unknown significance (VUSs), or variants that cannot be classified as either benign or pathogenic based on available information from reference databases and reported pathogenic mutations. These may represent rare, individual nonpathogenic variations or may be pathogenic but not yet reported. Further analysis is required to assess these variants: in silico prediction models, family screening of affected and unaffected members to segregate the variant in only affected members, and functional studies. Functional studies assess the significance of a VUS by evaluating its effect on the function of the protein product of the gene. This includes muscle biopsy with IHC and Western blot to assess for the reduction or absence of the protein product. Functional assays of the variant in animal models are used in the research setting but are not practical in the clinical setting.

Traditional evaluation of genetic NMD typically consists of muscle or nerve biopsy followed by genetic testing. This paradigm has shifted with the availability of NGS. For instance, because of the characteristic clinical picture of DMD or SMA, genetic testing is the preferred initial test almost universally. This eliminates the need for an invasive muscle biopsy in most of the patients. In a study of pediatric neuromuscular diseases, initial muscle or nerve biopsy provided a diagnostic yield of 34%. Genetic testing before biopsy showed pathogenic variants in 7.6%, and when genetic testing was directed by muscle biopsy findings, the yield rose to 47%. The authors concluded that the yield of genetic testing was higher when done after biopsy (Yang et al., 2019). Other studies suggest the converse: that initial genetic testing is more efficient and cost effective (Ankala et al., 2015; Chae et al., 2015; Haskell et al., 2018; Kitamura, Kondo, Urano, Aoki, & Saito, 2016). Overall, in heterogeneous NMD, NGS should probably be the initial diagnostic test if available and affordable. The use of targeted WES vs. WES depends on the clinical phenotype and the number of genes in the targeted WES panels. Muscle biopsy IHC and Western blot provide information about functional defects not only in the setting of VUS but also when no pathogenic mutation is identified and will then direct further genetic testing for confirmation of the diagnosis. Muscle biopsy findings may also be useful to understand the pathogenesis of novel mutations. In dystrophinopathies, the distinction between DMD and BMD is a clinical one, because up to 10% of cases do not follow the reading frame hypothesis (i.e., in-frame deletions manifest a DMD phenotype and out-of-frame deletions manifest a BMD phenotype) (Aartsma-Rus, Van Deutekom, Fokkema, Van Ommen, & Den Dunnen, 2006; Bladen et al., 2015). The amount of dystrophin on biopsy is therefore a better correlate of the clinical phenotype and a surrogate outcome measure for clinical trials of therapies seeking to restore dystrophin.

WGS will likely increase diagnostic yield due to its ability to detect mutations in noncoding regions and chromosomal rearrangements, but the incremental yield compared to WES remains to be established. In a study of a heterogeneous group of genetic disorders in children, WGS had an additive yield of 17% over conventional genetic testing (41% and 24%, respectively). A part of this cohort also underwent research-based WES; WGS identified all the variants that were identified by WES and, in 26% of cases, detected pathogenic variants that WES did not (Lionel et al., 2018).

Pretest and posttest genetic counseling is an important part of genetic testing. Pretest counseling for WES should provide the patient with results that may be obtained: a diagnosis may be established, a diagnostic variant may not be detected, one or more VUS may be detected, or secondary findings may be reported. The probability of an established diagnosis as described in the literature should be discussed in order to set expectations. The need for subsequent testing including family screening and functional assays such as muscle biopsy or enzymatic assay (e.g., α-glucosidase assay for Pompe disease) should be discussed. Finally, the issue of incidental, known, or expected pathogenic variants (now termed "secondary findings") has to be discussed. These are pathogenic variants unrelated to the clinical indication for testing. The American College of Medical Genetics and Genomics has published a minimum list of 59 "medically actionable" genes (i.e., disorders with either preventive or treatment strategies) that should be reported and informed to the patient. The three neurologic disorders in this list are tuberous sclerosis, neurofibromatosis, and Wilson disease. Patients should be counseled prior to testing regarding the reporting of secondary findings and should be given an opportunity to opt out of receiving these results (Kalia et al., 2017).

PRESYMPTOMATIC TESTING, CARRIER TESTING, AND NEWBORN SCREENING

Presymptomatic genetic testing is testing of the unaffected family members of a patient to assess risk of disease development. Carrier testing is genetic screening in the presence of a family history of a disorder, or ethnic predilection to a disorder, prior to planning pregnancy. While genetic testing in these populations may provide valuable information regarding their carrier status, risk for developing the disease, and risk of disease in offspring, care should be exercised before such testing. A discussion of the psychological, social, and legal implications of testing and shared decision making, taking into account the individual's values, is an important aspect of presymptomatic counseling. Skirton, Goldsmith, Jackson, and Tibben (2013) provide an excellent description of the presymptomatic counseling process and an evaluation of its quality.

Genetic newborn screening is the most common form of genetic testing. In the United States, all states have regulations for newborn screening for certain genetic and metabolic conditions that lend themselves to early treatment (e.g., sickle cell disease, phenylketonuria), although the number of screened conditions vary by state. A Recommended Universal Screening Panel (RUSP) identifies 34 core conditions and 26 secondary conditions for screening. In 2018, after the approval of nusinersen, SMA was added to the RUSP. In a study of newborn screening for DMD, there was strong support from parents and patients for screening (Chung et al., 2016).

ETHICAL AND REGULATORY ASPECTS OF GENETIC TESTING

Regulatory concerns surround both the standards for genetic testing and the effects of the results of genetic testing. In terms of standards, many genetic tests are locally

developed in laboratories. In the United States, the Centers for Medicaid and Medicare Services regulate quality control of laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) statute of 1988 via CLIA certification of laboratories. The US Food and Drug Administration (FDA) has discretionary oversight of laboratories and reviews commercially marketed diagnostic assays that are distributed to multiple laboratories. Several states require additional oversight (Ferreira-Gonzalez et al., 2008).

Direct-to-consumer (DTC) genetic tests are those that do not involve a health care professional and are offered directly for ancestry determination, heath-related purposes, or both, by commercial companies such as Ancestry, 23andMe, etc. Initially focused mainly on ancestry and family trees, these DTC tests have increasingly morphed into tests for genetic risk for disorders. Since 2017, the US FDA has granted authorization to companies to offer DTC genetic tests for risks of several conditions, including Alzheimer disease, Parkinson disease, and others. Health-related testing is often combined with ancestry testing (Gill, Obley, & Prasad, 2018). DTC genetic testing has advantages of easy access, low cost, and engagement of minorities. However, results may be less than accurate if strict quality control is not observed (CLIA certification). False-positives or -negatives may be a problem for non-European populations, because reference databases are skewed toward the European populations. The less sophisticated consumer may not be able to interpret the results accurately. The role of epigenetic and other factors in relation to the test results and risk of developing a condition is not addressed without a health care professional's input. Most of these tests are not integrated into medical records, and many health care professionals are not equipped to interpret the results of DTC genetic tests and advise patients (Feero & Wicklund, 2020). Confidentiality, privacy, and data security concerns grow with increased use of these tests. Data from DTC genetic testing have been used in law enforcement, and consumer privacy and confidentiality are dependent on company policies, which are variable. Regulations are required to protect the confidentiality of consumers' data (Hendricks-Sturrup, Prince, & Lu, 2019).

Another aspect of regulation is potential discrimination based on the accessibility of genetic testing reports to potential employers and insurance companies. This applies to both diagnostic testing and presymptomatic/carrier screening. The Genetic Information Nondiscrimination Act of 2008 prohibits the use of genetic information to determine eligibility or premiums for health insurance, but it does not address life, disability, or long-term care insurance (National Human Genome Research Institute, 2008). Countries vary in their methods of handling this issue. Klitzman, Appelbaum, and Chung (2014) provide an excellent overview of this issue.

Prenatal testing for pregnancy planning can be combined with prenatal pregnancy termination. Assisted reproductive technologies such as in vitro fertilization can be combined with preimplantation genetic diagnosis to prevent the birth of children with genetic diseases. This raises several ethical issues. The disability community has been very vocal on this issue, because of the view that the selection of an embryo based solely on a risk of developing a disorder associated with disability is unethical and unacceptable, implies that disabled persons are less valuable, and exemplifies an intolerance of diversity, leading to genetic selection. Additionally, it has been proposed that many negative facets of disabilities are culturally constructed rather than being actual features of the condition. Therefore, if society were aligned differently, people with disabilities would potentially encounter fewer drawbacks due to their disease and parents would not be inclined to make prenatal decisions based on disabilities (Edwards, 2004; Gyngell, Stark, & Savulescu, 2020; Hoffman, 2017). The contrary ethical argument is one of sovereignty and nonalienation (Enoch, 2017; Gyngell et al., 2020). Sovereignty refers to the concept that some decisions are a basic authority of individuals, no matter how they exercise these decisions. Reproductive choice is a form of bodily sovereignty, where decisions about whether to have children, access assisted reproductive technology, etc., are ultimately individual decisions (Enoch, 2017; Gyngell et al., 2020). Nonalienation describes the right of people to be in charge of their lives and to have a semblance of control of their life's path (Gyngell et al., 2020). Reproductive decisions have a profound effect on peoples' lives. Because having a child with a disability substantially affects a person's life, the principle of nonalienation suggests that a potential parent should be able to choose whether their child has a disability of not, in accordance with their preferences and values (Gyngell et al., 2020). Gyngell et al. (2020) provide an excellent review of these ethical issues as well as beneficence and justice both in genetic diagnosis and treatments, using SMA as an example.

GENETIC APPROACHES TO TREATMENT OF NEUROMUSCULAR DISORDERS

Approaches to treatment of genetic NMD include symptomatic treatments; those targeting shared pathways of muscle, nerve or neuromuscular junction degeneration; and treatments that aim to correct the underlying genetic defect. In this section, we discuss the approaches to genetic treatments of NMDs.

Mutations, or pathogenic variants in the genome, result in effects on the protein product of the gene leading to functional effects. AR mutations typically cause a loss of function of the protein product by inactivating the gene. In the normal genome, there are two alleles of a gene, both making normal gene product. In heterozygotes, with one normal and one mutated allele, the single normal allele may be able to synthesize sufficient normal gene product with a normal phenotype, while homozygous individuals manifest the effects of the loss of gene product. However, some loss-of-function mutations are dominant. In such cases, the single allele in the heterozygote cannot synthesize sufficient gene product, with resultant manifest disease. Less frequently, mutations may result in a gain-of-function, i.e., an increased or modified activity of the gene, or its expression at the wrong site or time. These mutations are usually AD (Lodish et al., 2000). Approaches to treatment of genetic NMD are generally directed towards replacing the deficient or dysfunctional protein product of the gene, or repairing the genetic defect.

OVERVIEW OF PROTEIN SYNTHESIS

Protein synthesis, regulated by RNA, consists of two steps: transcription and translation. During transcription, the

genetic code is copied from DNA to messenger RNA (mRNA). This occurs in the nucleus and is controlled by the enzyme RNA polymerase. First, a nucleotide sequence called pre-mRNA, containing both exons and introns, is formed. Pre-mRNA is then edited to remove introns and form mature mRNA transcript by a process called splicing. The number of proteins is vastly greater than the number of genes. This is possible because a single gene can express different forms of mRNA coding for divergent proteins by alternative splicing of pre-mRNA (Lander et al., 2001). Spliceosomes are complexes of proteins and RNA that mediate splicing (Bauman, Jearawiriyapaisarn, & Kole, 2009). Components of pre-mRNA such as splice sites, splicing enhancers, and silencers play a role in this process (Bauman et al., 2009). Once formed, mRNA travels from the nucleus to the cytoplasm, where protein translation occurs in the ribosomes. This process requires ribosomal RNA and transfer RNA. The ribosome is attached to a strand of mRNA, following which translation begins with the reading of the first triplet codon. Transfer RNA molecules bring in individual amino acids and attach them to mRNA and to each other, forming a chain of amino acids.

Strategies to address the genetic defect in inherited NMD may be classified into RNA-based and DNA-based therapies based on their mechanism and site of action.

RNA-BASED THERAPIES

RNA-based therapies primarily target RNA for therapeutic effects and include antisense oligonucleotides (ASOs) and RNA interference (small interfering RNA [siRNA] and micro-RNA [mRNA]). A related approach utilizes small molecules that alter the translation of mutant mRNA by inducing a partial read-through of nonsense mutations (Chery, 2016; McDonald et al., 2017).

ANTISENSE OLIGONUCLEOTIDES

ASOs are synthetic nucleic acid sequences that can bind to selected sequences of RNA through standard Watson-Crick base pairing and consequently regulate the expression of genes (Goyal & Narayanaswami, 2018). The term "antisense" refers to the fact that they are complementary to the "sense strand" or the strand that encodes amino acids for protein synthesis (Chery, 2016; Evers, Toonen, & van Roon-Mom, 2015; Geary, Norris, Yu, & Bennett, 2015). In their original form, they are rapidly degraded by endo- and exo-nucleases (Dagle, Weeks, & Walder, 1991; Eder, DeVine, Dagle, & Walder, 1991). Because of their large size and negative charge, intracellular uptake is limited (Saleh, Arzumanov, & Gait, 2012; Yokota et al., 2009). ASOs are therefore modified chemically to improve stability, prevent enzymatic degradation, increase cell penetrance, and target specificity and affinity. Based on these modifications, ASOs are termed first, second, and third generation ASOs (Table 11.2, Fig. 11.2) (De Clercq, Eckstein, & Merigan, 1969; Kurreck, 2003; Monia et al., 1993; Nielsen, Egholm, Berg, & Buchardt, 1991; Siva, Covello, & Denti, 2014; Summerton & Weller, 1997). ASOs act by several mechanisms and can restore deficient protein expression, reduce the expression of a toxic protein, modify the functional effects of proteins, or reduce the toxicity of mutant proteins (Evers et al., 2015) (Fig. 11.3). Genetic disorders are frequently due to mutations that modify splicing (Faustino & Cooper, 2003) and are therefore often amenable to ASO-mediated genetic modulation. ASOs used for gain-of-function disorders usually silence or "knock down" the causative gene. In loss-of-function disorders, ASOs usually work by splice modulation to restore function

Table 11.2 Antisense Oligonucleotide Chemistry and Properties

ASO Generation	Chemical Modification	Major Representative	Nuclease Resistance	Target-Binding Affinity	RNase-H Activation	Other
First Generation	Phosphate backbone	Phosphorothioate oligonucleotides	Yes	Poor	Yes	May stimulate immune response
Second Generation	Sugar modification	2'-*O*-Methyl and 2'-*O*-methoxyethyl ASOs, locked nucleic acids (LNAs)	Yes	Strong	No	LNA: poor target specificity
Third Generation	Phosphate, ribose, and nucleoside modifications	Peptide nucleic acids Phosphorodiamidate morpholino oligomers	Yes	Strong	No	
Gapmer	Central region of phosphate modification flanked by 2'-*O*-methyl modification regions		Yes	Strong	Yes	

RNase-H is an endonuclease present in the nucleus. It recognizes an RNA-DNA heteroduplex and catalyzes the cleavage of the RNA strand from the duplex. One mechanism action of ASOs is by activation of RNase-H, which results in degradation of the mRNA cleavage products both downstream and upstream of the initial cleavage site, therefore inhibiting protein translation.

Source: Goyal, N., & Narayanaswami, P. (2018). Making sense of antisense oligonucleotides. *Muscle & Nerve 57*: 356-370, Table 1, with permission from Wiley.

ASO, Antisense oligonucleotide; *RNAse-H*, ribonuclease H.

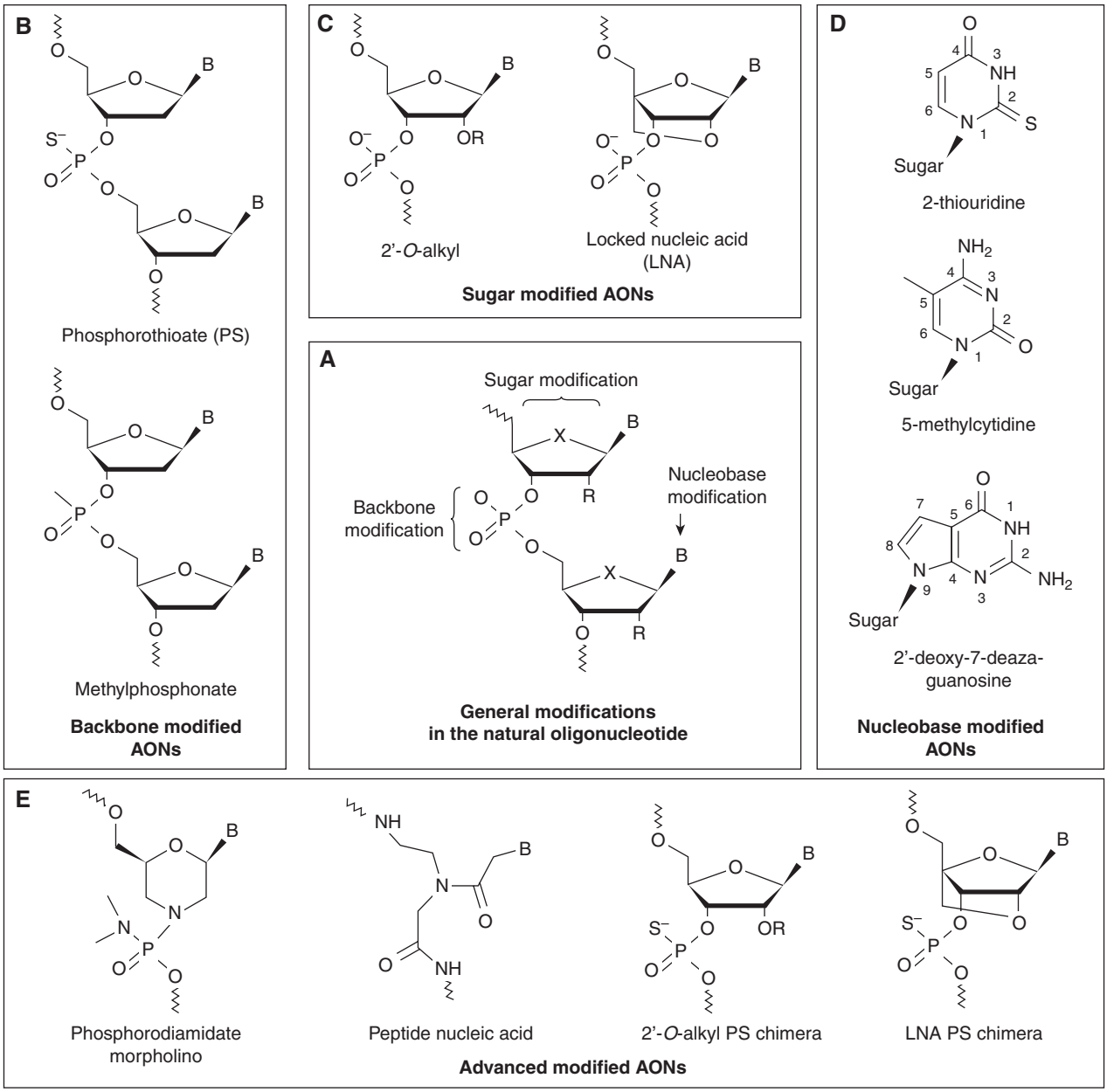


Fig. 11.2 Chemical structure of antisense oligonucleotides (ASOs, also known as AONs). (A) Modifications of the phosphate backbone, sugar moiety, or the organic nucleobase are used to increase ASO (AON) bioavailability, improve target specificity and affinity, and enhance cell penetration and nuclear accumulation. (B) First-generation ASOs: modifications of the phosphate backbone. Phosphorothioate oligonucleotides possess a sulfur atom instead of the nonbridging oxygen in the phosphate backbone. (C) Second-generation ASOs: additional modifications of the ribose sugar. 2'-*O*-methyl, 2'-*O*-methoxyethyl ASOs are formed by the addition of a methyl or a methoxyethyl group to the 20 oxygen atom of ribose, respectively. Locked nucleic acids are formed by creating a bridge between the 20 oxygen and 40 carbon atoms. (D) Nucleobase modified ASOs. (E) Third-generation ASOs: combined modifications of phosphate, ribose, and nucleoside. Phosphorodiamidate morpholino oligomers have a morpholine ring instead of ribose and phosphorodiamidate inter-nucleoside linkages instead of phosphodiester bonds. (From Goyal, N., & Narayanaswami, P. (2018.) Making sense of antisense oligonucleotides. *Muscle & Nerve, 57*, 356–370, Figure 2, with permission from Wiley.)

of the mutant protein or compensate for its loss (Du, Pollard, & Gatti, 2007; Evers et al., 2013, 2015; Singh, Singh, Androphy, & Singh, 2006; Zalachoras et al., 2013). Splice exclusion and splice inclusion have clinical applications in DMD and SMA, respectively, and are briefly discussed later.

In DMD, large deletions in the dystrophin gene result in disruption of the reading frame and a "frame shift" of the triplet codons by one or two nucleotides. This causes premature termination of mRNA translation and a near total absence of dystrophin. In BMD, the mutations maintain the reading frame, resulting in the translation of a truncated but partially functional dystrophin and a milder clinical phenotype (Bladen et al., 2015; Melis et al., 1998; Wood, Gait, & Yin, 2010). The principle of ASO therapies for DMD is to omit or "skip" the mutated exon alone or along with its flanking regions and convert the out-of-frame transcript to an in-frame one, restoring the reading frame and inducing the expression of a shorter and partially functional

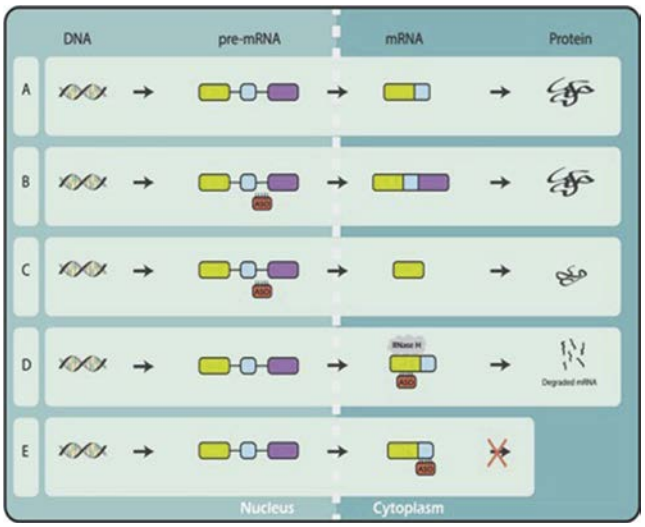


Fig. 11.3 Mechanisms of action of antisense oligonucleotides (ASOs). (A) Normal transcription and translation. The DNA is transcribed into pre-mRNA in the nucleus. The pre-mRNA spliced to form mature mRNA. mRNA enters the cytoplasm where protein translation occurs in the ribosomes. (B) Splice inclusion: The ASO binds to splice modulators on pre-mRNA, resulting in the inclusion of a previously excluded exon. Translation results in a modified protein with functional differences. (C) Splice exclusion or "exon skipping": The ASO binds to pre-mRNA and skips the mutated exons, thus converting an out-of-frame mutation to an in-frame one, resulting in the translation of a truncated but functional protein. (D) RNA knockdown: The ASO binds to mRNA and activates RNase-H-initiated breakdown of the target RNA, resulting in reduced levels of the toxic RNA and protein product. (E) Prevention of translation: The ASO binds to mRNA and directly inhibits translation. (From Goyal, N., & Narayanaswami, P. (2018). Making sense of antisense oligonucleotides. *Muscle & Nerve, 57*, 356–370, Figure 3, with permission from Wiley.)

dystrophin (Wood et al., 2010; Muntoni, Torelli, & Ferlini, 2003) (Fig. 11.4). Deletions in dystrophinopathies tend to be concentrated in "hot spots" along the gene. Approximately 70% are clustered between exons 45 and 55. Another "hot spot" is between exons 2 and 20 (14% of deletions) (Beggs, Koenig, Boyce, & Kunkel, 1990; Bladen et al., 2015; Muntoni et al., 2003). Exon 51 skipping restores the reading frame in approximately 14% of DMD patients with deletions of exons 50, 52, 52–63, 45–50, 48–50 or 49–50 (Aartsma-Rus et al., 2003; Bladen et al., 2015). Drisapersen was the first ASO to be studied in clinical trials for DMD. After a phase III randomized controlled trial (RCT), DEMAND III, an FDA review concluded that there was no proof of efficacy and there were concerns regarding adverse effects including renal toxicity and thrombocytopenia (Goemans, Campbell, & Kraus, 2013; Goemans et al., 2011; Niks & Aartsma-Rus, 2017; van Deutekom et al., 2007; Voit et al., 2014). The second ASO studied in DMD, eteplirsen, received conditional approval from the FDA in September 2016 following several clinical trials (Cirak et al., 2011; Kinali et al., 2009; Mendell et al., 2013, 2016). Eteplirsen is an ASO that "skips" or excludes exon 51 during pre-mRNA splicing, essentially changing the Duchenne pattern of dystrophin expression to a Becker pattern. Golodirsen is an ASO for the treatment of DMD in patients amenable to exon 53 skipping and was recently approved in the United States based on the results of a phase I/II clinical trial, discussed in Chapter 20. Viltolarsen is another exon-skipping medication that skips exon 53, under review by the US FDA, and is predicted to be useful in 8%–10% of patients with DMD (Roshmi & Yokota, 2019).

SMA is caused in approximately 96% of cases by loss-of-function homozygous deletions in the survival motor neuron 1 (SMN1) gene on chromosome 5q13, resulting in insufficient levels of the SMN protein (Lefebvre et al., 1995). Because of the presence of a closely related gene, SMN2, patients with SMA continue to express low levels of SMN protein. SMN2 differs from the SMN1 gene by five nucleotides. A single-nucleotide substitution at exon 7 affects splicing, resulting in exon 7 exclusion and the production of a truncated SMN2 protein that is rapidly degraded (Burnett et al., 2009; Lefebvre et al., 1995). The SMN2 gene may be present in varying numberd of copies, ranging from 0 to 8 (Butchbach, 2016). Interestingly, the SMN2 gene also produces up to 10% of full-length SMN protein due to normal splicing (Lefebvre et al., 1995). The amount of full-length functional SMN1 protein produced increases with increasing copies of the SMN2 gene, and this determines the SMA phenotype, with the most severe phenotype associated with the fewest copies of SMN2 (Feldkotter, Schwarzer, Wirth, Wienker, & Wirth, 2002). The principle of ASO treatment of SMA is to increase the inclusion of exon 7 in the mRNA of the SMN2 gene, thus increasing functional SMN protein. Intronic splicing silencer N1 (ISS-N1) inhibits the inclusion of exon 7 in SMN2 pre-mRNA. Consequently, ISS-N1 blockade results in greater inclusion of exon 7 into SMN2 mRNA transcript (Fig. 11.5). Intrathecal nusinersen, an ASO that blocks ISS-N1, was approved by the US FDA in December 2016 after several clinical trials (Chiriboga et al., 2016; Finkel et al., 2016; Spinraza, n.d.).

hATTR is caused by pathogenic single nucleotide mutations in the gene encoding transthyretin (TTR). The tetrameric TTR protein complex is destabilized and results in aggregation of monomers into insoluble, extracellular amyloid deposits. Progressive accumulation of both mutant and wild type amyloid leads to multiorgan dysfunction and death, with preferential involvement of the heart and peripheral nerves. The inheritance pattern of hATTR is AD, and the age of onset varies from early to late adulthood. In contrast, wild-type TTR amyloidosis is not genetic and TTR amyloid deposition occurs in older patients, mainly in the heart (Halatchev, Zheng, & Ou, 2018; Ruberg, Grogan, Hanna, Kelly, & Maurer, 2019). The ASO inotersen knocks down hepatic production of transthyretin. The US FDA approved inotersen for use in hATTR-PN in October 2018 based on the results of a large RCT (Benson et al., 2018).

As a group, the adverse effects of ASOs may be classified as hybridization dependent or hybridization independent. Hybridization-dependent toxicities can occur either at the target binding site or off-target, at an unintended target. Hybridization-independent toxicity is usually related to chemical modifications of the ASO and includes thrombocytopenia, nephrotoxicity, and hepatotoxicity (Bennett & Swayze, 2010). Animal studies and preliminary clinical studies in humans suggest that ASOs may have a role in many other NMDs, including SOD1-ALS, C9ORF72-ALS, and DM1 (Gotkine et al., 2013; Jiang et al., 2016; Jauvin et al., 2017; Klein et al., 2019; McCampbell et al., 2018; Miller et al., 2013). Clinical trials of ASOs in SOD1-ALS (NCT02623699, NCT03070119, clinicaltrials.gov) and C9orf72-ALS (NCT03626012) are in progress.

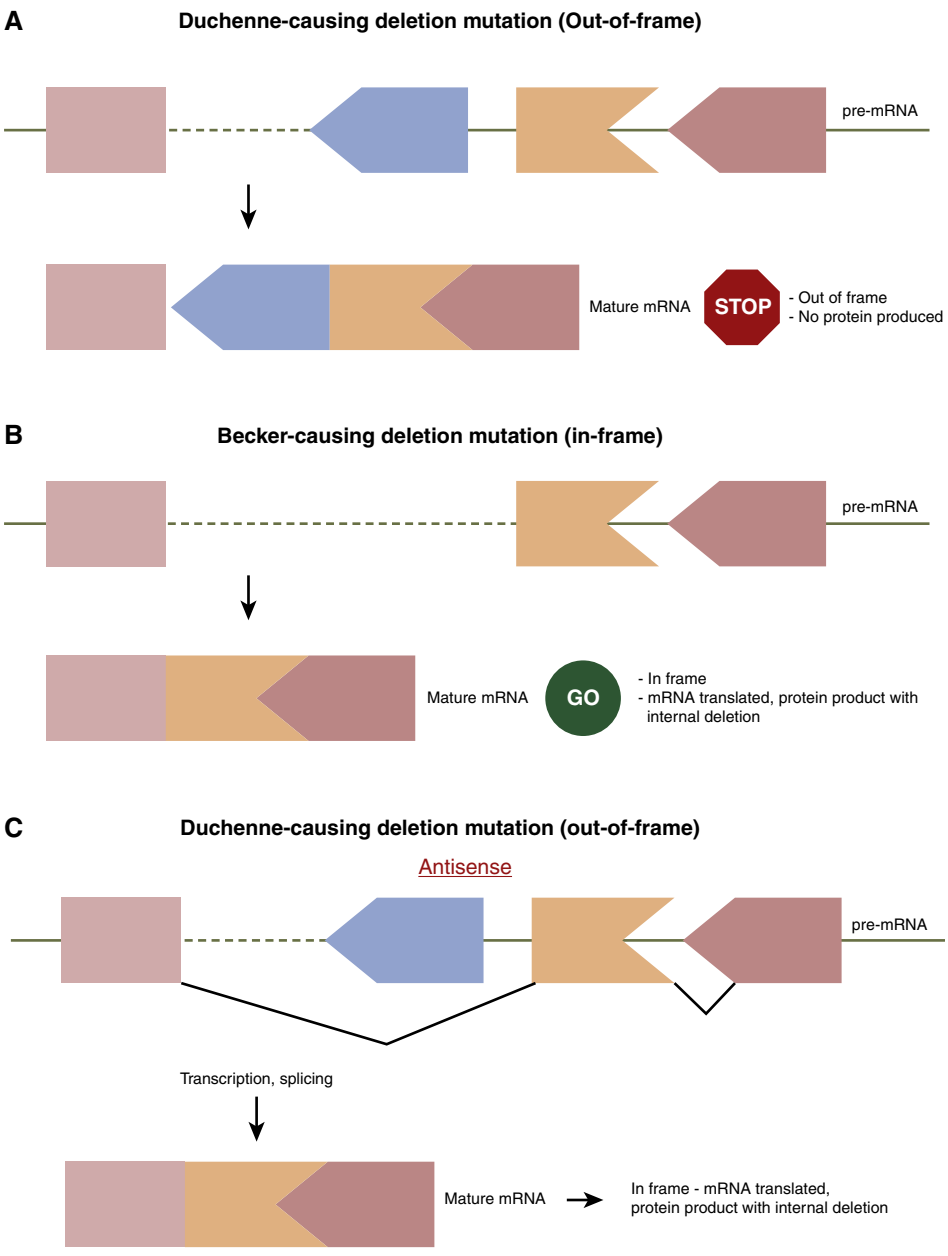


Fig. 11.4 Mechanism of action of antisense oligonucleotide (ASO) in Duchenne muscular dystrophy (DMD). (A) In DMD, an out-of-frame mutation disrupts the open reading frame (ORF) of the mRNA transcript. This leads to aberrant translation of mRNA because the triplet codon sequence is not maintained, resulting in the absence of dystrophin. (B) In Becker muscular dystrophy, an in-frame mutation that maintains the ORF leads to a truncated, partially functional protein. (C) ASO therapy of DMD aims to exclude or "skip" the mutated exon alone or together with its flanking regions and convert the out-of-frame transcript to an in-frame one, restoring the ORF and inducing the expression of a partially functional dystrophin. (With kind permission from Dr. MC Vila and Dr. AA Fiorillo, Center for Genetic Medicine Research, Children's Research Institute, Washington, DC.)

SMALL MOLECULES

Nonsense mutations occur due to the substitution of a single base pair in a triplet codon, leading to one of three stop codons (UAG, UAA, and UGA). The triplet codon coding for an amino acid is therefore altered to one that prematurely stops mRNA translation and results in a truncated protein. These codons are hence referred to as premature termination codon (PTC) (Siddiqui & Sonenberg, 2016). PTCs result in accelerated degradation of mRNAs through a mechanism called nonsense-mediated decay (Celik, Kervestin, & Jacobson, 2015). It has been estimated that up to 10%–15% of human genetic diseases may be related to nonsense mutations, including DMD, cystic fibrosis, and others (Kellermayer, 2006; Krawczak et al., 2000). Approximately 10%–15% of patients with DMD have a nonsense mutation, which introduces a PTC into the dystrophin mRNA, leading to the translation of a truncated, nonfunctional dystrophin (Pichavant et al. 2011). A small molecule, ataluren, with the ability to bypass, or "read through," PTCs, has been found to improve outcomes on timed functional tests in DMD (Bushby et al., 2014; Finkel et al., 2013; McDonald et al., 2017). Ataluren is approved for treatment of DMD in ambulatory patients over 2 years of age in Europe.

Risdiplam is an orally administered, centrally and peripherally distributed, small-molecule SMN2 mRNA splicing modifier. It promotes increases of functional SMN protein (Sturm et al., 2019). It was approved in 2020 as a first oral treatment for SMA patients 2 months of age and older (Dhillon, 2020).

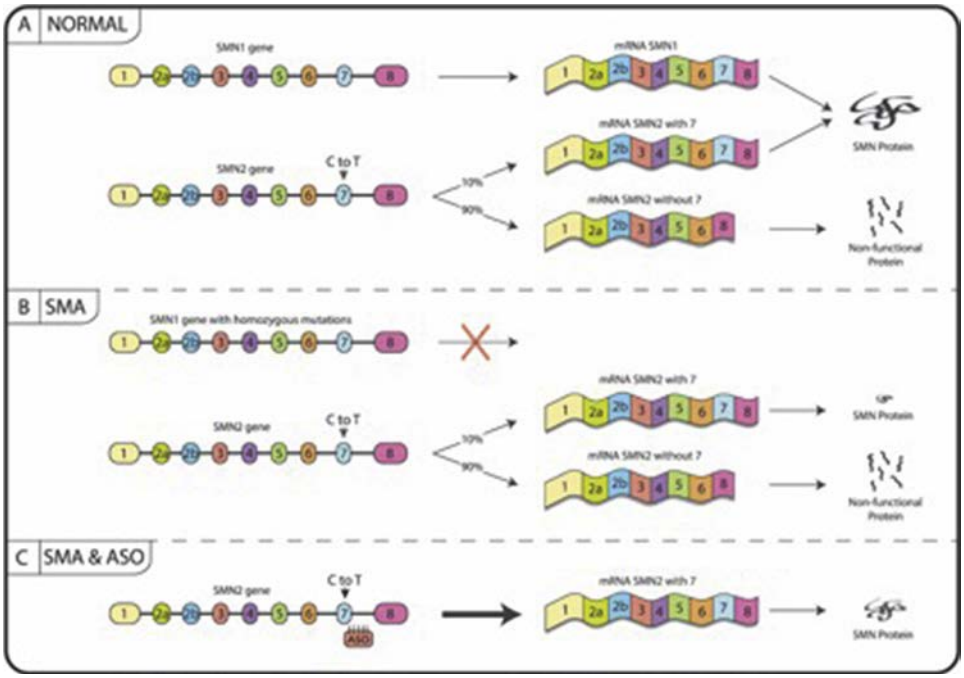


Fig. 11.5 Mechanism of action of antisense oligonucleotide (ASO) in spinal muscular atrophy (SMA). (A) In normal individuals, SMN1 gene transcription results in mRNA containing exon 7, which is translated to a fully functional SMN protein. The almost identical SMN2 gene lacks exon 7 in the majority (90%) of the transcribed mRNA due to a cytosine to thymine substitution at position 6 in exon 7. The translated SMN2 protein is unstable and rapidly degraded. (B) In patients with SMA, a homozygous deletion or mutation in the SMN1 gene results in insufficient levels of SMN protein. Because a small amount of the SMN2 transcript undergoes normal splicing, each copy of the SMN2 gene produces up to 10% of full-length SMN protein. SMA disease severity is modified by the number of SMN2 copies; as copy number increases, greater amounts of full SMN1 protein are produced, resulting in a less severe disease phenotype. (C) The aim of ASO treatment is to increase levels of full-length SMN protein expressed by the SMN2 gene. The ASO "switches" SMN2 splicing to retain exon 7 by blocking intronic splicing silencer N1 (ISS-N1) ISS-N1. This results in the inclusion of exon 7 and translation of greater amounts of full length SMN protein. (Goyal, N., & Narayanaswami, P. (2018). Making sense of antisense oligonucleotides. *Muscle & Nerve, 57*, 356–370, Figure 5, with permission from Wiley.)

A novel therapeutic approach for lysosomal diseases such as Pompe disease is the use of chaperone proteins, although not strictly a "genetic therapy." These small-molecule pharmacological chaperones promote folding, stability, and lysosomal trafficking of chaperone-responsive mutant enzymes (Parenti, Moracci, Fecarotta, & Andria, 2014). Chaperone proteins have also been shown to have a stabilizing effect with improved pharmacokinetics and pharmacodynamics of recombinant enzymes (Parenti et al., 2014).

Another small molecule, tafamidis meglumine, stabilizes the TTR tetramer, preventing its dissociation into amyloidogenic monomers. It was approved for treatment of early and intermediate stages of hATTR-PN in Europe (2011), Japan (2013), and Brazil (2016) based on the results of an RCT (Coelho et al., 2012). In the United States, tafamidis was approved in 2019 for the treatment of hATTR-related cardiomyopathy, but it is not approved for the treatment of hATTR-PN at this time (Maurer et al., 2018).

RNA INTERFERENCE

RNA interference (RNAi) is an innate cellular regulatory process that can prevent translation of genes into their protein product. RNAi is also used in the innate immune response of cells against viruses and bacteria (Chery, 2016; Ozcan, Ozpolat, Coleman, Sood, & Lopez-Berestein, 2015). This process is brought about by endogenous RNA molecules that induce sequence-specific inhibition of target gene expression or translation (Fig. 11.6) (Baulcombe, 1996). RNAi can also be induced by injection of exogenous RNA (Baulcombe, 1996; Montgomery & Fire, 1998). Interestingly, in contrast to ASOs, which are single stranded, double-stranded RNA (dsRNA) molecules appear to be more effective at achieving RNAi. The dsRNA sequence is homologous to that of the silenced gene (Fire et al., 1998; Elbashir et al., 2001; Elbashir, Lendeckel, & Tuschl, 2001). The mediators of RNAi interference are short dsRNA sequences 21 and 22 nucleotides long, derived by enzymatic cleavage from longer dsRNAs in a reaction mediated by ribonuclease III-like enzyme named Dicer (Elbashir, Harborth, et al., 2001; Elbashir, Lendeckel, et al., 2001; Nicholson, 2014). Three types of noncoding RNA that interfere with gene expression are described: siRNA, micro RNA (miRNA), and piwi-interacting RNAs (Castel & Martienssen, 2013; Jinek & Doudna, 2009).

Small Interfering RNAs (SIRNAS)

siRNA-based therapeutic approaches involve the introduction of a synthetic siRNA into the target cells to cause RNAi, consequently inhibiting the expression of mRNA to silence the corresponding gene (Behlke, 2006). However, in mammalian cells, the delivery of exogenous, long dsRNAs results in the activation of an interferon (IFN) response with nonspecific mRNA degradation and cellular apoptosis (Barik, 2005; Gantier & Williams, 2007). Direct introduction of synthetic siRNAs, instead of the

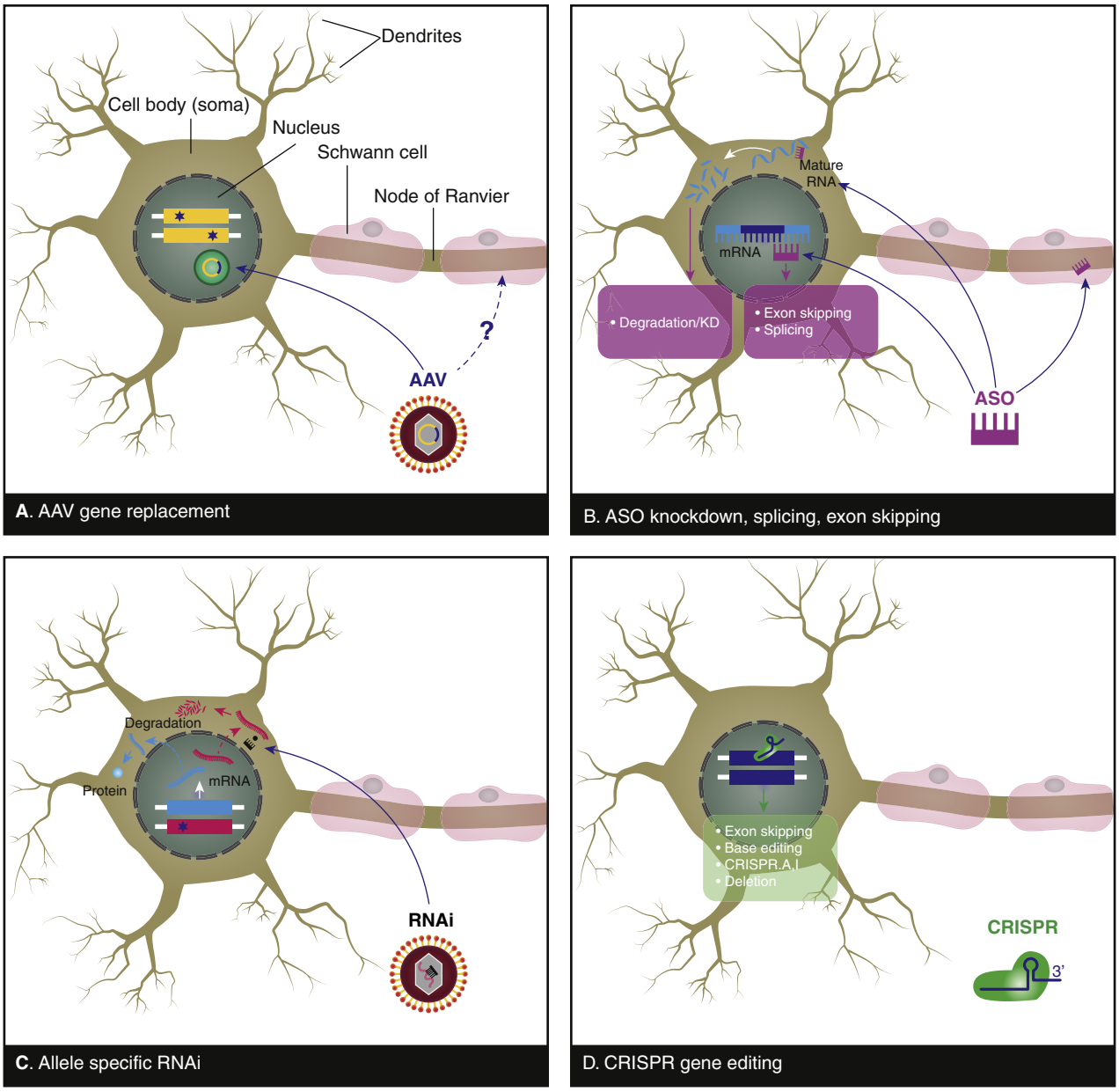


Fig. 11.6 Current and emerging gene therapy modalities. (A) Viral vectors for gene replacement can be used to restore gene expression, especially in recessive loss-of-function mutations. Adeno-associated virus (*AAV*) has been used extensively for this purpose, and the AAV9 serotype has good neurotropism. The viral payload persists in the nucleus as an extrachromosomal episome, providing long-term gene expression. (B) RNA interference (RNAi). Allele-specific RNAi sequences targeting mutant, but not wild-type, mRNA are expressed using a microRNA shuttle driven by a U6 promoter. This construct can be delivered using an AAV. (C) Gene editing. CRISPR-Cas9 is currently utilized only in preclinical studies and can potentially be used to promote exon skipping, base-editing, transcriptional activation (CRISPR-A) or inactivation (CRISPR-I), and gene deletion. *ASO*, Antisense oligonucleotide. (Modified from Morelli, K. H., Hatton, C. L., Harper, S. Q., & Burgess, R. W. (2020). Gene therapies for axonal neuropathies: Available strategies, successes to date, and what to target next. *Brain Research, 1732*, 146683, Figure 1.)

long dsRNAs, results in RNAi without activating the IFN response (Elbashir et al., 2001). Therefore, siRNAs have become useful tools to silence target genes. Unmodified siRNA is hydrophilic and needs to be transfected with cationic lipids or other types of nanoparticles to enter the cell (Dowdy, 2017). Alternatively, siRNA can be conjugated to a targeting ligand like *N*-acetylgalactosamine (GalNac), which binds to asialoglycoprotein receptors (Springer & Dowdy, 2018).

Patisiran is an siRNA targeting TTR, formulated as lipid nanoparticles for delivery to hepatocytes. It reduces the expression of mutant and wild-type TTR. Patisiran was approved in the United States and Europe in 2018 for the treatment of hATTR-PN, following the results of a large RCT that showed improvements in impairment, quality of life, and gait speed in patients treated with patisiran compared to placebo (Adams et al., 2018).

In acute intermittent porphyria (AIP), a liver-directed siRNA targeting the enzyme 5-aminolevulinic acid synthase (ALAS1), givosiran, was approved in December 2019 by the US FDA for acute hepatic porphyrias, including AIP, based on the results of the ENVISION trial (Scott, 2020).

Micro RNAs (miRNAs)

Similarly to siRNAs, miRNAs also inhibit posttranscriptional gene expression. The major difference between them is that the siRNAs inhibit the expression of one specific target mRNA, whereas miRNAs can regulate the expression of multiple mRNAs (Lam, Chow, Zhang, & Leung, 2015). miRNA expression may be dysregulated and their expression altered in specific patterns in several NMD. This dysregulation and altered expression is mirrored in serum miRNA profiles in various NMDs, providing a "signature" for a specific disease, which may have value both in diagnosis (especially when the genetic defect is not identified) and in following response to therapies such as ASOs (to evaluate for "normalization" of the miRNA profiles) (Alexander & Kunkel, 2015; Cacchiarelli et al., 2011; Eisenberg et al., 2007; Kye & Goncalves Ido, 2014; Zaharieva et al., 2013), miRNA-mediated gene regulation may also have potential for treatment of NMD caused by a toxic gain of function (Pourshafie et al., 2018).

DNA-BASED THERAPIES

DNA-based therapies work by inducing or inhibiting the expression of genes. Advances in adeno-associated virus (AAV) vector development have enabled the development of viral gene therapy in NMDs. The goal of gene therapy may be to replace the defective gene or to modify the gene using technologies such as CRISPR/Cas9 editing. Gene therapy may be used to correct a mutant gene by introducing and expressing its correct copy and, therefore, translating of the functional protein, or for DNA-based gene ablation, wherein the selected gene is switched off. Clinical use of gene replacement therapy is associated with challenges related to gene size and delivery modalities. Effective treatment depends on stable delivery and expression of the transgene in target tissue without pathogenicity or immunogenicity. It is unclear at this time if gene replacement and gene editing treatments will provide long-lasting or permanent benefit after a single treatment, or whether repeated treatments will be necessary to maintain benefit.

GENE REPLACEMENT

Gene replacement therapy involves the introduction of exogenous nucleic acids within living cells to reverse the genetic defect. The genomic material can be delivered by either viral or nonviral delivery systems, termed "vectors." The selection of a vector depends on factors such as the ability to attach to and enter the target cell, successful transfer to the nucleus, the ability to be expressed in the nucleus for a sustained time period, the size of the genomic material to be delivered, the interval to gene expression for therapeutic effect, and lack of pathogenicity and immunogenicity (Aguti, Malerba, & Zhou, 2018; Daya & Berns, 2008). The expression of the transgene is regulated by promoters. The role of promoters in the development of effective gene replacement therapy may be illustrated by the use of hybrid cytomegalovirus enhancer—chicken beta actin promoter in onasemnogene abeparvovec xioi for gene replacement in SMA. The promoter helps to maintain high, sustained human SMN expression by increasing the onset of transgene translation and promoting rapid and efficient transduction (Al-Zaidy & Mendell, 2019). AAVs are small viruses of the Parviridae family that have been the preferred vector for virus-based gene therapy in many clinical studies (Samulski & Muzyczka, 2014). AAV infection and replication require helper genes provided by coinfection with herpes simplex virus or adenovirus (Atchison, Casto, & Hammon, 1965). Without a helper virus, AAV becomes latent and integrates into the AAVS1 locus on chromosome 19 (19q13) of the human genome (Kotin, Linden, & Berns, 1992). AAV can infect both dividing and nondividing cells, including postmitotic neurons (Daya & Berns, 2008; Nishiyama, Mikuni, & Yasuda, 2017). Some serotypes of AAV such as AAV type 9 have high neurotropism (Addgene, n.d.; Bevan et al., 2011). AAV usually does not get integrated into the host genome, limiting potential adverse events. AAVs are small viruses with a nonenveloped capsid and linear single-strand DNA (ssDNA) genome in which three ORFs, *rep* (replication), *cap* (capsid), and *aap* (assembly activating protein), are flanked by two inverted terminal repeats (ITRs). ITRs are present at the origins of replication and are required for integration and genome packaging (Koczot, Carter, Garon, & Rose, 1973). Exogenous DNA is introduced into the AAV genome by replacing the *rep* and *cap* genes with the foreign DNA inserted between ITR sequences, producing a single-strand AAV (ssAAV) vector (Aguti et al., 2018). Inside the ssAAV vector, an ssDNA up to a maximum of 4.7 kb is packaged. After delivery into the cell, DNA polymerase synthesizes the second DNA strand and multiple vector genomes form concatemers of circular DNA (a long continuous DNA molecule that contains multiple copies of the same DNA sequence linked in series) (Fig. 11.6) (Duan et al., 1998). The time for synthesis of the complementary DNA strand delays transgene expression. Self-complementary AAV vectors have both DNA strands packaged within the vector, allowing faster transgene expression, but can hold only up to a 2.2 kb sequence (Meyer et al., 2015).

In SMA, AAV-9-vector-associated gene delivery has been demonstrated to replace the mutated gene and rescue the phenotype in mouse models after a single intravenous injection (McCarty, Monahan, & Samulski, 2001). Onasemnogene abeparvovec-xioi was approved by the US FDA in 2019 for the treatment of pediatric patients less than 2 years of age with SMA and biallelic mutations in the SMN1 gene based on a completed phase 1 and ongoing phase 3 trial (Hoy, 2019). In late 2019, the drug was placed on partial hold in clinical trials by the US FDA due to safety concerns on the basis of animal findings of dorsal root ganglia mononuclear cell inflammation, sometimes accompanied by neuronal cell body degeneration or loss (BioSpace, 2019). AAV-8-vector-associated gene therapy is being evaluated in a clinical trial (ASPIRO) for X-linked myotubular myopathy (NCT03199469). Aguti et al. (2018) provide a detailed review of gene therapies in NMD.

GENE EDITING

Gene editing refers to genetic engineering techniques to insert, delete, modify, or replace DNA in the genome. The clustered regularly interspaced short palindromic repeat (CRISPR)/CRISP-associated protein-9 (CRISPR-Cas9) system has generated great excitement because it is faster, cheaper, more accurate, and more efficient than older genome editing methods. Cas-9 is an endonuclease that is guided by single-guide RNA (sgRNA) to bind the targeted genomic locus and creates a double-strand break (DSB).

The DSB is then repaired by nonhomologous end joining, resulting in irregular insertion/deletion (indel) mutations, or homology-directed repair, which requires an exogenous DNA template to effect a precise modification at the target locus (Fig. 11.6). This technology has been studied in the mdx mouse model of DMD, using AAV vector delivery, and in cell culture studies. Gene correction in SMA, repeat snipping in C9orf72-ALS and DM1, and reducing PMP22 protein expression in CMT 1A are other potential applications being explored in preclinical studies. Long and colleagues provide a detailed overview (Long, Amoasii, Bassel-Duby, & Olson, 2016; Lee et al., 2020; Raaijmakers, Ripken, Ausems, & Wansink, 2019).

ETHICAL, POLICY, AND REGULATORY ASPECTS OF GENETIC TREATMENTS

With seven gene-based therapies approved for NMD between 2016 and 2019 (Table 11.3) and many more in the pipeline, these are exciting times for patients, parents, and clinicians who treat genetic NMD. However, the rapidly expanding science of genetic treatments also raises several ethical and regulatory challenges that accompany the approval and availability of these treatments. These include the uncertain and unknown long-term effects and adverse effects of these treatments, overly optimistic and unrealistic expectations due to the hype around these treatments, the high treatment costs and consequent implications, the ramifications for newborn screening, and effects on the standard of care (King & Bishop, 2017). For instance, the phase 3 trials of nusinersen in SMA that resulted in its approval were conducted in patients who were medically stable, without scoliosis or respiratory insufficiency. Although the rationale for selection of these study populations from a trial design perspective is justified, this limits the generalizability of results to other populations with SMA (Michelson et al., 2018). The limitations of available evidence with respect to efficacy in populations not studied hitherto in clinical trials, lack of information regarding long-term efficacy and optimal treatment duration, possible differential effects in patients with varying disease severity, and, most importantly, long-term adverse effects must be acknowledged. SMN protein is universally expressed in tissues; it is uncertain whether its restoration in the central nervous system alone in SMA will produce systemic effects such as cardiac disease in the long term because the systemic SMN protein deficit is not replaced (Hua et al., 2011).

Compelling stories from families or advocacy groups may lead to unrealistically high expectations of genetic treatments. The names of trials, such as ENDEAR, CHERISH, NURTURE, etc., may have a subliminal psychological effect on parents and patients. Relationships among researchers, industry, and advocacy organizations that fund trials raise issues of conflicts of interest and the potential for misrepresenting information. Patients and families should be counseled that these treatments are not curative. They change a severe phenotype into a less severe but chronic condition necessitating ongoing treatments and management of complications of long-standing disease (King & Bishop, 2017). The lack of long-term data makes quality-of-life discussions difficult.

The cost of genetic interventions is also an ethical consideration. Medical resources are finite, and demand often exceeds availability. How, then, should resources be allocated such that each person gets their due (the ethical principle of justice)? If one patient is treated with a costly treatment instead of one that is cheaper, it is at the expense of resources available to others. This indirectly harms others who could use this resource, which goes against an ethical obligation to use health resources cost-effectively (Gyngell et al., 2020). Practically, coverage of these treatments by third-party payers remains a concern. Insurance delays and denials are not uncommon. Hospitals administering drugs such as nusinersen may balk from accepting the risk of bearing unpaid costs. Varying insurance coverage results in varying availability of treatments, raising the ethical dilemma of the

Table 11.3 Genetic Therapies for Hereditary Neuromuscular Disorders

	Trade Name	Approved Indication for Use in the United States	Gene	Treatment Class	Approved by FDA
Nusinersen	Spinraza	Spinal muscular atrophy	SMN2	Antisense oligonucleotide	2016
Eteplirsen	Exondys51	Duchenne muscular dystrophy amenable to exon 51 skipping	Dystrophin	Antisense oligonucleotide	2016
Patisiran	Onpattro	Hereditary transthyretin amyloidosis cardiomyopathy	TTR	Small interfering RNA	2018
Inotersen	Tegsedi	Hereditary transthyretin amyloidosis-peripheral neuropathy	TTR	Antisense oligonucleotide	2018
Onasemnogene	Zolgensma	Spinal muscular atrophy	SMN	Gene replacement	2019
Givosiran	Givlaari	Acute hepatic porphyrias	ALA synthase 1	Small interfering RNA	2019
Golodirsen	Vyondys53	Duchenne muscular dystrophy amendable to exon 53 skipping	Dystrophin	Antisense oligonucleotide	2019
Risdiplam	Evrysdi	Spinal muscular atrophy	SMN2	Small molecule splicing modifier	2020

ALA, •••; *FDA*, Food and Drug Administration; *SMN*, survival motor neuron; *SMN2*, survival motor neuron 2; *TTR*, transthyretin.

just distribution of care (Burgart et al., 2018). Novel solutions such as public-private research and cost-sharing partnerships have been suggested. Other proposed solutions include long-term loans and risk sharing wherein payments are linked to treatment outcomes and increasing transparency around the costs of developing gene therapies (Richardson et al., 2019).

Genetic treatments have been categorized as ex-post and ex-ante treatments. Ex-post treatments are those administered after the diagnosis is made (e.g., nusinersen treatment instituted after a diagnosis of SMA), in contrast to ex-ante treatments that prevent cases of the disorder from occurring in live-born infants. Gyngell et al. (2020) provide an excellent discussion of the ethical issues surrounding these two types of treatments, using SMA as an example. Ethical aspects in clinical genetic research are increasingly recognized and, with them, the need for guidance on these issues. The TREAT-MD European Union network of excellence established the Project Ethics Council to address ethical issues that arise in drug trials of people, especially children with NMD (McCormack et al., 2013). As more genetic treatments are brought into clinical trials, ethical issues will also evolve. The problem with using placebo controls when a treatment has already been approved and the inability to carry out phase 1 trials in healthy volunteers are some research issues that arise (Goyal & Narayanaswami, 2018). Legislative and regulatory policy will be increasingly necessary to address trial design issues, access to treatments, costs, and appropriate clinical use of these interventions.

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PART 2

TREATMENT AND MANAGEMENT OF SPECIFIC NEUROMUSCULAR DISORDERS

12 Treatment and Management of Adult Motor Neuron Diseases

Laura Rosow, MD | Catherine Lomen-Hoerth, MD, PhD

Many diseases specifically affect the motor neurons, ranging from infectious processes such as polio and West Nile viruses to hereditary conditions such as spinal muscular atrophy (SMA) and Kennedy disease (Shook & Pioro, 2009). Radiation therapy can cause motor neuron degeneration many years later, mimicking the adult motor neuron disease amyotrophic lateral sclerosis (ALS) (Glenn & Ross, 2000). Sometimes, the motor neuron degeneration remains curiously restricted to just the cervical region, such as in Hirayama disease (Zhou, Chen, Fan, & Zhou, 2010). Central nervous system (CNS) lymphoma can directly infiltrate nerve roots, mimicking motor neuron disease. When motor neuron degeneration is accompanied by an adenocarcinoma, a paraneoplastic syndrome is suspected (Rowland & Shneider, 2001).

ALS is a disease that is still little understood despite first being described in the late 1800s. It affects 1 in 100,000 people, with a slight male predominance and no ethnic or geographic preference. Incidence of ALS peaks between 60 and 75 years of age (Chiò et al., 2013). Typically, the disease is sporadic, but familial cases occur 5%–10% of the time. The most common gene mutations implicated in ALS involve the chromosome 9 open reading frame 72 (*C9orf72*) gene and the superoxide dismutase 1 (*SOD1*) gene, further discussed later in this chapter. Several other genes have been discovered, causing an even smaller proportion of familial cases (Kwiatkowski, Bosco, & Leclerc, 2009; Zou et al., 2017; Vance et al., 2009).

In ALS, weakness typically starts in a limb or less frequently in the bulbar region and progressively spreads contiguously until respiratory depression and death occur, approximately 3 to 5 years from symptom onset unless invasive ventilation is desired. Cognitive and behavioral changes can be seen as well. The range of progression is variable, and death can occur within a couple of months from the first symptom or up to decades later. Prognosis may be more favorable in pure upper motor neuron variants of ALS (Agarwal et al., 2018). Diagnosis is difficult, particularly early in the disease course, because many conditions mimic ALS, and no definitive test is available.

No available treatments significantly alter the fatal outcome of the disease; however, tremendous strides have been made in the management of symptoms through technology and medications, leading to an improved quality of life. Furthermore, ongoing research into the pathogenesis of ALS and related neurodegenerative conditions provides fertile ground for drug development. In particular, TAR DNA-binding protein, or TDP-43, found in both ALS and frontotemporal dementia (FTD), provides clues to the pathogenesis of these diseases and will hopefully lead to improved treatments in the future (Bartoletti et al., 2019). Lastly, research into stem cell therapy keeps patients and physicians hopeful that we may have a meaningful therapy for ALS even before fully understanding its underlying mechanisms (Baloh, Glass, & Svendsen et al., 2018; Rowland & Shneider, 2001)

DIAGNOSIS AND EVALUATION

Despite the lack of curative treatments available, prompt diagnosis of motor neuron disease is important to allow patients to access specialized care, enroll in clinical trials, and make plans for their future. Unfortunately, given the clinical heterogeneity of ALS and lack of a definitive diagnostic test, delay in diagnosis is all too common. In fact, the mean time from symptom onset to diagnosis has been shown to range from 10.2 to 16.1 months (Palese, Sartori, Logroscino, & Pisa, 2019). The evaluation of a potential motor neuron disease patient is primarily based on the clinical presentation (Figs. 12.1–12.3 and Table 12.1). Important features to determine what type of workup is needed include the rate of progression of the weakness, the pattern of weakness, family history, associated symptoms such as parkinsonism or dementia, and the age of onset. The degree of upper versus lower motor neuron involvement is critical to identify; the symptoms of such involvement are shown in Fig. 12.2. Once the degree of upper and lower motor neuron involvement is established and all ALS mimics are excluded, the revised El Escorial criteria can be used to establish the diagnosis (see Fig. 12.1). The different types of ALS presentations and the workup recommended in each case are described here and also diagrammed in Fig. 12.3.

FAMILY HISTORY

When there is a known family history of progressive weakness, it is important to determine the age of onset in family members, the disease duration, and the rate and pattern of the spread of weakness. It is also important to inquire about any family history of dementia or psychiatric disturbances, given co-occurrence of/pathogenetic overlap between FTD and ALS (Murphy, Henry, & Lomen-Hoerth, 2007).

Symmetric proximal greater than distal lower motor neuron weakness in the limbs and bulbar involvement that is slowly progressive may indicate Kennedy disease. This is an X-linked, trinucleotide repeat, genetic disorder that occurs in 1 in 50,000 males and involves progressive degeneration of anterior motor neurons. Androgen receptor function is impaired, the severity of this impairment correlating with

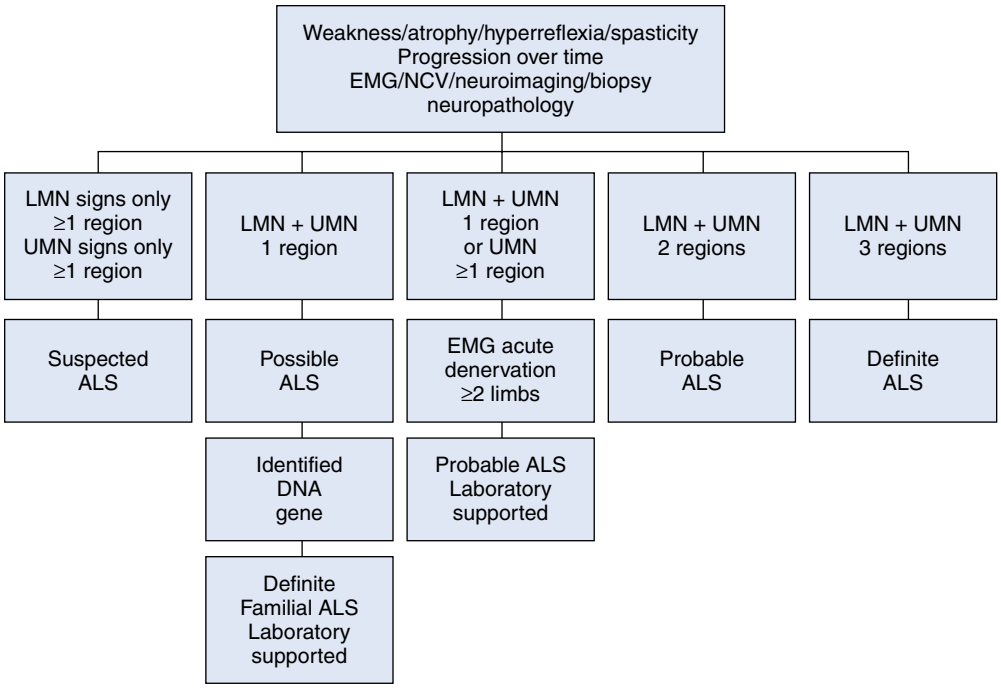


Fig. 12.1 El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *ALS*, Amyotrophic lateral sclerosis; *EMG*, electromyography; *LMN*, lower motor neuron; *NCV*, nerve conduction velocity; *UMN*, upper motor neuron. (From Brooks, B. R., Miller, R. G., & Swash, M., for the World Federation of Neurology Research Group on Motor Neuron Diseases. (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, 1*, 293-299.)

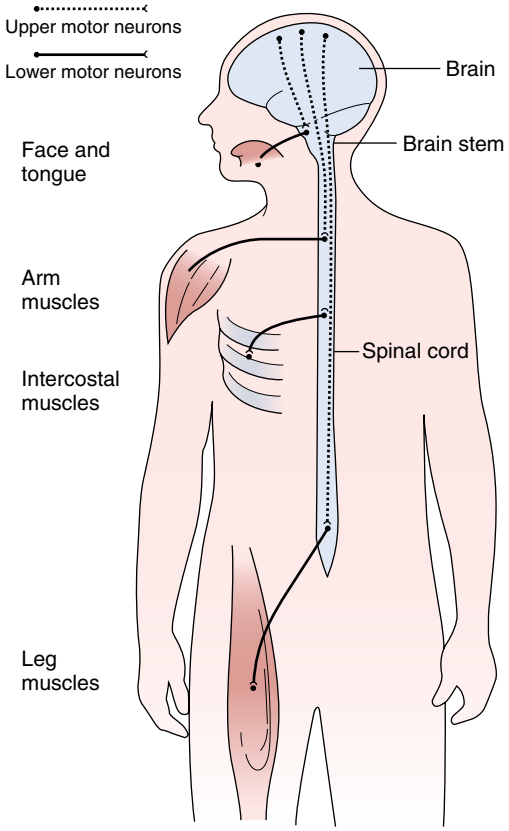


Fig. 12.2 Upper motor neuron findings include slow speech, brisk gag and jaw jerk reflexes, brisk limb reflexes, spasticity, and Hoffmann or Babinski signs. Lower motor neuron findings include atrophy, fasciculations, and weakness.

the length of the expansion of the CAG repeat within the receptor. There is also an inverse correlation between the number of CAG repeats and the age of onset of the disease. The key features include gynecomastia (in more than 50% of cases), areflexia, a subtle sensory neuropathy, and progressive, proximal greater than distal weakness in the limbs and bulbar muscles. Onset is usually in the third or fourth decade of life but may occur in the teenage years or later in life. Muscle cramps often occur years before the onset of weakness; fasciculations are common, particularly in the lower face and tongue. Creatine kinase (CK) measurements may be up to 5 times the upper limit of normal. Tremor of the limbs and chin is reported. Dysphagia and dysarthria usually occur later (10 to 20 years after symptoms start). Life expectancy in Kennedy disease is not particularly reduced unless complicated by aspiration pneumonia, so it is critical for the prognosis to distinguish this disorder from ALS. Testes may be small, and infertility is common. There can be associated diabetes (Lee, Shin, & Park, 2005; Manganelli, Iodice, & Provitera, 2007; Sinnreich & Klein, 2004). Treatment is largely based on symptoms because treatment with testosterone makes the symptoms worse (Kinirons & Rouleau, 2008). Although antisense oligonucleotide treatment shows promise in animal models of Kennedy disease, no such therapeutics have yet advanced to clinical trials (Ravi et al., 2019).

If the weakness has an onset in childhood or late adulthood and the patient has a pure lower motor neuron presentation that is predominately proximal, SMA should be considered along with familial ALS. SMA is an autosomal recessive disorder with a defect in the survival motor neuron (*SMN1*) gene on chromosome 5 (Cuscó, Barceló, & Rojas-García, 2006). It can also occur in infants, in whom it can be rapidly fatal. Due to the pattern of weakness and age of presentation, it can be difficult to distinguish from the limb-girdle muscular dystrophies without electromyographic (EMG) studies. Treatment for SMA had, for many years, been primarily supportive. However, in recent years, three different disease modifying therapies have been Food and Drug Administration (FDA) approved for treatment of SMA. Nusinersen, an antisense oligonucleotide, modifies splicing of the *SMN2* gene and promotes increased

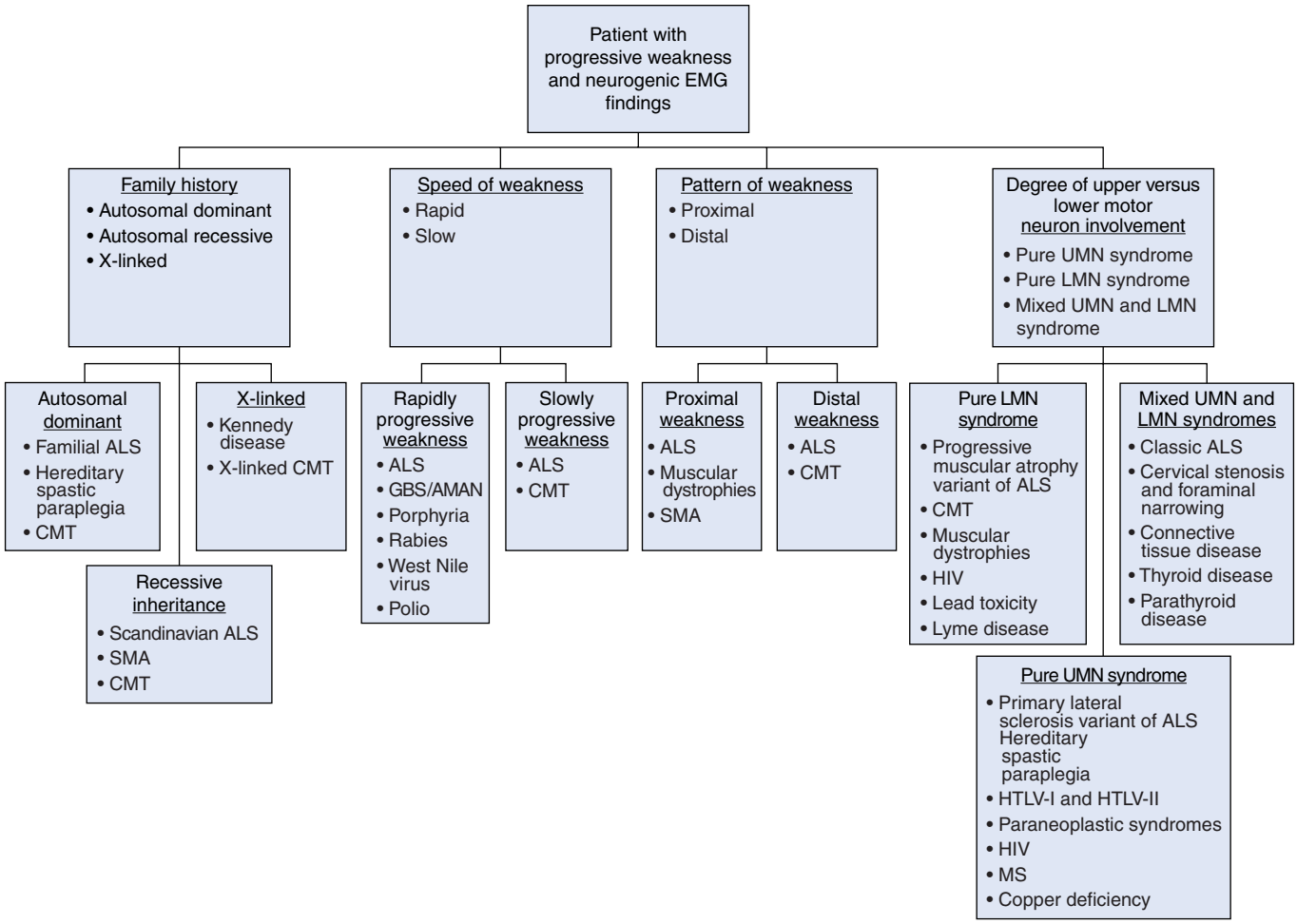


Fig. 12.3 Critical questions for the workup of possible amyotrophic lateral sclerosis (*ALS*). *AMAN*, Acute motor axonal neuropathy; *CMT*, Charcot-Marie-Tooth disease; *EMG*, electromyography; *GBS*, Guillain-Barré syndrome; *HIV*, human immunodeficiency virus; *HTLV*, human T-cell lymphotropic virus; *LMN*, lower motor neuron; *MS*, multiple sclerosis; *SMA*, spinal muscular atrophy; *UMN*, upper motor neuron.

production of full-length SMN protein, which is deficient in this condition (Finkel et al., 2017). Risdiplam, the first orally administered drug for treatment of SMA, also modifies SMN2 splicing to increase levels of functional SMN protein. This was FDA approved in 2020 for patients 2 months of age and older (Dhillon, 2020). Onasemnogene abeparvovec, a gene replacement therapy, utilizes a viral vector to replace mutated *SMN1* with normal *SMN1* and is currently FDA approved only for children under the age of 2 with biallelic mutations (Mendell et al., 2017).

Other inherited conditions that can be confused with ALS include adult-onset Tay-Sachs disease, Charcot-Marie-Tooth disease (CMT), and adult polyglucosan body disease. Adult-onset Tay-Sachs disease is caused by a mutation in the gene for hexosaminidase A and may cause upper more than lower motor neuron involvement. This disease tends to be slowly progressive; cerebellar atrophy on neuroimaging is a clue to this diagnosis. CMT can present with myriad clinical features that can be confused with those of ALS, including a mixture of upper and lower motor neuron involvement in rare cases and vocal cord paralysis. Adult polyglucosan body disease can also mimic ALS and should be included in the differential, particularly in patients of Ashkenazi Jewish background with associated dementia (McDonald, Faust, & Bruno, 1993). Commercially available genetic tests can exclude many of these possibilities. Muscular dystrophies may also be confused with ALS, particularly facioscapulohumeral muscular dystrophy (FSHD). FSHD is an autosomal dominant disorder affecting 1 in 20,000 persons. Many patients are unaware of their condition, and new mutations can also occur, making it difficult to rely on family history to help with the diagnosis. FSHD is caused by a deletion of tandem 3.3 kb repeats on chromosome 4q35. This results in the overexpression of upstream genes due to loss of binding of a transcriptional repressor protein. It is variable in severity and age of onset but is generally slowly progressive, with only about 20% of patients eventually needing a wheelchair. Typical onset is in the second or third decade, with a nearly normal or normal life span. The facial muscles are involved, causing difficulty closing the eyes, smiling, and whistling. The face can appear to be pouting. The shoulder and upper arm muscles are affected, with relative sparing of the deltoid muscles and significant scapular winging. Foot drop occurs in the scapuloperoneal variety; interestingly, the extensor digitorum brevis muscle tends to be hypertrophied rather than atrophic as in neurogenic causes of foot drop. In the arms, the extensors are also affected more than the flexor muscles. The weakness can progress slowly with periods of arrests. Asymmetry of the weakness is not unusual. EMG studies show a myopathic pattern. CK level may be normal or only mildly elevated, despite inflammation found on muscle biopsy (Dmitriev, Lipinski, & Vassetzky, 2009).

Table 12.1 Workup for Adult Motor Neuron Disease

Symptom	Workup
Pure lower motor neuron syndrome	EMG and nerve conduction studies of at least one arm and one leg, tongue, and thoracic paraspinal muscles Neuroimaging of the affected body segments Routine blood work[a] Genetic testing for Kennedy's, ALS, and SMA if familial or if clinical presentation is classic in the absence of a family history HIV test if patient has risk factors Anti-GM1 antibodies Spinal tap with fluid sent for cytology, cell count, protein, glucose, and IgG index
Pure upper motor neuron syndrome	EMG and nerve conduction studies of at least one arm and one leg, thoracic paraspinal muscles, and tongue Neuroimaging of the affected body segments Routine blood work[a] Genetic testing for hereditary spastic paraplegia if familial Spinal tap with fluid sent for cytology, cell count, protein, glucose, IgG index, HTLV-I and -II, and VDRL Serum copper Paraneoplastic antibody tests HIV test if patient has risk factors
Progressive bulbar palsy	EMG and nerve conduction studies of at least one arm and one leg, thoracic paraspinal muscles, and tongue Neuroimaging of the brain Routine blood work[a] MuSK antibody if EMG not clearly neurogenic Spinal tap with fluid sent for cytology, cell count, protein, glucose, and IgG index
Upper and lower motor neuron syndrome	EMG and nerve conduction studies of at least one arm and one leg, thoracic paraspinal muscles, and tongue Neuroimaging of the affected body segments Routine blood work[a] Genetic testing for ALS if familial

[a]Routine blood work: complete blood count, electrolytes, calcium, thyroid-stimulating hormone, vitamin B12, liver function tests, serum protein electrophoresis, immunofixation, urine protein electrophoresis, glucose, blood urea nitrogen, creatinine, creatine kinase, erythrocyte sedimentation rate, antinuclear antibody, and Lyme antibody (if in endemic area).

ALS, amyotrophic lateral sclerosis; *EMG*, electromyography; *HTLV*, human T-cell lymphotropic virus; *IgG*, immunoglobulin G; *SMA*, spinal muscular atrophy; *VDRL*, Venereal Disease Research Laboratory.

With advances in commercially available genetic testing and many testing companies offering financial assistance, genetic testing for ALS is now an option for most patients with a compelling family history. Genetic testing can assist in the diagnosis of at-risk family members, can help diagnose potential comorbidities (e.g., FTD) earlier, and can allow patients and family members to make informed decisions regarding family planning. It can also provide opportunities for patients to participate in clinical trials targeting patients with particular gene mutations, several of which are currently ongoing or in development. Over 40 ALS-causing gene mutations have been identified. Most of these gene mutations are inherited in an autosomal dominant fashion, although autosomal recessive and X-linked mutations have been described. Genetic counseling should be obtained both before and after testing, given potential profound implications for other family members. The incidence of different genetic mutations varies across different ethnic populations. In European populations, *C9orf72* mutations are most common, followed by *SOD1* gene mutations, while *SOD1* gene mutations are more common in Asian populations (Zou et al., 2017). Other gene mutations frequently implicated in familial ALS involve the TAR DNA binding protein (*TARDBP*) gene, fused in sarcoma (*FUS*) gene, FIG4 phosphoinositide 5-phosphatase (*FIG4*) gene, and (*ANG*) gene. These different gene mutations can have certain phenotypic associations. For example, patients with *C9orf72* mutations have an earlier mean age of onset and a substantially higher rate of comorbid FTD than ALS patients without this mutation (Byrne et al., 2012). The *SOD1* gene has over 180 identified mutations, with considerable phenotypic variability among them, from very rapidly progressive symptoms in the *A4V* variant to very slowly progressive with sensory involvement in the *D90A* recessive Scandinavian type. Although it is frequently requested, asymptomatic genetic testing is not covered by insurance. Because genetic testing will not identify a gene mutation in all familial cases, it is important to also screen for more common etiologies of weakness and not automatically assume that the weakness is from familial ALS rather than cervical radiculopathy, for example.

PURE LOWER MOTOR NEURON SYNDROME

When patients present with a pure lower motor neuron syndrome and no family history, it is important to still consider the differential discussed in this chapter for cases with a family history, because many patients with Kennedy disease and various muscular dystrophies are not aware of any family

history until they are diagnosed themselves. This is not necessarily due to new sporadic mutations but may be due to incomplete penetrance or undiagnosed cases that are too mild to seek clinical attention.

It is also important to consider the most common cause of lower motor neuron weakness—a polyradiculopathy. Neuroimaging of the affected areas is critical to look for this possibility. West Nile virus, Lyme disease, porphyria, diphtheria, Creutzfeldt-Jakob disease, acute motor axonal neuropathy (AMAN syndrome), and polio all cause a pure lower motor neuron syndrome, but the time from onset to deficit is much more rapid than in typical ALS, and they are usually easily distinguishable from that disorder. Botulism also presents with rapidly progressive weakness but has characteristic findings on EMG and nerve conduction studies that distinguish this entity from motor neuron disease. Monoclonal gammopathies can be difficult to differentiate clinically but can be screened by testing serum protein electrophoresis, immunofixation, and urine protein electrophoresis. Myasthenia gravis can easily be identified on nerve conduction studies with a decremental response on repetitive stimulation, and antibodies can be sent for the acetylcholine and MuSK receptors. Of note, ALS can sometimes cause decrement on repetitive nerve, particularly if rapidly progressive, and so EMG studies may still be necessary to differentiate myasthenia gravis from ALS. If an incremental response is seen on high-frequency repetitive stimulation, suggesting a presynaptic disorder, then antibodies can be tested for the calcium channel. Lambert-Eaton syndrome presents with symmetric limb weakness and decreased reflexes, which can be confusing in the differential diagnosis of a pure lower motor neuron syndrome. Myopathies and muscular dystrophies can also be differentiated based on EMG studies and muscle biopsy. Blood should be tested for the presence of human immunodeficiency virus (HIV), particularly in patients with risk factors for HIV (Shook & Pioro, 2009).

When patients with a history of polio and residual weakness in a limb present later in life with new weakness, it is important to differentiate postpolio syndrome from other neurologic processes, including superimposed ALS. Postpolio syndrome occurs in a moderately severe or severely weak limb and usually involves small changes in the degree of strength that can sometimes lead to significant functional changes. It never occurs in a limb that is full strength, is not rapidly progressive, and does not occur in patients who have never had polio or had polio and recovered fully (Halstead, 1991).

One of the most important conditions to consider in the differential is multifocal motor neuropathy with conduction block; this is a highly treatable condition that mimics ALS. Patients have fasciculations; progressive weakness, typically in the distal upper limbs; preserved or brisk reflexes; and abnormalities on nerve conduction studies to support the diagnosis. Antibodies are produced to gangliosides, such as anti-GM1, which then, it is hypothesized, cause focal demyelination of motor nerves. When nerves are stimulated electrically at multiple points, a dropoff in the amplitude of the CMAP signifies conduction block, and, ideally, this is demonstrated at a noncompressible site. Anti-GM1 levels may be elevated or normal, making it difficult to achieve a definitive diagnosis with this test. To confound the issue more, patients with a classical clinical presentation but no conduction block identified on nerve conduction studies are sometimes responsive to intravenous immunoglobulin (IVIg), the treatment most typically given in this condition, with a 94% response rate (Cats et al., 2010). In contrast to chronic inflammatory demyelinating polyneuropathy, the spinal fluid protein in a patient with multifocal motor neuropathy with conduction block is typically normal. Sometimes a 3-month trial of IVIg at 2 g/kg/month is warranted to look for a treatment response in patients with a pure lower motor neuron syndrome where conduction block is not found on nerve conduction studies but the patient otherwise fits the clinical syndrome.

Inclusion body myositis (IBM) may be mistaken for motor neuron disease, as patients often present with asymmetric limb weakness, muscle atrophy, and dysphagia. CK may be mildly elevated, as can also be the case in motor neuron disease. In more severely affected muscle groups, it is not uncommon for EMG to show a "chronic neurogenic" pattern of findings such as long duration, polyphasic motor unit action potentials, likely due to extensive muscle fiber splitting (Rosow & Amato, 2016). Certain features are helpful in differentiating IBM from motor neuron disease, including the pattern of muscle involvement (predominantly deep finger flexors and quadriceps in IBM), lack of fasciculations, and myopathic findings on EMG—particularly in less severely affected muscle groups. The diagnosis can be readily made via muscle biopsy and/or testing for anti-NT5c1A antibodies (Amlani et al., 2019). In younger patients with weakness restricted to one limb, the clinician may consider a diagnosis of Hirayama disease (also known as "cervical flexion-induced myelopathy"), a form of monomelic or focal amyotrophy. Weakness typically progresses over a period of years, then plateaus and remains restricted to the one limb. This condition most commonly involves a single arm, although it rarely may affect a single leg instead. Dynamic MRI may demonstrate asymmetric cord flattening in the neutral position and forward displacement of the dura with neck flexion (Lehman et al., 2013). Treatment is controversial, but some clinicians advocate use of a cervical collar to help prevent neck flexion that may theoretically accelerate progression of weakness (Tokumaru & Hirayama, 2001).

After all the ALS mimics are excluded, patients with a pure lower motor neuron presentation of ALS are considered to have progressive muscular atrophy variant of ALS. This condition often starts with limb weakness; sometimes these patients progress more slowly than those with typical ALS, with progression more like that seen with SMA, but other times they progress just as rapidly as typical ALS patients. Over time, these patients may develop upper motor neuron signs and bulbar involvement, changing the diagnosis to classic ALS (Berg-Vos, Visser, & Kalmijn, 2009; Kim, Liu, & Sandner, 2009). Development of these signs may change management of the disorder; for example, baclofen may be added to the treatment regimen to help with spasticity. In addition, the change in diagnosis may allow patients to be eligible for ALS clinical trials, because currently most trials exclude patients with a pure lower or upper motor neuron presentation and require a diagnosis of probable or definite ALS (see Fig. 12.1).

PURE UPPER MOTOR NEURON SYNDROME

Patients with a pure upper motor neuron syndrome need a fairly aggressive workup to exclude mimics of *primary lateral*

sclerosis, the term used for a pure upper motor neuron presentation of ALS. EMG studies should initially be performed in these patients to look for any subclinical motor neuron involvement, which might help to narrow the workup. If the EMG is normal or shows suprasegmental weakness (an interference pattern on EMG that is proportional to effort, consistent with an upper motor neuron pattern of weakness), extensive neuroimaging is critical to look for multiple sclerosis, tumor, or a compressive spinal cord lesion. Some conditions, such as spinal arteriovenous malformation or dural arteriovenous fistula, can be missed if the quality of the magnetic resonance study is poor or the neuroradiologist is inexperienced. These conditions may present with a more stepwise pattern of weakness. A lumbar puncture can help guide the workup, looking for elevated protein, IgG, and cells. The spinal fluid can also be tested for human T-cell lymphotropic virus 1 and 2 (HTLV-1 and HTLV-2), as well as syphilis with the VDRL. Serum can also be examined for the presence of HTLV-1. Copper deficiency is a very rare cause of upper motor neuron syndrome, but it can be tested by examining serum copper levels. Paraneoplastic syndromes are also important to consider; measuring antineuronal antibodies is a typical part of the workup. It is also important to assess HIV status, as with pure lower motor neuron presentations (Shook & Pioro, 2009).

Hereditary spastic paraplegia can mimic an upper motor neuron presentation of ALS and can be difficult to distinguish from that disorder. Patients with spastic paraplegia usually have an earlier age of onset and a strong autosomal dominant family history, which is helpful in diagnosis. There can also be a superimposed neuropathy and cognitive deficits, and, despite the name, arm involvement can occur. Vitamin B_{12} deficiency can cause a motor myelopathy, as can thyroid disease; these disorders can easily be ruled out with blood testing (Salinas, Proukakis, Crosby, & Warner, 2008).

As with the pure lower motor neuron presentation of ALS, patients with a pure upper motor neuron form can develop lower motor neuron involvement over time, even decades later. EMG studies at diagnosis and every 1 to 2 years can be useful in helping identify subclinical lower motor neuron involvement. This can allow patients to be eligible for clinical trials if their diagnosis changes to ALS based on their EMG results (see Fig. 12.1).

PROGRESSIVE BULBAR PALSY

Progressive bulbar palsy is a condition presenting with bulbar weakness. The differential is quite broad because patients can present with either pure lower motor neuron or pure upper motor neuron findings. Detailed neuroimaging is critical in a pure upper motor neuron presentation to look for any evidence of a structural lesion, such as stroke, tumor, or multiple sclerosis. In a pure lower motor neuron presentation, the Miller-Fisher variant of Guillain-Barré syndrome, myasthenia gravis, Lyme disease, and tumor infiltrating the cranial nerves are part of the differential. MuSK-positive antibody myasthenia gravis is particularly difficult to distinguish from bulbar ALS because patients have proximal weakness, bulbar involvement, and sometimes significant muscle atrophy. Fasciculations, however, are not present in this condition (Sanders, El-Salem, & Massey, 2003). A lumbar puncture, with a large volume of cerebrospinal fluid sent for cytology, is important to aid in the diagnosis if neuroimaging is negative. When both upper and lower motor neuron findings are present and basic blood work, neuroimaging, and lumbar puncture results are negative, there is not much utility in further evaluations, because ALS is the most likely diagnosis. However, it may take years for the disease to involve the limbs. An EMG study can be useful to document the lower motor neuron involvement in the tongue and to establish any subclinical disease in the limbs.

FLAIL ARM AND FLAIL LEG

Brachial amyotrophic diplegia, also called "flail arm" syndrome, manifests primarily as asymmetric, progressive lower motor neuron weakness that typically spreads proximally to distally. Flail leg syndrome, also known as "pseudopolyneuritic" motor neuron disease, causes asymmetric lower motor neuron leg weakness, usually starting distally and spreading upward. Both flail arm and flail leg syndromes tend to progress more slowly to respiratory involvement than typical limb-onset ALS. While median survival of limb-onset ALS patients in one research cohort was found to be 31 months, it was 66 months for patients with flail arm syndrome and 71 months for patients with flail leg syndrome (Wijesekera et al., 2009).

FACIAL-ONSET SENSORY AND MOTOR NEURONOPATHY

First reported in 2006, facial-onset sensory and motor neuronopathy is a rare variant of motor neuron disease that is characterized by gradually progressive facial-onset sensory impairment that can then go on to involve the neck, upper extremities, and trunk. Sensory abnormalities are eventually accompanied by lower motor neuron findings of atrophy, fasciculations, and weakness. Corneal reflexes will be characteristically reduced or absent. Electrodiagnostic testing is notable for delayed or absent blink reflexes, low or absent sensory responses in affected limbs, and active and chronic motor axonal changes on EMG. Extensive evaluations are often indicated to rule out disease mimics, including brain and cervical spine MRI and cerebrospinal fluid analysis (Zheng, Chu, Tan, & Zhang, 2016).

CONFOUNDING FEATURES

When patients have features in addition to those described in the revised El Escorial criteria shown in Fig. 12.1, the term used is *ALS plus* (McCluskey et al., 2014). This classification is unsatisfactory because it is not descriptive of the myriad associated findings patients can have in addition to the classic upper and lower motor neuron findings. The number of affected patients ranges from 3% to more than 50% of total patients with ALS, depending on the study published and the types of neuropsychological testing performed. The severity of frontotemporal deficits is on a continuum, with a significant proportion of ALS patients possessing a gradation of behavioral and cognitive changes (Table 12.2) (Murphy et al., 2007). Beyond being of interest for researchers, the associated cognitive and behavioral changes significantly affect survival due to their effects on compliance with treatment recommendations (Olney, Murphy, & Forshew, 2005). Obviously, before concluding that a patient has cognitive or behavioral problems due to ALS, a careful workup to exclude confounders,

Table 12.2 Axis II: Cognitive/Behavioral Characterization

Frontotemporal Lobar Degeneration with ALS			
ALS-FTD	ALS-bvFTD	ALS-dementia*, FTD-MND	ALS patient meeting either the Neary criteria (51) or Hodge criteria (2) for FTD
	ALS-PNFA		ALS patient meeting Neary criteria for PNFA
	ALS-SD		ALS patient meeting Neary criteria for SD
ALSbi			ALS patient meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria (51) or Hodge criteria (2) for FTD
ALSci			Evidence of cognitive impairment at or below the fifth percentile on at least two distinct tests of cognition that are sensitive to executive functioning
FTD-MND-like			A neuropathologic diagnosis in which FTLD is the primary diagnosis but in which there is neuropathologic evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-dementia			
		ALS-dementia (ALS-D)[a]	ALS with dementia, not typical of FTLD
	ALS-AD		ALS in association with AD
	ALS-vascular dementia		ALS in association with vascular dementia
	ALS-mixed dementia		ALS in association with a mixed dementia (e.g., AD-vascular dementia)
ALS-parkinsonism dementia complex		Western Pacific variant of ALS; Lytico-Bodig disease	ALS concurrent with dementia or parkinsonism occurring in hyperendemic foci of the Western Pacific

From Strong, M. J., Grace, G. M., Freedman, M., Lomen-Hoerth, C., Woolley, S., Goldstein, L. H., et al. (2009). Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis, 10*, 131–146, erratum in *Amyotrophic Lateral Sclerosis 10*, 252, 2009.

*Note that the term "ALS-dementia" has been used generically within the literature to imply the presence of any clinical or neuropathologic evidence of cognitive or behavioral impairment and thus appears in two synonymous categories. The participants recommend restriction of the use of ALS-dementia to refer to specific dementias.

AD, Alzheimer disease; *ALS*, amyotrophic lateral sclerosis; *ALSbi*, amyotrophic lateral sclerosis with behavioral impairment; *ALSci*, amyotrophic lateral sclerosis with cognitive impairment; *bvFTD*, behavioral variant, frontotemporal dementia; *FTD*, frontotemporal dementia; *FTLD*, frontotemporal lobar dementia; *MND*, motor neuron disease; *PNFA*, progressive nonfluent aphasia; *SD*, semantic dementia.

such as structural CNS causes, depression, nocturnal desaturations, sleep deprivation, and medication side effects, is critical. Although extensive progress has been made in developing screening studies to identify patients with cognitive and behavioral impairments in the clinic, the gold standard is still detailed neuropsychological testing and caregiver interviews.

ELECTRODIAGNOSTIC STUDIES

Electrophysiology is the key to diagnosis in many cases. As demonstrated in Fig. 12.1, the revised El Escorial criteria allow EMG findings to be included as identifying subclinical lower motor neuron involvement. Active and chronic denervation is required in at least two limbs. The denervation needs to be in at least two body segments innervated by different nerve roots in the limbs for a diagnosis of probable ALS (see Fig. 12.1). In the tongue and thoracic paraspinal muscles, this is not a requirement. EMG of the sternocleidomastoid and trapezius has been proposed to establish lower motor neuron cranial nerve involvement with greater sensitivity than the tongue muscle (Sonoo, Kuwabara, & Shimizu, 2009). Awaji criteria further allow fasciculations on EMG testing to document lower motor neuron involvement in bulbar and thoracic muscles, thereby increasing the diagnostic sensitivity of EMG in ALS (Costa, Swash, & de Carvalho, 2012). In addition to establishing the degree of lower motor neuron involvement, the EMG and nerve conduction studies are required to exclude some of the mimics of ALS, such as myopathies, myasthenia gravis, muscular dystrophies, and neuropathies such as multifocal motor neuropathy. For some conditions such as polyradiculopathy, the EMG findings are indistinguishable from those of ALS, and detailed neuroimaging is critical.

LABORATORY EVALUATIONS

The laboratory evaluations are performed based on the clinical presentation and, in some cases, with serial testing to prevent costly workups (see Table 12.1). Basic blood work is important to test in most cases, including complete blood count, CK, erythrocyte sedimentation rate, glucose, liver function tests, electrolytes, kidney function tests, thyroid-stimulating hormone, and protein electrophoresis (serum and urine). Other specialized tests can be ordered on a case-by-case basis. For example, if Kennedy disease is highest in the differential diagnosis, then the androgen receptor DNA test would be performed before ordering other tests. Rapidly progressive weakness should prompt evaluations of various infectious causes. Remember: ALS is a clinical diagnosis based on the exclusion of other causes; there is currently no direct testing that can be done to confirm the diagnosis in non-familial ALS.

HOW TO DELIVER THE DIAGNOSIS

During the evaluation process, it is important to be careful about the delivery of information to the patient and family. If the diagnosis of ALS is confirmed, the clinician should allow plenty of time for the discussion, pace the discussion appropriately based on the reactions of the patient and family, and allow opportunity for questions to be asked. At the end of the discussion, it is important to provide hope with the offer of symptomatic and experimental therapies. Handouts are useful because patients may not absorb information well after hearing the diagnosis *ALS*. It is important to provide reassurance that the doctor and management team will be present throughout the disease course, that second-opinion requests will be honored if desired, and that the disease will likely progress at the same rate without suddenly speeding up. Both the Muscular Dystrophy Association (MDA) and the ALS Association (ALSA) have many resources available for patients, including support groups, educational materials, and financial assistance for equipment needs (www.mda.org; www.alsa.org).

TREATMENT AND MANAGEMENT

DRUG THERAPIES

Treatments to slow disease progression include riluzole. This glutamate antagonist was shown in a large clinical trial with hundreds of ALS patients to slow disease progression by 10% (Bensimon, Lacomblez, & Meininger, 1994; Rowland, 1994). The dose of riluzole is typically 50 mg BID; if the patient experiences side effects of somnolence, taking one tablet at night may be sufficient. Liver function tests should be monitored at regular intervals to monitor for transaminase elevations. Patients may experience nausea and abdominal pain, and the clinician can try temporarily reducing the dose or holding the medication entirely for a period of time to see if these symptoms resolve off treatment. Taking the medication with food also typically relieves the nausea and abdominal pain and minimally reduces the absorption of the drug.

Edaravone is a free radical scavenger that is thought to reduce oxidative stress in ALS. This was shown in clinical trials to slow disease progression in certain subsets of ALS patients, primarily those with milder disease and shorter duration of illness (Writing Group & Edaravone (MCI-186) ALS 19 Study Group, 2017). This medication is given via IV over several days per month, usually necessitating placement of long-term venous access, such as a port. In certain circumstances, home infusions can be arranged, which many patients and caregivers prefer for convenience. An oral preparation of edaravone is currently under investigation, which could make this treatment substantially more accessible for patients and their caregivers.

EXPERIMENTAL TRIALS

Experimental drug trials have historically been disappointing in ALS and in other motor neuron diseases (such as Kennedy disease). A large number of potentially beneficial therapies, such as several neurotrophic factors, antioxidant agents (such as coenzyme Q_{10}), anti-inflammatory agents (such as celecoxib [Celebrex]), topiramate (Topamax), and the caspase-1 inhibitor minocycline, have had negative results or have accelerated progression in ALS (Brooks, 2009). A recent noteworthy exception is the combination of sodium phenylbutyrate and taurursodiol, drugs that mitigate endoplasmic reticulum stress and mitochondrial dysfunction. In the 6-month CENTAUR phase 2 clinic trial, this combination was found to slow the progression of ALS significantly, with the treatment group demonstrating an absolute difference of 2.32 points on the 48-point ALSFRS-R scale compared to the placebo group and an increase in ventilator-free survival of 6.5 months (Paganoni et al., n.d., 2020). Given these significant findings, the drug is currently under review with the FDA for potential approval.

More targeted therapy is possible for the familial forms of ALS where the genes are known, such as SOD1 and C9orf72. Tofersen, an antisense oligonuclerotide delivered intrathecally to decrease SOD1 protein synthesis, showed promising results in a recent phase 1–2 clinical trial (Miller et al., 2020). CSF SOD1 protein decreased in patients receiving the highest dose of tofersen in this 12-week study. While the study was not powered to demonstrate a clinical effect, patients on treatment had some slowing of the ALSFRS-R decline, which accelerated once the treatment was stopped at the end of the study. A trial using antisense oligonucleotides for patients with confirmed *C9orf72* mutations is also in progress at this time.

A particularly promising innovation in ALS research was the launch of the HEALEY ALS Platform Trial in 2020. This ongoing multisite trial utilizes specialized statistical methods to allow the simultaneous study of multiple pharmaceutical agents against one placebo control, with a goal of reducing start-up and execution times as well as study costs for any given drug. This trial format also minimizes the number of patients needing to be randomized to placebo.

In addition, basic science research is evaluating novel pathogenic mechanisms for motor neuron disease, including the possible role of inflammatory cytokine pathways and the gut microbiome. This research may provide novel therapeutic targets for clinical trials (Blacher et al., 2019; Trageser, Smith, Herman, Ono, & Pasinetti, 2019). The ALSA,

MDA, and National Institutes of Health Web sites are excellent sources for information on ongoing clinical trials for ALS (www.alsa.org, www.mda.org, and www.nih.gov). Placebo-controlled trials are important in ALS because previous trials have tested drugs that were safe in the general population, such as Topamax and minocycline, but these drugs caused decreased survival in ALS (Cudkowicz, Shefner, & Schoenfeld, 2003; Gordon, Moore, & Miller et al., 2007).

Nonpharmaceutical trials in ALS are also ongoing. In particular, early trials of intraspinal and intrathecal stem cells show promise and offer great hope for improvement of already weak muscles rather than strictly slowing down disease progression, which has been the sole focus of pharmaceutical trials in ALS (Baloh et al., 2018; Chen, Sakowski, & Feldman, 2016).

EXERCISE AND PHYSICAL THERAPY

Exercise has been shown to be beneficial for both prolonging life and improving quality of life in ALS (de Almeida, Silvestre, Pinto, & de Carvalho, 2012). A carefully constructed program is important to avoid overexercising weak muscles or underexercising strong muscles. Ideally, a physical therapist familiar with neuromuscular disease can work with the patient to help guide the exercise program at the beginning and throughout the disease process as weakness changes. Patients should be counseled that the goal of physical therapy in motor neuron disease is not to increase the strength of already weakened muscles, but to optimize mobility, retain independence, and prevent injury. Massage, water therapy, and use of recumbent bicycles are helpful adjuncts to physical therapy. Timely implementation of appropriate splints, adaptive equipment, and assistive devices can further increase mobility and independence, prevent contractures and injuries, and improve quality of life.

NUTRITIONAL MANAGEMENT

Proper nutrition in patients with ALS is important to prevent weight loss that can accelerate progression of weakness, as well as to maintain proper hydration and prevent constipation. Advances in placement of percutaneous endoscopic gastrostomy (PEG) tubes have made it possible for even those patients with low forced vital capacity (FVC) to obtain PEG tubes safely, although it is advisable to pursue PEG placement before the FVC drops below 50% if possible for maximal safety. PEG tube placement is usually recommended before patients lose weight and should be considered when swallowing or bringing food to the mouth is burdensome due to weakness (Miller et al., 2009). Advances in nutritional supplements and equipment have made maintaining weight easier even without a PEG tube (see also Chapter 4).

BREATHING MANAGEMENT

Supporting breathing with noninvasive breathing machines has prolonged survival in ALS by several months (Miller et al., 2009). Typically, these machines are recommended for patients once their breathing function declines to an FVC less than 50% or when their maximal inspiratory flow (MIF) is less than −60 cm H_2O. Most patients can acclimate to these machines over time if different interfaces are tried and saliva is well managed. In additional to inquiring about dyspnea and orthopnea, the clinician can ask about daytime somnolence, poor sleep (e.g., frequent awakenings, waking up fatigued), morning headaches, and confusion, as these may all represent sequelae of respiratory weakness and should prompt further evaluation. If spirometry testing does not qualify a symptomatic patient for noninvasive ventilatory support, additional testing can be obtained, such as supine vital capacity, sniff nasal inspiratory pressure, and nocturnal oximetry. In general, supplemental oxygen should not be utilized in ALS patients without also providing concurrent noninvasive ventilator support, as the primary ventilatory issue in ALS is typically one of hypercapnea rather than hypoxia. Daytime hypoxia is unusual in ALS and should usually prompt evaluation for pneumonia or a comorbid pulmonary condition. At the point of the FVC declining to 30% of expected, patients are presented with the choice of pursuing invasive ventilation or enrolling in hospice. If a patient does not wish to pursue invasive ventilation and is troubled by dyspnea, low-dose oral morphine can be considered for symptomatic relief. Artificial ventilation is discussed in detail in Chapter 2, and hospice is discussed in this chapter.

SYMPTOMATIC MANAGEMENT

Many ALS symptoms, including cramps, excessive saliva, spasticity, urinary urgency, pseudobulbar affect, constipation, pain, depression, and anxiety, can be managed with medications (Table 12.3). Symptomatic therapies are also appropriate for any of the motor neuron diseases. Few direct comparison studies have been done to determine the most effective medications to treat these symptoms, but a small range of drugs are typically tried (Forshew & Bromberg, 2003; Lomen-Hoerth, 2008).

Pseudobulbar affect is a condition of easy laughing and crying, which is common in ALS and is sometimes disabling. The combination drug dextromethorphan-quinidine, dosed twice daily, is quite effective in treating pseudobulbar affect (Ahmed & Simmons, 2013). If dextromethorphan-quinidine (Nuedexta®) is not available or is contraindicated, other possible treatments for pseudobulbar affect include tricyclic antidepressants such as amitriptyline and selective serotonin-reuptake inhibitors (SSRIs).

Cramps, a very common symptom in ALS, were well controlled with quinine sulfate until it was pulled from the market in the United States due to safety concerns. Tonic water contains small amounts of quinine and may be effective in patients with mild cramps. Mexiletine has been shown to cause significant improvement in cramp frequency and severity in ALS (Weiss et al., 2016). Carbamazepine and baclofen may also be effective in some cases.

Excessive saliva becomes a problem in ALS due to difficulty swallowing. It is usually treated with glycopyrrolate at first. Sublingual atropine drops are added when glycopyrrolate is no longer effective or if pills can no longer be safely swallowed. A typical dose of glycopyrrolate is 1 to 2 mg three times daily as needed. Atropine is given in 1% drops every 4–6 hours as needed. It is safe to take both medications together, but constipation inevitably occurs with these drugs. These treatments become less effective as swallowing worsens further; at that point, botulinum toxin injections into the parotid and submandibular glands are effective in drying

Table 12.3 Symptom Management in ALS

Symptom	Treatment
Sialorrhea	Amitriptyline (Elavil) 10–50 mg HS Atropine 1% solution 1–2 drops q4h Glycopyrrolate (Robinul) 1–2 mg TID Scopolamine patch Radiation therapy to the salivary glands Botulinum toxin injection (Botox) to the parotid and submandibular salivary glands
Cramps	Tonic water containing quinine Mexiletine 150 mg BID Carbamazepine 100–200 mg TID
Spasticity	Baclofen 10–30 mg TID Diazepam (Valium) 10–40 mg HS Tizanidine (Zanaflex) 4–12 mg TID Baclofen pump titrated to patient's spasticity
Urinary urgency	Oxybutynin (Ditropan) 5–10 mg BID TID Tolteridine (Detrol) 2 mg BID
Pseudobulbar affect	Dextromethorphan/Quinidine (Nuedexta®) 20 mg/10 mg BID Amitriptyline (Elavil) 10–50 mg HS
Constipation	Stool softeners, fluids, fiber, polyethylene glycol 17 g daily, and lactulose 20–40 g BID
Sleep	Bilevel positive airway pressure at least 4 hours/day Mirtazapine (Remeron) 15–30 mg HS Trazodone 50–200 mg HS Zolpidem (Ambien) 5–10 mg HS Diazepam (Valium) 10–40 mg HS
Depression	Selective serotonin reuptake inhibitors (SSRIs) varying doses Mirtazapine (Remeron) 15–30 mg HS Trazodone 50–200 mg HS
Anxiety	Lorazepam (Ativan) 0.5–1 mg q4h prn Buspirone 10–30 mg BID SSRIs varying doses

ALS, Amyotrophic lateral sclerosis; *BID*, two times day; *HS*, at bedtime; *TID*, three times a day.

up saliva (Jackson, Gronseth, & Rosenfeld, 2009). When the saliva is dried with these medications, it often becomes thick; it can be thinned by using a humidifier, increasing fluids, and taking guaifenesin (Mucinex). Mucinex is available over the counter in liquid and pill forms and can be taken up to 400 mg every 4 hours. Additional, less frequently used treatments for excessive saliva include scopolamine patches and low-dose radiation to the parotid glands (Garuti et al., 2019).

For patients with significant upper motor neuron involvement, spasticity even more than weakness can limit mobility. It is important to caution patients that relieving their spasticity may cause the legs to become too limp if that spasticity is the main factor keeping them upright. It is a delicate balance between keeping patients from being too stiff or too loose to maximize function, and it is a continuously changing problem as the disease progresses. Baclofen, diazepam, and tizanidine are the main drugs used in the management of spasticity. Diazepam is usually started at 10 mg per night and increased as tolerated. Baclofen is usually started at 5 mg TID and gradually increased until maximum effectiveness. Tizanidine has more side effects than the other two drugs and is usually started at 4 mg TID. When patients have maximized medical therapy and still have refractory spasticity, a baclofen pump is considered if felt appropriate (i.e., given the patient's functional status and rate of decline). Usually a trial is performed with intrathecal injections of increasing doses of baclofen and careful monitoring of the patient's ability to walk. A bell-shaped curve is desired to best predict response to pump placement. Sometimes, this treatment is so effective that patients can eliminate their oral medications.

Urinary difficulties in ALS typically manifest as increased urinary urgency, but it is unusual to have incontinence unless the patient cannot reach the bathroom in time due to mobility issues. Tolterodine (Detrol) and oxybutynin (Ditropan) may be prescribed for bladder control; a urinal or condom catheter may be useful for male patients. Prostate hypertrophy needs to be excluded as a cause for urinary urgency in men because treatment for that condition is very different. Frank incontinence or urine retention should be evaluated by a urologist because these are unusual for ALS.

Sleep disturbances are a major problem in ALS, with often multifactorial causes. Mobility issues prevent patients from being able to turn in bed, causing discomfort. A hospital bed with an air mattress can be helpful; more sophisticated turning beds are also available, but sometimes the only solution is having caregivers turn the patient throughout the night. In addition, difficulty breathing can cause disrupted sleep and fatigue. Breathing difficulties can be determined from FVC and MIF measurements along with the clinical history, and, if needed, a nocturnal oximetry study can be done at home during sleep to look for nocturnal desaturations. Noninvasive mechanical ventilation is an easy solution to the problem in these cases.

Sometimes, even when breathing and mechanical problems are resolved, patients may still have trouble sleeping. In these cases, sedating medications such as zolpidem (Ambien), mirtazapine (Remeron), and trazodone may be effective. Although depression rarely occurs in ALS, when present it is usually responsive to antidepressants (Kurt, Nijboer, & Matuz, 2007; Rabkin, Albert, & Bene, 2005). Anxiety may be a sign of comorbid FTD or executive dysfunction. It is best managed with behavioral therapy and SSRIs but is often hard to fully control (Kurt et al., 2007; Olney et al., 2005). Fatigue can be managed by improving sleep, conserving energy, and taking modafinil (Rabkin, Gordon, & McElhiney, 2009).

Lastly, constipation should be managed well to avoid unnecessary discomfort. It frequently occurs in ALS due to decreased fluid intake, constipating medications, and mobility issues. Initially, a high-fiber diet, hydration, and stool softeners work, but later in the disease course, stronger medications such as polyethylene glycol are often needed to maintain regular bowel movements.

EQUIPMENT MANAGEMENT

Advances in equipment for patients with ALS have been tremendous in recent years. A myriad of options for power

wheelchairs are available, including those that fold in the trunk. In addition, manual wheelchairs have become lighter and more compact. Ramps and lifts are now cheaper and more easily installed in the home for patients with stairs. Communication devices range from a simple laser pointer with an alphabet board to eye-gaze systems and even implanted brain chips. Home physical therapy and occupational therapy allow patients to receive professional guidance before remodeling their home or purchasing equipment.

SOCIAL MANAGEMENT

Social work involvement is critical for managing the financial, emotional, and physical impacts of the disease. The financial consequences of an ALS diagnosis can be severe. Patients may lose their jobs due to progressive weakness, and it is critical to connect them with all the social services for which they are eligible, such as compensation from the Veterans Administration if they are veterans, Social Security disability, Medicare, long-term care insurance, and early payout of life insurance benefits. Patients with ALS are immediately eligible for Medicare, and veterans with ALS receive full-service connection. Counseling is often beneficial to help the patient and family cope with the stress at the time of diagnosis and as the disease progresses. The time of diagnosis has been determined to be the most stressful time of the disease process. It is important to provide patients and families as many resources as possible at this critical time.

MULTIDISCIPLINARY CARE

Several studies have shown the benefit of multidisciplinary care in affecting both the quality and quantity of life in ALS (Mayadev, Weiss, & Distad, 2008; Zoccolella, Beghi, & Palagano, 2007). The typical multidisciplinary team includes a speech pathologist, communication specialist, dietitian, social worker, respiratory therapist, ALS nurse, neurologist, physical therapist, and occupational therapist. Other members of the team available as needed for consultation include a neuropsychologist, gastroenterologist, equipment specialist, and pulmonologist. Unfortunately, insurance reimbursement is not robust for coverage of these specialists, and few medical centers are able to offer comprehensive services for ALS patients. Both the MDA and the ALSA recognize those centers with comprehensive care, and details regarding the closest center can be obtained from either the ALSA or MDA Web sites.

END-OF-LIFE CONSIDERATIONS

Once the patient's FVC is less than 30% of normal, he or she qualifies for hospice, because typically life expectancy will be less than 6 months at this point. Hospice is able to provide psychological support for the patient and family as well as other services to ensure comfort.

Many hospitals now have palliative care teams that can be employed for patients desiring to die in the hospital rather than at home or for those patients whose discomfort cannot be managed easily with home hospice. Inpatient hospice is available in some areas and is a good alternative for patients who may not have the social support or resources to be able to be maintained at home during the end stages of the disease. ALS patients rarely choose long-term ventilation, mostly due to the costs of the care, which can easily be as high as $250,000 per year. If they do choose long-term ventilation, most patients do so only for a limited time, perhaps to reach a significant milestone in their family life or until the disease progresses to the point that quality of life is not optimal (see also Chapter 8).

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Treatment and Management of Spinal Muscular Atrophy and Congenital Myopathies

13

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INTRODUCTION

Although spinal muscular atrophy (SMA) and the congenital myopathies (CMs) have different etiologic features, they have similar clinical characteristics, and the decision to address them together is consistent with the similarities in the supportive management of these two groups. Advances in gene-based therapies over the last few years have significantly altered the therapeutic management and natural course of these disorders, in particular SMA. We will discuss the distinctions in medical management, as well as future directions for therapies.

Common clinical features include early onset, proximal, symmetrical weakness, hypotonia, and, in most, preserved mentation.

Some of the severe, neonatal forms of CM resemble SMA type 1. Without therapeutic interventions, respiratory support is frequently necessary for both groups and there is high rate of morbidity and mortality related to restrictive lung disease (RLD). Prior to the development of gene-based therapies for SMA, the prognosis of severe forms of CM was more favorable than that for SMA type 1. However, with treatment, the natural history of all types of SMA is changing and course of disease is more stable or less severe. There is much more to learn about the long-term outcomes of patients with SMA who have been treated with novel gene therapies.

DIAGNOSIS AND EVALUATION

SMA is an autosomal recessive neuromuscular disorder of infancy, childhood, and young adulthood. Its incidence is estimated to be 1 in 11,000 live births. SMA was first described at the end of the nineteenth century (Hoffmann, 1893; Groger, 1990), and its causative gene, *SMN1*, was discovered in 1995 (Lefebvre et al., 1995). Homozygous deletion or other mutations of the *SMN1* gene located on chromosome 5q cause degeneration of anterior horn motor neurons. 5q SMA represents 95% of all SMAs. The rest represent a heterogeneous group of disorders sharing the same involvement of anterior horn motor neurons, such as SMA with distal involvement, Kennedy disease, SMA with respiratory distress (SMARD), Hirayama disease, and juvenile amyotrophic lateral sclerosis. Clinical entities with established genetic linkage are included in Table 13.1. SMA is characterized by progressive, predominantly proximal symmetrical muscle weakness with normal sensation, depressed or absent reflexes, and preserved cognition. Prior to gene-based therapies, an acute phase of rapid decline in muscle strength was noted, followed by a phase of relative stabilization, which extended over long periods of time.

Since the initial classification in 1961 (Byers & Banker, 1961), multiple classification systems have been described. Prior to the emergence of gene therapies, the most accepted classification included types 1 to 4, and these were described based on onset of symptoms and highest motor function achieved (Iannaccone et al., 2000). This phenotypical classification may no longer apply since gene-based therapies have an effect on phenotype, prognosis, and survival. It is perhaps more useful to describe SMA type based on the ability to sit or walk, for example, "nonsitters," "sitters," and "walkers." Another possible option is a classification based on the number of copies of the SMN2 genes. Without any treatment, type 1 patients have symptom onset in the first 6 months, are unable to sit independently, have early feeding and breathing difficulties, and die by age 2 years. Pectus excavatum or carinatum, bell-shaped chest, and paradoxical breathing are common (Figs. 13.1 and 13.2). Type 2 SMA is characterized by onset between 6 and 18 months; patients sit unsupported and survive into young adulthood or later. They have proximal symmetrical muscle weakness of the lower extremities more than upper. They often present with failure to achieve the ability to walk. Type 3 patients have onset after 18 months of age, walk independently at some time, and can have normal life expectancy. Some lose ambulation by midadolescence and some develop RLD. This clinical heterogeneity was in great part explained with the discovery of the *SMN2* gene, whose transcription produces a small amount of full length (fl-) SMN protein. In general, the more copies of *SMN2* gene, the less severe and the later the onset of the disease (Mailman et al., 2002).

SMA diagnosis used to rely on electrodiagnostic studies (denervation with normal motor and sensory nerve conductions) and muscle biopsy (grouped atrophy). Currently, targeted mutation analysis is used to detect deletion of exons 7 and 8 of the *SMN1* gene and to determine the number of copies of the *SMN2* gene. A homozygous *SMN1* deletion is diagnostic. This is the initial test in an infant or child with a typical presentation and should be performed as soon as a diagnosis is suspected. SMA was added to the Federal Recommended Uniform Screening Panel for newborn

Table 13.1 Clinical Motor Neuron Entities with Established Genetic Linkage

Clinical Entity	Gene	Chromosome	Age at Onset	Clinical Features
Proximal SMA—autosomal recessive				
SMA type 0	SMN	5q13	Prenatal	Severe. Congenital heart defects. Death around 30 days.
SMA type 1	SMN	5q13	<6 months	Severe. Never sit, and fatal before age 2.[a]
SMA type 2	SMN	5q13	6–18 months	Sit independently, never walk.[a] LE predominance.
SMA type 3	SMN	5q13	>18 months	Walk independently.
Congenital with arthrogryposis	SMN	5q13	Congenital	Severe. Facial weakness, respiratory failure at birth, contractures. Death around 30 days.
SMA + congenital fractures Type 1	TRIP4	15q22	Prenatal	Severe. Pulmonary hypoplasia, congenital heart defects ± facial dysmorphisms. Death at 2 to 16 months.
SMA + congenital fractures Type 2	ASCC1	10q22	Prenatal	Severe. Pulmonary hypoplasia, congenital heart defects ± facial dysmorphisms. Death at 2 to 16 months.
SMA + myoclonus epilepsy	ASAH1	8q22	3 to 30 years	Seizures, proximal weakness, tongue fasciculations, respiratory insufficiency later in the disease.
SMA + pontocerebellar hypoplasia Type 1A	VRK1	14q32	First decade. Some prenatal	May walk but then lose ambulation. Feeding difficulties. Ataxia and nystagmus. In severe cases, death before 6 months.
SMA + pontocerebellar hypoplasia Type 1B	EXOSC3	9p11	Congenital	Muscle wasting, distal contractures, microcephaly, and oculomotor apraxia.
Spinal muscular atrophy with hypomyelination and cerebellar hypoplasia	EXOSC8	3q13	2–4 months	Severe weakness, failure to thrive, hearing and vision impairment, death caused by respiratory failure before 20 months.
Proximal SMA—autosomal dominant				
Adult	VAPB	20q13	30–60 years	Proximal LE weakness and atrophy. Fasciculations and reduced reflexes. Slow progression.
SMAJ adult onset	CHCHD10	22q11	30–70 years	Proximal > distal and abdominal weakness. Cramps and fasciculations.
Bulbar SMA with gynecomastia	?	?	Second to third decade	Asymmetric, proximal weakness + tibialis anterior. Nasal voice and tremors. Limb and tongue fasciculations.
HMN8	TRPV4	12q24	Congenital	LE weakness only; proximal > distal. Arthrogryposis ± vocal cord paresis.
HMSN-P (Okinawa type)	TFG	3q12	17 to 50 years	Symmetric proximal > distal weakness. Progression to severe disability and wheelchair.
SMA with LE predominance (SMALED 1)	DYNC1H1	14q32	Early childhood	LE weakness and wasting. Delayed walking. Decreased patellar reflexes.
Recessive X-linked SMA				
Bulbospinal SMAX 1 (Kennedy disease)	Androgen receptor	Xq12	20–40 years	Gynecomastia, bulbar involvement, hyperlipoproteinemia.
SMAX 2 Infantile	UBE1	Xp11	Neonatal—early infantile	Severe. Arthrogryposis and fractures.
Distal SMA—autosomal recessive				
SMA + diaphragm paralysis (SMARD1)	GHMBP2	11q13	Infantile	Severe. Early respiratory failure.
DHMNJ (Jerash type)	?	9p21	6–10 years	LE weakness progressing to UE. Brisk patellar reflexes and absent ankle. + Babinski earlier on.
Type 3	?	11q13	Infancy to early adult	Distal weakness progressing to proximal and truncal weakness.

Table 13.1 Clinical Motor Neuron Entities with Established Genetic Linkage—cont'd

Clinical Entity	Gene	Chromosome	Age at Onset	Clinical Features
Type 4	PLEKHG5	1p36		Generalized weakness, contractures, scapular winging, lordosis. Progresses to severe disability over a decade.
Type 5	DNAJB2 (HSJ1)	2q35	First to fourth decades	Severe, distal, LE weakness (foot drop; bulbar and respiratory weakness later in course).
Distal SMA + ataxia telangiectasia	ATM	11q22	Second decade	Distal weakness, LE > UE, resting tremor.
Distal SMA + encephalopathy	TBCE	1q42	Neonatal to 14 months	Global developmental delay, distal UE and LE weakness, spasticity, ± ataxia, ± optic atrophy. Progressive.
Distal SMA—autosomal dominant				
Calf predominant (HMN2D)	FBXO38	5p31	13–48 years	Calves, hands, and feet weakness. Slowly progressive.
SMALED2A	BICD2	9q22	Congenital	Symmetric, proximal > distal, LE > UE weakness; ankle contractures; most patients are ambulant.
Distal SMA + macular changes	FBLN5	14q32	First to ninth decades	Macular degeneration and weakness (70%).
Distal SMA + hearing loss	MYH14	19q13	4–23 years	Symmetric distal weakness, hoarseness, and hearing loss.
Scapuloperoneal neuropathy	TRPV4	12q24		Scapuloperonal and distal weakness. Laryngeal palsy.
Distal SMA—X-linked				
SMAX 3	ATP7A	Xq21	1–61 years	Distal (tibioperoneal) weakness. Hand weakness later in disease. Slow progression.
Distal SMA—mitochondrial inheritance				
MTATP6 variant syndrome	MTATP6	N/A	First to second decade	Distal, LE > UE weakness; progressive. Brisk reflexes.

DHMNJ, Distal hereditary motor neuropathy, Jerash type; *HMN8*, Distal Hereditary Motor Neuronopathy type 8; *HMSN-P*, Hereditary Motor and Sensory Neuropathy with Proximal Predominance; *LE*, lower extremities; *SMA*, spinal muscular atrophy; *SMAJ*, Spinal Muscular Atrophy, Jokela type; *UE*, upper extremities.
[a]Without treatment.



Fig. 13.1 Paradoxical breathing (www.ehealthwall.com).

screening in 2018. Currently, several states have adopted and implemented newborn screening for SMA (Cure SMA, 2020). Establishing a diagnosis early is of vital importance as the treatment outcomes are better the earlier an individual is treated. Serum creatine kinase (CK) can be normal or mildly elevated in SMA. If targeted mutation analysis detects one copy of the *SMN1* gene in an otherwise typical patient, gene sequencing is necessary as a small proportion of SMA patients (2%–5%) may have an intragenic mutation of *SMN1*. Occasional patients with double heterozygote *SMN1* point mutations are seen. *SMN1* gene sequencing should be considered in typical patients with two *SMN1* copies and negative SMARD genetic testing. If SMA genetic testing is negative, then 5q SMA is not confirmed and further genetic testing, electrodiagnostic studies, or muscle and nerve biopsies should be pursued.

CMs are a genetically and pathologically heterogeneous group of muscle disorders that share a similar clinical picture dominated by neonatal or infantile weakness and hypotonia and characteristic morphologic changes on muscle biopsy (Table 13.2). The incidence of CM is suspected to be at least 1–25,000 with core myopathies, and specifically RYR1 mutations being the most common (Amburgey et al., 2011;

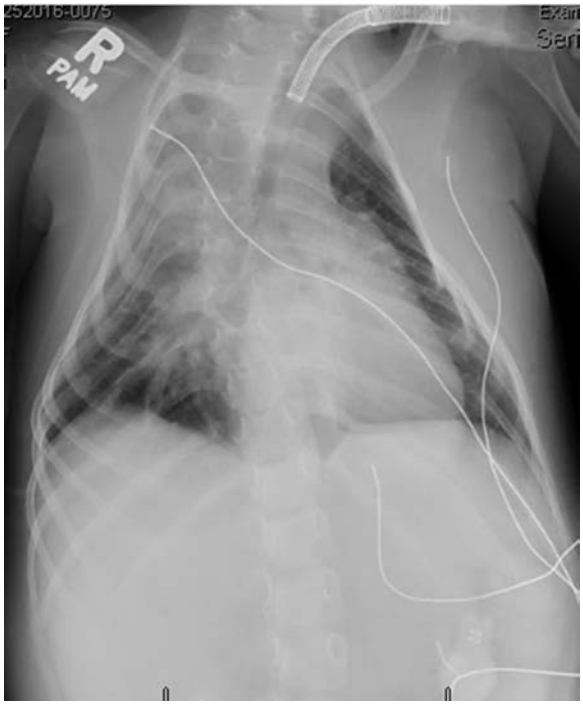


Fig. 13.2 Bell-shaped chest in a patient with spinal muscular atrophy type 1. (Courtesy Diana Castro, MD, Archive.)

Witting, Werlauff, Duno, & Vissing, 2017). Facial weakness, bulbar weakness, and ptosis are common. Ophthalmoparesis is not typical but has been described with some mutations (DMM2, MTM1, and autosomal recessive [AR] RYR1 mutations). Other common characteristics include decreased or absent reflexes, respiratory insufficiency, early feeding problems, small muscle bulk, craniofacial deformities, and spine and limb deformities. Cardiomyopathy and malignant hyperthermia are associated with some forms of CM. Sensation and cognition are typically preserved. The spectrum of severity of CM extends from fatal neonatal forms to minimally symptomatic adult forms. In severe forms of CM, symptoms can start prenatally with reduced fetal movements and polyhydramnios, leading to craniofacial dysmorphisms, arthrogryposis, or pulmonary hypoplasia (Cassandrini et al., 2017; Maggi et al., 2013). Most CMs have a nonprogressive course, although some forms may show progressive weakness.

As with SMA, the diagnosis of CM used to rely on clinical exam, history, electrodiagnostic studies, and muscle biopsy. The emergence of next-generation sequencing has led to faster and less invasive diagnosis when a myopathy is clinically suspected. Many novel genes have been discovered using this technology, and to date, there are at least 32 genes that are associated with a definitive clinical and histopathologic diagnosis of CM (Pelin & Wallgren-Pettersson, 2019).

Genetic testing yields a diagnosis in approximately 60%–80% of the clinical cases. Comprehensive neuromuscular gene panels are currently the most effective for genetic diagnosis. However, whole exome sequencing is more widely used (Pelin & Wallgren-Pettersson, 2019). Creatine kinase (CK) levels, electrodiagnostic studies, and muscle biopsy still play a role in diagnosing atypical cases, when variants of unclear clinical significance are found and need pathologic correlation, or when a genetic cause is not identified. CK levels are usually normal or slightly elevated (less than 5 times the upper limit of normal); higher levels should raise suspicion for an alternative diagnosis such as muscular dystrophy. Nerve conduction studies show usually normal sensory responses, and motor studies may show normal or low amplitude units. Electromyography shows myopathic changes. Muscle ultrasound and muscle magnetic resonance imaging can be used as a screening tool and to help differentiate between CM types. Ultrasound may be particularly useful in younger patients as it does not require sedation. The detection of pathological changes can be helpful in guiding muscle biopsy, and the description of the muscle involvement pattern might help in the differential diagnosis (Colombo et al., 2015; Wattjes, Kley, & Fischer, 2010).

A genetic diagnosis has important benefits beyond the diagnostic value. It allows for counseling for carrier status and family planning, prognosis, and risk for other organ involvement; with current gene-based therapy advances, it may help identify treatments for specific gene mutations in the future.

Traditionally, CMs have been classified by characteristic morphologic changes on muscle biopsy (Table 13.2). The most common and better described are central core disease, nemaline myopathy (NM), centronuclear myopathy (CNM), and congenital fiber-type disproportion (CFTD). The increased identification of genetic mutations causing CM has demonstrated an overlap between the different genetic changes and traditional histologic subtypes on muscle biopsy. In other words, multiple gene mutations can cause the same histologic changes, and some gene mutations can cause more than one pathologic change. Furthermore, some genetic changes are not associated with any of the classical pathologic changes. It is also now recognized that cases arising from mutations in genes traditionally associated with CM can also lead to a congenital muscular dystrophy phenotype (Cassandrini et al., 2017; Colombo et al., 2015; Pelin & Wallgren-Pettersson, 2019; North et al., 2014). In the last several years, the use of muscle biopsies has declined, decreasing the association of pathological features with specific gene mutations, and it has therefore become more common to refer to CM by its causative gene, rather than the traditional pathological changes, e.g., *ACTA1*-disease, *RYR1*-related diseases, and titinopathies.

Central core myopathies are histologically characterized by foci lacking oxidative enzymes in myofibers. These are usually seen in type 1 muscle fibers by light microscopy. They are further divided into central core and multiminicore myopathies. Most core myopathies are associated with autosomal dominant or AR gene mutations in the ryanodine receptor (RYR1) gene (De Cauwer, Heytens, & Martin, 2002; Herman, Finegold, Zhao, de Gouyon, & Metzenberg, 1999). Phenotypes are variable ranging from mild to severe, and severity of phenotype can vary within members of the same family. AR mutations are clinically more severe. Most individuals with RYR1 mutations have mild to moderate weakness with a static or slowly progressive course. Patients with this mutation may also be at risk for malignant hyperthermia. There are severe neonatal core myopathies that can present with marked joint laxity, severe weakness, muscle atrophy, respiratory insufficiency, and failure to thrive. There are some reports of cases that present with fetal akinesia and congenital arthrogryposis (De Cauwer et al., 2002).

Table 13.2 The Genetics of Congenital Myopathies

Gene	Subtype	Inheritance Pattern	Protein	Primary Subcellular Involvement	Possible Pathogenesis
ACTA 1	• Nemaline myopathy (NM) • Cap disease (NM variant) • Zebra body myopathy (NM variant) • Congenital fiber type disproportion	AD, AR AD AD AD	Actin, alpha skeletal muscle	Thin filament involvement	Abnormal thin filament structure
TPM3	• Nemaline myopathy (NM variant) • Cap disease (NM variant) • Congenital fiber-type disproportion	AD, AR AD AD	Tropomyosin 3		
TPM2	• Nemalin myopathy (NM) • Cap disease (NM variant)	AD AD	Tropomyosin 2 (beta)		
TNNTI	• Nemalin myopathy (NM)	AR	Troponin T type 1 (skeletal, slow)		
NEB	• Nemaline myopathy (NM) • Core–rod myopathy	AR	Nebulin		Thin filament remodeling ± stability
LMOD3	• Nemalin myopathy (NM)	AR	Leiomodin 3		
KBTBD13	• Nemalin myopathy (NM)	AD	Kelch repeat and BTB (POZ) domain containing protein 13		
CFL2	• Nemalin myopathy (NM)	AR	Cofilin 2 (muscle)		
KLHL40	• Nemalin myopathy (NM)	AR	Kelch-like family member 40		
KLHL41	• Nemalin myopathy (NM)	AR	Kelch-like family member 41		
MYO18B	• Nemalin myopathy	AR	Myosin 18B	Unknown	Unknown
RYR1	• Central core myopathy • Multiminicore myopathy • Core–rod myopathy • Nemalin myopathy • Congenital fiber type disproportion • Centronuclear myopathy • Congenital neuromuscular disease with uniform type 1 fiber	AD, AR AR AD, AR AR AR AR AD	Ryanodine receptor I	Triad involvement	Abnormal EC coupling
CACNASI	• Congenital fiber type disproportion	AR	DHPR		
STAC3	• Native American myopathy	AR	SH3 and cysteine-rich domain containing protein 3		
ORA11	• Tubular aggregate myopathy	AD	Transmembrane protein 142A		Abnormal SOCE
ST1M1	• Tubular aggregate myopathy	AD	Stromal interaction molecule 1		
SEPN1	• Multiminicore myopathy • Congenital fiber type disproportion	AR AR	Selenoprotein N1		Oxidative defects
CCDC78	• Centronuclear myopathy	AD	Coiled coil domain containing protein 78		Abnormal EC coupling?
BIN 1	• Centronuclear myopathy	AR, AD	Amphiphysin		Membrane remodeling ± stability.
DNM2	• Centronuclear myopathy	AD	Dynamin 2		
MTM1	• Myotubular myopathy	XR	Myotubularin 1		
MTMR14[a]	• Centronuclear myopathy		Myotubularin-related protein 14		
SPEG	• Centronuclear myopathy with dilated cardiomyopathy	AR	*SPEG* complex locus		

Continued

Table 13.2 The Genetics of Congenital Myopathies—cont'd

Gene	Subtype	Inheritance Pattern	Protein	Primary Subcellular Involvement	Possible Pathogenesis
PTPLA (=HCDA1)	• Congenital myopathy related to *PTPLA*	AR	Protein tyrosine phosphatase-like (3-hydroxyacyl-CoA dehydratase)		
TTN	• Centronuclear myopathy • Congenital myopathy with fatal cardiomyopathy	AR AR	Titin		
MYH7	• Myosin storage myopathy • Myosin storage myopathy with cardiomyopathy • Congenital fiber type disproportion	AD AR AD	Myosin, heavy chain 7, cardiac muscle, b		Abnormal ATPase and actin-binding properties Structural abnormalities
MYH2	• Myosin IIa myopathy	AD, AR	Myosin, heavy-chain 2, skeletal muscle	Heavy-chain neuromuscular junction (NJ)	Abnormal ATPase and actin-binding properties
CNTN1	• Compton-North congenital myopathy	AR	Contactin-1		Structural abnormalities Aberrant NJ adhesion?
MEGF10	• Early-onset myopathy, areflexia respiratory distress and dysphagia • Minicores	AR AR	Multiple EGF-like domains 10	Satellite cells	Abnormal regulation of satellite cells
ZAK	• Congenital fiber type disproportion	AR	Sterile alpha motif and leucine zipper containing kinase AZK	Unknown	Mitogen-activated protein kinase (MAPK) signaling pathway

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Adapted from Kaplan, J. C., & Hamroun, D. (2015). The 2016 version of the gene table of monogenic neuromuscular disorders (nuclear genome). *Neuromuscular Disorders, 25*, 991-1020.

[a]Until now *MTMR14* has been proven to produce a myopathy only in animal models.

AD, Autosomal-dominant; *AR*, autosomal-recessive; *AZK*, Sterile alpha motif and leucine zipper containing kinase; *BTB*, Broad-Complex, Tramtrack and Bric a brac; *DHPR*, dihydropyridine receptor; *EC*, excitation–contraction; *EGF*, epidermal growth factor; *POZ*, Pox virus and Zinc finger; *SOCE*, store-operated calcium entry; *XR*, X-linked recessive.

Multiminicore myopathies also have variable phenotypes with onset typically in childhood or adolescence. The most common type presents with axial weakness, scoliosis, respiratory involvement, and torticollis. The degree of weakness does not typically correlate with the severity of respiratory insufficiency (Chudley, Rozdilsky, Houston, Becker, & Knoll, 1985; Kim, Armstrong, & Fishman, 1994).

Nemaline myopathies are histologically characterized by electron-dense nemaline bodies or rods within myofibers. Variants include cap myopathy, zebra body myopathy, and core rod myopathy (Wallgren-Pettersson, 1989). Clinical phenotypes are highly variable. Most NMs present with axial and limb-girdle weakness progressing to distal muscles. Congenital forms present with facial, respiratory, axial, and proximal muscle weakness. Some present with arthrogryposis and dilated cardiomyopathy. Many patients succumb because of respiratory failure or aspiration pneumonia in the first year of life. There are some forms of NM that present with hypertonia and muscle stiffness. There are several genes associated with NM. Mutations of the Nebulin (NEB) are the most common form of recessive "typical" nemaline rod myopathy. Other genes like α-Actin (ACTA1) represent 20% of rod myopathies, usually inherited in an AR fashion, but dominant and sporadic forms have been identified (Hutchinson, Charlton, Laing, Ilkovski, & North, 2006).

Centronuclear myopathies are histologically characterized by centrally located nuclei that resemble fetal myotubules. Myotubular myopathy refers to the X-linked form and is caused by mutations in the myotubularin (*MTM*) gene. It mostly affects boys and can present in utero with polyhydramnios and decreased fetal movements (Herman et al., 1999). Boys are born with hypotonia, arthrogryposis, pronounced facial weakness, ophthalmoplegia, respiratory insufficiency, and axial muscle weakness. It has high mortality and morbidity rates from pulmonary complications in the first year of life (de Gouyon et al., 1997). Autosomal CNM myopathies have a greater genetic heterogenicity and variable phenotypes. De novo mutations have been described and have an earlier onset and more severe phenotype. Most present in childhood or adulthood with slow progression of weakness, fatigue, and exercise intolerance. Some cases of asymmetric weakness have been described. Mutations in SPEG can also cause cardiomyopathy. Individuals with some subtypes of CNM may have neuromuscular junction (NMJ)

features and respond to anticholinesterase therapy (Dowling, Gonorazky, Cohn, & Campbell, 2018).

CFTD:fiber type disproportion can be seen with several types of myopathies, central nervous system disorders, and metabolic disorders. However, the difference in caliber is typically smaller than with CFTD, which is defined by type 1 fibers being consistently smaller in diameter than type 2 fibers by more than 35% to 40% in the absence of other histopathologic abnormalities. Most CFTD myopathies are static or slowly progressive. They present with variable degrees of hypotonia, respiratory insufficiency, facial diplegia, dysphagia, and ophthalmoparesis (Mah & Joseph, 2016).

Other histologic features have been described, including hyaline body or myosin storage, neck lace fiber, radial sarcoplasmic strands, actin aggregates, cylindrical spirals, and lobulated myofibers.

TREATMENT AND MANAGEMENT

Until 2016, no treatment was available for SMA, and management consisted of supportive measures: providing adequate nutrition and respiratory support, and preventing complications of weakness. There are now three novel gene therapies for SMA, and more therapies are being studied for treatment of SMA and some types of CM. In addition to treatment with these novel therapies, symptomatic management remains a vital part of caring for patients with both SMA and CM. The goal is to manage the complications of weakness and hypotonia while maintaining quality of life (Dowling et al., 2018; Mah & Joseph, 2016; Wang et al., 2012). Management is multidisciplinary and should take place in specialized neuromuscular clinics under direct supervision of a pediatric subspecialist (usually a pediatric neurologist) with expertise in SMA and CM. Specialties involved should include orthopedics, pulmonology, and gastroenterology as well as physical, occupational, and speech therapists. Patient and parent education is paramount and should start at the time of diagnosis. Parents should be exposed to all available options of treatment and palliation and supported to make the best decisions in their particular circumstance. They should have a clinic contact number and clear guidelines for when to seek medical attention and fast access into the specialty hospital. Families should also talk to a specialist prior to major procedures that may require anesthesia, as some CMs are associated with malignant hyperthermia and/or are more sensitive to sedatives.

SYMPTOMATIC MANAGEMENT

DEVELOPMENTAL DELAY

Muscle weakness leads to developmental delay. Gross motor milestones are predominantly affected with sparing of cognitive and social skills. Fine motor skills are variably affected. With few exceptions, CMs have a stable, nonprogressive course, while regression of motor milestones is the hallmark of SMA. Regression may not be obvious in infants with type 1 SMA as no significant milestones are achieved. SMA type 2 and 3 patients lose milestones (sitting/walking) after variable periods of time. This is changing since the emergence of gene-based therapies.

Children with SMA have normal intelligence, demonstrate good social skills, and often appear more mature than their peers. Their verbal intelligence quotient (IQ) is higher than average by adolescence, probably as a compensation to their physical disability (von Gontard, Zerres, et al., 2002). With some exceptions, CM patients have normal intelligence. Proper educational placement is important. Too often, their normal intelligence is overlooked, and school placement is based on their motor handicaps. This leads to deficient education and psychological trauma in these children, who are already at high risk for low self-esteem. When in doubt, formal neuropsychological testing should be used to guide school placement. The level of education correlates with level of employment as adults (Fowler et al., 1997).

FAILURE TO THRIVE AND GASTROENTEROLOGICAL COMPLICATIONS

Thirty-seven percent of patients with SMA type 2 have weight 2 SDs below normal (Messina et al., 2008). Most of the CM patients are underweight as well, some of them severely. The main causes for failure to thrive (FTT) are dysphagia, fatigue during feeding, chewing difficulties, and limitation in mouth opening (seen especially in older patients with SMA). Other factors, including depression, hypersalivation, and poor dentition, may have a role. In older patients, weakness of the arm may affect feeding. All these factors may lead to long feeding times and decreased caloric intake. Increased effort of breathing induces increased energy expenditure. FTT exacerbates muscle weakness and increases susceptibility for infections. Greater awareness of malnutrition (low basal metabolic index, body mass index) and its deleterious effects justifies an aggressive approach with early percutaneous gastrostomy placement. Gastrostomy plays a role in increased survival in patients with SMA type 1 (Finkel et al., 2018; Iannaccone, Smith, & Simard, 2004; Mercuri et al., 2018; Messina et al., 2008).

Assessment of feeding and swallowing by a speech therapist should be considered in every child with SMA and CM. Simple questioning about change in diet, feeding time, and choking or coughing during feeding, although very important, may fail to identify dysphagia. Observing the patient during feeding can be informative. A modified barium swallow test (video fluoroscopy) is necessary for suspected dysphagia and when there is recurrent or aspiration pneumonia. Barium swallow test not only proves swallowing dysfunction and micro aspiration but also guides interventions. An upper gastrointestinal series is recommended before placement of the gastrostomy tube. Initial interventions include change in food consistency and caloric content, small frequent meals, and adjustment in positioning during and after feeding. In patients with severe swallowing difficulties, institution of an alternate feeding route is indicated (Tilton, Miller, & Khoshoo, 1998). There are currently no randomized clinical trials to evaluate the efficacy of different methods of treatment for dysphagia; current recommendations are based on expert opinion (Bach, Baird, Plosky, Navado, & Weaver, 2002; Birnkrant, Pope, Martin, Repucci, & Eiben, 1998; Mercuri et al., 2018). When conservative measures fail and high risk of aspiration persists, gastrostomy placement remains the preferred alternative. Occasionally, the older patient may choose intermittent NGT placement instead of permanent gastrostomy. Temporary NGT can be used in patients awaiting gastrostomy placement.

There is disagreement among experts about the timing of gastrostomy placement in SMA (Birnkrant et al., 1998; Hill, Hughes, & Milford, 2004; Mercuri et al., 2018). Early placement of gastrostomy tube has the advantage of better respiratory status at the time of intervention. In addition, early gastrostomy placement may prevent episodes of pneumonia or aspiration. A minimally invasive procedure, such as percutaneous endoscopic gastrostomy, is preferred. When simultaneous Nissen fundoplication is necessary, a laparoscopic approach is preferred to open surgical approach.

Delayed gastric emptying and gastroesophageal reflux (GER) are frequent in type 1 and severe type 2 SMA as well as severe CM. Frequent "spitting up" and vomiting, food regurgitation, and chest discomfort as well as frequent pulmonary infections are common presentations of GER. Fatal episodes of aspiration pneumonia are well-recognized complications in these children. Treatment of GER can be medical or surgical. Stable patients may benefit from a trial of antireflux medication (i.e., proton pump inhibitors or histamine blockers). However, a recent study reveals increased incidence of pneumonia in patients taking gastric acid inhibitors for GER disease (Canani et al., 2006). Those with severe reflux and respiratory compromise will benefit from a combined laparoscopic gastrostomy and an antireflux procedure like Nissen fundoplication. Gastric emptying can be improved with erythromycin and metoclopramide.

As a consequence of abdominal muscle weakness, hypotonia, and immobility, constipation is common in type 1 and type 2 SMA and severe forms of CM. It is usually associated with abdominal distention and bloating that together may negatively affect respiratory status. In general, constipation in SMA responds to dietary changes, increased fiber intake, and hydration. Ambulatory patients are less likely to develop constipation.

Often overlooked, xerostomia causes discomfort and predisposes to dental breakdown and can be treated with artificial saliva. Excessive salivation can be treated with glycopyrrolate and atropine.

ORTHOPEDIC DEFORMITIES

Although infrequent in young "nonsitters," scoliosis develops in a majority of type 2 and type 3 SMA patients as a consequence of weakness and immobility. The age of onset is around 4 and 9 years for the "sitter" group and "walker" group, respectively. It remains mild while the patient is ambulatory and rapidly worsens once wheelchair bound (Granata, Merlini, Magni, Marini, & Stagni, 1989). Typically, scoliosis seen in SMA is a single, C-shaped curve that predominantly involves the thoracolumbar segments (Fig. 13.3) (Kouwenhoven, Van Ommeren, Pruijs, & Castelein, 2006). As it progresses, sacrum can be involved with consequent pelvic obliquity (Evans, Drennan, & Russman, 1981). Often, scoliosis has a progressive course despite the nonprogressive weakness of many forms of CM. Scoliosis worsens RLD, impedes sitting and mobility, causes ischial bursitis, leads to back and chest wall pain, and may cause functional loss of the arm. Although there is only weak evidence that spinal orthotics slow progression, orthotics are often recommended in young patients with curves larger than 40 degrees (Sucato, 2007). Scoliosis worsens at different rates despite bracing, progressing faster (8 degrees/year) in type 1 SMA and slower (3 degrees/year) in milder cases (Merlini et al., 1989). Spinal bracing in SMA patients with type 1 and type 2 may cause decreased tidal breathing. Initial fitting with a spinal brace and subsequent adjustments should be coordinated with the pulmonary team. In order to minimize the effect on tidal breathing, spinal orthotics should have an abdominal cutout to allow free diaphragm movements.

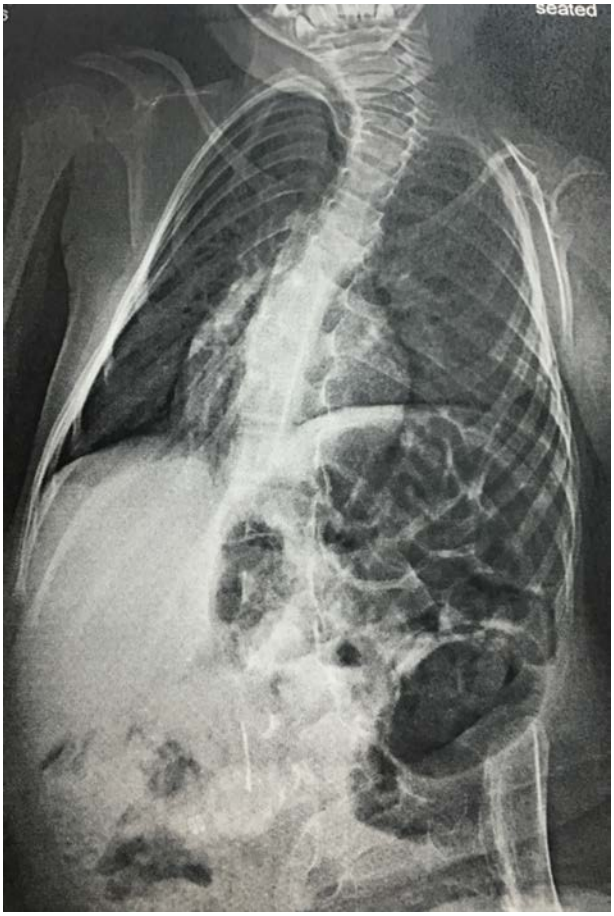


Fig. 13.3 Neuromuscular scoliosis with thoracolumbar curvature in a patient with spinal muscular atrophy type 1. (Courtesy Diana Castro, MD, Archive.)

Surgical correction of scoliosis is generally recommended once the curvature worsens to over 50 to 60 degrees (Phillips, Roye, Farcy, Leet, & Shelton, 1990). In patients with severe scoliosis, surgical intervention may have a palliative goal of relieving the pain secondary to impingements on the ribs. Preoperative evaluation should include respiratory, neurologic, and rehabilitation assessment in order to achieve the best possible functional status. Evidence exists for beneficial effects of surgical correction of scoliosis in this population (Fig. 13.4). The benefits include improved sitting balance, improved endurance (Phillips et al., 1990), improved aesthetic appearance, and an increased sense of well-being (Granata, Cervellati, Ballestrazzi, Corbascio, & Merlini, 1993). A majority of studies report a correction of 40% to 60% of the preoperative angle of curvature (Aprin, Bowen, MacEwen, & Hall, 1982; Granata et al., 1993). Respiratory function continues to deteriorate after surgery, but the rate of deterioration appears to be slower (Chng et al., 2003). With advances in noninvasive ventilation and assisted cough devices, spine surgery is relatively safe even in type 1 SMA patients. More frequent complications of spine



Fig. 13.4 Status post spinal fusion in a patient with spinal muscular atrophy type 2.

surgery include pseudarthrosis, failed correction, infectious complications, and respiratory failure. Frequently, surgical intervention in flexible patients is preceded by traction to decrease the curve as much as possible prior to surgery. Traction has a positive effect on respiratory function as well (Aprin et al., 1982). Spine surgery should be undertaken under continuous somatosensory evoked potential monitoring to avoid permanent motor dysfunction. A posterior approach with fusion and segmental instrumentation is preferred for correction of neuromuscular scoliosis. An anterior approach may be necessary in the most severe cases but requires good respiratory function (Sucato, 2007). Harrington and Luque rod instrumentation is frequently used. Fusion to the pelvis is advocated in order to prevent further worsening of pelvic obliquity. Postoperative immobilization can be avoided if new techniques of posterior segmental fixation (pedicle screw fixation, sublaminar wires) are used instead of posterior fusion and instrumentation (Mullender et al., 2008). Young children with significant scoliosis may benefit from a dual growing rod technique that allows spinal growth while maintaining the initial correction. This approach may avoid subsequent lengthening procedures (Akbarnia, Marks, Boachie-Adjei, Thompson, & Asher, 2005).

Hip dislocation is common in nonambulatory children with both SMA and CM. Age of onset varies with severity of their weakness, ranging from 3 to 4 years in nonsitters to teenage years in sitters. It can be unilateral or bilateral. Mildly affected patients can develop hip subluxation (Evans et al., 1981). A relationship of causality between pelvic obliquity and hip dislocation has not been not proved (Granata et al., 1989). Surgical correction of hip dislocation is not recommended in patients with type 2 SMA (Sporer & Smith, 2003; Zenios, Sampath, Cole, Khan, & Galasko, 2005). There is a high rate of recurrent dislocation after surgical correction in patients with SMA (Thompson & Larsen, 1990; Zenios et al., 2005). Treatment of hip dislocation in various forms of CM is not well studied, with both conservative and surgical approaches being used. In general, a more aggressive stance is needed in patients with milder disease.

Congenital clubfoot occurs occasionally in patients with genetically proven SMA as well as some CMs (Echenne, Rivier, Roubertie, & Carson, 2004; Schwentker & Gibson, 1976; Zanette, Robb, Zadra, Zanette, & Manani, 2007). A combination of serial casting and surgical repair may be effective.

Acquired equinovarus deformity is frequently seen in nonambulatory SMA patients. Type 3 SMA patients may develop equinovarus deformity that responds well to ankle-foot orthoses (Evans et al., 1981). Myotubular myopathy (MM) patients have a high incidence of equinovarus deformity, with onset from birth to 6 years. The deformity responds well to treatment with ankle-foot orthoses but may require Achilles tendon lengthening (Cahill, Rinella, & Bielski, 2007).

Large joint contractures are frequently seen in SMA and CM. The joints most frequently and severely involved are hips and knees and are directly related to the amount of time spent sitting. Upper extremity joint contractures tend to remain mild. A flexion contracture of more than 45 degrees is considered intractable. Stretching and passive range-of-motion exercises are the recommended initial intervention. However, night splints that apply tension to stretch tendons during sleep can be much more effective than passive stretch. Otherwise, surgical soft tissue release can be performed, keeping in mind that there is a significant risk of recurrence without postoperative bracing. The treatment goal should be adjusted to the patient's functional status and potential for ambulation. Because most patients are unlikely to ambulate independently, the goals should be improving sitting, preventing hip subluxations, and reducing pain.

Congenital fractures have been reported in SMA type 1 and congenital NM. Congenital fractures in SMA are secondary to intrauterine immobility, although recent studies suggest an intrinsic role of *SMN1* in bone remodeling (Shanmugarajan et al., 2007). Patients with SMA may have the lowest bone mineral density of all neuromuscular patients (Khatri, Chaudhry, Seikaly, Browne, & Iannaccone, 2008). As a consequence, SMA type 2 and 3 patients have significantly increased risk of bone fractures compared to the general population. Common locations for fractures include vertebrae, femur (with a relative risk of 15.1 when compared with the general population), lower leg, and arm. Approximately one fifth of fractures result in loss of function. The main predictor of fracture is the use of a wheelchair, consistent with the importance of ambulation for bone health (Vestergaard et al., 2001). Frequent fractures were noted in patients with MM (Cahill et al., 2007), NM, and other forms of CM.

Dual-energy x-ray absorptiometry scans can be useful for assessment of bone mineral density and identification of patients at risk for fractures (Khatri et al., 2008). However, there are still issues to be resolved regarding the validity of this test

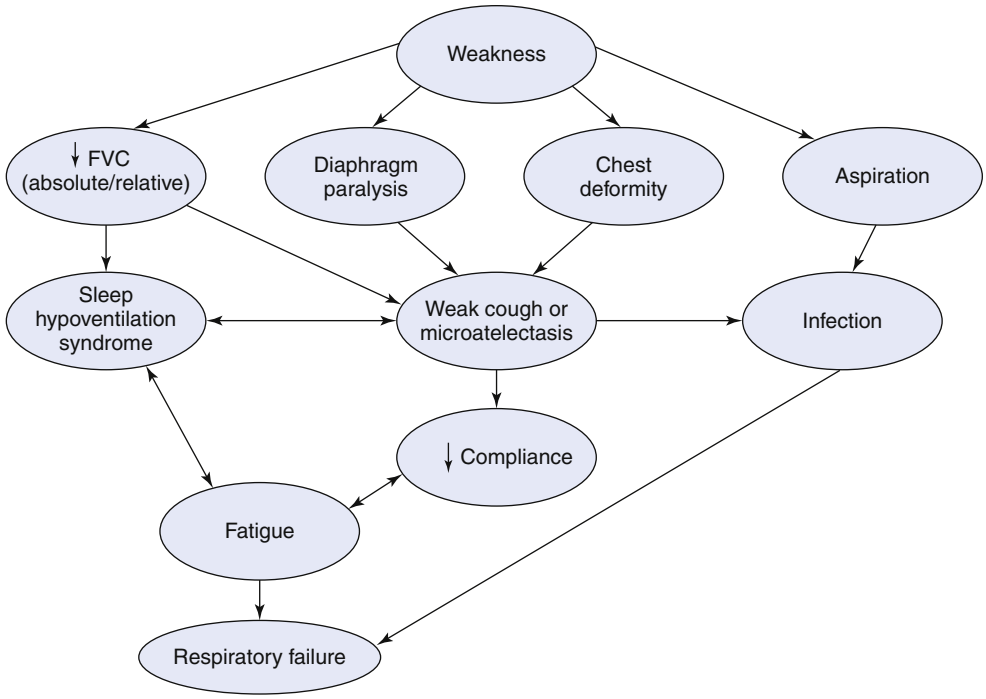


Fig. 13.5 Algorithm for pulmonary deterioration in a child with neuromuscular disease and restrictive lung disease. *FVC*, forced vital capacity.

in SMA patients. Maintaining ambulation is probably the most important factor in prevention of bone fractures, and monitoring dietary calcium and vitamin D intake is important.

FACIAL AND JAW DEFORMITIES

Craniofacial abnormalities are secondary to facial weakness. Frequently encountered deformities in CM include high, narrow palate; micrognathia; retrognathia; temporomandibular joint contracture; and open mouth. Although craniofacial abnormalities are prominent in CM, they occur in SMA as well (Houston, Buschang, Iannaccone, & Seale, 1994). The main consequences are malocclusion and jaw deformities. An open mouth and taking nothing by mouth (NPO) predispose patients to dental problems and occasionally create significant air leak that may interfere with proper mask ventilation.

PULMONARY MANAGEMENT

The past two decades have brought major technological advances for children with SMA and CM. Such advances include interfaces (masks) made of patient-friendly materials, in all sizes for all ages, as well as portable ventilators and bilevel positive airway pressure (BiPAP) and devices for airway clearance. The pathophysiology of respiratory failure in SMA is depicted in Fig. 13.5.

WEAK COUGH

Weakness of inspiratory and expiratory muscles results in ineffective cough, which may lead to atelectasis and predispose the patient to pneumonia. Cough ability is further impaired during respiratory infections (Mier-Jedrzejowicz, Brophy, & Green, 1988). Weak cough is one of the initial manifestations of RLD in patients with SMA and CM. While a peak cough flow (PCF) of 160 to 200 L/min is considered sufficient for airway clearance, a PCF of 270 L/min may be necessary to overcome cough impairment during respiratory infections (Wallgren-Pettersson, Bushby, Mellies, & Simonds, 2004).

Simple measures such as proper air humidity and good hydration decrease mucus viscosity.

Manual techniques for secretion mobilization include chest physiotherapy and postural drainage, often used together. The caregiver should be taught these techniques as well as the use of oximetry and PCF measurements to help guide therapy. Postural drainage and chest percussion remain useful, especially in young patients with SMA and CM who cannot actively participate in therapy (Langenderfer, 1998). Mechanical chest percussion devices are available, and some of them are designed for neonates and young infants (Neo-Cussor, General Physical Therapy, St. Louis, MO).

Different respiratory muscle training techniques (autogenic drainage, positive expiratory pressure therapy, and flutter valve), as well as devices that use oscillations of air column (Acapella, Smiths Medical Inc., Carlsbad, CA; and Quake, Thayer Medical, Tucson, AZ), rely on good respiratory muscle function and are unlikely to be useful in SMA and CM, except in mildly affected patients.

Augmentation of a patient's expiratory cough effort with a few abdominal thrusts provided by a caregiver improves PCF in neuromuscular patients with RLD. If, in addition, an inspiratory assist is provided, the PCF is further increased. This can be accomplished by a number of modalities (glossopharyngeal breathing, air stacking, use of Ambu-bag, or intermittent positive pressure breathing [IPPB] device). IPPB devices are scarce but can be used at home as well as in hospital and are inexpensive. At home, IPPB therapy is usually performed two to four times a day, depending on the patient's clinical status. Pressures used in one study in children varied between 22 and 40 mbar (Dohna-Schwake, Ragette, Teschler, Voit, & Mellies, 2006). Higher pressures are not recommended because of risk of pneumothorax.

Of the mechanically assisted cough devices, Cough Assist (mechanical insufflator-exsufflator [MI-E]) has gained

popularity within the SMA population and is helpful for all patients with RLD. This device provides a deep insufflation, followed abruptly by application of a negative, expiratory pressure mimicking the rate and flow of air during natural cough. MI-E was proved beneficial for both adults (Bach, 1993) and children (Miske, Hickey, Kolb, Weiner, & Panitch, 2004) with ineffective cough secondary to neuromuscular weakness. MI-E was well tolerated in children at pressures as high as 40 cm H_2O/−40 cm H_2O, with significant improvement in a number of respiratory parameters (sniff nasal inspiratory pressure, PCF/peak expiratory flow) (Fauroux et al., 2008). MI-E can be used prophylactically, but it is especially useful in the setting of infection and atelectasis. Early use can prevent hospitalizations and shorten recovery time. However, there is significant cost difference between the relatively inexpensive IPPB and MI-E. Appeals to insurance carriers are often successful in finding reimbursement for individual cases.

Other devices, such as The Vest (Hill-Rom, Batesville, IN) and Impulsator Percussionator Ventilator (IPV) (Percussionaire, Sandpoint, ID), loosen secretions in the small airways and may be helpful in preparation for assisted cough. IPV use reduced days of antibiotic requirement and hospitalization for respiratory infection in adolescents with neuromuscular disease (Reardon, Christiansen, Barnett, & Cabral, 2005).

The use of different airway clearance techniques and devices should be individualized for each patient. They should be instituted as soon as the PCF drops. Patients with mild impairment may require airway clearance only during respiratory infection, while those more affected may benefit from daily use. In hospital, these techniques must be used aggressively for treatment of any respiratory congestion. Use preoperatively, postoperatively, and at the time of extubation may be crucial.

RECURRENT INFECTIONS

As a consequence of weak cough, children with SMA and CM develop respiratory infections more frequently than people in the general population. Most episodes of pneumonia and atelectasis follow upper respiratory infections when excessive secretions accumulate and become secondarily infected. Lower lobe pneumonia is frequent. Its clinical appearance is initially mild, with only low-grade fever and tachypnea. Guidelines for treatment of acute respiratory infections in patients with neuromuscular weakness have been published (Wallgren-Pettersson et al., 2004). Aggressive therapy should be initiated at home with use of assisted cough devices. This, by itself, may prevent hospitalization (Birnkrant, Pope, & Eiben, 1999). Treatment with broad-spectrum antibiotics should be initiated early, but oral antibiotics are generally ineffective. In the hospital, the patient will require frequent clinical evaluations and continuous monitoring of oxygen saturation and blood gases. Supplemental oxygen may be necessary in the face of hypoxemia secondary to pneumonia or atelectasis. However, supplemental oxygen without ventilation should not be used without a clear indication. Careful monitoring for hypercapnia and respiratory rate is mandatory. Aggressive airway clearance should be instituted under respiratory care coordination. With persistent hypoxemia, mechanical ventilation may be necessary. First consideration should be given to noninvasive positive pressure ventilation via mask. In hospital, this is usually accomplished with a pressure-controlled ventilator with a backup rate and delivered through a face mask or nasal mask. Continuous noninvasive ventilation is initiated for patients with respiratory failure ($P_{CO_2} > 50$ mm Hg). With improvement, over several days, a slow wean of noninvasive ventilation to the premorbid level is done. Only if this fails or there are clear contraindications to noninvasive ventilation should intubation follow. The relative contraindications for noninvasive ventilation include high risk of aspiration, mental status change, life-threatening hypoxemia, and cardiac instability. Nutritional support is important in critically ill patients. Since respiratory distress increases the risk of aspiration, patients should be NPO. A nasogastric tube (NGT) or nasojejunal tube should be placed (Birnkrant et al., 1999). Some patients may require total parenteral nutrition for a few days.

ASPIRATION

Aspiration secondary to dysphagia, weak cough, and GER is a significant cause of morbidity and death in these patients. It can take the form of the life-threatening event or a silent, repeated event. Fatal aspiration can occur in the setting of mild pulmonary disease. Repeated microaspirations are often responsible for an increased incidence of chest infection. Early placement of gastrostomy tube and concomitant Nissen fundoplication is well tolerated even in children with type 1 SMA and may decrease the number of admissions and optimize quality of life (Durkin, Schroth, Helin, & Shaaban, 2008; Yuan, Wang, Trela, & Albanese, 2007). IPV has been successfully used in treatment of refractory segmental atelectasis secondary to aspiration (Birnkrant, Pope, Lewarski, Stegmaier, & Besunder, 1996).

SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (SDB) is an early and common complication of neuromuscular RLD. Early recognition and treatment of SDB improve quality of life and chance of survival (Mellies, Dohna-Schwake, Stehling, & Voit, 2004). SDB is a direct consequence of sleep-related changes: decreased muscle tone especially during the REM (rapid eye movement) stage, decrease of the respiratory drive, and increase in upper airway resistance. These changes pose a significant burden on the already limited respiratory reserve of these patients. SDB evolves over time from REM-associated hypopneas to REM hypopneas and hypoventilation and finally to non-REM nocturnal hypoventilation. Nocturnal hypoventilation will often progress to daytime hypoventilation and respiratory failure in SMA patients (Ragette, Mellies, Schwake, Voit, & Teschler, 2002). In SMA, the diaphragm is relatively spared; this is not the case in CMs, in particular NM. Involvement of the diaphragm puts patients at high risk for nocturnal hypoventilation, especially during REM sleep, when the diaphragm remains the main respiratory muscle. Occasional patients with CM may have decreased respiratory drive of central origin, independent of muscle weakness (Wilson, Sanders, & Dauber, 1987). Severe nocturnal hypoventilation with hypercapnia and cor-pulmonale was described in NM with diaphragm paralysis despite relatively normal gross motor function. Patients responded well to nocturnal noninvasive ventilation (Maayan et al., 1986).

Until recently, SDB in children was frequently overlooked and intervention delayed until after the onset of daytime hypoventilation (Guilleminault, Philip, & Robinson, 1998). New care guidelines for children with RLD include annual monitoring of forced vital capacity (FVC) and polysomnography. For young

patients who cannot cooperate with spirometry, a history of frequent chest infections, early-morning end tidal CO_2 measurement, and blood gases help in assessing the risk of SDB. FVC less than 65% predicted indicated a high risk of SDB in children with RLD. Nocturnal hypoventilation may be confirmed with polysomnography or overnight oximetry (Wallgren-Pettersson et al., 2004). If nocturnal noninvasive ventilation is started, regular, at least annual, reevaluation with overnight oximetry or polysomnography should be performed in order to assess effects and guide adjustments as the child grows. A number of CM and type 1 SMA patients will have a superimposed pattern of upper airway obstruction secondary to facial and cranial abnormalities or bulbar weakness. Fortunately, the treatment for nocturnal hypoventilation and obstructive apnea is similar. If untreated, nocturnal hypoventilation may progress to daytime hypoventilation and often causes daytime somnolence and poor school performance (Ward, Chatwin, Heather, & Simonds, 2005). Nocturnal ventilation is initiated with BiPAP. Occasionally, as patients reach late adolescence, BiPAP may be replaced by a pressure-controlled ventilator using the same interface (Iannaccone, 2007).

PSYCHOSOCIAL ISSUES

Secondary to motor deficits, wheelchair use, and dependence on respiratory technology, children with SMA and CM cannot participate in many age-related physical and social activities. Their physical, social, and school functioning is reduced with a decreased quality of life when compared to healthy children. This not only creates a degree of isolation but also represents a challenge for their self-esteem. Owing to their normal intelligence, these children are able to adapt. Normal mother-infant bonding requires close contact, nursing, and intimacy; this is often compromised in SMA infants. Stress in families affected by SMA is high secondary to a number of factors (social isolation, conflicts within family, permanent commitment to the child in need, job-related problems, and financial factors), but it does not appear to be affected by use of home mechanical ventilation (Mah, Thannhauser, Kolski, & Dewey, 2008). Interestingly, the healthy siblings of patients with SMA seem to suffer from more behavioral problems than SMA patients (Laufersweiler-Plass et al., 2003). Somewhat unexpected, depression appears to be rare in children with SMA. However, when there is loss of mobility, adolescents express disappointment (Iannaccone, 2007). In general, children and adolescents with SMA have a low rate of psychiatric comorbidity, not different from control individuals (von Gontard, Backes, et al., 2002) The most common psychiatric comorbidity was separation anxiety disorder (Laufersweiler-Plass et al., 2003). A number of studies revealed that the quality of life of children with neuromuscular disorders is higher than expected (Kohler et al., 2005; Bach, Vega, Majors, & Friedman, 2003).

CURRENT THERAPIES

SPINAL MUSCULAR ATROPHY

Over the last few years, three medications have been approved by the US Food and Drug Agency for the treatment of SMA. Intrathecal Spinraza (nusinersen), the first medication approved, in December 2016, increases the production of full-length survival motor neuron (SMN) protein by promoting the inclusion of Exon 7 in the SMN2 gene. Zolgensma (onasemnogene abeparvovec-xioi) was the second medication approved, in May 2019. Zolgensma is a one-time gene-replacement therapy (GRT) designed to deliver a fully functional copy of the human SMN gene (Fig. 13.6). The third medication, Risdiplam (Evrysdi) was approved in August 2020. This is an oral SMN2 splicing modifier, that similarly to Spinraza, increases the levels of functional SMN protein.

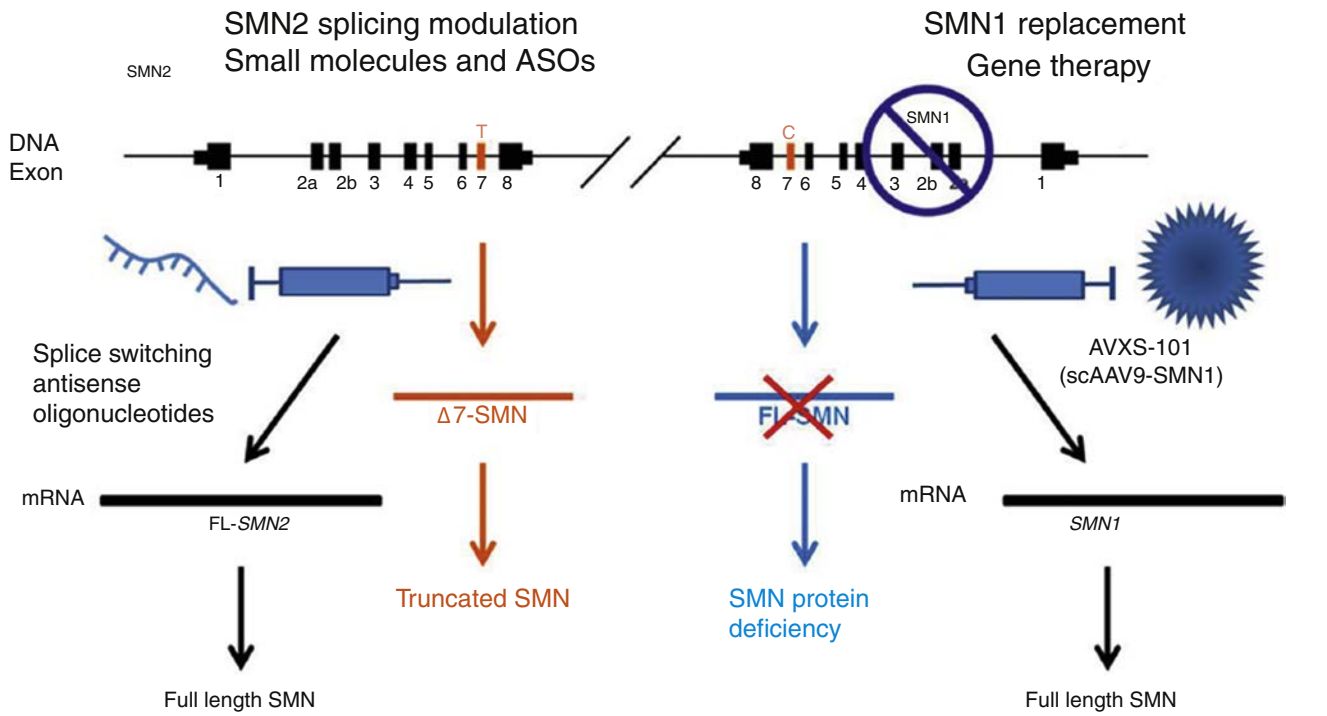


Fig. 13.6 Mechanism of action of splicing modulating agents (Spinraza) and SMN Gene Replacement Therapy (Zolgensma). *ASO*, Antisense oligonucleotide. (Reprints and permissions: www.sagepub.co.uk/journalsPermissions.nav.)

SMN1 (telomeric) and *SMN2* (centromeric) genes have a single nucleotide difference (C to T transition), which causes production of a truncated protein that lacks exon 7 (delta 7-SMN) by *SMN2*. The severity of SMA is ameliorated by *SMN2* copies. Milder cases have more *SMN2* copies (Monani et al., 1999). The *SMN2* gene produces only a small amount of full-length SMN mRNA.

Nusinersen is a 2'-*O*-methoxyethyl (2"MOE) modified antisense oligonucleotide, designed to target a heterogeneous nuclear ribonucleoprotein (hnRNP)-A1/A2–dependent splicing silencer, ISS-N1, in intron 7 of the SMNpre-mRNA. Nusinersen displaces hnRNP proteins from the ISS-N1 site on theSMN2pre-mRNA, facilitating accurate splicing of SMN2 transcripts, increasing the synthesis of transcripts containing exon 7 and resulting in increased production of full-length SMN protein (Chiriboga et al., 2016).

Nusinersen has been studied in a wide population of patients with SMA, including presymptomatic infants (NURTURE), symptomatic infants <6 months of age (ENDEAR), and symptomatic SMA type 2 and 3 (CHERISH). Currently, there are two ongoing trials, NURTURE for presymptomatic and SHINE, which compiled all the patients from ENDEAR and CHERISH, for long-term follow up.

ENDEAR was the pivotal study for the approval of nusinersen. This was a multicenter, randomized, double-blind sham-procedure control, phase III study in 121 patients younger than 6 months with symptomatic infantile onset SMA, most likely to develop SMA type 1. Patients randomized to treatment (81) received an intrathecal injection of 12 mg on days 7, 15, 29, 64, 183, and 302. The primary endpoints were motor-milestone response (by Hammersmith Infant Neurological Examination [HINE]) and event-free survival (time to death or use of permanent ventilation).

The secondary endpoints included the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Compound Motor Action Potentials (CMAP).

The HINE evaluates the overall neurologic function in infants. Section 2 of the HINE (HINE-2) measures the attainment of motor milestones (Bishop, Montes, & Finkel, 2018; Haataja et al., 1999). The patients were categorized as responders if they met the following two criteria: improvement in at least one category (increase in the score for head control, rolling, sitting, crawling, standing or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening (Finkel et al., 2017).

An interim analysis showed that a higher percentage of infants treated with nusinersen, 21 of 51 (41%), had a motor milestone response compared to the ones in the sham group, 0 of 27 (0%). The trial was terminated, and all the patients were treated with nusinersen. The final analysis showed a higher percentage of responders in the treated group, 37 of 73 (51%) vs. 0 of 37 (0%) in the sham group.

Event-free survival was higher in the nusinersen group than in the sham group. Death or need for permanent ventilation (tracheostomy or >16 hours a day of ventilation) occurred in 39% of the infants treated with nusinersen and 68% in the control group.

Adverse events were similar in the two groups. The most common adverse event was fever and respiratory infections (Finkel et al., 2017).

NURTURE is a multisite, open-label, single-arm, phase II study in 25 presymptomatic infants less than 6 weeks of age at first dose. Fifteen of these patients had two copies of SMN2 and 10 had three copies of SMN2. At this interim analysis, the median age was 34.8 months of age. All patients were alive, and none required permanent ventilation or tracheostomy. All the patients achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently (De Vivo et al., 2019).

These two studies, as well as the long-term follow up (SHINE), demonstrate the efficacy and safety of nusinersen for the treatment of SMA. Currently, nusinersen is approved for the use in pediatric and adult patients with SMA type 1, 2, or 3.

Initial loading dose with 12 mg of nusinersen occurs at 2-week intervals for the first three doses and the last loading dose 1 month after the third dose. After this loading period, the patient receives nusinersen 12 mg intrathecally every 4 months for their lifetime.

The second approved therapy is Zolgensma (onasemnogene abeparvovec-xioi). Zolgensma is an intravenous one-time GRT based on a nonreplicating recombinant adeno-associated virus serotype 9 (AAV9) containing the human SMN gene.

AVXS-101 was the pivotal study for the approval of onasemnogene. This was an open-label, single-center, phase I–II study in 15 infants with SMA type 1 less than 6 months of age. Participants were divided into two cohorts that received either 6.7 e13 vg/kg (3 patients) or 2.0 e14 vg/kg (12 patients), delivered as a single intravenous administration. Patients were treated with prednisone 1 mg/kg the day before the infusion and 30 days after the therapy administration. The primary endpoint was safety and the secondary endpoint was time between birth and death or time to permanent ventilation (more than 16 hours a day of non-invasive ventilation or tracheostomy) (Mendell et al., 2017).

The exploratory outcomes included motor function by CHOP INTEND and motor milestones compared to historical cohorts. By the end of the study (2014–2017), all 15 patients were alive and event free, compared to only 8% survival in historical controls. CHOP INTEND scores improved from baseline (9.8-point increase at 1 month and 15.4-point increase at 3 months, mean baseline scores for the low cohort was 16 and for the higher cohort was 28).

Of the 12 infants treated with the higher dose, 11 were able to sit without support, 9 could roll over, 11 could feed orally and speak, and 2 walked independently.

Side effects included increased aminotransferase levels, controlled with oral prednisone.

Other studies include STR1VE, an open-label, single-arm, multicenter, phase 3 study for symptomatic patients with SMA type 1 less than 6 months of age. This study enrolled 22 patients. SPR1NT was open-label, single-arm, multicenter, phase 3 study for presymptomatic patients with two or three copies of SMN2 and younger than 6 weeks of age. This study also enrolled 22 patients (10 with two copies of SMN2 and 12 with three copies of SMN2).

STRONG is a phase 1/2a study for children with three copies of SMN2, able to sit independently for more than 10 seconds per World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) criteria but cannot stand or walk independently. Patients were divided in three cohorts (dose A: low dose, dose B: mid dose, and dose C: high dose). Participants received the medication intrathecally instead of intravenously.

The most recent approved medication (August 2020) for SMA patients 2 months and older is Evrysdi (Risdiplam). Risdiplam is a centrally and peripherally distributed oral SMN2

Table 13.3 Current Clinical Trials

Clinical Trials.Gov Identifier	Sponsor	Study	Drug	Phase	Type/Status	Description
NCT03032172	Hoffmann-La Roche	A study of RO7034067 in adult and pediatric participants with SMA (Jewelfish)	Risdiplam	II	Interventional Active Not recruiting	Multicenter, exploratory, noncomparative, and open-label study to investigate the safety, tolerability, PK, and PK/PD relationship of risdiplam in adults, children, and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime, or AVXS-101.
NCT03779334	Hoffmann-La Roche	A study of risdiplam in infants with genetically diagnosed and presymptomatic SMA (Rainbowfish)	Risdiplam	II	Interventional Active recruiting	Open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK/PD of risdiplam in infants aged from birth to 6 weeks who have been genetically diagnosed with SMA but are not yet presenting with symptoms. There will be a screening, treatment, open-label extension (OLE) phase, and a follow-up period for any participants who withdraw early. All participants will receive risdiplam orally once daily for 2 years followed by an OLE phase of at least 3 years (with a follow-up of 1 year for those participants who withdraw early), with a total treatment duration of at least 5 years for each participant enrolled.
NTC03921528	Scholar Rock, Inc.	Active treatment study to evaluate the efficacy and safety of SRK-015 in patients with later-onset SMA (TOPAZ)	Anti-pro myostatin monoclonal antibody (mAb)	II	Interventional Active Not recruiting	Multicenter study to evaluate the efficacy and safety of SRK-015 in patients with later-onset SMA. Three cohorts. Active treatment, randomized, double blind for cohort 3.
NCT03819660	Catalyst Pharmaceuticals, Inc.	Long-term safety study of amifampridine phosphate in ambulatory patients with SMA type 3	Amifampridine phosphate	II	Interventional Active Enrolling by invitation	Open-label, long-term safety study is designed to evaluate the safety of amifampridine phosphate in ambulatory patients diagnosed with SMA type 3 over an extended period. The study is planned to include approximately 12 male and female SMA type 3 patients. The planned duration of participation for each patient may be up to 1 year. Patients must have demonstrated benefit during the initial SMA-001 trial.

pre-mRNA splicing modifier than increases levels of functional SMN protein. Risdiplam's safety, tolerability, and efficacy have been studied in more than 450 patients with SMA types 1, 2, and 3.

FIREFISH is a two-part, multicenter, open-label trial of infantile-onset SMA (SMA type 1). Part 1 was the exploratory, dose-finding portion, which enrolled 21 patients between 3 and 7 months of age at the start of treatment. In this part, efficacy was also established on the ability to sit without support for at least 5 seconds as measured by Item 22 of the BSID-III gross motor scale and on the basis of survival without permanent ventilation.

In part 1, 41% (7/17) achieved the ability of sitting without support for more than 5 seconds, and 90% (19/21) were alive and without permanent ventilation at 12 months.

Part 2 enrolled 41 patients, and the primary endpoint was achievement of a motor milestone at 12 months, as measured by Item 22 of the BSID-III gross motor scale.

SUNFISH is a two-part, randomized, multicenter, placebo-control trial of later-onset SMA (types 2 and 3). Part 1 was an exploratory, dose-finding portion and included both ambulatory (14% [n = 7]) and nonambulatory patients (65% [n = 33] sitters and 21% [n = 11] nonsitters). Part 2 (n = 180) was the confirmatory portion and included nonambulatory patients who had mild to severe scoliosis (67% [n = 120] total), 32% (n = 57) of whom had severe scoliosis. Participants were randomized 2:1 to receive either the recommended dose of Risdiplam established in Part 1 or placebo for 12 months before switching to Risdiplam. The primary endpoint was mean change from baseline in motor function score at 12 months, as measured by MFM-32.

The patients randomized to Risdiplam had a 1.36-point increase, compared to the patients randomized to placebo who had a 0.19-point decrease in the MFM-32 scale.

Other therapies, currently in clinical trials, are summarized in Table 13.3. This includes oral small molecules to modified SMN2 splicing, myostatin inhibitors, and medications acting in the NMJ, like amifampridine (NIH, 2020).

CONGENITAL MYOPATHIES

Progress in experimental therapies for CMs is hindered by the great genetic heterogeneity.

Two interventional studies in CMs have been completed or are actively enrolling.

The first one was to investigate the efficacy of *N*-acetylcysteine (NAC) in decreasing elevated oxidative stress and increasing physical endurance in patients with ryanodine receptor 1-related myopathies (RYR1-RM). There was an initial 6-month natural history assessment of 37 patients followed by a 6-month randomized, double-blinded, placebo-controlled trial. Sixteen participants were randomized to NAC (adult dose: 2700 mg/day; pediatric dose: 30 mg/kg/day), and 17 participants to placebo. The primary endpoint was urine 15-F2t isoprostane concentration and the coprimary endpoint was 6-minute walk test (6MWT) distance.

Patients with RYR1-RM had elevated baseline 15-F2 isoprostane concentrations and decreased 6MWT distance. NAC treatment did not improve 6MWT distance or 15-F2t isoprostane concentration, which means it did not improve oxidative stress. NAC was well tolerated (Todd et al., 2020).

The second study evaluated gene transfer therapy for X-linked myotubular myopathy (XL-MTM). This is a phase 1/2, randomized, open-label, ascending-dose, delayed treatment concurrent control clinical study evaluating the safety and efficacy of intravenous AT132, an AAV8-delivered gene therapy. This study is currently enrolling patients with XL-MTM aged less than 5 years. The study is being conducted in two parts. Part 1 is a dose escalation phase to evaluate the safety and efficacy of AT132 at doses of 1 × 1014 vg/kg and 3 × 1014 vg/kg. Part 2 is a pivotal expansion cohort to confirm the safety and efficacy of AT132 at a dose of 3 × 1014 vg/kg (NIH, 2020).

CONCLUSION

SMA and CM are incurable disorders that affect children more than adults. Recent advances in clinical management may improve quality of life and survival for many patients.

The approval of effective therapies for SMA is radically changing the landscape. New issues are now emerging, like treatment cost, reimbursement, and poor understanding from patients and families about these therapies being disease modifiers but not cure. Standard of care is essential for the success of these therapies; new phenotypes are now emerging with entirely new complications and comorbidities.

It is very likely that combination therapies providing SMN-directed and SMN-independent treatments are going to be the best approach in the future.

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14 Treatment and Management of Hereditary Neuropathies

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OVERVIEW OF INHERITED NEUROPATHIES

Hereditary neuropathy remains a major cause of neuropathy in patients referred to tertiary centers, estimated to represent 25% to 40% of all causes of neuropathy. With a prevalence of 1 per 2500, Charcot-Marie-Tooth (CMT) is the most common inherited neurologic disorder, affecting approximately 150,000 Americans. The advent of next-generation sequencing technologies and its use in gene discovery and primary diagnosis has sustained an explosion in the number of genes and alleles associated with hereditary neuropathy. The characterization of genetic mutations underlying these familial diseases has led to an understanding of disease pathogenesis and has heralded a new era of rational targeted therapies. Recent Food and Drug Administration (FDA) approvals of biologic therapies for spinal muscular atrophy (SMA) and hereditary transthyretin (hTTR) amyloidosis have energized patients, advocacy groups, physicians, and drug developers and have spurred interest in a wide range of hereditary neuromuscular diseases without approved therapies. While targeted therapies still benefit only a small subset of inherited neuropathy patients, most patients benefit from symptomatic therapies and referral to specialists with expertise in treating hereditary neuropathy.

In this chapter, we will take a practical approach to caring for patients with familial neuropathy. We will discuss the clinical presentation, diagnosis, and treatment of these diseases. We will cover both disorders specifically affecting peripheral nerves (referred to as *nonsyndromic inherited neuropathies*, listed in Table 14.2) and systemic genetic disorders in which peripheral neuropathy is a major clinical feature (referred to as multiple system-inherited or *syndromic neuropathies*, listed in Table 14.3). We will first consider the hereditary motor and sensory neuropathies (HMSNs), also called CMT disease, and hereditary sensory and autonomic neuropathies (HSANs), summarized in Table 14.2. Since there is considerable overlap between hereditary motor neuropathies (HMNs) and motor neuron diseases, these disorders will be briefly discussed here, and specific management of motor neuron diseases is discussed in Chapters 12 (amyotrophic lateral sclerosis [ALS]) and 13 (SMA). As shown in Table 14.3, the list of *syndromic neuropathies* is long, and we will focus on inherited syndromes in which neuropathy is a primary feature and in which specific treatments are available or in the clinical pipeline: familial amyloid polyneuropathy (FAP), Friedreich ataxia (FRDA), Fabry disease, metachromatic leukodystrophy (MLD) and Krabbe disease, X-linked adrenomyeloneuropathy, Refsum disease, and porphyric neuropathy.

To lay a foundation for our disease-focused discussions, we will discuss targeted therapies and their treatment paradigms and give examples of early successes in the clinic. The list of genetic causes of neuropathy is continuously expanding, making their molecular diagnosis increasingly subspecialized (see Tables 14.2 and 14.3). The online database OMIM (Online Mendelian Inheritance in Man, Johns Hopkins University School of Medicine, www.omim.org) is an extremely useful reference for clinicians; it is a publicly funded, up-to-date, searchable database in which a physician can enter a patient's clinical findings and potential inherited diseases can be rapidly identified. As more variants are identified in the clinic, the shared resource ClinVar can sometimes help determine whether variants of undetermined significance have been associated with the same phenotype in other families; the Inherited Neuropathy Variant Browser is a CMT-focused effort to do the same (http://hihg.med.miami.edu/code/http/cmt/public_html/#/).

DIAGNOSIS OF INHERITED NEUROPATHIES

Treatment of inherited neuropathy relies on making the correct diagnosis. Far too often, patients are started on expensive and potentially harmful immune therapies for unrecognized inherited neuropathies. Distinction between inherited and acquired neuropathies is therefore paramount. Clinical recognition of inherited peripheral neuropathy includes defining the time course of the illness, determining which fiber types are affected, characterizing the distribution of symptoms, determining electrophysiologic pattern (demyelinating or axonal), obtaining family history, and searching for risk factors for acquired causes of peripheral neuropathy. The key differentiating historical and diagnostic features between inherited and acquired peripheral neuropathies are outlined in Table 14.1. Rather than merely asking general questions as to whether family members have neuropathy or similar symptoms, patients should be asked if their parents or siblings had foot deformities, remained mobile or were confined to a wheelchair, or dragged their feet when they walked. When possible, family members should be interviewed and examined and, if appropriate, should have electrodiagnostic studies performed.

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Table 14.1 Distinguishing Features of Inherited and Acquired Neuropathies

	Inherited	Acquired
Time course *Onset and progression*	Long-standing (several years), slow progression	Acute, subacute, or chronic (~months–years)
Distribution *Symmetric* *Distal, proximal* *Unusual sites—vocal cords, phrenic nerve*	Symmetric; distal > proximal; presence of foot deformities	Symmetric or asymmetric; may have similar proximal and distal involvement
Fiber types *Sensory—small fibers* *Sensory—large fibers* *Motor* *Autonomic*	Motor > sensory; sensory signs > sensory symptoms	Depends on etiology; commonly sensory > motor
Electrophysiology *Axonal* *Demyelinating* *Uniform* *Entrapment sites* *Conduction block*	Axonal or demyelinating; findings uniform from segment to segment and between adjacent nerves Physiology often worse than clinical phenotype	May be axonal or demyelinating; may be uniform or nonuniform Severity of physiological findings generally correlates with clinical phenotype
Family history	Positive	Negative; although family members may have diabetic, alcohol-related, or other acquired neuropathies

Most inherited neuropathies are long standing (often with onset during childhood or adolescence) and slowly progressive over years. Involvement of motor fibers is usually greater than sensory fibers, and sensory symptoms are often minimal despite marked sensory findings on examination and electrophysiology. Findings are usually symmetric with greater distal than proximal involvement. Musculoskeletal malformations that are the result of long-standing distal neuropathy can include high arches, hammer toes, and clawed hand. Characteristic electrophysiological findings include uniform length-dependent demyelinating or axonal findings on nerve conduction studies (NCSs).

TIME COURSE

While HMSN and CMT are characteristically symmetric and slowly progressive, it is important to recognize that not all inherited neuropathies fit this pattern. Patients with hereditary neuropathy with liability to pressure palsies (HNPPs) may present with acute onset of recurrent painless, focal neuropathy at usual sites of entrapment (median at wrist, ulnar at elbow, and peroneal at knee). Similarly, patients with hereditary neuralgic amyotrophy (HNA) (caused by mutations in *SEPTIN9*) may present with acute onset of pain and weakness localizing to the brachial plexus of one arm. Patients with SCN9A-related inherited erythromelalgia may have pain, redness, warmth, and swelling in the feet occurring in an episodic manner. Acute intermittent porphyria (AIP) (caused by mutations in *HMBS*) may present with acute onset of weakness in the arms and legs, along with abdominal pain and mental status changes. There can be episodic worsening in the distribution of affected nerves during attacks. Genetic variants can cause neuropathy through many divergent mechanisms, and it is fitting that there is a wide range of presentations.

DISTRIBUTION

Most inherited neuropathies present with length-dependent symmetric sensorimotor symptoms and signs. However, onset in hands, vocal cord paresis, deafness, optic atrophy, and non-length-dependent sensory ataxia may be the presenting symptoms. These atypical features can suggest specific genetic causes (Table 14.2).

FIBER TYPES

Most inherited neuropathies involve sensory and motor fibers in a length-dependent manner (HMSN). However, pure motor neuropathies (dHMN), small fiber neuropathies (hereditary sensory neuropathy [HSN]), pure sensory large fiber neuropathies (ataxic neuropathies), small fiber sensory neuropathies (Fabry, amyloidosis, inherited erythromelalgia), autonomic neuropathies (HAN), and sensory and autonomic neuropathies (HSAN) need to be recognized.

ELECTROPHYSIOLOGY

The original subdivision into CMT1 and CMT2 relied on the presence or absence of slowing of nerve conduction velocity below 38 m/second in an upper extremity motor nerve. Intermediate nerve conduction velocities (between 25 m/second and 45 m/second) occur with CMTX and HNPP (and other intermediate CMTs). Most inherited neuropathies cause uniform and diffuse involvement. This is in contrast to acquired neuropathies, where the findings are nonhomogeneous, can vary between adjacent nerves, and can vary within different segments of the same nerve. Conduction block, a reflection of nonhomogenous involvement within a nerve, is generally a feature of acquired demyelinating neuropathies but may occur with CMTX and CMT1B. In addition to defining an axonal or demyelinating pattern, electrophysiology is

Table 14.2 Nonsyndromic Inherited Neuropathies

Disease	Inheritance Pattern	Gene or Locus	Clinical Features
Hereditary Motor and Sensory Neuropathies (HMSN)			
Demyelinating			Forearm NCV usually <38 m/second
CMT1	AD		Young adult onset, NCV 10–35 m/second
CMT1A		PMP22 (usually duplication)	Most common (70% of all CMT1) Mutations also cause CMT3
CMT1B		MPZ (P_0)	Mutations also cause CMT2 and CMT3
CMT1C		LITAF/SIMPLE	
CMT1D		EGR2	Broad clinical spectrum (also CMT3)
CMT1F		NEFL	DSS phenotype common
CMT1 plus		FBLN5	Macular degeneration; cutis laxa
CMT1		PMP2	Classic CMT1
SNCV/CMT1		ARHGEF10	Asymptomatic slowed NCVs
HNPP	AD	PMP22 (usually deletion)	Adult onset episodic entrapment neuropathies, mild slowing (NCV 40–50 m/second)
CMT3			Severe, early-onset demyelinating
DSS	AD/X AR	CMT1 genes PRX, MTMR2	Onset before age 3 years old
CHN	AD AR	PMP22, MPZ EGR2	Congenital onset AR-CHN, also known as CMT4E
CMT4	AR		Childhood onset, usually severe
CMT4A		GDAP1	Both axonal and demyelinating types
CMT4B1		MTMR2	Biopsy shows focally folded myelin
CMT4B2		SBF2/MTMR13	Same as above ± early-onset glaucoma
		SBF1/MTMR5	
CMT4C		SH3TC2	Scoliosis often severe, also axonal types
CMT4D		NDRG1	Dysmorphic features, deafness
CMT4E		EGR2	
CMT4F		PRX	DSS phenotype
CMT4G		HK1	
CMT4H		FGD4	
CMT4J		FIG4	
		SURF-1	
		CTDP1	
Slow NCV	AD	ARHGEF10	Asymptomatic NCV slowing
Intermediate			NCV 25–45 m/second
CMTX	X		
CMTX1		GJB1/Cx32	Similar to CMT1, but males more severely affected, CNS involvement common
CMTX2, Cowchuck syn		AIFM1	MR, deafness, axonal
CMTX5		PRPS1	Axonal CMT, deafness, optic atrophy
CMTX6		PDK3	Axonal CMT
CMTX		DRP2	Intermediate MCVs
CMTDI	AD		
DI-CMTA		10q24	
DI-CMTB		DNM2	Neutropenia
DI-CMTC		YARS	

Table 14.2 Nonsyndromic Inherited Neuropathies—cont'd

Disease	Inheritance Pattern	Gene or Locus	Clinical Features
DI-CMTD		MPZ	
DI-CMTE		IFN2	Focal segmental glomerulosclerosis
DI-CMTF		GNB4	
CMTRI	AR		
CMTR1A		GDAP1	
CMTR1B		KARS	
CMTR1C		PLEKHG5	
CMTR1D		COX6A1	
Axonal			NCV >38 m/second
CMT2	AD		Young adult onset
CMT2A		MFN2 KIF1B (rare)	Most common; also HMSN V (optic atrophy), VI (spasticity), and early onset
CMT2B		RAB7	Severe sensory loss like HSAN-1
CMT2C		TRPV4	Vocal cord/diaphragm weakness
CMT2D		GARS	Arm > leg, motor predominant, similar to dHMN caused by BSCL2 mutations
CMT2E		NEFL	Allelic with CMT1E; variable phenotype
CMT2F		HSP27 (HSPB1)	Motor predominant
CMT2G		12q12-13.3	Proximal > distal weakness
CMT2H, K		GDAP1	Allelic with CMT4A
CMT2I, J		MPZ (P_0)	Cough, pain, autonomic/pupil, deafness
CMT2L		HSP22 (HSPB8)	Motor predominant, allelic with HMNIIa
CMTDIB, CMT2M		DNM2	Intermediate or CMT2; cataracts; ophthalmoplegia; ptosis
CMT2N		AARS	
CMT2P		LRSAM1	
CMT2Q		DHTKD1	
CMT2U		MARS	Late onset
CMT2V		NAGLU	Late onset painful sensory predominant
CMT2W		HARS	
CMT2Y		VCP	
CMT2Z		MORC2	Pyramidal signs
CMT2			
CMT2 with giant axons		DCAF8	Childhood onset
CMT2		TUBB3	
CMT2		DGAT2	
CMT2		JAG1	Vocal fold paralysis
SPG10, CMT2		KIF5A	
HMSNP		TFG	Proximal > distal
AR-CMT2	AR		
CMT2B1		LMNA	Also called CMT2B1 and CMT4C1
CMT2B2		MED25	
NMAN		HINT1	
CMT2R		TRIM2	
CMT2S		IGHMBP2	

Continued

Table 14.2 Nonsyndromic Inherited Neuropathies—cont'd

Disease	Inheritance Pattern	Gene or Locus	Clinical Features
CMT2T		HSJ1	
CMT2X		KIAA1840	
AR-CMT2	AR/AD	MME	Dominant mutations cause late onset
Hereditary sensory and autonomic neuropathies (HSANs)[a] and HMNs			
HSAN			Sensory (± autonomic) neuropathy
HSAN1A	AD	SPTLC1	Late onset, slowly progressive sensory axonal neuropathy ± SNHL, weakness
HSAN1B	AD	3p24-p22	Variant with cough, GERD, deafness
HSAN1C	AD	SPTLC2	
HSAN1D/SPG3A	AD	ATL1	
HSAN2A	AR	HSN2	Congenital sensory loss, acral mutilation
HSAN3	AR	IKBKAP	Severe dysautonomia, Ashkenazi Jews
HSAN4	AR	TRKA	Anhidrosis, acral mutilation, ± CNS
HSAN5	AR	NGFB	Congenital insensitivity to pain
HSAN6	AR	DST	Severe autonomic dysfunction, death by age 2
HSAN7	AD	SCN11A	Congenital insensitivity to pain, hyperhidrosis, GI dysfunction
HSAN8	AR	PRDM12	Congenital insensitivity to pain
HMN/dSMA			Distal wasting and weakness
HMNIIa	AD	HSPB8(HSP22)	Adult onset, allelic with CMT2L
HMNIIb	AD	HSP27(HSPB1)	Allelic with CMT2F
HMNVa	AD	GARS	Upper limb predominant
HMNVb	AD	BSCL2	Allelic with SPG17/Silver Syndrome
HMNVI	AR	IGHMBP2	Severe infantile respiratory distress/SMARD
HMNVIIa	AD	2q14	Adult onset, vocal cord paralysis
HMNVIIb	AD	DCTN1	Same as above
HMNX	X	Xq13.1-q21	
HMNJ	AR	9p21.1-p12	Childhood-onset (Jerash type)
SBMA	X	Androgen Receptor (CAG rpt)	Adult onset bulbar symptoms, proximal weakness, sensory neuronopathy, gynecomastia

This table lists the inherited neuropathies that are generally considered to exclusively or predominantly affect the peripheral nerve, although as shown in the Clinical Features column, many of these diseases affect the CNS and other tissues. For the columns, in "Disease" column, name is usually abbreviated, full names below; inheritance pattern is listed as autosomal dominant (*AD*), autosomal recessive (*AR*), or X-linked (*X*); and for gene or locus, the affected gene(s) is listed if known; otherwise, the chromosomal locus is listed. In cases where the mutation is not a missense mutation, the type of mutation is listed in parentheses (duplication, deletion, or CAG repeat). The diseases are grouped according to phenotype:

HMSN, hereditary motor and sensory neuropathy; *HS(A)N*, hereditary sensory and (± autonomic) neuropathy; *HMN,* hereditary motor neuropathy, also called dSMA (distal spinal muscular atrophy); *SBMA*, spinal bulbar and muscular atrophy. The HMSNs are further divided into demyelinating, axonal, and intermediate forms based on the usual range of nerve conduction velocity (*NCV*).

CHN, Congenital hypomyelinating neuropathy; *CMT*, Charcot-Marie-Tooth disease; *CMTDI*, dominant intermediate CMT; *CNS*, central nervous system; *DSS*, Dejerine-Sottas disease; *GERD*, gastroesophageal reflux disease; *HNPP*, hereditary neuropathy with liability to form pressure palsies; *MCV*, motor conduction velocity; *MR*, mental retardation; *rpt*, repeat; *SMARD*, spinal muscular atrophy with respiratory distress; *SNHL*, sensorineural hearing loss; *SPG*, hereditary spastic paraplegia; *syn*, syndrome (see Table 14.3).

[a]See also Table 5.4, where the chromosomal loci of these disorders are also listed.

helpful in detecting relative involvement of sensory and motor nerves, whether the neuropathy is length dependent or length independent, and in characterizing the severity.

GENETIC STUDIES

Genetic testing is usually best done along with a genetic counselor who can discuss the risks and benefits of genetic testing with multiple family members. Patients need to

Table 14.3 Syndromic Neuropathies

Disease	Inheritance Pattern	Gene or Locus	Clinical Features
HNA	AD	SEPT9	Recurrent brachial neuritis, dysmorphic features in some
Friedreich ataxia (FRDA)	AR	Frataxin-GAA repeats	Ataxia, sensory large fiber axonal neuropathy, positive Babinski sign, cardiomyopathy
AVED	AR	TTPA	FRDA-like, vitamin E deficiency
SCAN1	AR	TDP1	Spinocerebellar ataxia, sensory neuropathy
Ataxia-Telang.	AR	ATM	Ataxia, telangiectasias, malignancy, infections
SCA			Sensory neuropathy variable in most
SCA3/MJD	AD	ATXN3	Ataxia, spasticity, severe axonal neuropathy
SCA4	AD	PLEKHG4	Prominent axonal sensory neuropathy
SCA10	AD	ATXN10	± Sensorimotor neuropathy
SCA25	AD	2p21-p13	Prominent axonal sensory neuropathy
SCA27	AD	FGF-14	Mild axonal sensory neuropathy
HSP			"Complicated HSP" with neuropathy
SPG2	X	PLP	CNS white matter disease ± neuropathy
SPG7	AR	Paraplegin	± Neuropathy, dysarthria, dysphagia
SPG9	AD	10q23.3-24.1	Amyotrophy, cataracts, GERD
SPG10	AD	KIF5A	± Distal atrophy
SPG11	AR	Spatacsin	MR, nystagmus, thin corpus callosum
SPG14	AR	3q27–q28	Distal motor neuropathy, MR, visual agnosia
SPG15	AR	Spastizin	Pigmented maculopathy, MR, dysarthria
SPG17	AD	BSCL2	(Silver's syndrome) hand atrophy prominent
SPG20	AR	Spartin	(Troyer syndrome) distal atrophy, dysarthria
FAP			
TTR	AD	TTR	Early adult onset painful sensorimotor and autonomic neuropathy, entrapment neuropathy, cardiomyopathy, GI symptoms
(Iowa)		ApoAI	Similar to TTR, but progressive renal failure
(Finnish)		Gelsolin	Cranial neuropathies, corneal dystrophy
Fabry's	X	α-Gal-A	Child-onset painful SFSN, renal failure, cardiac disease, strokes
Leukodystrophies			Some associated with demyelinating neuropathy
GLD/Krabbe	AR	GALC	Progressive MR, hyperreflexia, sz, optic atrophy
MLD	AR	ARSA	Same as above, though CNS sx less severe
PCWH/Wartenburg's	AD	SOX10	CHN, central dysmyelination, Waardenberg and Hirschprung syndrome
Adrenomyelo-neuropathy	X	ABCD1	Spastic paraparesis, large fiber sensory loss, bowel and bladder incontinence
Merosin def	AR	LAMA2	Neuropathy and muscular dystrophy
Refsum disease	AR	PAHX PEX7	Ataxia, retinitis pigmentosa, demyelinating neuropathy, cardiac, deafness, ichthyosis
AMACR deficiency	AR	AMACR	Adult-onset sensory and motor neuropathy, retinitis pigmentosa, seizures, ataxia, developmental delay, acute and relapsing encephalopathy with headache
Mitochondrial diseases			Neuropathy common, axonal or demyelinating
Leigh disease	ARmito	Multiple genes	Early onset CPEO, ptosis, ataxia, MR, pyramidal signs, demyelinating neuropathy

Continued

Table 14.3 Syndromic Neuropathies—cont'd

Disease	Inheritance Pattern	Gene or Locus	Clinical Features
NARP	Mito	MTATP6	Sensory neuropathy, ataxia, retinitis pigmentosa
MNGIE	AR	ECGF1 POLG	Ptosis, CPEO, leukoencephalopathy, neuropathy, myopathy, GI dysmotility
Porphyria	AD		
AIP		PBGD	Acute neuropathy, abdominal pain, psychosis, sz
Copro		CPO	Similar to AIP, but also skin photosensitivity
Variegate		PPOX	Similar to AIP, but also skin photosensitivity
Tangiers disease	AR	ABC1	Orange tonsils, organomegaly, low HDL, atherosclerosis
Abetalipoprot.	AR	MTTP	Ataxia, acanthocytosis, steatorrhea, low LDL
Hypobetalipo.	AD	Apo-B	Ataxia, sensory axonal polyneuropathy
GAN	AR	Gigaxonin	MR, kinky hair, biopsy shows giant axons
ACCPN	AR	KCC3	Agenesis of corpus callosum, French Canadian
CCFDN	AR	CTDP1	Congenital cataracts, facial dysmorphism

This table lists the inherited neuropathies in which the neuropathy is part of a systemic disease. For the columns, in "Disease," the name is usually abbreviated, with full names below; in "Inheritance Pattern," data are listed as autosomal dominant (*AD*), autosomal recessive (*AR*), X-linked (*X*), or mitochondrial (maternal) (*mito*); and for "Gene or locus," the affected gene(s) is listed if known; otherwise, the chromosomal locus is listed.

Abetalipoprot., Abetalipoproteinemia; *ACCPN*: agenesis of the corpus callosum and peripheral neuropathy, also known as Anderman syndrome; *AIP*, acute intermittent porphyria; *AMACR*, alpha-methylacyl-CoA racemase; *AVED*, ataxia with isolated vitamin E deficiency; *CCFDN*: congenital cataracts, facial dysmorphism, neuropathy; *CHN*, congenital hypomyelinating neuropathy; *CNS*, central nervous system; *Copro*, coproporphyria; *CPEO*, chronic progressive external ophthalmoplegia; *FAP*, familial amyloidotic polyneuropathy; *FRDA*, Friedreich ataxia; *GAN*, giant axonal neuropathy; *GERD*, gastroesophageal reflux disease; *GI*, gastrointestinal; *GLD*, globoid-cell dystrophy; *HDL*, high-density lipoprotein; *HNA*, hereditary neuralgic amyotrophy; *HSP*, hereditary spastic paraplegia; *LDL*, low-density lipoprotein; *MLD*, metachromatic leukodystrophy; *MJD*, Machado-Joseph disease; *MNGIE*, mitochondrial neurogastrointestinal encephalopathy syndrome; *MR*, mental retardation; *NARP*, neuropathy, ataxia, and retinitis pigmentosa; *PCWH*, peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschprung disease; *SCA*, spinocerebellar ataxia; *SCAN1*, spinocerebellar ataxia with axonal neuropathy 1; *SFSN*, small fiber sensory neuropathy; *SPG*, spastic gait; *sx*, symptoms; *sz*, seizures; *Telang*, Telangiectasia; *TTR*, transthyretin; *Variegate*, variegate porphyria.

be well educated regarding the implications of a molecular diagnosis, both for themselves and for family members. Genetic testing is of utmost relevance to family members of childbearing age, because for most well-defined monogenic disorders, preimplantation or in utero genetic testing is available. It is worth noting that the first genetic nondiscrimination law (Genetic Information Nondiscrimination Act [GINA]) was signed into law in 2008, giving patients protection from discrimination by employers and health insurance companies. In most cases, unaffected minors should not be offered genetic testing to determine future health or reproductive risks, unless screening provides a clear and timely medical benefit with minimal psychosocial risks.

Although testing can be expensive and sometimes is not covered by insurance, genetic diagnosis is extremely valuable to many patients and clinicians. The balance and landscape of cost and gene coverage are constantly changing, and helping navigate this is one of the important roles genetic counselors play. The exponential decreases in cost of next generation testing have also made it so that unbiased exome sequencing can compete on price with more focused panel testing. This adds complexity to the decision of how and when to test, which has been covered in a new chapter in this edition (Chapter 11). Carrier screening panels are also starting to include recessive and X-linked neuropathy genes, which may help decrease the incidence of some of the most severe forms of the disease.

Having a molecular diagnosis continues to have many benefits. First, it can potentially give a definitive diagnosis not available by any other means and can obviate invasive testing (e.g., nerve biopsy) and unnecessary treatment (e.g., intravenous gamma globulin). More recently, the advent of FDA-approved therapies for hereditary transthyreitin amyloidosis (hATTR) has also introduced the possibility that genetic diagnosis could identify a potentially treatable cause of neuropathy. This has been another driver toward affordable panel and exome testing, spurring collaborations between pharmaceutical companies and genetic diagnostic companies to defray the cost to patients and make it easier to test.

Knowing the cause of their symptoms can often empower patients to follow research progress, take part in natural history studies, and enroll in clinical trials. This chapter will discuss genetic tests that are commercially available. The National Center for Biotechnology Information's Genetic Testing Registry Web site (https://www.ncbi.nlm.nih.gov/gtr/) is a valuable resource for identifying gene tests, both those available clinically and those

performed on a research basis, and includes online reviews of most diseases (GeneReviews).

IMAGING STUDIES

Magnetic resonance imaging (MRI) studies are able to show increased size of the nerves in CMT patients and normal magnetic resonance signal without enhancement. This is opposed to acquired neuropathies such as chronic inflammatory demyelinating polyneuropathies (CIDPs) in which enlarged nerves are associated with enhancement or hyperintensity of the T2 signal. Nerve root hypertrophy may cause compressive myelopathy or radiculopathy in CMT patients. Ultrasound is being used more frequently in clinical practice to show that the cross-sectional areas of the nerves are increased.

TREATMENT

Unfortunately, most *syndromic* and *nonsyndromic inherited neuropathies* do not yet have specific pharmacologic therapies available. Given that the first genes causing CMT were first discovered in the early 1990s, and given the magnitude of discoveries achieved since then, there is certainly reason to be optimistic that therapies will continue to enter clinical trials and the clinic in the coming years.

In addition to targeted potentially disease-modifying therapies, symptomatic therapies are available, mostly to treat the orthopedic complications that arise. These psychiatric and surgical therapies are covered in detail in Chapters 8 and 9, respectively, and will only briefly be discussed here as they relate to specific disorders. Neuropathic pain is uncommon in most inherited neuropathies and is treated in the same way as in acquired neuropathies; however, in a few inherited neuropathies, pain may be the presenting symptom, particularly in Fabry disease and FAP. Chapter 6 discusses treatment of painful neuropathy.

Importantly, there are several patient support groups that can offer valuable services to patients and their families. The Muscular Dystrophy Association (www.mdausa.org/) supports patients with CMT and FRDA, and this organization can be very helpful to patients. Other patient resources include the Charcot-Marie-Tooth Association (www.charcot-marie-tooth.org/), the Hereditary Neuropathy Foundation (www.hnf-cure.org/), and the Neuropathy Association (www.neuropathy.org/).

THERAPEUTIC PARADIGMS FOR NEUROPATHY

This chapter will cover both available and experimental treatments, as it is expected that the principles of drug development will apply to new therapies for inherited neuropathies in the future. This chapter is organized by disease subtype and reviews the clinical presentation, diagnosis, and treatment of each of these diseases of the peripheral nervous system. Understanding these disease-specific approaches requires a baseline understanding of the treatment paradigms and targeted therapy approaches that are being used across the field. To set the stage for our review of each disease subtype, we will start with a review of treatment paradigms and then discuss the specific approaches that are under investigation in each disease area.

Therapeutic development usually needs to start with a deep understanding of the disease mechanism. Fig. 14.1 shows a schematic of the drug discovery process, beginning with identification of the mutated gene. Identification of the genetic mutations causing inherited neuropathies is the critical step to the development of disease-specific therapy. The next critical question is whether the mutations cause a loss of function or a gain of function. While this can be straightforward (most autosomal recessive and X-linked recessive diseases are the result of a loss of function), it can be more complicated in dominantly inherited diseases because (1) loss of one copy of a gene alone can cause dominantly inherited diseases (haploinsufficiency, or semidominant), (2) loss of function can contribute to the pathology of a disease that is primarily driven by toxicity of the mutant allele, (3) loss of function can be the result of mutant protein influencing the function of the wild-type allele via a dominant-negative mechanism, or (4) loss of function can have no influence on toxicity (Fig. 14.2).

To tease the contributions of loss and gain of function to gather this basic mechanistic understanding of disease, it is often necessary to have animal models that reflect both loss of the protein and those that express the mutant protein (knock-in or overexpression) (Fig. 14.2). Most genes known to cause neuropathy are highly conserved in mammals, and many are even conserved in simple genetic model systems such as yeast and fruit flies. Thus, studies of the basic biology and pathogenesis of inherited diseases in animal models have proven to be especially relevant to our understanding of inherited human diseases. Finally, faithful cellular, invertebrate, and mammalian models of disease are necessary for testing small and large molecule therapeutics.

Fig. 14.3 outlines a range of biologic-therapy approaches to treating genetic disease based upon the understanding of the mechanism of disease. We review both small molecule and biologic therapeutics discovery in the following subsections.

GENE REPLACEMENT STRATEGIES

Loss-of-function mutations can be treated with gene or protein replacement strategies, whereas gain-of-function mutations require a strategy to reduce the toxicity of the mutated or duplicated gene product (e.g., antisense oligonucleotides [ASOs] in CMT1A). There are viral and nonviral gene replacement strategies (Fig. 14.3). Adeno-associated viral vectors have been the first to reach the clinic, with FDA-approved AAV9 vectors for SMA and AAV2 vectors for *RPE65*-linked retinal dystrophy. The adeno-associated virus (AAV) serotype reflects different capsid proteins and influences viral tropism, infectivity, and immunogenicity. The mode of administration also influences the therapeutic dose, distribution, and potential toxicity. AAV2-*RPE65* is delivered by subretinal injection (Maguire et al., 2009), for example, while AAV9-SMN1 is delivered intravenously (Mendell et al., 2017). Many groups are working to improve the tropism of AAV serotypes to the central and peripheral nervous system. Several AAV subtypes have also been shown to effectively infect motor and sensory neurons with local injection, intrathecal injection, and systemic administration, although delivery to Schwann cells has proven more difficult.

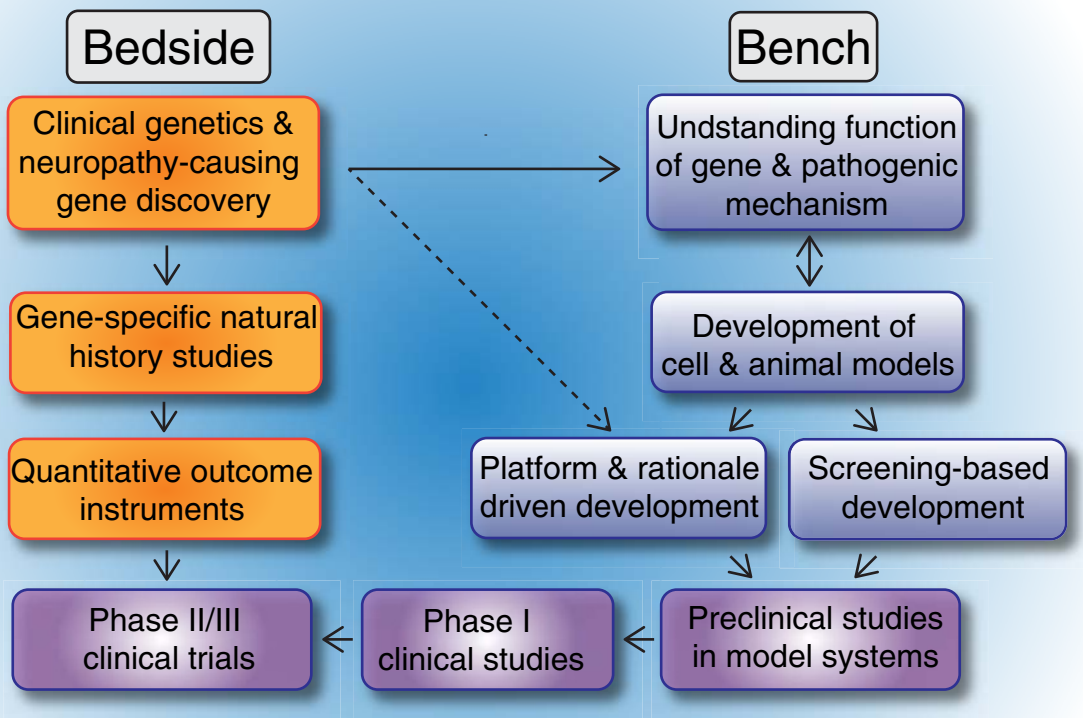


Fig. 14.1 Drug development for inherited neuropathies: from bedside to bench, and back. The initial step in drug development involves the identification and characterization of the gene that is mutated in disease. By introducing these mutations into animals or cells, animal models can be developed and validated, which can assist in understanding the basic biology of the disease. One can then identify therapeutic targets and design drugs based on a rationale-driven approach using small molecule or biologic therapies. Alternatively, animal or in vitro models can be screened with pharmaceutical and chemical libraries to identify novel potential therapeutics, which then undergo preclinical testing in animal models to show efficacy and safety. Once candidate compounds pass these tests, they can then be tested in clinical trials. Gene-specific natural history studies, quantitative outcome instruments, and biomarkers of disease are important requisites for successful phase 2 and 3 studies.

Nonviral gene delivery systems are also under preclinical development but have not yet been taken to the clinic for neuromuscular diseases. These approaches often require liposomal vehicles to facilitate transfer of mRNA or linear or plasmid DNA. These approaches would require repeat dosing but do not have the risks associated with immune response to the virus, and these approaches do allow dose titration and re-dosing.

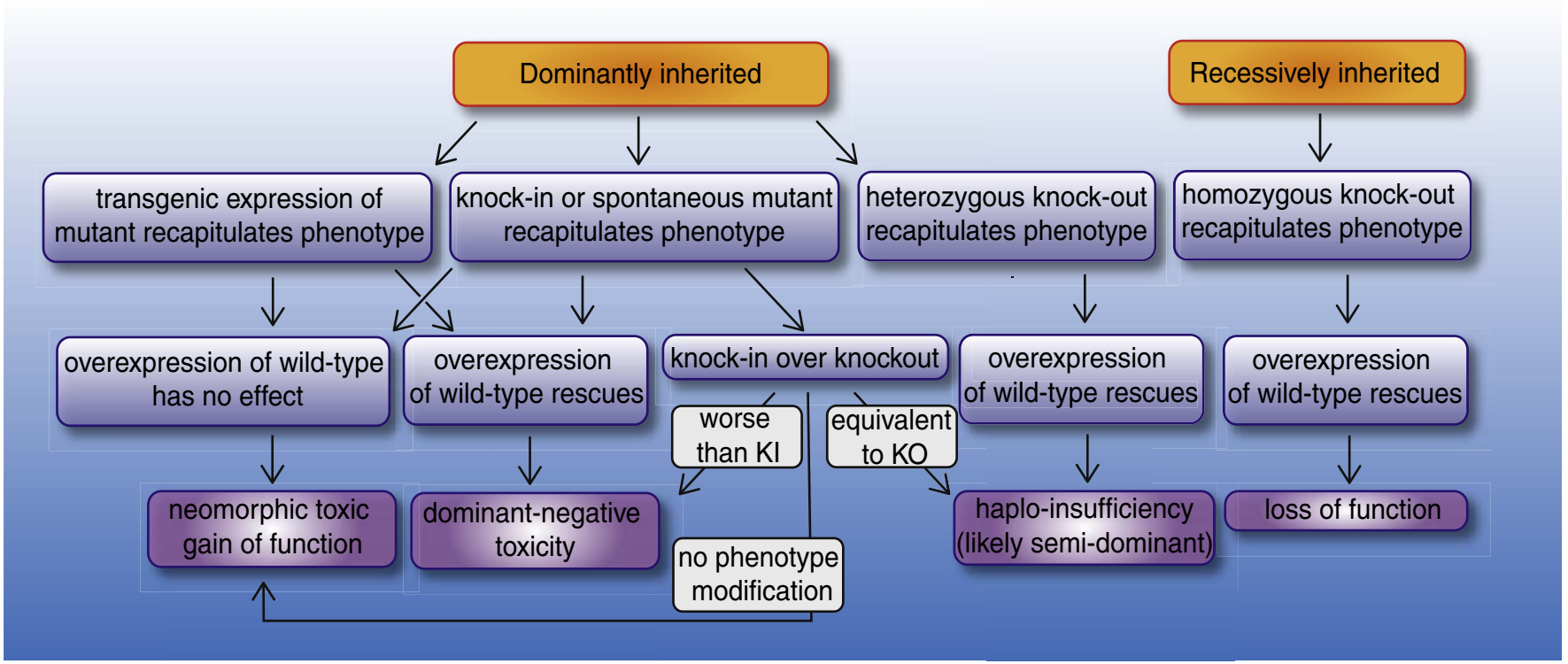


Fig. 14.2 Using cell and animal models to determine the contributions of loss or gain of function in the mutated gene. One of the key questions to determine the appropriate therapeutic approach is the whether the disease phenotype is the result of a loss of function in the mutated gene product or a gain of function in the mutated gene product. Dominantly inherited diseases can be the result of a loss or gain of function of the gene product. Haplo-insufficiency occurs when one wild-type allele does not produce enough protein for normal function. It is therefore loss of function of the mutant allele that eliminates 50% of the gene product and results in a disease phenotype. Hereditary neuropathy with liability to pressure palsies (HNPP) is the result of haplo-insufficiency of the PMP22 gene. Dominant negative mechanisms suggest that the mutant allele is acting to prevent normal function of the wild-type allele and thus can be corrected by overexpression of the wild-type protein. If the amount of wild-type protein does not modify the phenotype when the mutant allele is present, and expression of the mutant allele with a transgene recapitulates the phenotype, this is suggestive of a toxic gain of function independent of normal protein function. Autosomal recessive and X-linked recessive diseases are usually caused by a partial or complete loss of function. This can be confirmed using animal model systems, and the expectation would be that homozygous knock-out recapitulates the phenotype, and restoration of expression rescues the phenotype.

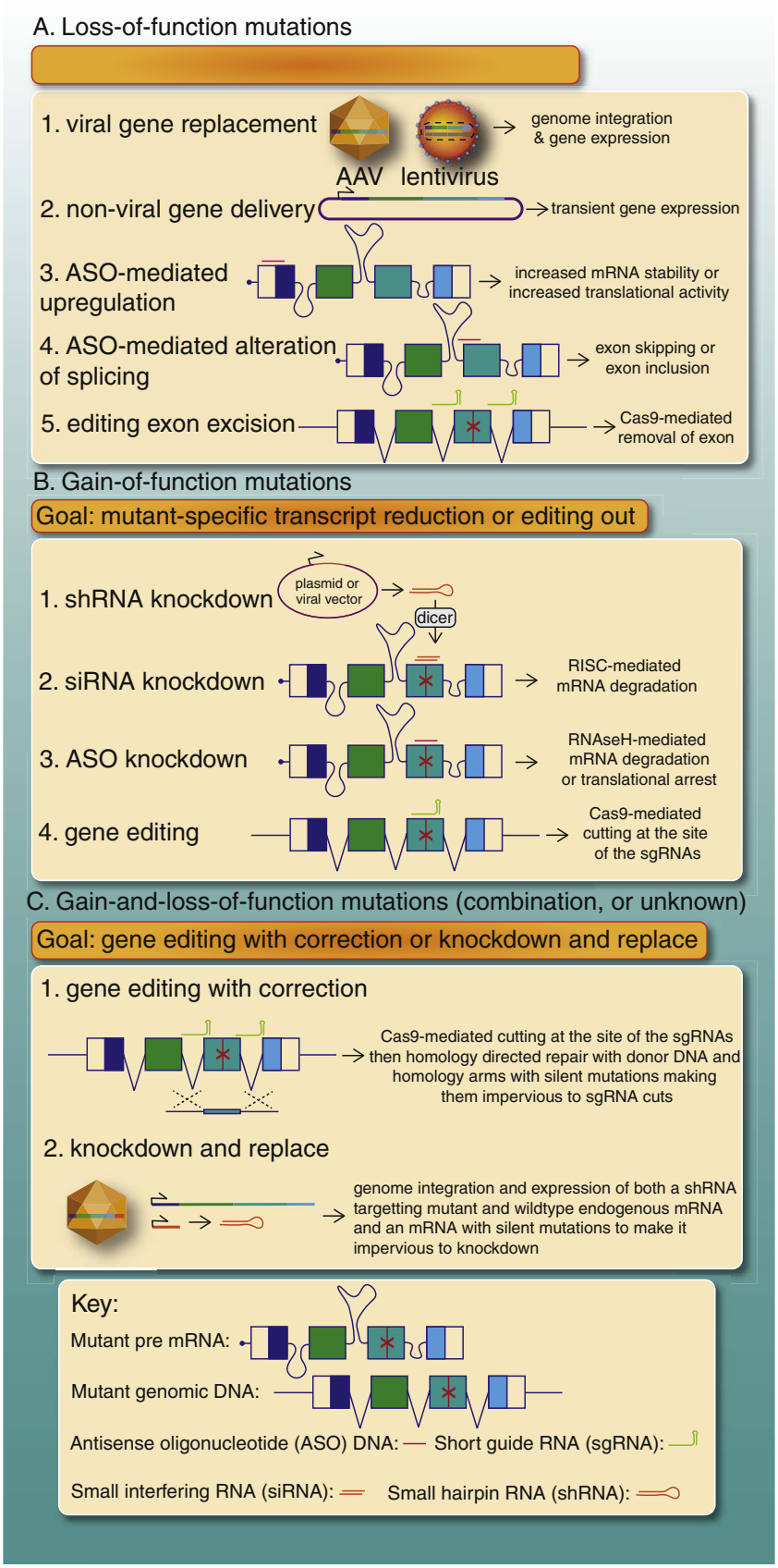

A. Loss-of-function mutations
1. viral gene replacement
AAV
lentivirus
genome integration & gene expression
2. non-viral gene delivery
transient gene expression
3. ASO-mediated upregulation
increased mRNA stability or increased translational activity
4. ASO-mediated alteration of splicing
exon skipping or exon inclusion
5. editing exon excision
Cas9-mediated removal of exon
B. Gain-of-function mutations
Goal: mutant-specific transcript reduction or editing out
1. shRNA knockdown
plasmid or viral vector
dicer
2. siRNA knockdown
RISC-mediated mRNA degradation
3. ASO knockdown
RNAseH-mediated mRNA degradation or translational arrest
4. gene editing
Cas9-mediated cutting at the site of the sgRNAs
C. Gain-and-loss-of-function mutations (combination, or unknown)
Goal: gene editing with correction or knockdown and replace
1. gene editing with correction
Cas9-mediated cutting at the site of the sgRNAs then homology directed repair with donor DNA and homology arms with silent mutations making them impervious to sgRNA cuts
2. knockdown and replace
genome integration and expression of both a shRNA targetting mutant and wildtype endogenous mRNA and an mRNA with silent mutations to make it impervious to knockdown
Key:
Mutant pre mRNA:
Mutant genomic DNA:
Antisense oligonucleotide (ASO) DNA:
Short guide RNA (sgRNA):
Small interfering RNA (siRNA):
Small hairpin RNA (shRNA):

Fig. 14.3 Gene-targeted therapy paradigms. There has been a great proliferation in the number of approaches to treating genetic diseases and these approaches are making their way to the clinic in many genetic neurological diseases. These same tools are likely to be used for the treatment of peripheral neuropathies. Strategies for the treatment of loss-of-function mutations are focused on gene replacement or transcript regulation (A). These include (1) virally mediated gene replacement that harness the ability for viruses to stably deliver DNA to cells. The most advanced platforms in neurological disease applications are adeno-associated virus (AAV) and lentivirus based. (2) Nonvirally mediated delivery tools are also in development to deliver mRNA or plasmid DNA to the affected cells and often harness liposomal preparations of DNA. Antisense oligonucleotide (*ASOs*) are versatile therapeutic tools and can be used to (3) upregulate gene expression, a strategy that would work for diseases caused by haploinsufficiency where upregulation of the wild-type allele would be therapeutic, (4) mediate splicing to include exons whose splicing decreases the stability of the protein product (as is the case with the SMN2 gene targeted by nusinersen), or to skip exons whose inclusion causes premature termination or frame shift (as is the case with the DMD gene targeted by eteplirsen). Finally, emerging gene editing strategies can be used to remove mutant exons for a more definitive and permanent approach than exon skipping. Approaches are being attempted to use two guides to remove frameshift containing exons (5). Strategies for the treatment of gain-of-function mutations are focused on mutant gene silencing (B). These include (1) short hairpin RNA (*shRNA*) knockdown and (2) small interfering RNA (*siRNA*) knockdown. shRNAs are converted into siRNAs by Dicer, and siRNA knockdown of mRNA transcripts is mediated by RISC. ASOs can be used to perform both allele-specific and non–allele-specific knockdown mediated by RNAseH cleavage (3). If toxicity of the allele is pathogenic and premature truncation improves the phenotype, gene editing tools can be used to cut the mutant gene to prevent production of the mutant (4). When the mechanism results in both a loss of function and a gain of function, or when the mechanism is ambiguous, there are approaches that can be used that both eliminate the mutant and restore wild-type function. These include gene editing approaches that correct the allele to a wild-type allele, which is challenging and requires homologous recombination (1), and virally delivered shRNA with a gene replacement in the same vector (2).

ANTISENSE OLIGONUCLEOTIDE AND RNAI-BASED APPROACHES (THIS AND GENE THERAPY ARE DISCUSSED IN DETAIL IN CHAPTER 11)

The success of nusinersen for the treatment of SMA has further increased enthusiasm for ASO therapies for neuromuscular diseases and neuropathies. Nusinersen binds to an intronic sequence in the SMN2 gene to prevent splicing of exon 7 and encourage production of full-length protein (Sumner & Crawford, 2018). Eteplirsen binds to exon 51 in transcripts from the Duchenne muscular dystrophy-associated gene (DMD) and facilitates skipping of mutant exon 51 containing a premature termination codon or frameshift and results in restoration of the reading frame (Mendell et al., 2013). This demonstrates two ways ASOs can be used to restore protein function by modulating splicing in opposite ways, exon inclusion and exon skipping. ASO therapies can also be used to facilitate RNaseH-mediated degradation of target mRNA.

Small interfering RNA (siRNA) and short hairpin RNA (shRNA) therapies are less versatile because they facilitate RNA-induced silencing complex (RISC)-mediated mRNA degradation and cannot be used to modulate splicing or expression. shRNAs are generally delivered in vectors and converted into siRNAs by Dicer. siRNA, shRNA, and ASOs can be used to drive degradation of mRNAs before they are translated into toxic proteins. Both the first FDA-approved siRNA therapy, patisiran, and one of the first FDA-approved ASO therapeutics, inotersen, target mutant and wild-type hTTR. Allele-specific knockdown of only the mutant allele using ASO, siRNA, or shRNA therapies is possible, but achieving efficient knockdown with good specificity has proven challenging for missense variants and only a few such examples have been published (Schwarz et al., 2006). Allele-specific knockdown also requires more tailored therapeutics development to match missense changes or associated single nucleotide polymorphisms (SNPs) linked to disease. Nevertheless, it is an appealing approach in diseases caused by mutations in genes that are required for survival and function of the targeted cell type (e.g. MFN2, AARS).

SMALL MOLECULE APPROACHES

While rational and platform-based biologic therapeutic approaches have stolen much of the spotlight in recent years, there continue to be advantages to small molecule approaches. Most notably, the parameters for bioavailability, tissue access, and penetrance are well known to drug developers. In addition, massively parallel screening is possible with small molecules. There are generally two approaches to small molecule drug discovery: target-based approaches, and phenotype or expression-screening approaches. With confidence in the target and mechanism, several complementary approaches are often used to identify the best medicines. The technologies for drug discovery are constantly improving and multiple approaches are often used simultaneously to find hits, to verify hits and characterize toxicity to identify lead compounds, and to perform lead optimization to select compounds ready for clinical testing.

Once a mechanism of pathogenesis is proposed and animal models are developed, the drug development process can begin using either a target-based approach or a phenotype-driven approach (see Fig. 14.1). Target-based approaches utilize our understanding of the basic biology and disease pathogenesis to screen molecules for a desired effect on a protein target. Transthyreitin protein in the liver functions as a tetramer, and disease pathogenesis requires dissociation of monomeric protein from the tetramer and release from the liver. Several groups performed screens for small molecules that increase the stability of the transthyreitin tetramer. Increasing its stability prevents dissociation of the monomer from its tetrameric structure, release of the mutant monomer from the liver, and accumulation of the amyloidogenic monomer in heart and peripheral nerve.

Another approach is phenotype or expression-based screening. For example, PMP22 duplication is the most common cause of CMT and results in excess expression levels of PMP22. Researchers performed an expression-based screen for FDA-approved molecules that reduce PMP22 expression. The result was the identification of three FDA-approved compounds (fenretinide, olvanil, and bortezomib) that reduced PMP22 mRNA and protein (Jang, Lopez-Anido, MacArthur, Svaren, & Inglese, 2012). The criticism of phenotype and expression-based systems is that it is difficult to determine the

molecular target of the effect, and therefore, it is difficult to improve upon the molecule in the ways that traditional drug development is performed. To our knowledge, these compounds have not been tested clinically. Bortezomib, one of the compounds that were found to decrease PMP22 expression in this screen, is known to cause a severe acquired neuropathy and would therefore be a poor candidate for clinical testing.

Drug development in other therapeutic areas may identify compounds that will slow disease progression of hereditary neuropathies. Therapeutics targeting generally neuroprotective pathways will be promising for neuropathy patients. Since the publication of the last edition, our understanding of the pathways mediating axon degeneration has improved significantly. Axodegenerative programs mediated by the SARM1 protein that trigger Wallerian degeneration are attractive therapeutic targets and, if found, may serve as effective therapies in many hereditary neuropathies. Conversely, candidate compounds with general neuroprotective or neuroregenerative properties identified in research efforts for hereditary neuropathies may also be effective in acquired neuropathies.

GENE EDITING

Gene editing has great therapeutic potential, but many challenges remain before it will be a viable therapeutic approach in hereditary neuropathy. Even with gene editing, delivery of the editing proteins to relevant tissues will continue to be a challenge and will rely on the successes of gene therapies that precede them to ensure delivery of Cas9 and related proteins and short guide RNAs. Another caveat is that gene editing targets that require correction rather than simply elimination of an exon or repeat will not be early targets because of the challenges of recombination-based repair and correction. Second- and third-generation editing tools may skirt the requirement for repair or recombination by performing specific substitutions in DNA or RNA, but transformation of the cells with exogenous editing proteins will still be early hurdles. As a result, hereditary neuropathies will not be early targets for CRISPR-based approaches.

MECHANISM AGNOSTIC APPROACHES

Some drug development paradigms for dominant diseases have skirted the need to definitively parse the contributions of gain and loss of function. These include gene editing, and a "knockdown and replace" strategy (Fig. 14.3). In addition to the hurdles discussed in the section on gene editing earlier, replacing portions of genomic DNA with wild-type sequence will require either homology-directed repair with an oligo template or homologous recombination with a double-stranded template. The efficiencies of these approaches will need to be improved before they can be used therapeutically.

The "knockdown and replace" approaches use viruses to deliver oligonucleotides that knock down endogenous mRNA and simultaneously deliver gene replacement with transcripts that harbor synonymous mutations that make them impervious to knockdown. Several CMT2 genes are essential genes and lend themselves to this approach.

CLINICAL DEVELOPMENT

After candidate drugs are identified and undergo rigorous toxicity, efficacy, and dosage testing in animal models, they can then be tested in clinical trials. An often-underappreciated part of drug development to complement bench science and preclinical development is concomitant definition and characterization of natural history, biomarkers, and quantitative disease metrics (Fig. 14.1). This is critical so that investigators can identify subpopulations whose disease progresses rapidly enough to show an effect in a feasible study duration.

Most drugs fail in phase 2 clinical studies, where efficacy signal is needed for advancement. The reasons are multifold, but without a good understanding of a disease's natural history, selection of the correct patient population, ability to predict effect size, and adequate power, even the most effective preclinical therapies will fail and result in disappointment for patients and clinicians. These are particularly challenging obstacles for treatments for inherited neuropathies. These diseases individually are rare, and adequately powering a study can be challenging. The development of large consortia that can enroll many patients from sites around the world is now allowing much larger studies to be performed with more uniform tracking of outcomes in many modalities. The slowly progressive nature of many of these disorders with varied and clinical parameters that can be difficult to measure makes it difficult to quantitate the treatment effects. Another obstacle to the advancement of biologic therapies into the clinic has been the absence of tools to facilitate large molecule delivery to motor and sensory neurons and Schwann cells.

With these in mind, it is not surprising that hTTR amyloidosis has been an attractive target. The liver, the source of amyloid protein production, is an easier tissue to target than anterior horn cells, dorsal root ganglion cells, or Schwann cells, for both small molecules and biologics, and the disease course is rapidly progressive based on existing natural history data.

The development of quantitative scales to measure disease severity and the ability to assay biomarkers that are relevant to disease pathogenesis are improving the quality of clinical trials in these diseases. A validated primary clinical outcome used in current studies is the CMT Neuropathy Score (CMTNS) (Shy et al., 2005), which was improved with an updated second version (CMTNS2) (Murphy et al., 2011). There is also the overall neuropathy limitation score (ONLS) (Graham & Hughes, 2006). Oftentimes, both the CMTNS and ONLS are used concomitantly in clinical studies. There is also the modified Neuropathy Impairment Score +7 (mNIS+7), which is tailored to trials of FAP (Dyck et al., 2017).

Biomarkers are another important part of clinical development that can be used to measure target engagement or to more sensitively measure the desired therapeutic effect. There has been significant work to improve quantitative assays for neurofilament light (NfL) chain and to characterize serum and CSF levels in control and patient populations. In CMT, plasma NfL has been established as a reliable biomarker of disease activity that stratifies with disease severity and genetic subtypes (Sandelius et al., 2018). There is also great interest in its use in many neurodegenerative disease of the central (e.g., multiple sclerosis and Alzheimer disease) and peripheral nervous systems.

Thus, through continued advancements in our understanding of inherited neuropathies, and building on the

success of the FDA-approved therapy for hTTR amyloidosis and improvements in the design and implementation of clinical trials, effective therapies for inherited neuropathies can be expected to advance through the development pipeline.

NONSYNDROMIC INHERITED NEUROPATHIES

HEREDITARY MOTOR AND SENSORY NEUROPATHIES (HMSNS)

Hereditary motor and sensory neuropathy, commonly referred to as Charcot-Marie Tooth disease, is the most common inherited neurologic disease, affecting 1 in 2500 people, and encompasses the largest group of inherited neuropathies. These diseases are commonly classified based on clinical presentation (age of onset and inheritance pattern) and pathology/electrophysiology; for example, autosomal dominant neuropathies are classified as primarily demyelinating (CMT1) or axonal (CMT2). X-linked CMT is classified as CMTX, and autosomal recessive CMT is CMT4. The term "CMT3" refers to severe, congenital, or early childhood onset CMT and is best considered a variant of CMT1, as the genes that are mutated are the same. About 70% of CMT is demyelinating, and about 70% of demyelinating CMT is due to a duplication of the PMP22 gene (CMT1A). Thus, while between 80 and 120 genetic loci have been described in CMT patients, almost half of patients with CMT have a single, well-characterized mutation. However, with the discovery of the genetic basis for most of these disorders, it has become evident that different mutations in the same gene can cause multiple, distinct phenotypes, referred to as genetic pleiotropy. Conversely, the same phenotype is often caused by mutations in different genes (see Table 14.2 for a list of HMSN genes). For example, mutations in the myelin protein zero (MPZ) gene have been found in all forms of CMT (axonal and demyelinating, dominant and recessive). Thus, classification based on the genetic mutation and molecular pathogenesis of the disease may be more relevant than the clinical presentation when discussing therapeutic options.

CLINICAL PRESENTATION

Most patients with CMT develop slowly progressive weakness and atrophy in their feet beginning in childhood or early adulthood. Pain or sensory loss is variable but is usually not a chief complaint. Foot deformities (pes cavus, or high arches, and hammertoes) are common and may lead to disability (see picture in Chapter 9). Mildly affected patients may be limited only in their ability to walk on their heels and play sports, whereas more severely affected patients will have foot drop and steppage gait (hence the initial description of this disease as peroneal muscular atrophy). However, due to the insidious nature of this disease, many patients do not complain of motor or sensory symptoms until late in the disease course, and most remain ambulatory. Thus, it is not uncommon to find asymptomatic family members with classical examination and electrophysiologic features of CMT.

On examination, patients typically have distal weakness and atrophy in the feet, areflexia, and length-dependent sensory loss of both large and small-fiber sensory modalities. More severely affected patients will develop sensory ataxia or tremor (Roussy-Levy syndrome), palpably enlarged nerves (demyelinating CMT), and weakness, atrophy, and sensory loss of the hands. Patients with motor findings only and without evidence of sensory involvement on examination or electrodiagnostic testing are classified as having HMN, whereas patients with sensory findings only and without evidence of motor involvement are classified as HSN or HSAN (see Table 14.2 and later). Less commonly, patients can have a severe form of CMT (CMT3) that is congenital (congenital hypomyelinating neuropathy [CHN]) or with onset before age 3 (Dejerine-Sottas syndrome [DSS]). Some forms of CMT have unusual features, such as central nervous system (CNS) involvement in CMTX, vocal cord paralysis with CMT2C, and specific thenar involvement in CMT2D (see Table 14.2).

Whereas CMT1A is caused by a duplication of the PMP22 locus, HNPP is caused by a deletion of the same locus (Chance et al., 1993). As the name suggests, these patients often present with painless, recurrent entrapment neuropathies, often precipitated by minor trauma or compression. HNPP patients usually also have a mild length-dependent demyelinating neuropathy. Another disorder occasionally confused with HNPP is HNA. These patients present essentially the same as those with idiopathic brachial neuritis (Parsonage-Turner syndrome) with episodic, painful weakness and numbness of one upper extremity, often triggered by an infection, exercise, or stress.

DIAGNOSIS

CMT is usually suspected when there is a family history of peripheral neuropathy, as most forms of CMT are autosomal dominant. However, mutations causing CMT occur de novo in about a third of patients. This is primarily driven by high rates of de novo duplication of the PMP22 gene via nonallelic homologous recombination (Pentao, Wise, Chinault, Patel, & Lupski, 1992), but de novo inheritance has also been observed in other CMT genes (Meggouh, Bienfait, Weterman, de Visser, & Baas, 2006; Motley et al., 2016) and can be a valuable tool in identifying the disease-causing gene in small families with neuropathy. CMT should be considered in patients with slowly progressive peripheral neuropathy even in the absence of family history. Thus, CMT is underdiagnosed in sporadic cases and is a common diagnosis made in tertiary referral centers of patients with undiagnosed peripheral neuropathy (Pareyson, 2003). Less commonly, CMT can be X-linked or autosomal recessive. Careful history taking, pedigree drawing, and examination, coupled with electrodiagnostic testing of as many affected and asymptomatic family members, can often be extremely helpful in determining the inheritance pattern of neuropathy.

As shown in the diagnostic algorithm flowchart (Fig. 14.4), when CMT is clinically suspected the most useful initial test to perform is an NCS. Classification of the disease as axonal or demyelinating can potentially limit the genetic testing required, as the common mutations causing CMT1 (demyelinating) are, in general, different from those causing CMT2 (axonal). History and clinical examination cannot reliably distinguish these distinct forms of CMT, although an early age of onset and palpable nerves would favor a diagnosis of demyelinating CMT. In addition to classifying the disease as primarily axonal or demyelinating, NCSs

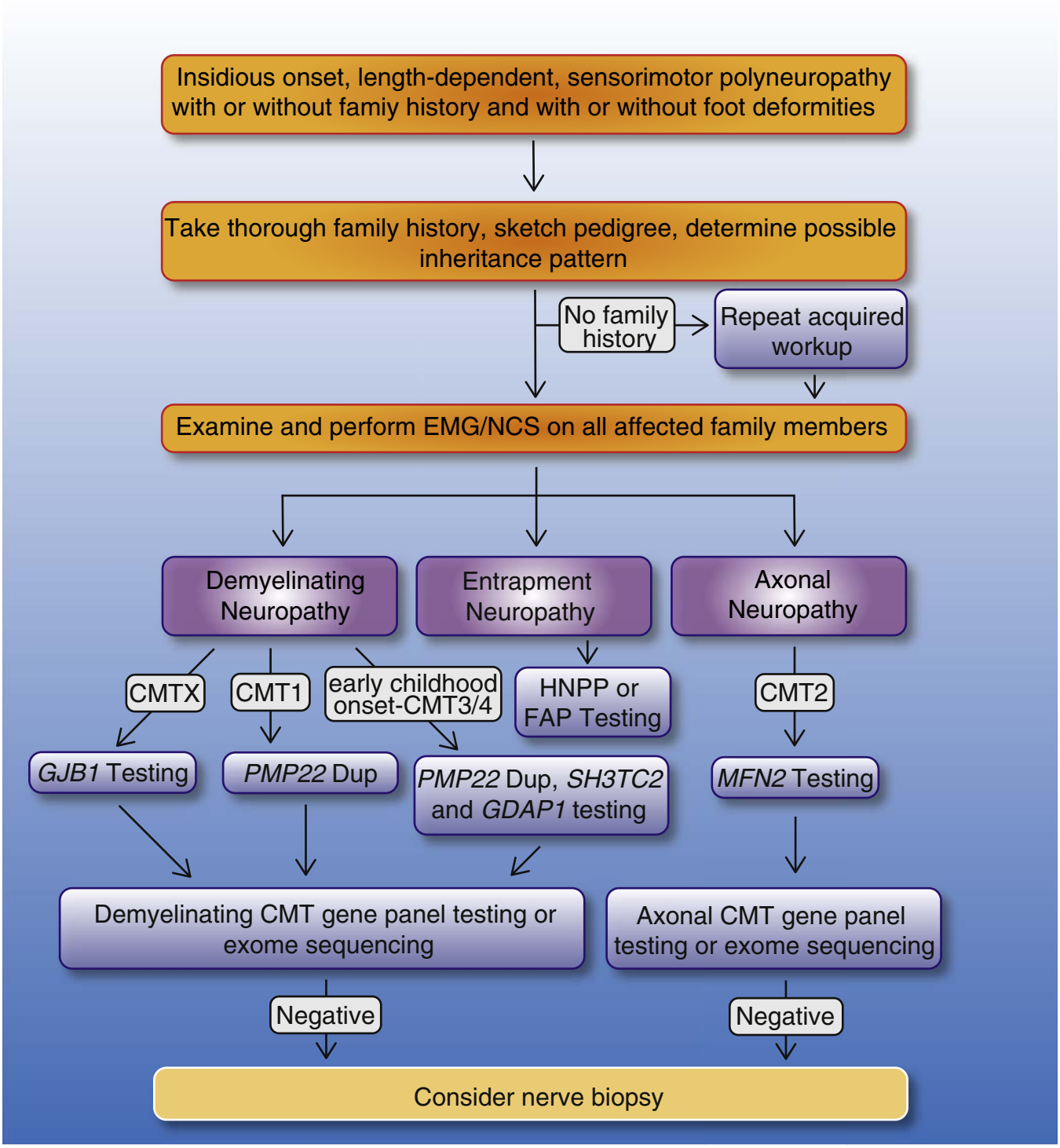


Fig. 14.4 Diagnostic algorithm for suspected Charcot-Marie-Tooth disease (CMT). Patients and family members with possible CMT should undergo examination and neurophysiologic testing (electromyography/NCS) to evaluate for the presence and type of neuropathy. Depending on age of onset, inheritance pattern, and physiological characteristics, patients can be divided into different disease types. CMT3 and CMT4 (CMT3/4) are severe, early-onset, autosomal dominant (AD) (CMT 3) or autosomal recessive (AR) (CMT4) demyelinating neuropathies. CMT1 and CMTX (CMT1/X) are less severe, late childhood or adult onset demyelinating neuropathy with AD (CMT1) or X-linked (CMTX) inheritance. The presence of multiple entrapment neuropathies in a family suggests the possibility of hereditary neuropathy with liability to pressure palsy or familial amyloid polyneuropathy. CMT2 is considered in axonal neuropathies in which acquired causes have been ruled out. As the cost of panel and exome sequencing has decreased and as the likelihood of capturing a mutation with these methods has improved, this has moved higher in the diagnostic algorithm. Here, we suggest single gene tests only when they can capture a significant portion of patients. Nerve biopsy is occasionally helpful in difficult cases. If genetic testing and biopsy do not confirm an inherited neuropathy, a repeat evaluation for acquired causes of neuropathy is warranted, particularly diabetes (glucose tolerance test), vitamin deficiency, and toxin exposure. *EMG*, Electromyography; *NCS*, nerve conduction study.

may identify features suggestive of an acquired neuropathy such as CIDPs, including asymmetry and conduction block. The most common form of CMT, CMT1A, typically shows severe, uniform reduction of motor and sensory conduction velocities (usually 15–30 m/second). In congenital or early childhood cases (CMT3), the conduction velocity is usually less than 20 m/second. HNPP shows only mild slowing of conduction velocities but frequently shows focal slowing or conduction block at common sites of entrapment.

When electrophysiology suggests a uniform, symmetric demyelinating polyneuropathy (forearm conduction velocities <38 m/second), the clinical diagnosis of CMT can be made and can usually be confirmed with genetic testing. When discussing the potential benefits of genetic testing, it is important that patients be educated that although there are currently no proven, specific therapies currently available for CMT, there are ongoing clinical trials for patients with specific forms of CMT in which they may be eligible to participate. The diagnostic yield for a single genetic test, i.e., testing for the PMP-22 duplication, for a patient with CMT1 is very high (~70%), whereas the yield of complete sequencing of all known CMT2 genes in a family with CMT2 is low (<20%) (Rossor, Polke, Houlden, & Reilly, 2013). Thus, the chances of making a definitive molecular diagnosis in a patient with CMT1 are quite high, whereas it remains low in CMT2, as additional genes remain to be discovered.

A reasonable diagnostic algorithm for the diagnosis of CMT is shown in Fig. 14.4; an American Academy of Neurology practice parameter on diagnostic testing of distal symmetric polyneuropathy is now a decade old (England et al., 2009). Our approach favors single-gene or small panel testing only when likely to capture a meaningful portion of patients, then reflexing to broad panel or exome testing. This is reflective of the decreasing costs of unbiased testing and the increasing need for molecular diagnoses.

In patients with uniformly demyelinating neuropathy on NCSs, a reasonable diagnostic approach is to first test for the PMP22 duplication/deletion, as this will be positive in the majority of patients. The second most common genetic cause of demyelinating polyneuropathy is CMTX1, with mutations in the gap junction beta 1 (GJB1) gene (also called connexin 32), responsible for about 7% of cases. These mutations are X-linked dominant, and females are often affected, although often with milder phenotypes than males with the same mutation. While usually clinically indistinguishable from other CMTs, a few families have been described with CNS demyelination presenting with ataxia, dysarthria, aphasia, disorientation, weakness, and hearing loss, especially in males. Spontaneously resolving confluent white matter changes may be seen on brain MRI. Furthermore, peripheral nerve demyelination is less severe than in CMT1A, with forearm nerve conduction velocities of 30 to 40 m/second in males and 30 to 50 m/second in females; nonuniform slowing and conduction block mimicking findings of CIDP may occur. If CMTX is suspected, it is reasonable to first sequence the GJB1 gene. If this test is negative, one should consider performing genetic testing for the other genes associated with the CMT1 or CMTX phenotype (see Fig. 14.4 and Table 14.2). The autosomal recessive demyelinating neuropathies usually have an earlier onset than autosomal dominant forms and may give an early childhood (DSS) or CHN phenotype.

Interestingly, while CMT2 patients with axonal physiology usually have mutations in genes distinct from CMT1, mutations in several of the above-mentioned genes mutated in CMT1 and expressed in Schwann cells can also cause CMT2. This finding highlights the dependence of Schwann cell–axon interactions on axonal health. The most common form of CMT2, CMT2A, is caused by mutations in the mitofusin 2 gene (MFN2) and may be the second most common cause of CMT overall (Verhoeven et al., 2006). Mitofusins are mitochondrial GTPases that regulate fusion of mitochondria, and many genes causative of axonal CMT are implicated in either mitochondrial function, axonal transport, or both (Baloh, Schmidt, Pestronk, & Milbrandt, 2007; Züchner & Vance, 2005). Although many genes causing CMT2 are ubiquitously expressed, the phenotype is believed to be selective to peripheral nerve due to profound energy demand along axons at long distances from the cell soma. Other genes found mutated in CMT2 are listed in Table 14.2. Several genes have been described that cause dominant intermediate CMT, in which the conduction velocity is intermediate between CMT1 and CMT2, similar to that of CMTX discussed earlier. Many genes that cause CMT2 still await discovery. Clinical exome sequencing analyzes only known genes but gathers data for all genes. With research consent, a good family history, and multiple samples from within the family, there is potential to identify novel causes of CMT with the help of clinical neurogeneticists and neurogenetics researchers.

Acquired causes of distal axonal sensorimotor polyneuropathy are more common than inherited causes. The diagnosis of CMT2 is usually made by first excluding other causes of axonal neuropathy such as diabetes mellitus, alcoholism, heavy metal and drug toxicity, nutritional deficiency, monoclonal gammopathy, and renal disease. When the available genetic tests are negative, nerve biopsy may be useful in selected cases in determining the etiology. For example, uniform onion bulb formations are the pathological hallmark of demyelinating CMT and, if present, would strongly support the diagnosis of CMT. In patients with a severe early-onset neuropathy, CNS involvement, and tightly curled hair, biopsy findings of giant axonal swellings are diagnostic of giant axonal neuropathy. Furthermore, findings of amyloid deposition (see section on FAP) or inflammation would point to an alternative diagnosis. One should also reconsider acquired causes of neuropathy and repeat blood tests for vitamin B_1, B_6, B_{12}, and E levels, glucose tolerance test, and serum and urine immunofixation. In cases in which an exhaustive search is negative, one should consider toxins, such as alcohol. When a clear diagnosis cannot be made, referral to a tertiary center is recommended rather than a trial of immunotherapy for possible diagnosis of CIDP, as the expense and/or risks of intravenous immunoglobulin or steroids rarely justify empiric use of these drugs in slowly progressive cases. It is important to recognize that the electrophysiological features associated with acquired CIDP can also occur with certain forms of inherited neuropathy. For example, CMT1B, CMTX1, CMT4C, HSAN1A, and CMT1D are examples of inherited neuropathies whose physiology may resemble that of an acquired neuropathy with nonuniform demyelinating findings (for associated genes, refer to Table 14.2).

TREATMENT

There are no specific therapies for CMT currently available. Physical and occupational therapy should be offered to patients since orthotics including ankle bracing and aids to improve dexterity (e.g., button and zipper holders) may improve quality of life. Orthopedic surgery for correction of foot deformities is often recommended, although surgery is not always necessary (see Chapter 9 for surgical management of neuropathies). Surgery such as tendon transfers may help prevent pressure ulcers or relieve pain caused by severe pes cavus, inverted feet, or other deformities. Well-made, specially fitted shoes and daily inspection of feet may be all that is required to prevent ulcers and pain over pressure points. Physical and occupational therapy are often helpful with regard to orthotics and exercises to maintain muscle bulk and coordination; however, evidence showing a benefit for most orthotics is lacking (Sackley et al., 2009). Exercise has generally shown benefit, but there is risk in excessive exercise, which can result in overwork weakness (Burns et al., 2017; Mori et al., 2019; Sman et al., 2015).

Patients in whom pain is a significant complaint may benefit from medications used for neuropathic pain, such as antiepileptics or antidepressants (see Chapter 6). Even though weak ankles and decreased sensation often affect balance, most patients remain ambulatory and the life expectancy is not shortened. A certified genetic counselor should be available to advise and help in the management of these patients and their families.

Physicians are often asked whether drugs prescribed for other purposes may potentially be harmful in CMT. Neurotoxic drugs, especially the chemotherapeutic agents paclitaxel, vincristine, and cisplatin, should be avoided if possible, but evidence demonstrating adverse effects of other drugs is limited. The CMT Association website (https://www.cmtausa.org/living-with-cmt/managing-cmt/medications/) lists drugs that have been reported to exacerbate CMT, although this potential risk should be weighed against any benefit. Regardless of whether the underlying pathophysiology is primarily demyelinating or axonal, disability in CMT correlates with axon loss. Thus, reductions in compound motor action potential (CMAP) amplitude and muscle atrophy are a much more important measure of functional status than conduction velocity on nerve conduction studies or demyelination on biopsy. Chronic demyelination eventually leads to axonal degeneration through an unclear mechanism, although one that is an area of active investigation. Thus, therapies targeted at promoting neuronal survival and preventing axonal degeneration may be broadly applicable to all causes of inherited and acquired neuropathies.

There are reports of patients with CMT1 developing superimposed CIDP with acute or subacute progression, proximal involvement, or markedly elevated CSF protein, asymmetric NCSs, and an inflammatory sural nerve biopsy. Whether there is an increased association of CIDP with CMT is unclear, but prednisone, immunoglobulin, or other immunotherapies should be considered in patients who develop rapid clinical deterioration (Dyck, Swanson, Low, Bartleson, & Lambert, 1982; Ginsberg et al., 2004). There is evidence in mouse models that the immune system may play a role in the pathogenesis of CMT (Gabriel, Gregson, Wood, & Hughes, 2002); however, there is no evidence that immunosuppressive therapies are beneficial in typical CMT.

Counseling patients with HNPP and HNA to avoid compression of the nerves at susceptible sites is of utmost importance because of their susceptibility to develop entrapment neuropathies (see Chapter 17 regarding specific therapies). As in noninherited entrapment neuropathies, the most common sites of compression are the wrist, elbow, knee, and shoulder. Patients should be advised to avoid repetitive and strenuous use of these joints and to avoid static and/or awkward positioning. Focal neuropathies usually recover spontaneously, although the recovery is often incomplete; surgical release of the entrapment is controversial (Grossman, Feinberg, DiCarlo, Birchansky, & Wolfe, 2007) but is generally not advisable because nerves are especially vulnerable to manipulation and minor trauma.

EXPERIMENTAL THERAPIES FOR CMT: A GROWING PIPELINE OF TARGETED THERAPIES

As the molecular basis of inherited neuropathies becomes better understood, specific therapies will likely become available. The best example of this rational therapeutics approach applied to CMT is the development of modifiers of PMP22 gene expression. The gene dosage of PMP22 is critical for peripheral nerve myelination, as a duplication of the PMP22 locus (increasing gene expression by only 50%) causes CMT1A, whereas a deletion of this locus (reducing expression by 50%) causes HNPP. The relatively high frequency of CMT1A can be explained by the genomic location of the PMP22 gene, in a region of chromosome 17 that is flanked by two tandem duplications, thereby increasing the frequency of unequal crossing-over during meiosis (Saifi, Szigeti, Snipes, Garcia, & Lupski, 2003).

CMT1A is the most common inherited neuropathy, responsible for about half of all CMT cases, and may be caused by both duplication of (most common) and point mutations in PMP22. Transgenic mice and rats overexpressing human PMP22 replicate many of the pathologic features of CMT1A and thus have been used to model human CMT.

Ascorbic acid (vitamin C) had previously been shown to be required for in vitro myelination of axons by Schwann cells in culture (Carey & Todd, 1987), and vitamin C, along with other antioxidant vitamins, is believed to have neuroprotective properties (Grandis & Shy, 2005). Passage and colleagues showed in 2004 that administration of high-dose ascorbic acid to mice overexpressing PMP22 led to marked improvement of locomotor deficits and reduced demyelination (Passage et al., 2004). Interestingly, ascorbic acid, but not other antioxidants, specifically inhibits PMP22 gene expression, and thus, ascorbic acid may treat the underlying cause of CMT1A. However, a 2-year study of 277 patients with CMT1A randomized to receive either 1.5 g ascorbic acid or placebo showed no difference in the CMTNS, nor a series of secondary endpoints (Pareyson et al., 2011).

A similar approach was carried out with progesterone antagonists, shown to decrease PMP22 expression in Schwann cell cultures and transgenic mice and rats (Horste et al., 2007; Sereda, Horste, Suter, Uzma, & Nave, 2003). The available progesterone antagonist, onapristone, shows severe toxicity in humans (Klijn, 2000), and thus, new progesterone antagonists are currently under development.

A third drug repositioning effort in CMT1A is in development and has shown efficacy in early clinical studies. This work is based on in silico analysis performed to computationally

identify compounds that would impact signaling pathways known to be important for myelin gene expression (e.g., cAMP dependent, neurosteroid, and Akt/Erk signaling). Working backward from the pathways they wished to modulate, they constructed a model whereby G protein–coupled receptor (GPCR)-based signaling results in PMP22 gene expression through a series of intermediate effector molecule signaling pathways. The group that performed this work hypothesized that targeting multiple GPCRs with FDA-approved compounds would have a synergistic effect on PMP22 gene expression. After selecting only those medicines that would be tolerated when used chronically, they narrowed the list to three drugs: baclofen, naltrexone, and D-sorbitol. In a coculture system with dorsal root ganglion neurons and Schwann cells derived from a PMP22 transgenic rat model of CMT1A, it was determined that this cocktail of compounds decreases the expression of PMP22 relative to MPZ and housekeeping genes. All three compounds independently increased myelination, decreased Pmp22 mRNA levels (without affecting MPZ levels), and acted in concert to produce the best response when combined. Oral treatment of the CMT1A rat model demonstrated a statistically significant improvement in behavioral and pathological measures of disease (Chumakov et al., 2014).

As a cocktail of repurposed medicines, this entered clinical testing in a phase 2 study of 80 patients with CMT1A who were randomized to receive either 6 mg baclofen, 0.7 mg naltrexone, and 210 mg sorbitol (low-dose PXT3003); 12 mg baclofen, 1.4 mg naltrexone, and 420 mg sorbitol (high-dose PXT3003); or placebo. The highest dose group showed evidence of improvement in the CMTNS and the ONLS. Patients were less likely to deteriorate in the treatment arms. Although not yet published, press releases suggest that a phase 3 study of PXT3003 has been performed (15-month placebo-controlled study of 323 patients randomized to placebo, low-dose, and high-dose PXT3003 at a 1:1:1 ratio), and another release has suggested that the FDA has requested another late-stage trial because of formulation and stability concerns that impacted dropout rate in one arm of the study.

The work on repurposing small molecules demonstrates how identification of the underlying gene defect in CMT1A, understanding of the basic biology of myelin formation, and development of animal models can rapidly translate to clinical trials for patients (see Fig. 14.1).

Despite much work on small molecule approaches, gene-targeted approaches are likely to offer more direct and impactful therapies in CMT1A. RNA or ASO therapies targeting *PMP22* are likely to be the first to reach investigational trials. The development of a *PMP22*-targeted therapy is likely to be aided by the utility of a peripheral biomarker in *PMP22* mRNA levels in skin biopsies (Nobbio et al., 2014). ASO therapy has shown benefit in mouse and rat models of increased PMP22 copy number (Zhao et al., 2018). Systemic administration will be required for Schwann cell targeting, and systemic administration can be limited by toxicities in liver and kidney.

While the previous therapies address the root cause of CMT1A, there is considerable evidence that the cause of disability in CMT is due to secondary axon loss rather than demyelination, suggesting that axon protection is another path to therapeutic intervention. This is believed to be due to disruption of interactions between Schwann cells and axons. Thus, therapies of neurotrophic factors devised to prevent axonal degeneration may also be efficacious in inherited demyelinating neuropathies (Chao, Rajagopal, & Lee, 2006).

One such trophic factor that has shown promise in CMT1A is neurotrophin 3 (NT-3). NT-3 is a small peptide produced by Schwann cells that autoregulates their proliferation and differentiation. Sahenk and colleagues performed a single-blinded pilot study of NT-3 in eight CMT1A patients. They reported that subcutaneous administration of NT-3 (5 μg/kg tiw) led to a significant improvement of sensory symptoms and reflexes, but no change in motor outcome (Sahenk et al., 2005). Furthermore, NT-3 increased axonal regeneration in two CMT1A animal models. Although this therapy shows promise, larger studies are needed to determine the efficacy of NT-3. The national clinical trials registry suggests that recruitment will soon open for a gene therapy trial to deliver NTF3 (the gene encoding NT-3) using an AAV1 vector (ClinicalTrials.gov, NCT03520751).

While most approaches in therapeutics development focus on the degenerating nerve in hereditary neuropathy, some have focused on maintaining and improving muscle strength as a means of preventing weakness. Follistatin promotes muscle growth by sequestering multiple tumor necrosis factor-beta ligands that inhibit growth. ACE-083 is a recombinant protein biologic therapy that is a fusion of follistatin to the IgG2 Fc domain to induce dimerization. It has shown benefit in the Trembler-J mouse model of CMT1A (Pearsall et al., 2019). Intramuscular injection of ACE-083 is in a clinical trial for tibialis anterior injection in CMT (ClinicalTrials.gov, NCT03124459).

Preclinical data in several additional CMT subtypes show great promise. Intrathecal viral gene therapy has shown benefit in rodent models of CMTX1 (Kagiava et al., 2018, 2019) and CMT4J (Lutz et al., 2019). In CMT2A, determining the structure of mitofusin 2 allowed determination of fusion-constrained and fusion-permissive conformations of the protein. Based upon this determination, a minipeptide was designed to destabilize the fusion-constrained conformation of mutant MFN2, thereby restoring function in cells (Franco et al., 2016). More recently, small molecules that allosterically mimic the peptide and promote mitochondrial fusion have been identified that can reverse some of the mitochondrial fusion and transport defects seen in mouse models of the disease (Rocha et al., 2018). These small molecules have the potential to help patients with mutations in the heptad repeat domains but are not capable of improving MFN2 function for patients with GTPase domain mutations (the more common site of mutation).

A recent publication on CMT outlined a paradigm for accelerated preclinical experiments for personalized therapies. A patient with a unique *GARS* mutation and a severe form of CMT2D was identified, a mouse with an equivalent mutation was generated using CRISPR/Cas9, and an allele-specific miRNA delivered with self-complementary AAV9 showed benefit in this model (Morelli et al., 2019). This shows how novel genetic engineering tools might compress preclinical development pipelines for individualized therapies. It can be difficult to imagine a landscape where individual neuropathy patients could

receive tailored therapies. Despite this, recent work in a fatal neurodegenerative disease called neuronal ceroid lipofuscionsis (Kim et al., 2019) suggests that the obstacles to this sort of personalized therapy are no longer scientific. It will be interesting to see if pharmaceutical companies, regulators, and payers are able to catch up to the pace of research and forge a path for these truly personalized therapies.

Promising results in animal models do not always translate into effective human treatments, as was shown with ascorbic acid, and as has been shown too often in clinical trials for ALS (Petrov, Mansfield, Moussy, & Hermine, 2017); thus, caution must be taken when counseling patients regarding the promise of experimental drugs until their registration and approval.

HEREDITARY MOTOR NEUROPATHIES (HMNS)

The term "hereditary motor neuropathy" primarily refers to degenerative disorders of lower motor neurons that innervate *distal* muscles, whereas when proximal muscles are preferentially affected, the disorder is referred to as SMA, discussed in Chapter 13. Because HMNs are about 10 times less common than SMA, these disorders are often referred to as distal SMA to emphasize this distinction from typical SMA. Not surprisingly, there is significant overlap between HMN and CMT2, including several allelic disorders that differ in their classification depending on whether there is sensory involvement (e.g., GARS mutations cause both CMT2D and HMN-Va). There is also overlap in clinical presentation of some hereditary forms of ALS with HMN; for example, ALS-4 is a juvenile form of ALS with very slowly progressive distal muscle weakness and atrophy (see Chapter 12). Genetic testing is now available for most of these disorders (see Table 14.2). There are no specific therapies yet available, but patients' symptoms are treated similarly to patients with CMT discussed earlier.

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSANS)

The HSANs comprise a group of rare disorders with the primary manifestation of peripheral sensory loss and/or autonomic dysfunction (also discussed in Chapter 5). These disorders must be distinguished from inherited neuropathies of large primary afferent sensory neurons with or without cerebellar and/or spinocerebellar neurons (spinocerebellar degeneration such as Friedreich or spinocerebellar ataxia). As shown in Table 14.2, HSAN is typically classified based on inheritance pattern into autosomal dominant (type 1) and autosomal recessive (types 2–5) forms.

CLINICAL PRESENTATION

The autosomal dominant and recessive forms of HSAN have very different clinical presentations. Autosomal dominant HSAN (HSAN type 1, also called hereditary sensory neuropathy type 1 or HSN-1) presents as a slowly progressive, length-dependent sensory axonal neuropathy (Auer-Grumbach, 2008). Onset is usually in the second or third decade of life. Motor and autonomic manifestations (usually loss of sweating) are variable but are usually much less severe than the sensory symptoms. Examination also reveals distal loss of reflexes and sensation of all modalities, and foot ulcers are common. In addition, there are characteristic but variable findings seen in subtypes of HSAN 1. Patients with a mutation in the serine palmitoyltransferase long chain gene (SPTLC1) frequently develop hearing loss, peroneal weakness, and hyperhidrosis (Klein et al., 2005). Another locus on chromosome 3 has been found in families with prominent cough and gastroesophageal reflux, variable sensorineural hearing loss, and lack of motor involvement (Spring et al., 2005).

In contrast, the autosomal recessive forms of HSAN (types 2–4) are usually congenital in onset, with a generalized loss of sensory and autonomic fibers (Axelrod & Simson, 2007). An insensitivity to pain frequently causes severe acral mutilation and arthropathy, frequently leading to more severe morbidity than the CMT patients discussed previously. HSAN type 2 is a rare autosomal recessive disorder characterized by congenital sensory loss and severe acral mutilation. HSAN type 3, also known as familial dysautonomia, is probably the most common form of HSAN and is seen almost exclusively in the Ashkenazi Jewish population. Infants present with hypotonia and profound dysautonomia, causing poor feeding, high fevers, skin blotching, and cardiovascular instability. Pain and temperature sensation are less affected than in other forms of HSAN. HSAN type 4 is characterized by anhidrosis causing recurrent high fevers and characteristic skin thickening, severe ulceromutilation and arthropathy due to pain insensitivity, and CNS involvement in more severely affected patients.

DIAGNOSIS

HSAN type 1 can be difficult to distinguish from other causes of slowly progressive, length-dependent sensory neuropathies. This diagnosis should be considered in patients developing a sensory-predominant axonal neuropathy at a young age (often second or third decade of life) or with an autosomal dominant inheritance pattern. The chronicity and severity of the sensory loss lead to severe foot complications in some kindred, including plantar ulcers, spontaneous fractures, and osteomyelitis. Electrodiagnostic testing is performed to confirm the presence of a sensory axonal neuropathy, and laboratory testing including a glucose tolerance test is helpful in excluding more common acquired sensory neuropathies. Skin biopsy and sudomotor testing may be helpful in confirming small fiber sensory and autonomic involvement, respectively. Nerve biopsy may be helpful in difficult cases to exclude amyloidosis and vasculitis. In HSAN types 2–5, diagnosis is usually based on the constellation of clinical signs.

As with other inherited neuropathies, genetic testing should be performed for definitive diagnosis if possible. Exome sequencing and panel testing are available for HSAN patients. Carrier testing is also available for familial dysautonomia/HSAN 3 (IKBKAP) and is encouraged in the Ashkenazi Jewish population, where carrier frequency estimated to be about 1 in 30 (Rubin & Anderson, 2007).

TREATMENT

The mainstay of treatment in HSAN types 1 and 2 is in preventing ulcerations, the major cause of morbidity. The same general precautions and treatments of diabetic feet

are recommended (see Chapters 8 and 21) because sensory loss is length dependent in HSAN type 1. In contrast, in HSAN 2 and 4, prevention and treatment of self-mutilation is much more difficult given the infantile onset and generalized symptoms. Smoothing of teeth or tooth extractions may be required in children with severe ulcero-mutilation. A case study demonstrated a 98% reduction of self-injurious behavior in an 11-year-old boy using habit-reversal behavioral therapy (Kuhn, Hagopian, & Terlonge, 2008). Braces may be helpful to prevent osteoarthropathy of weight-bearing joints. Treatment of dysautonomia in patients with HSAN types 3 and 4 is particularly challenging and is discussed in detail in Chapter 5.

SPTLC1 and SPTLC2, two genes mutated in patients with HSAN 1, encode serine palmitoyltransferase enzymes. Mutant SPTLC1 enzymes show a shift in avidity favoring L-alanine as a substrate instead of L-serine. The products of the reaction of L-alanine catalyzed by palmitoyltransferase are neurotoxic deoxysphingolipids. In vitro studies demonstrate that increases in L-serine concentration can shift the kinetics to favor the serine substrate and reduce the production of neurotoxic compounds (Garofalo et al., 2011). A pilot study of 14 patients demonstrated that L-serine supplementation reduced levels of toxic deoxyspingolipids (Garofalo et al., 2011). There is preclinical evidence that ASOs can be used to correct the splicing defect in a common IKBKAP mutation that causes familial dysautonomia (Sinha et al., 2018).

SYNDROMIC INHERITED NEUROPATHIES

FAMILIAL AMYLOID POLYNEUROPATHY

Like HSAN type 1, FAP is also an autosomal dominant, adult-onset polyneuropathy, predominantly affecting small caliber sensory and autonomic fiber (Sekijima et al., 2018). Unlike HSAN, though, FAP is a systemic disease, and patients frequently develop restrictive cardiomyopathy, nephropathy, ocular symptoms, or involvement of other tissues. In addition to inherited amyloidoses, acquired forms of systemic amyloidosis also cause neuropathy (Kapoor, Rossor, Jaunmuktane, Lunn, & Reilly, 2019). Approximately 20% of patients with immunoglobulin light chain (AL) amyloidosis develop neuropathy, and even more of these patients have symptoms of carpal tunnel syndrome or other entrapment neuropathies. Also, patients on chronic dialysis can develop amyloidosis and carpal tunnel syndrome from deposition of β_2-microglobulin. Here, we will focus on the inherited amyloid neuropathies.

FAP is most commonly caused by a missense mutation in transthyretin (TTR), an abundant plasma protein synthesized in the liver that binds and transports thyroid hormone and vitamin A (Planté-Bordeneuve, 2017). Over 100 missense mutations in TTR have been described that are believed to cause instability of the TTR tetramer, misfolding of the monomeric protein, and a propensity to form amyloidogenic fibrils that are deposited extracellularly. This form of FAP is referred to as hTTR amyloidosis. A V30M mutation is by far the most common mutation, although there is little correlation between genotype and phenotype, with a few exceptions. Two other genes have been shown to be mutated in a few families with FAP: apolipoprotein AI (ApoAI) and gelsolin, which both have distinctive clinical features discussed later (see Table 14.3). The mechanism whereby amyloid induces neuropathy is unclear but is believed to be due to a direct toxic effect of amyloid oligomers on neurons.

CLINICAL PRESENTATION

Patients with hTTR amyloidosis typically present in their second or third decade with slowly progressive pain and allodynia in their limbs (Andrade, 1952). Patients may also develop autonomic symptoms including impotence and orthostatic hypotension. Like in diabetic neuropathy, this initial small fiber neuropathy typically progresses to involve large myelinated sensory fibers, and later in the disease patients develop a length-dependent axonal sensorimotor polyneuropathy. Carpal tunnel syndrome is rarely a presenting complaint in families with the V30M mutation but is common in families with several other mutations. The course of the disease is usually slowly progressive, although cases of rapidly progressive disease have been reported. Patients typically become wheelchair bound by an average of 10 years after onset and may succumb to infection or cardiovascular collapse.

The involvement of other systems is variable and depends upon the tissues in which the amyloid becomes deposited. Involvement of the cardiovascular system is very common, and patients frequently develop progressive conduction abnormalities and restrictive cardiomyopathy, often leading to arrhythmias and heart failure, respectively. In addition to being produced in the liver, TTR is also produced at lower levels in the retina and choroid plexus, explaining the finding of amyloid deposits in the vitreous and leptomeninges, respectively. Some patients may develop CNS involvement due to leptomeningeal amyloid deposits and may have elevated CSF protein and meningeal enhancement on MRI. The gastrointestinal system may be affected due to both involvement of autonomic nerves supplying the gut and amyloid deposition in the bowel wall causing a protein-losing enteropathy. Although other organs such as the kidneys frequently develop amyloid deposits in patients with TTR mutations, these deposits are usually asymptomatic.

Patients with mutations in ApoAI develop a clinical presentation that is very similar to that of patients with TTR mutations; however, these patients also develop progressive renal failure (Van Allen, Frohlich, & Davis, 1969). Patients with gelsolin mutations have a very distinctive clinical presentation, initially presenting with a pathognomonic lattice corneal dystrophy, often leading to diagnosis. These patients usually develop cranial neuropathies in their fourth or fifth decade and later develop a length-dependent polyneuropathy (Hornigold, Patel, Ward, & O'Connor, 2006).

DIAGNOSIS

Early diagnosis of FAP depends on it being considered in all patients who present with an otherwise unexplained progressive sensorimotor axonal polyneuropathy, particularly in patients with autonomic or cardiovascular symptoms, early small fiber involvement, or a family history of neuropathy. Considering FAP early in the diagnostic workup is particularly important now that treatments for hTTR amyloidosis have become available. The primary differential diagnostic considerations are acquired amyloidosis, diabetes, HIV, leprosy, and toxic neuropathies. In a cohort of 90 FAP patients

who presented without family history, the most common misdiagnosis was chronic inflammatory demyelinating polyneuropathy, likely due to elevated CSF protein, slowed nerve conduction velocities, or negative biopsy (Planté-Bordeneuve et al., 2007). Other inherited neuropathies that may mimic FAP are HSAN and Fabry disease, discussed later in this chapter.

If there is a family history of FAP, diagnosis is best made with genetic testing. However, in the majority of cases in which there is not a positive family history, historically the first step towards making the diagnosis once it is considered has been to perform a tissue biopsy, although a negative biopsy does not rule out this diagnosis. Sural nerve biopsy has been reported to be insensitive for making the diagnosis of amyloidosis in one small cases series (Simmons et al., 1993), but in several other studies, nerve biopsy has been shown to be as sensitive, if not more sensitive, than biopsies from other sites, with a sensitivity of about 80 (Planté-Bordeneuve et al., 2007). Other tissues such as rectum, labial salivary gland, and subcutaneous fat pad have been reported to have a similar sensitivity and can also be examined. Skin biopsy is useful in evaluating small fiber neuropathy and has been shown to be a sensitive and specific tool for detection of amyloid in FAP (Ebenezer et al., 2017; McArthur, Stocks, Hauer, Cornblath, & Griffin, 1998). Biopsies stained with Congo Red reveal amorphous deposits of congophilic material that are apple-green birefringent under polarized light. However, due to the patchy nature of the deposits, multiple sections may be required to identify the amyloid.

Historically, testing for hTTR mutation would follow nerve biopsy and pathological diagnosis of amyloid. As the cost of genetic testing has come down, many physicians at tertiary care centers perform genetic testing before biopsy and have a higher threshold to consider invasive biopsy as the sensitivity of genetic testing has improved. Biopsy often follows negative genetic testing, and in patients with amyloid on biopsy, immunohistochemistry for light chains, *TTR*, and serum amyloid A protein is occasionally useful in determining the nature of the amyloid deposit. Serum and urine immunofixation electrophoresis should be performed to evaluate for a monoclonal plasma cell dyscrasia causing light chain amyloid. If the diagnosis of FAP is confirmed by DNA sequencing, further genetic counseling of the patient and family members should be performed. The presence of cardiac involvement should be determined with EKG and echocardiogram.

TREATMENT

Since the first edition of this volume, the treatment of hTTR has been revolutionized by targeted therapies. Among hereditary neuropathies, hTTR has been an attractive target because the liver is more accessible than the motor and sensory neurons of the peripheral nervous system.

Patisaran is a double-stranded siRNA in a lipid complex administered intravenously. Patisaran results in knock-down of *TTR* mRNA transcripts, decreasing liver production of mutant and wild-type TTR protein. Intravenous patisaran showed significant benefit in a phase 3 randomized, placebo controlled study of 225 patients (randomized to placebo and patisiran at a 1:2 ratio) with TTR mutations measured by mNIS+7 and other secondary endpoint (Adams et al., 2018). This was the first FDA-approved siRNA-based therapy.

Similar to patisaran, inotersen is another nucleotide-based therapy that is approved for hTTR. Inotersen is a 2′-*O*-methoxyethyl–modified ASO that binds TTR mRNA and prevents its translation, decreasing levels of wild-type and mutant TTR. Subcutaneous injection of inotersen showed benefit in mNIS+7 and other secondary endpoints (Benson et al., 2018).

The next therapies in late-stage hTTR clinical studies, tafamidis and AG10, are orally bioavailable small molecules that stabilize the TTR tetramer to prevent dissociation, release from the liver, and deposition. Tafamidis was studied in neuropathy in one study of 125 patients and showed modest benefit but did not cross the threshold of significance (Coelho et al., 2012). Both stabilizers are at different stages of clinical development for hTTR cardiomyopathy and it is uncertain whether their developers will apply for registration for neuropathy.

Historically, the only therapy proven to be effective in FAP had been liver transplantation. In this era of effective targeted therapies, the risk-benefit ratio will probably make liver transplantation far less common. In a large series of 84 patients undergoing transplantation for FAP in Sweden over a 15-year period (1990–2005), less than 10% had improvement in symptoms, although in over half, transplantation halted the progression of the disease (Yamamoto et al., 2007). In patients who do not respond to transplantation, the progression is thought to be due to continued deposition of wild-type TTR. Patients with ApoAI mutations who also develop severe renal involvement may benefit from combined liver and kidney transplant (Gillmore et al., 2001), and patients with gelsolin amyloidosis may be effectively treated with corneal transplantation.

Since FAP is a systemic disease, there are also many symptomatic treatments to consider. As in acquired painful neuropathies, neuropathic pain may respond to antiepileptic and antidepressant medications (see Chapter 6). Vitrectomy is often effective for ocular amyloidosis. A pacemaker may be required for patients who develop arrhythmias or cardiomyopathy.

FRIEDREICH ATAXIA

Inherited diseases causing degeneration of the spinocerebellar tract have many genetic causes and are commonly associated with peripheral neuropathy (Table 14.3). Large fiber sensory neuropathy is a common clinical feature of FRDA and spinocerebellar atrophy with axonal neuropathy (SCAN1) and is a variable finding in most other spinocerebellar ataxias and ataxia telangiectasia. Vitamin E deficiency (either acquired or rare inherited forms abetalipoproteinemia and ataxia with vitamin E deficiency, see below and Table 14.3) can mimic the neurologic manifestations of FRDA and should be considered in the differential diagnosis given that patients respond to high-dose vitamin E (100 mg/kg/day) and fat restriction. Here, we will focus on FRDA, the most common genetic ataxia in North America and Europe.

CLINICAL PRESENTATION

FRDA is an autosomal recessive neurodegenerative disease characterized by progressive ataxia, dysarthria, nystagmus, and sensory loss. Loss of sensory neurons in the dorsal root

ganglion occurs early, followed by degeneration of the spinocerebellar tract, posterior columns, and pyramidal tracts. Although the clinical picture is usually dominated by ataxia, large fiber neuropathy is a common cause of disability. Patients usually develop progressive proprioceptive loss, foot deformity, and kyphoscoliosis and on examination classically have absence of deep tendon reflexes with extensor plantar reflexes. Other common clinical findings include hypertrophic cardiomyopathy, a common cause of morbidity and mortality in FRDA, diabetes, sensorineural hearing loss, and optic neuropathy (Pandolfo, 2008b).

DIAGNOSIS

Genetic testing of the frataxin gene (*FXN*) reveals an expansion of the GAA triplet-repeat in the first intron, causing a reduction in frataxin levels. Normally, there are fewer than 33 GAA repeats, whereas in patients, repeats are from 67 in length to over 1000. Rarely (~3% of cases), one allele contains a point mutation elsewhere in the gene rather than an expanded triplet repeat (Lynch, Farmer, Balcer, & Wilson, 2002). Electrodiagnostic testing shows a sensory axonal neuropathy/neuronopathy (non–length-dependent decrease in sensory amplitudes), and sural nerve biopsy shows axonal atrophy with mild demyelination and remyelination.

EMERGING TREATMENTS

As the molecular etiology of FRDA becomes elucidated, targeted pharmacotherapies affecting specific pathogenic pathways and gene-targeted therapies addressing the underlying gene defect become increasingly promising (see Fig. 14.5) (Clay, Hearle, Schadt, & Lynch, 2019; Strawser et al., 2017). FRDA is often considered a mitochondrial disease caused by mutations in a nuclear-encoded gene because the disorder is thought to be due to loss of frataxin function in mitochondria. Increasing evidence suggests that, like in Fragile X syndrome, the triplet-repeats in noncoding portions of the gene causes the DNA to form a "sticky" triple helical structure, leading to decreased expression of frataxin (Wells, 2008). There are several downstream consequences of the loss of FXN expression and function in mitochondria. Broadly speaking, therapies in the development pipeline try to (1) decrease oxidative stress or increase mitochondrial function or (2) increase FXN protein expression. There has been a great deal of interest in this disease because of its relatively high prevalence among orphan diseases. The FRDA research alliance lists over 20 approaches that are being pursued by academic or industry groups (Strawser et al., 2017) (curefa.org). Here, we will focus on the approaches that have undergone clinical efficacy testing and those that we feel are most promising to address the root causes of the disease.

Approaches to Increase Mitochondrial Function or Decrease Oxidative Stress

The most investigated therapy in FRDA, studied even before the frataxin gene was discovered, is antioxidant therapy (Pandolfo, 2008a). One of the early rationales for this treatment was the similarity of symptoms between FRDA and vitamin E-deficient ataxia. Once the increase in reactive oxygen species (ROS) was identified in FRDA and oxidative stress became a widely believed mechanism of neurodegeneration, antioxidant therapy became widely used in patients despite the lack of evidence of efficacy. Many early studies performed with antioxidant agents in FRDA were uncontrolled, underpowered, and without clearly defined clinical endpoints. The use of multiple standardized rating scales (the International Cooperative Ataxia Rating Scale [ICARS] and Friedreich Ataxia Rating Scale [FARS]) and the establishment of international consortia have significantly improved the quality of clinical studies.

The most well-studied antioxidant therapy is idebenone, a synthetic coenzyme Q analog that has showed inconsistent results in early phase clinical trials. Higher doses are generally very well tolerated (Di Prospero, Sumner, Atkinson, Fischbeck, & Taylor, 2005), although there are reports of neutropenia that is reversible upon drug cessation (Di Prospero, Baker, Jeffries, & Fischbeck, 2007). Thus, patients taking high doses should have routine monitoring of blood counts. There was a significant effect of idebenone on ICARS in patients who were not yet wheelchair bound, but analysis including all patients did not show significant differences in ICARS, FARS, nor activities of daily living total scores (Di Prospero et al., 2007). Another 6-month study of high doses of idebenone failed to confirm this benefit in ambulatory patients (Lynch, Perlman, & Meier, 2010) and showed no impact on ejection fraction and cardiac function (Lagedrost et al., 2011). EPI-743 is an enhanced version of idebenone with structural similarity to vitamin E that has similarly ambiguous results in the clinic (Zesiewicz et al., 2018). In conclusion, there is still uncertainty about whether idebenone and other coenzyme Q–like antioxidants offer benefit to patients with FRDA. With so many other approaches under clinical investigation with more direct therapeutic rationale, it may be difficult to justify any additional larger trials.

In addition to oxidative stress, there are several well-defined downstream consequences of frataxin loss. Frataxin functions in iron metabolism and is required for the mitochondrial generation of iron-sulfur clusters, cofactors essential to the function of several enzymes of the respiratory chain and Kreb cycle such as aconitase. Decreased frataxin expression causes iron overload in mitochondria, and the abnormal iron chemistry generates increased ROS and sensitivity to oxidative stress. As shown in Fig. 14.5, all of these consequences of frataxin loss are investigational targets for FRDA drug therapy.

Iron chelation therapy to reduce iron overload has been attempted. Iron accumulation has not been proven to be the driver of disease pathogenesis in FRDA and iron chelators have had mixed results in the clinic, where early compounds failed because of poor cell permeability (Richardson, 2003). Deferiprone has been tried alone and in combination with idebenone and has shown mixed results depending on the dose, and no large placebo-controlled studies have been performed to establish its efficacy (Arpa et al., 2014; Pandolfo & Hausmann, 2013; Velasco-Sánchez et al., 2011).

PGC1α is a transcription factor that is a master regulator of mitochondrial biogenesis and acts in part by increasing the expression of NRF2. The expressions of both PGC1α and NFR2 are reduced in FRDA patients (D'Oria et al., 2013; Marmolino et al., 2010; Paupe et al., 2009; Shan et al., 2013). NRF2 directs the expression of a broad antioxidant and anti-inflammatory gene signature. Omaveloxolone inhibits KEAP1 and slows the degradation of NRF2, thereby increasing its activity. A 2-year phase 2 double-blind

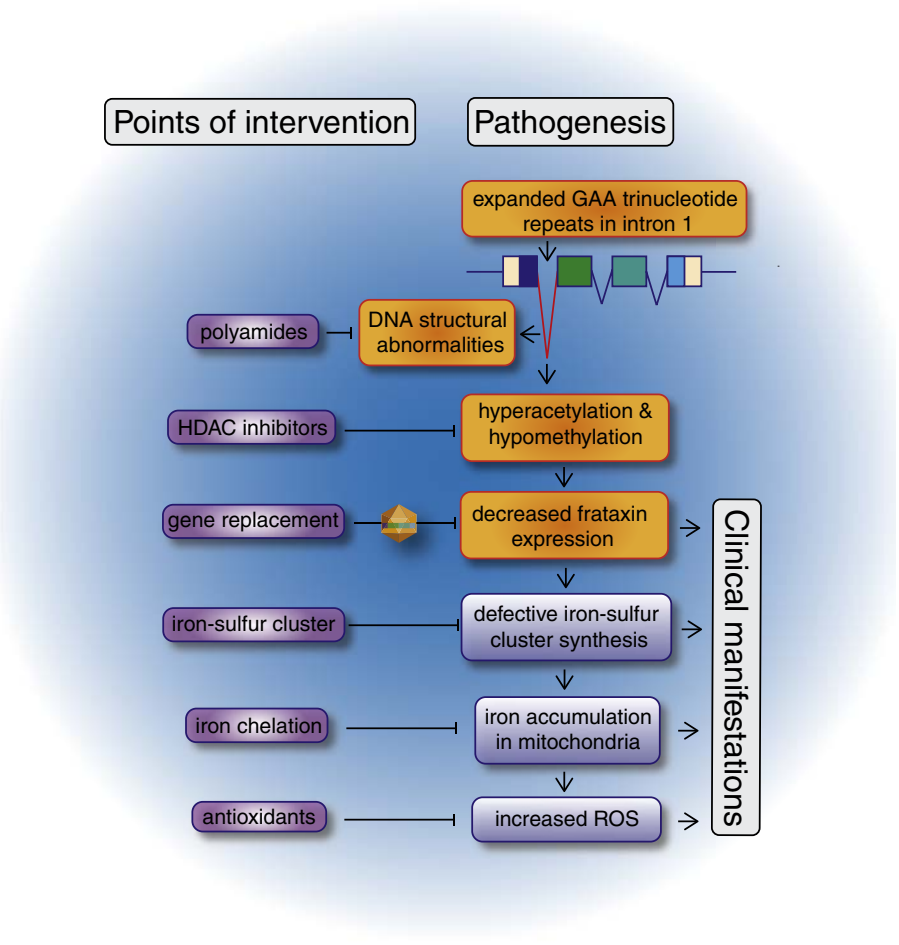


Fig. 14.5 Pathogenesis and therapeutic development of Friedreich ataxia. The *arrows* designate a hypothesized pathogenic cascade of Friedreich ataxia in which the cause of disease is believed to be due to decreased frataxin expression. An expansion of the GAA triplet repeat causes DNA structural changes that cause the DNA to become hypoacetylated and hypermethylated, thereby reducing gene expression. Reduced frataxin protein leads to defective iron (Fe) sulfur cluster synthesis, mitochondrial iron accumulation, and increased reactive oxygen species (*ROS*). Each of these abnormalities may contribute to the disease phenotype directly and indirectly (thus multiple arrows leading to clinical manifestations), and it is likely that an effective therapy will target multiple pathogenic steps. Therapies currently under development are listed below each pathogenic step and described in the text. ⊣ indicates therapy to ameliorate this pathogenic step.

placebo-controlled registrational study has been conducted with omaveloxolone in FRDA, but the results have not yet been published. Press releases from the developers of omaveloxolone have indicated a statistically significant improvement in the primary endpoint, a modified version of the FARS. Initial clinical testing suggested that those patients with pes cavus had a less robust response to the therapy (perhaps because of their inability to participate in a portion of the rating scale) (Lynch et al., 2019a) and were thus excluded from the study. Those patients with pes cavus are likely those with the most significant neuropathy, and thus it will be difficult to determine what the possible effects of this therapy might be on the neuropathic component of the disease. Despite these limitations, the significance of a potential positive readout in a registrational trial should not be underestimated, and this may well become the first FDA-approved therapy for FRDA.

Increase the Expression of FXN Gene or Replace FXN

Although antioxidant therapies and other therapies targeted toward the downstream effects of frataxin deficiency have shown promise, most experts believe that the goal of new investigational agents for FRDA should be to restore frataxin levels and thereby target the underlying cause of the disease. Work to increase FXN expression has focused on (1) approaches to increase FXN expression by modifying DNA and its epigenetic modifications, (2) repositioning screens for registered molecules that increase FXN gene expression, and (3) gene replacement strategies.

The structural changes in the repeat DNA disrupt expression through intramolecular DNA-DNA self-associations. Researchers have tried to use synthetic polyamides to disrupt the sticky confirmations and restore FXN expression in vitro (Burnett et al., 2006). More recently, bifunctional conjugates have been made that link a polyamide and a BRD4 ligand to increase frataxin expression through chromatin remodeling (Erwin et al., 2017). Furthermore, these abnormal triple helix structures are subject to deacetylation and hypermethylation of DNA, thereby condensing local chromatin and decreasing gene expression. Thus, histone deacetylation (HDAC) inhibitors or DNA demethylation agents could potentially treat the underlying cause of these diseases, and indeed, small molecule drugs are in various stages of preclinical development. Indeed, specific HDAC inhibitors have been shown to normalize frataxin expression in patient-derived lymphoid cell lines (Herman et al., 2006). FRDA mouse models have been generated that replicate many of the epigenetic and pathologic changes seen in human patients (Butler & Napierala, 2015; Puccio et al., 2001), and HDAC inhibitors fed to a mouse model restore frataxin expression without signs of toxicity (Rai et al., 2008). Nicotinamide, or vitamin B_3, is a class III HDAC inhibitor

that has also been shown to upregulate the FXN gene in lymphocytes (Chan et al., 2013). In a small open-label study, nicotinamide was shown to significantly increase FXN levels in plasma, but the study was underpowered and not long enough to determine efficacy (Libri et al., 2014).

Screening is also being undertaken to identify FDA-approved molecules and novel small molecules that increase frataxin expression. Interferon gamma, resveratrol, and erythropoietin have all been found to increase expression of FXN in vitro and are in different stages of development. Interferon-gamma showed promise in mice (Tomassini et al., 2012) but did not show benefit in a placebo-controlled study of 92 adults (Lynch et al., 2019b). Resveratrol was also found to upregulate FXN levels in a screen (Li et al., 2013), and while this effect on FXN levels was not confirmed in an open-label study with high doses, it may have shown some clinical benefit that would need to be confirmed with a randomized trial (Yiu et al., 2015). Resveratrol is a potent antioxidant, so there are other plausible mechanisms of action that may have influenced these hints of a clinical effect. A recent study determined that patient-derived induced pleuripotent stem cells (iPSCs) had widely varied responses in FXN expression to resveratrol and nicotinamide. This suggests that there could be an in vitro way to determine those patients most likely to respond to therapy, which could open more directed patient selection strategies for future studies (Georges et al., 2019).

Erythropoietin (EPO) has also been shown to increase frataxin expression in patient-derived cell lines through an as-yet-unclear mechanism (Sturm et al., 2005), yet two double-blind placebo-controlled studies of EPO failed to show benefit in FRDA patients (Boesch et al., 2014; Mariotti et al., 2012). These studies help determine the pharmacodynamic properties of EPO on FXN that may facilitate an improved trial design, and the trials may have been underpowered for efficacy (Boesch & Indelicato, 2019). FRDA has been an intriguing target of gene therapy because relatively modest increases in frataxin levels can translate to meaningful improvement, and overexpression is not toxic in mice. In addition to CNS penetration, transfection of cardiac myocytes is critical because cardiomyopathy is a life-threatening consequence of the disease. AAV9 and HSV1 vectors have been tested in FRDA preclinical models and show promise (Gérard et al., 2014; Lim et al., 2007). The success of AAV9 delivery in other neurodegenerative diseases makes this vector more likely to be tested in clinical trials.

Symptomatic Approaches

Despite the promise that these investigational agents have shown in early studies, there is, as of yet, no proven pharmacotherapy for FRDA. As in other inherited neuropathies, orthopedic procedures and devices are critical to the maintenance of mobility (see Chapters 8 and 9). This is particularly true in FRDA, as foot deformities may compound the imbalance caused by the underlying ataxia. In one series of patients, while surgery to correct equinovarus foot deformity was effective in improving function (predominantly ability to transfer independently), 3 of 7 patients had life-threatening complications (aspiration pneumonia or pulmonary embolus) (Delatycki et al., 2005). Thus, aggressive physiotherapy to prevent foot deformity is paramount. In a large series of patients undergoing treatment for scoliosis, surgical fusion was effective whereas bracing was not (Milbrandt, Kunes, & Karol, 2008). Furthermore, the primary cause of death in these patients is related to cardiac complications, and thus prevention and treatment of hypertrophic cardiomyopathy is paramount. Finally, patients should be screened for glucose intolerance due to the risk of developing diabetes.

LYSOSOMAL STORAGE DISEASES: FABRY DISEASE

Lysosomal storage diseases (LSDs) constitute a diverse group of over 40 inherited disorders with multiorgan involvement that frequently involve the nervous system. Peripheral nerve involvement is especially prominent in the sphingolipidoses, including Fabry disease, MLD, and Krabbe disease or globoid cell leukodystrophy (GLD), but has also been reported in many other LSDs. Many LSDs present with progressive neurodegeneration beginning in early childhood, but some have adult-onset forms. Although individually uncommon, as a group, they make up a significant portion of inherited neuropathies, and many of these diseases are potentially treatable with enzyme replacement therapy (ERT) or hematopoietic stem cell transplant. Thus, LSDs should be considered in the differential diagnosis of unexplained neuropathy, especially in those with CNS or other organ involvement.

Fabry disease is one of the more common lysosomal storage disorders, and painful small-fiber neuropathy is the earliest and often the most disabling symptom of this multisystem disease. This disease is X-linked, and while symptoms occur earlier and are more severe in men, female carriers are variably affected, partially due to skewed X-inactivation. Fabry disease is caused by a deficiency of α-galactosidase A, leading to accumulation of globotriaosylceramide (Gb3) in vascular endothelium and other tissues. The lysosomal storage of Gb3 in blood vessels is believed to cause ischemic damage in multiple tissues.

CLINICAL PRESENTATION

The symptoms of Fabry disease begin in childhood (usually about 5 years old in boys and late childhood or early adulthood in girls) with painful paresthesias in the hands and feet, decreased sweating, and gastrointestinal symptoms (nausea, abdominal pain, postprandial diarrhea), frequently leading to difficulty in school. Pain is typically chronic with episodic exacerbations or "crises," often triggered by environmental stimuli (e.g., heat, exercise, or stress). Untreated patients develop progressive disease of the kidneys, heart, and brain, usually leading to premature death in the 40s to 50s. Renal disease starts with proteinuria and progresses to renal insufficiency and end-stage renal disease if untreated. Early cardiac manifestations include left ventricular hypertrophy and mitral insufficiency and often progress to coronary artery disease, hypertrophic cardiomyopathy, and arrhythmias. Patients are at approximately a 10-fold increased risk for transient ischemic attacks and strokes, and brain MRI frequently shows evidence of microvascular ischemic disease. Boys usually have multiple angiokeratomas, punctate red telangiectasias commonly found on the skin of the lower trunk, buttocks, and scrotum. Other signs and symptoms include sensorineural hearing loss, corneal opacities, endocrine dysfunction, and mood disorders. As with other LSDs, there are rare late-onset variants of this disease, usually affecting only

the heart or kidney, and recently a family with adult-onset cramp-fasciculation syndrome was shown to have Fabry disease (Nance et al., 2006).

DIAGNOSIS

Diagnosis is frequently missed or delayed due to the nonspecific nature of the initial symptoms. In this regard, the neurologist or neuromuscular specialist is well suited to make the diagnosis when evaluating the patient for neuropathy. The diagnosis should be considered in children presenting with progressive length-dependent small fiber neuropathy, particularly if there are associated angiokeratomas, gastrointestinal symptoms, sweating abnormalities, exercise intolerance or fatigue, and a family history of renal failure, cardiovascular disease, and stroke. NCSs show mildly reduced conduction velocity in about two-thirds of patients, and sural nerve biopsies show a selective loss of small myelinated and unmyelinated fibers. In boys, diagnosis can reliably be made by testing α-galactosidase A activity in peripheral leukocytes or plasma; however, in girls, genetic testing is required to make the diagnosis.

Due to the multiorgan nature of the disease, patients are best served in a multidisciplinary clinic where they can be seen with cardiologists, nephrologists, and neurologists familiar with the disease. Cardiac monitoring with EKG and echocardiogram should be performed at least every 2 years, and renal function monitoring including measurement of creatinine clearance and urine protein should be performed on an annual basis. Brain MRI/magnetic resonance angiography is performed to evaluate for subclinical strokes and cerebrovascular disease, and unmyelinated fiber density may be followed with physical examination of pain and temperature sensation.

TREATMENT

LSDs are uniquely amenable to ERT, as lysosomal enzymes can be secreted extracellularly and endocytosed into lysosomes by binding to the mannose-6-phosphate receptor on the surface of the cell. Two recombinant α-Gal A preparations are available: agalsidase b (Fabrazyme) and agalsidase a (Replagal). Both of these therapies have proven effective and are available in Europe, and no significant differences have been shown between them; nonetheless, only Fabrazyme has been FDA approved in the United States.

In a randomized, placebo-controlled, double-blind, multicenter trial of 58 adult patients, agalsidase b given IV every two weeks for 20 weeks led to clearance of Gb3 deposits from the microvascular endothelium of kidneys, skin, and heart in 69% of patients, compared to 0% in the placebo group (Eng et al., 2001). A 3-year phase IV open-label extension of this study showed sustained safety and efficacy of agalsidase b with improvements in renal function and Gb3 clearance (Wilcox et al., 2004). In a similarly designed placebo-controlled study of 26 adult patients, IV agalsidase a given every 2 weeks significantly reduced pain and renal pathology, increased creatinine clearance, and reduced plasma and urinary sediment Gb3 levels (Schiffmann et al., 2001). Subsequent studies have substantiated a beneficial effect of ERT in Fabry disease, including a decrease in cardiac hypertrophy and decrease in the frequency of pain crises (Banikazemi et al., 2007; Beck et al., 2004). Furthermore, these studies have suggested that the earlier the initiation of therapy, the greater the treatment effect.

In addition to a reduction in pain described earlier, a few studies have specifically investigated the effects of ERT on neuropathy. Studies performing quantitative sensory and sudomotor testing on Fabry patients suggest a modest but significant improvement in thermal sensation and sweating with ERT (Hilz, Brys, Marthol, Stemper, & Dütsch, 2004; Schiffmann et al., 2003). However, an analysis of intraepidermal nerve fiber (IENF) density in the distal thigh did not show a treatment effect over the 6 months of the placebo-controlled trial (Schiffmann et al., 2006); there was no evidence of IENF regeneration with therapy, and, in fact, patients had a significant reduction in IENF density after 18 months of treatment.

These medications are well tolerated, with the most concerning adverse effect being an allergic infusion reaction. These symptoms can often be prevented with pretreatment with antihistamines and hydrocortisone, and the incidence decreases with repeated infusions. Initially, agalsidase b is infused slowly over 4–6 hours to ensure that the drug is tolerated, but with subsequent infusions, the rate can be significantly increased. A significant number of patients (55%–80%) generate IgG antibodies against the enzyme (as would be expected in patients who do not produce detectable levels of the enzyme); however, it is unclear whether antibody production reduces the efficacy of the treatment, and antibody titers decrease over time, suggesting induction of immune tolerance.

Despite these encouraging results, many open questions remain. The optimal dosing of these drugs has not been determined, and no well-designed head-to-head trials have been performed to determine if one preparation has advantages over the other. Furthermore, although measurements of Gb3 levels from blood and urine have been used as a biomarker in clinical trials, there is significant variability in levels that do not allow it to be a reliable measurement to assess ERT response in individual patients. One critical question is when treatment should be initiated in females. There is considerable evidence in Fabry disease and other LSDs that much of the pathology is irreversible and that earlier treatment does confer benefit. The decision of when to initiate treatment has become more complicated as more asymptomatic patients have been identified by newborn screening. These challenging clinical decisions require subspecialty care at centers dedicated to the care of patients with LSDs.

Chaperone therapy aims to increase the lysosomal delivery of the mutant enzyme, as most of the more than 200 mutations in α-Gal A are missense mutations that produce a misfolded but enzymatically active protein that is retained in the endoplasmic reticulum and degraded. The molecular chaperone therapy migalastat has demonstrated efficacy in clinical studies and been FDA approved. Migalastat (Galafold) binds to the active site of agalactosidase and stabilizes mutant enzymes with missense mutations facilitating trafficking to lysosomes. Sixty-seven patients were randomized to receive migalastat or placebo for 6 months with a 6-month open-label extension (followed by an additional 12-month open-label extension). The patients had been selected using a first-generation cell-based screening assay to determine whether they harbored mutations amenable to chaperone treatment. It did not reach its primary endpoint (GL-3 inclusions per kidney interstitial capillary) but did show benefit in improvements in left-ventricular-mass index (Germain et al., 2016). Investigators later

realized that the first-generation assay was flawed when a good laboratory practice (GLP)-validated cell-based assay was developed that yielded different results from the initial screen. Analysis of the data from the same study with new patient selection criteria demonstrated efficacy across a wide range of surrogate and clinical endpoints (reviewed here; McCafferty & Scott, 2019). Migalastat has become an important tool for physicians treating patients with Fabry disease (especially because of its oral administration).

Other potential treatments for Fabry disease and other LSDs in preclinical trials include substrate reduction therapies and gene therapy (Miller, Kanack, & Dahms, 2020). The idea of substrate reduction therapy is that toxic levels of Gb3 can be reduced by inhibiting its synthesis. Furthermore, continuous delivery of enzyme replacement would likely be more efficacious and physiologic than a bolus infusion every other week. Such a delivery would be possible via gene therapy, and indeed, because much of the breakdown of Gb3 normally occurs in the reticuloendothelial system, gene replacement therapy via hematopoietic stem cells (HSCs) is a promising future therapy currently in clinical trials (NCT02800070). Systemic in vivo gene therapy approaches are also being studied in clinical trials (NCT04046224). In the future, it is likely that a combination of approved therapies will be the standard of care for patients with Fabry disease.

LYSOSOMAL LEUKODYSTROPHIES: METACHROMATIC LEUKODYSTROPHY AND KRABBE DISEASE

CLINICAL PRESENTATION

Lysosomal leukodystrophies are autosomal recessive LSDs with a specific defect in the breakdown of both CNS and peripheral nervous system (PNS) myelin and include MLD and GLD, also called Krabbe disease. The most common, infantile-onset forms of these diseases present with progressive walking difficulty beginning in infancy, followed by progressive mental retardation, pyramidal signs, seizures, and blindness due to optic atrophy. However, LSDs have variable presentations, including juvenile and adult-onset forms. Rarely, patients may initially present with progressive neuropathic symptoms including neuropathic pain of the extremities, areflexia, and weakness in the absence of other symptoms (Comabella et al., 2001; Haberlandt et al., 2009). Patients with GLD have a similar presentation as in MLD, although the CNS involvement usually begins earlier and is more severe. The peripheral nervous system involvement was classically thought to be less profound in GLD, although a recent electrophysiologic study has shown that demyelinating peripheral neuropathy occurs early, is profound, and correlates in severity with that of CNS involvement (Siddiqi, Sanders, & Massey, 2006b).

DIAGNOSIS

Diagnosis is usually suspected based on clinical history and brain MRI showing nonspecific periventricular demyelination. Occasionally, these patients may be misdiagnosed with an inflammatory demyelinating polyneuropathy, as lumbar puncture reveals markedly elevated CSF protein and NCS shows evidence of demyelination (however, nerve conduction velocities are usually severely and uniformly reduced to 10 to 20 m/second). MLD is caused by a deficiency of arylsulfatase A, leading to progressive central and peripheral demyelination. A blood test is available for diagnosing arylsulfatase A deficiency in leukocytes and can be confirmed by genetic testing to identify mutations in the arylsulfatase A gene or in the activator protein, saposin B. Diagnosis of GLD can be made by testing galactosylceramide-β-galactosidase activity in blood leukocytes or with genetic testing. Although nerve biopsy is not necessary for diagnosis, toluidine blue staining shows demyelination and remyelination and in MLD will show metachromatic (brown) lysosomal granules due to the accumulation of sulfatide in Schwann cell perikarya. EEM performed on thin sections of nerve or skin biopsies shows characteristic lysosomal inclusions in both MLD and GLD.

TREATMENT

One important limitation of ERT (see Fabry disease earlier) is that intravenously delivered enzymes generally do not cross the blood-brain barrier. To circumvent this problem, patients can undergo a hematopoietic stem cell transplant (HSCT), as bone marrow–derived microglia can enter the CNS and secrete lysosomal enzymes that can enter affected cells. However, these therapies have significant risks, are extremely expensive, rely on the ability of stable enzyme to be secreted extracellularly, and are usually effective only if patients are treated early in the course of the disease, preferably presymptomatically.

HSCT was first shown to have efficacy in treating Hurler syndrome (mucopolysacchyridosis type 1) in 1981, long before the molecular defect was understood (Hobbs et al., 1981). Since that time, HSCT has shown variable efficacy in treating several LSDs, including GLD and MLD (Cartier & Aubourg, 2008). The safety and efficacy of HSCTs have improved over the last decade, and banking of umbilical cord blood allows the possibility of rapidly identifying a suitable donor.

In principle, both GLD and MLD can be treated with allogeneic HSCT. However, in practice, HSCT has been much less effective in MLD even when treated presymptomatically. The reasons for this difference are not known, but may be due to low amounts of stable arylsulfatase secreted by microglia. Supporting this hypothesis, bone marrow–derived HSCs from an arylsulfatase A–deficient mouse genetically engineered to produce high levels of the enzyme dramatically improved the neurologic outcome of these mice treated with HSCT, while peripherally delivered enzymes produced from hepatocytes did not deliver enzyme to the CNS (Biffi et al., 2004). In contrast, patients with the infantile, juvenile, and late-onset forms of GLD have shown improved neurologic outcomes after HSCT when compared with patients receiving no therapy (Escolar et al., 2005; Krivit et al., 2009). In a study of infantile GLD patients treated with umbilical cord blood stem cells, asymptomatic newborns had a marked response to HSCT, with only a few having delays in expressive language and motor function. Important to our focus on neuropathy, an electrodiagnostic study showed a significant improvement in the neuropathy in Krabbe patients treated with HSCT, demonstrating an ability for these patients to regrow and myelinate axons with treatment (Siddiqi, Sanders, & Massey, 2006a). In comparison, infants treated after the onset of symptoms had minimal neurologic improvement.

Promising gene therapy approaches under investigation for both GLD and MLD include ex vivo gene transfer using lentiviral vectors to transduce autologous HSCs and intrathecal AAV gene transfer (Mikulka & Sands, 2016; Rosenberg, Kaminsky, Aubourg, Crystal, & Sondhi, 2016).

In summary, because LSDs associated with neuropathy are potentially treatable if identified early, these diagnoses should be considered and tested for, particularly in children with unexplained demyelinating neuropathy.

PEROXISOMAL DISORDERS: ADRENOMYELONEUROPATHY AND REFSUM DISEASE

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are different clinical presentations of the same X-linked genetic disease characterized biochemically by accumulation of saturated very long chain fatty acids (VLCFAs) (reviewed by Raymond, Moser, & Fatemi, 2018). The mutated protein, known as ABCD1, is a member of the ABC transporter family and is believed to function by transporting VLCFAs into the peroxisome, where they undergo beta-oxidation. However, the mechanism of disease pathogenesis is unclear. Refsum disease (also known as heredopathia atactica polyneuritiformis and previously designated HMSN IV) is characterized by an accumulation of specific branched chain fatty acids called phytanic acids. Phytanic acids are exclusively derived from the diet and normally undergo alpha-oxidation in the peroxisome. Refsum disease is a rare autosomal recessive disorder usually caused by deficiencies in phytanoyl-CoA hydroxylase (*PHYH*) or the peroxisomal targeting signal 2 receptor (*PEX7*) (Wanders, Waterham, & Leroy, 2006).

ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY: CLINICAL PRESENTATION

The classic childhood onset ALD phenotype affects boys age 4 to 8 years old with an initial onset of ADHD and other behavioral symptoms, followed by rapidly progressive cortical blindness, spastic paraparesis, deafness, seizures, and adrenal insufficiency. Pathologically, the brains of these patients show intense inflammatory demyelination beginning in the occipital lobes and progressing anteriorly. The intense CD8+ T cell infiltrate and cytolytic death of oligodendrocytes has led to the hypothesis that immune recognition of abnormal VLCFAs causes an autoimmune response; however, myeloablation does not slow progression of the disease (Nowaczyk, Saunders, Tein, Blaser, & Clarke, 1997). These children do not develop neuropathy.

In contrast, AMN develops in adults with a slowly progressive spastic paraparesis, large fiber sensory loss, and bowel and bladder incontinence. The pathological characteristics are very different in this disease, with evidence of a non-inflammatory distal axonopathy affecting the corticospinal tract, dorsal columns, and peripheral nerve. AMN frequently affects males in their 20s and 30s and, surprisingly, also affects about 50% of carrier females in their 30s and 40s. Most patients do not develop cerebral manifestations; however, about 20%–40% of males will develop cerebral inflammatory demyelination later in the course of their disease. Magnetic resonance spectroscopy imaging studies have shown that even patients with "pure AMN" have metabolic changes evident in the corticospinal tract and parieto-occipital white matter (Dubey et al., 2005).

Almost 500 mutations in the ABCD1 gene have been described (see https://adrenoleukodystrophy.info/ for an updated list), and there is almost no correlation between mutation and phenotype, suggesting that additional modifier genes or environmental factors determine whether a given patient develops ALD or AMN or remains asymptomatic. However, the majority of patients with both ALD and AMN (~70%) develop adrenal insufficiency usually preceding neurological symptoms. Symptoms include nausea, vomiting, fatigue, hyperpigmentation, and hyponatremia.

ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY: DIAGNOSIS

Childhood cerebral ALD is difficult to diagnose in its early stages, as it must be distinguished from ADHD, autism spectrum disorder, and other neuropsychiatric disorders. However, with its inexorable progression, once brain MRI is performed revealing the posterior demyelination, the diagnosis is quickly suspected. Adult-onset AMN must be distinguished from other causes of myelopathy and myeloneuropathy and may be misdiagnosed as multiple sclerosis, particularly if abnormalities are seen on brain MRI. The differential diagnosis also includes vitamin deficiencies such as copper and vitamin B_{12}, primary lateral sclerosis and ALS, HTLV1 infection, and hereditary spastic paraparesis.

Diagnosis is made using a plasma VLCFA assay. Both affected and asymptomatic males have a markedly elevated C26:0 level and an increased ratio of C24:0 and C26:0 to C22:0. Female carriers may also have elevated VLCFAs, but false-negative tests do occur in about 20% of heterozygous females, so DNA sequencing is recommended. Once a mutation is identified, other family members can be rapidly tested for the presence of that mutation. VLCFAs are elevated in chorionic villus cells and cultured amniocytes, allowing prenatal diagnosis with chorion villus sampling and amniocentesis. Neonatal screening assays have been developed and this test was added to the recommended uniform screening panel in 2015 (Raymond, Jones, & Moser, 2007).

The neuropathy of AMN is mild relative to the myelopathy and is frequently overlooked given the brisk reflexes. However, careful examination identifies evidence of a length-dependent peripheral neuropathy in most AMN patients. NCSs show mixed multifocal demyelination and axonal loss (Chaudhry, Moser, & Cornblath, 1996), consistent with the AMN pathology initially described by Griffin, Goren, Schaumburg, Engel, and Loriaux (1977). Interestingly, NCS abnormalities correlated with disability status and plasma VLCFA levels.

Once the diagnosis of AMN is made, patients should be evaluated and regularly monitored for adrenal insufficiency. Testing is done by measuring serum adrenocortitrophin hormone (ACTH) level and, if equivocal, performing an ACTH-stimulation test. Serum cortisol levels are not sufficiently sensitive for detecting adrenal insufficiency in these patients. Furthermore, MRI of the brain should be performed on a regular basis to evaluate for cerebral inflammation. Newer imaging modalities including magnetization transfer imaging and diffusion tensor imaging show promise in quantifying and following axonal pathology in the brain and spinal cord.

ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY: TREATMENT

Because about 70% of males with X-ALD develop adrenal insufficiency, which is potentially fatal if untreated, the most critical treatment of these patients is corticosteroid replacement if needed. This treatment is usually in the form of glucocorticoids (e.g., hydrocortisone 10–40 mg/day in divided doses) without mineralocorticoids. Testosterone treatment may also be effective in patients with hypogonadism. However, steroid treatment has no effect on the neurologic manifestations. Other symptomatic treatments include treatment of spasticity (e.g., baclofen) and bowel and bladder symptoms.

HSCT has been shown to benefit patients with early symptomatic X-ALD (Moser, Raymond, & Dubey, 2005). In about 50% of X-ALD boys treated with HSCT, disease progression is halted, and this effect is long-term. The earlier transplant is performed, the greater the likelihood of clinical effect. However, as discussed earlier, HSCT is a risky procedure with a mortality rate of 10%–20%, and therefore, the risk-to-benefit ratio is considered unfavorable in patients with pure AMN. Nonetheless, HSCT should be considered as an option for AMN patients who develop cerebral inflammation if discovered early (e.g., subclinically with MRI).

More recently, ex vivo gene therapy has been shown to be a safe and effective alternative to HSCT. Seventeen patients between the ages of 3 and 14 were treated with CD34+ HSCs that had been transduced with a lentiviral vector containing the *ABCD1* cDNA under the control of the MND promoter (a synthetic promoter element derived from viral promoters that are highly active in the hematopoetic compartment–myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted) (Eichler et al., 2017). Most patients were treated with granulocyte colony-stimulating factor after the infusion of the cell product to promote engraftment. Of 17 patients, 15 saw stabilization of their neurological function, and 12 of those 17 patients also had stabilization of their Loes score, a radiographic score of white matter lesion accumulation. Those patients with the highest Loes scores at the start of the study were more likely to be among the patients with radiographic evidence of disease progression, suggesting that early treatment will be critical. Two patients progressed and died of disease-related, but not treatment-related, events. Those patients did have among the lowest vector copies per diploid genome, suggesting that a combination of more advanced disease and a less potent cell product may have combined to decrease the efficacy (Eichler et al., 2017).

REFSUM DISEASE: CLINICAL PRESENTATION, DIAGNOSIS, AND TREATMENT

Refsum disease typically presents in late childhood with worsening night vision, although age of onset is variable, ranging from infancy to late adulthood. Constant and early disease features include pigmentary retinopathy and anosmia. Although symptoms of neuropathy are usually not present initially, a distal, demyelinating sensorimotor and autonomic polyneuropathy invariably develops as the disease progresses in untreated patients, often occurring subacutely. Other common findings include optic atrophy, cataracts, deafness, skin changes (ichthyosis), shortened bones in hands and feet, cardiac conduction defects, and cardiomyopathy.

Although Refsum disease is rare, this diagnosis should be considered in patients with retinitis pigmentosa as this disease is treatable. Elevated plasma phytanic acid over 200 μmoL/L (normal is <30 μmoL/L) is pathognomonic for this disease. Because phytanic acid is solely derived from the diet, plasma levels can be markedly lowered and the disease treated by reducing dietary intake. Patients are advised to take less than 10 mg/day (normal is about 100 mg/day) by avoiding foods with high levels of phytanic acid, including dairy products, beef and lamb, and certain fatty fish. Abrupt weight loss or fasting should be avoided as mobilization of fat releases phytanic acid into the blood. In patients who develop subacute worsening of symptoms, plasmapheresis reduces phytanic acid levels and reportedly has led to a dramatic improvement in symptoms in small case series. Patients should be counseled that they can prevent progression of the disease by strictly adhering to the diet.

PORPHYRIC NEUROPATHY

CLINICAL PRESENTATION

Hepatic porphyrias are autosomal dominant disorders of heme metabolism that typically present with the triad of acute neuropathy, psychiatric symptoms, and abdominal involvement (Albers & Fink, 2004). Variegate porphyria and hereditary coproporphyria are distinguished by the presence of skin blisters and bullae in about 50% of patients, whereas patients with the more common AIP do not develop skin manifestations. Patients are usually asymptomatic between attacks, and episodes can occur spontaneously or be precipitated by factors that increase heme synthesis (and thereby increase the toxic porphyrin metabolites). Exacerbating factors include stress, hormonal factors, reduced caloric intake, and certain drugs. The active site of cytochrome P450 contains heme, and therefore drugs that induce hepatic synthesis of cytochrome P450 (e.g., barbiturates) also trigger synthesis of toxic heme intermediates and are potent triggers of attacks. The earliest signs of an episode are usually abdominal pain, constipation, vomiting, and mental status changes. The peripheral neuropathy associated with porphyria has an acute onset and may be preceded or accompanied by autonomic manifestations such as tachycardia, hypertension, and postural hypotension. The neuropathy usually progresses over 2–4 weeks to cause diffuse weakness (often proximal > distal and upper > lower extremities) and areflexia. Sensory loss is generally mild and may be more prominent proximally in a "bathing trunk" distribution (Thadani, Deacon, & Peters, 2000).

DIAGNOSIS

The disease is named after the Greek word "porphuros" for purple, and, indeed, urine of patients with hepatic porphyria turns purple/red when exposed to air and light due to oxidation of excess porphyrin precursurs. Spinal fluid is similar to Guillain-Barré syndrome with an albuminocytologic dissociation, and in fact some experts recommend screening all patients with the Guillain-Barré clinical syndrome for porphyria. Acute attacks are invariably associated with increased urinary excretion of aminolevulinic acid and/or porphobilinogen, and a random urine test for porphobilinogen is a useful screen for acute porphyria. While this test is sensitive, it lacks specificity, and porphyrins can be elevated secondary to many drugs and alcohol in addition to chronic diseases such as diabetes mellitus, liver disease, and iron-deficiency anemia. Measuring 24-hour urinary excretion of porphobilinogen

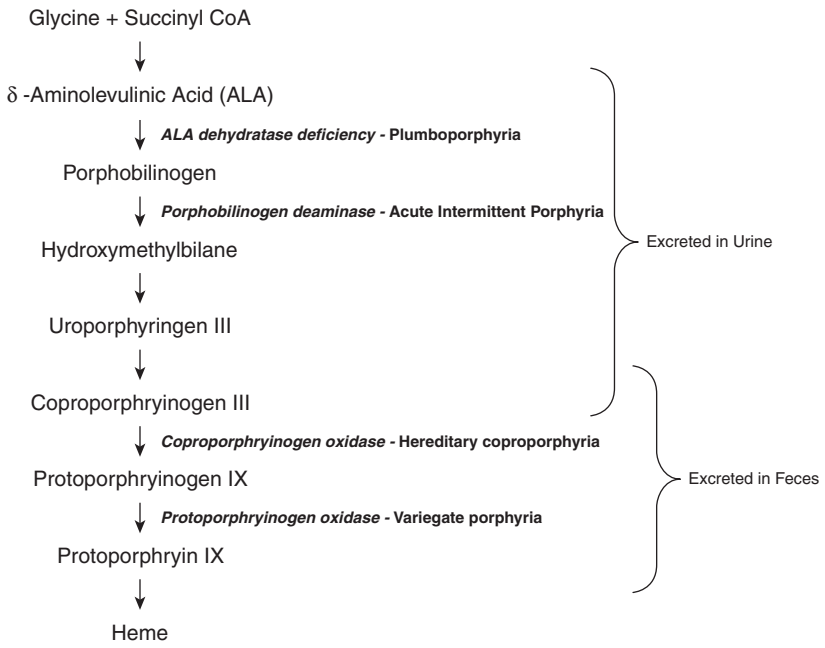


Fig. 14.6 Heme biosynthesis pathway and sites of defects for the porphyrias resulting in neurological dysfunction.

Table 14.4 Diagnosis of Porphyric Neuropathies

	Acute Intermittent Porphyria	Hereditary Coproporphyria	Variegate Porphyria	ALA Dehydratase Deficiency
Inheritance	AD	AD	AD	AR
Enzyme deficiency	PBG deaminase	Copro oxidase	Proto oxidase	ALA dehydratase
Photosensitivity	None	Present	Present	None
Porphyrin excretion				
Urine	ALA, PBG, Uro	ALA, PBG, Uro, Copro	ALA, PBG, Uro, Copro	ALA, Copro
Feces	Normal	Copro > Proto	Proto > Copro	Normal

Porphyrias can be diagnosed by urinary and fecal porphyrin excretion. As shown in Fig. 14.6, hereditary coproporphyria and variegate porphyria are distinguished by the fecal porphyrin measurement.
AD, Autosomal dominant; *ALA*, ∂-aminolevulinic acid; *Copro*, coproporphyrinogen; *PBG*, porphobilinogen; *Proto*, protoporphyrin; *uro*, uroporphyrin.

and aminolevulinic acid and 24-hour fecal excretion of protoporphyrin and coproporphyrin during a symptomatic period is the definitive test for porphyria and can distinguish between variegate porphyria and hereditary coporphyria (Fig. 14.6 and Table 14.4). Since porphyrins are light sensitive, specimens must be stored in the dark and tested as soon as possible. In difficult diagnostic cases or to diagnose latent porphyria in an asymptomatic patient, enzyme activity can be measured in erythrocytes, and genetic testing is available.

TREATMENT

Treatment of acute porphyria involves a three-pronged approach of (1) removing the disease trigger, (2) specific therapy aimed at decreasing hepatic porphyrin synthesis (now including targeted therapies for AIP), and (3) supportive care. The most important treatment during the acute crisis is supportive care including fluid management, ventilatory support, management of heart rate and blood pressure (autonomic dysfunction), and avoidance of medications that are known to precipitate or worsen an acute attack. Identifying safe drugs can be difficult, as most anticonvulsants and many analgesics and hypnotics may exacerbate porphyria. The offending agent should be identified, which is usually a drug known to induce cytochrome P450 synthesis. Other triggers include menstrual cycles, fasting, and alcohol. Pharmacological therapy including oral or intravenous glucose (300 to 500 g/day) and heme arginate (hematin) should be instituted as soon as possible. Hematin is administered in daily infusions of 4 mg/kg over a period of 3–5 days. Only one placebo-controlled study has been performed which showed a modest benefit of hematin, which was greatest if started early (Herrick, McColl, Moore, Cook, & Goldberg, 1989). Recovery from an acute attack may take several months. Patients need to be educated to avoid triggers of

acute attacks, and patients whose attacks correspond with the menstrual cycle can be treated with low-dose estrogen or gonadotropin-releasing hormone agonist therapy. Since the last edition, an RNAi-based therapy targeting *ALAS1* has been shown to reduce the frequency of attacks and was recently FDA approved for patients with *HMBS* mutations. Published results from a three-part phase I study showed meaningful changes in mRNA levels of the target and normalization of ∂-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels (Sardh et al., 2019). Phase 3 results that were the basis for FDA approval have not yet been published, but press releases suggest a 74% reduction in annualized rates of attacks; 50% of patients in the givosiran group were attack-free during the 6-month study, while only 16.3% of patients in the placebo arm were attack-free. Biomarker readouts were also impressive, with ~90% ALA and PBG reduction from baseline. Neuropathy endpoints were not examined.

CONCLUSIONS

Every year, additional genetic causes of peripheral neuropathy are being discovered, and we are learning more about the pathophysiology of inherited neuropathies. The clinical presentation of hereditary neuropathies is quite variable, and inherited disease should always be considered in the differential diagnosis of unexplained neuropathy, even in the absence of family history. This is especially true as the cost of next-generation genetic testing continues to decrease. Genetic testing is available to diagnose many hereditary neuropathies, and there are significant efforts to perform subtype-specific natural history studies and gene-targeted therapeutic trials.

The syndromic neuropathies section of the chapter introduced several gene-targeted therapies (employing a range of modalities outlined in earlier in the chapter) that are FDA approved or nearing approval based on recent pivotal data. With improved cell and animal models and increased understanding of these diseases, there is optimism that new gene-targeted therapies for nonsyndromic hereditary neuropathies will be proven to be efficacious and to gain FDA approval before the publication of the next edition of this book.

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15 Treatment and Management of Autoimmune Neuropathies

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INTRODUCTION

Autoimmune peripheral neuropathies (APNs) develop when immunologic tolerance to key antigenic sites on myelin, axon, nodes of Ranvier, or ganglionic neurons is lost (Dalakas, 2011b, 2013b). These conditions may manifest either acutely or in a more chronic manner; symptoms may include motor, sensory, and autonomic in isolation or in concert. The classic prototypical syndromes are the Guillain-Barré syndrome (GBS)—an acute postinfectious sensorimotor neuropathy—and chronic inflammatory demyelinating polyneuropathy (CIDP)—a subacute to chronic autoimmune sensorimotor neuropathy. There are multiple notable variants of each of these forms, as well as additional distinct conditions distinguished by specific antibodies, mechanism of action, concurrent systemic diseases, or sites of extraperipheral damage. The pathogenesis, diagnosis, and treatment vary among these conditions despite their overlapping symptomatology.

ACUTE AUTOIMMUNE PERIPHERAL NEUROPATHIES

GBS is an acute, monophasic, paralyzing illness, reaching its nadir within 4 weeks of onset. It is the most common and most severe acute paralytic neuropathy, with about 100,000 people developing the disorder every year worldwide. The annual incidence rate increases with age (0.6 per 100,000 per year in children and 2.7 per 100,000 per year in people aged 80 years and over), and the disease is slightly more frequent in males than in females (Willison, Jacobs, & van Doorn, 2016). GBS is a heterogeneous disorder with multiple variants (Figs. 15.1 and 15.2), according to whether the main clinicopathologic involvement is centered on motor or sensory nerve fibers and whether it affects predominantly the myelin or the axon (Dalakas, 2011b, 2013b; Hughes & Cornblath, 2005; Yuki and Hartung, 2012) (Table 15.1). There is an antecedent infection with *Campylobacter jejuni* (*C. jejuni*) as the most frequently identified precipitant, followed by viruses (Cytomegalovirus, Epstein-Barr virus [EBV]) and other bacteria (*Haemophilus influenzae, Mycoplasma pneumoniae*) (Bourque, Chardon, & Massie, 2015). Zika virus has been reported to cause GBS and other parainfectious polyneuropathies (Barbi, Coelho, Alencar, & Crovella, 2018; Cao-Lormeau et al., 2016; Medina et al., 2016). During 2015 and early 2016, Zika GBS incident rate significantly increased in South and Central America (Barbi et al., 2018; Cao-Lormeau et al., 2016).

GUILLAIN-BARRÉ SYNDROME SUBTYPES

Acute inflammatory demyelinating polyneuropathy (AIDP): the prototype variant of GBS and accounts for 85% of cases (Willison et al., 2016; Yuki & Hartung, 2012). Immune injury takes place at the myelin sheath and related Schwann cell components (Fig. 15.3).

It is characterized by progressive ascending quadriparesis and often by prominent sensory symptoms (Bourque et al., 2015). Pain is a significant symptom. It can be muscle pain or radicular pain and can precede weakness in about a third of patients (Liu, Wang, & McNicol, 2013; Oh, Kurokawa, de Almeida, Ryan, & Claussen, 2003; Ruts et al., 2010). Exam shows hypotonic paraparesis and reduced or absent muscles reflexes (van den Berg, Fokke, Drenthen, van Doorn, & Jacobs, 2014) or quadriparesis and cranial nerve involvement in severe cases resulting in facial, oculomotor, or bulbar weakness (Oh et al., 2003; Ruts et al., 2010; van den Berg, Fokke, et al., 2014). Autonomic dysfunction may lead to cardiac arrhythmia, excessive sweating, blood pressure instability, or ileus (van den Berg, Walgaard, et al., 2014). During the progressive phase, 20%–30% of patients develop respiratory failure and need ventilation at an intensive care unit (ICU) (Fokke et al., 2014).

Nerve conduction studies (NCSs) show multifocal demyelination. Demyelination and conduction block (CB) proximally at the level of the lumbar and cervical nerve roots explain the proximal weakness. CB along motor axons explains the bilateral ascending weakness (Delmont et al., 2017; Fokke et al., 2014; Sejvar et al., 2011; van Doorn, 2013).

The cerebrospinal fluid (CSF) typically reveals a normal white blood cell count with moderate elevation of the protein content (albumino-cytologic dissociation). This is the likely consequence of a deficient blood-nerve barrier (BNB), particularly at the level of the spinal nerve roots. Currently, there are no specific antibody biomarkers (Uncini, Susuki, & Yuki, 2013).

Patients are typically treated with either plasma exchange (PE) or intravenous immunoglobulins (IVIg) (Guillain-Barré Syndrome Study Group, 1985; Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997; The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome, 1997; Van der Meché & Schmitz, 1992). Neither treatment is better than the other, nor is the combination of IVIg and PE at the same time better than either treatment alone. Multiple clinical trials have failed to show any benefit for steroids (Guillain-Barré Syndrome Steroid Trial Group, 1993; Hughes et al., 2007). Although the

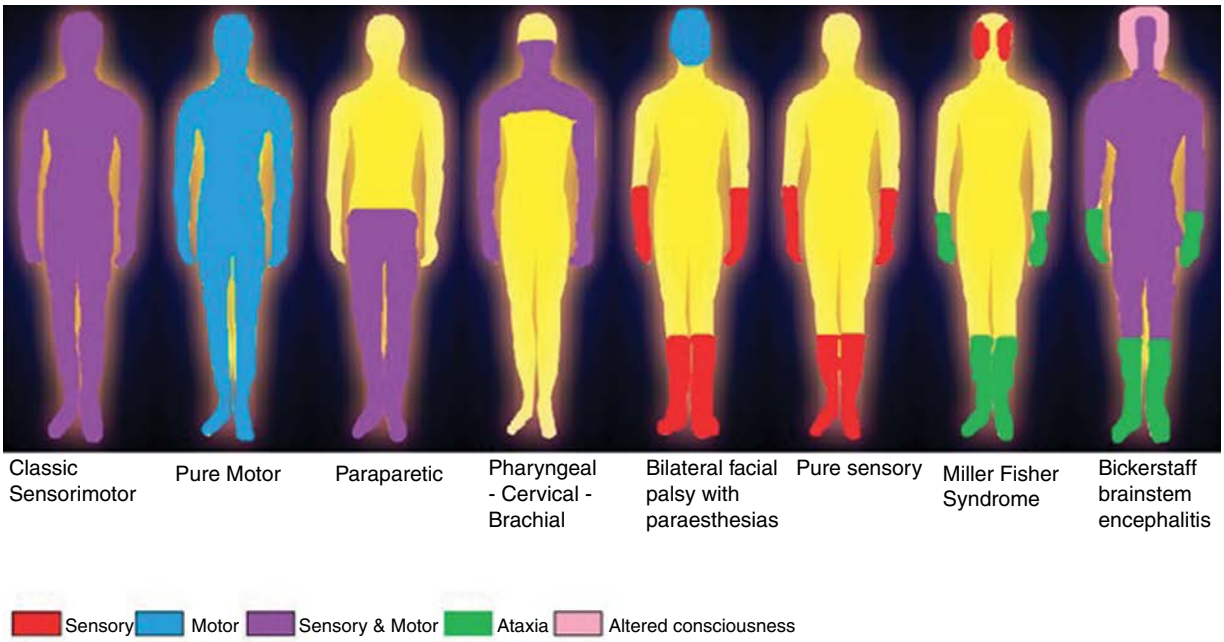


Fig. 15.1 Pattern of symptoms in variants of Guillain-Barré syndrome (GBS). Graphic representation of the pattern of symptoms typically observed in the different clinical variants of Guillain-Barré syndrome (GBS). Symptoms can be purely motor, purely sensory (rare), or a combination of motor and sensory. Ataxia can be present in patients with Miller Fisher syndrome, and both decreased consciousness and ataxia can be present in patients with Bickerstaff brainstem encephalitis. Symptoms can be localized to specific regions of the body, and the pattern of symptoms differs between variants of GBS. Although rare, bilateral facial palsy with paraesthesias, the pure sensory variant, and Miller Fisher syndrome are included in the GBS spectrum, they do not fulfill the diagnostic criteria for GBS.

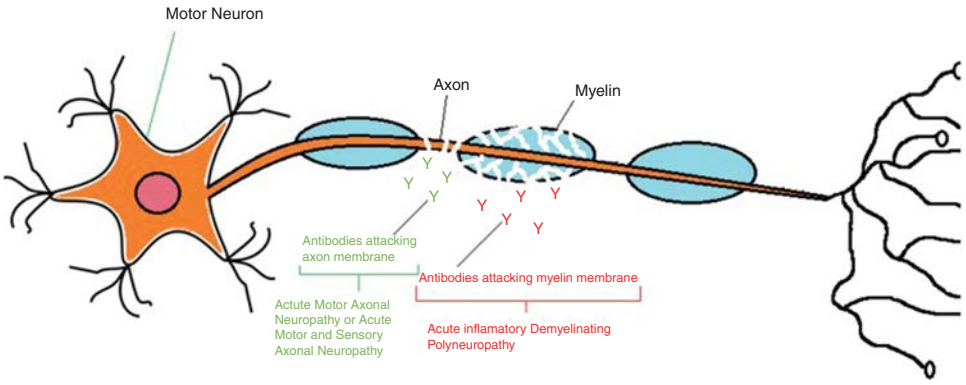


Fig. 15.2 Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways, including complement activation, cause glial or axonal membrane injury with consequent conduction failure

prognosis of GBS is generally favorable, there is still mortality in the range of 5% and disability beyond 1 year in approximately 20% of patients (Hughes et al., 2007).

Acute motor axonal neuropathy (AMAN): characterized by pure motor involvement and absence of evidence of demyelination on electrophysiological tests (Kuwabara & Yuki, 2013). It is characterized by rapidly progressive weakness, often with respiratory involvement and usually good recovery.

AMAN accounts for 5%–10% of cases in the Western Hemisphere and 50% in Asia (Nagasawa et al., 2006). There is a strong association with preceding *C. jejuni* and Zika virus infection (Rees, Gregson, & Hughes, 1995; Watrin et al., 2016). The primary immune attack is humoral and selectively acts on the motor axons and the axolemma at the nodes of Ranvier (Griffin et al., 1996; Willison et al., 2016). Reflexes can initially be normal (Yuki et al., 2012). The clinical course and prognosis are otherwise similar to classical AIDP (Bourque et al., 2015). GD1a, GM1, or GD3 ganglioside autoantibodies are found in roughly 50% of cases (Jacobs et al., 2008; Willison & Yuki, 2002). The antibodies fix complement, recruit macrophages, and deposit membrane attack complex (MAC) in the axolemmal membrane (McGonigal et al., 2010), thus disrupting the axolemma at the nerve terminals and nodes of Ranvier with resulting disruption of nodal sodium channel clusters and detachment of paranodal myelin terminal loops (Rees, Gregson, et al., 1995; Watrin et al., 2016). Consequently, there is a nerve conduction blockade. This blockade is reversible and, pathophysiologically, initially predominates over axonal degeneration in AMAN (McGonigal et al., 2010). This makes it the prototype of the newly described nodo-paranodopathies triggered by molecular mimicry (Wolf et al., 2010).

Table 15.1 Brighton Criteria for Diagnosis of Typical GBS

	Level of Diagnostic Certainty			
Diagnostic Criteria	**1**	**2**	**3**	**4**
Bilateral and flaccid weakness of limbs	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset and nadir 12 hours to 28 days	+	+	+	+/-
CSF cell count <50/μL[a]	+	+	-	+/-
CSF protein concentration > normal value[a]	+	+/-	-	+/-
NCS findings consistent with one of the subtypes of GBS	+	+/-	-	+/-
Absence of alternative diagnosis for weakness	+	+	+	+

Brighton criteria account for the level of diagnostic certainty based on the combination of examination, history, laboratory, and electrodiagnostic findings in typical GBS. A level of 1 is most certain, while a level of 4 is least certain and reported as GBS, possibly due to insufficient data for further classification. + indicates present; -, absent; +/-, present or absent.
[a]If CSF is not collected or results are not available, nerve electrophysiology results must be consistent with the diagnosis GBS.
CSF, Cerebrospinal fluid; *GBS*, Guillain-Barre syndrome; *NCS*, nerve conduction study.

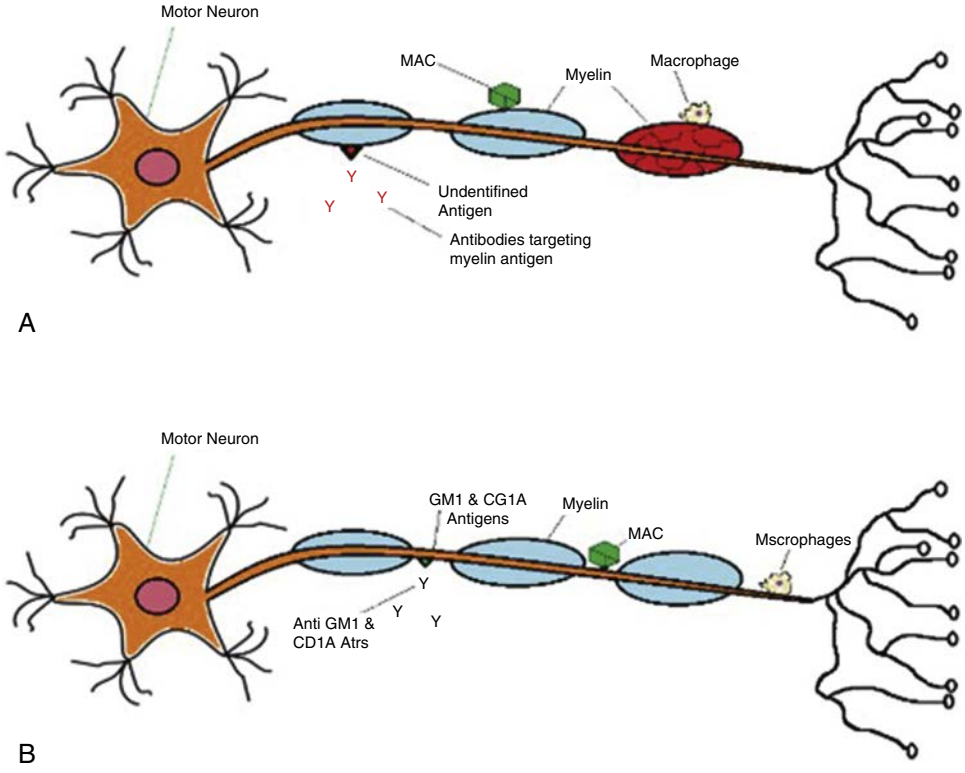


Fig. 15.3 (A) Proposed immune attack in acute inflammatory demyelinating polyneuropathy (AIDP). Autoantibodies are suspected to bind to myelin antigens and activate complement. The formation of a membrane attack complex (*MAC*) on the outer surface of Schwann cells leads to vesicular degeneration, with subsequent removal of myelin debris by macrophages. (B) shows a different pathogenesis proposed for acute motor axonal neuropathy (AMAN). Anti-GM1 or anti-GD1a antibodies are shown binding to the nodal axolemma. This may affect voltage-gated sodium (Nav) channels. Additional disruption of paranodal myelin may also contribute to conduction failure. Macrophages may subsequently invade the periaxonal space.

Electrophysiologically, the reduction of distal compound muscle action potential (CMAP) amplitude may be seen in the absence of the other features of demyelination.

Pure motor GBS can occur in patients with AMAN or with AIDP (van den Berg, Walgaard, et al., 2014).

Acute motor-sensory axonal neuropathy (AMSAN): a rare variant of GBS, less than 10% of AMAN cases. It is associated with antecedent *C. jejuni* infection (Vucic, Kiernan, & Cornblath, 2009). This disease shows some association with anti-GD1a. The presentation is with acute onset of distal weakness, loss of deep tendon reflexes, and sensory symptoms (Vucic et al., 2009). The primary pathology is in motor and sensory axons (Ho et al., 1995). In AMAN and AMSAN, the pathologies are very similar (Yuki, Kuwabara, Koga, & Hirata, 1999), where macrophages invade the space between the Schwann cell and axon, leaving the myelin sheath intact (Vucic et al., 2009). It shows a more serious clinical course and, owing to its axonal pathology, is associated with slow and incomplete recovery compared to the demyelinating variant (Bourque et al., 2015; Vucic et al., 2009).

Miller Fisher syndrome (MFS): accounts for 5% of cases (Gilmore, Doherty, Kimpinski, & Rice, 2018) and is the second most common variant of GBS (Mori, Kuwabara, Fukutake, Yuki, & Hattori, 2001). There is male predominance (Mori et al., 2001) with median age in the fifth decade (Snyder,

Rismondo, & Miller, 2009). It is characterized by acute onset of ophthalmoplegia, gait ataxia, and areflexia (Dalakas, 2011b, 2013b; Hughes & Cornblath, 2005; Yuki & Hartung, 2012). It is preceded by upper respiratory tract infection in 56%–76% of the patients, mostly *C. jejuni* (Ito et al., 2008; Koga et al., 2005) and *Haemophilus influenzae* (Bukhari & Taboada, 2017). A diagnosis of MFS can be made with compatible clinical history and cardinal symptoms and the presence of albumino-cytologic dissociation in the CSF (Ito et al., 2008). The disease then progresses until a clinical nadir is reached (range of 2–21 days) (Mori et al., 2001). The immune attack takes place at the paranodal myelin epitopes strongly expressed in oculomotor nerves, dorsal root ganglia, muscle spindles, and neurons in the cerebellar molecular layer, a distribution that fits well with cardinal clinical manifestations (Chiba, Kusunoki, Shimizu, & Kanazawa, 1992; Liu, Willison, & Pedrosa-Domellöf, 2009). MFS is strongly associated with serum antibodies to GQ1b in up to 85% of cases (Chiba et al., 1992; Chiba, Kusunoki, Obata, Machinami, & Kanazawa, 1993; Nishimoto, Odaka, Hirata, & Yuki, 2004; Willison, Veitch, Paterson, & Kennedy, 1993), a ganglioside component of nerves that is disproportionately enriched in the extramedullary regions of the ocular motor nerves and some large neurons of dorsal root ganglia (Chiba et al., 1993; Kusunoki, Chiba, & Kanazawa, 1999; Liu et al., 2009; Wakerley & Yuki, 2015; Wong et al., 2015). The antibodies also block acetylcholine release from the motor nerve terminals. Levels are proportionate to the disease activity and can be used as a diagnostic marker (Chiba et al., 1992). MFS is frequently accompanied by other cranial nerve involvement and can progress to weakness of the limbs (Miller Fisher-Guillain-Barre overlap syndrome) (Kronlage et al., 2017).

While MFS is considered as a pure peripheral cranial polyneuropathy, in some patients concomitant central nervous system (CNS) involvement is suggested by magnetic resonance imaging (MRI) abnormalities of hyperintense lesions on T2-weighted and hypointense on T1-weighted images in the cerebral white matter, brainstem, and cerebellum (Echaniz-Laguna, Battaglia, Heymann, Tranchant, & Warter, 2000; Tezer, Gurer, Karatas, Nurlu, & Saribas, 2002) and electroencephalography abnormalities (Giroud, Mousson, Chalopin, Rifle, & Dumas, 1990; Ito et al., 2008; Petty, Duncan, Jamal, Hadley, & Kennedy, 1993).

Incomplete forms with acute ophthalmoparesis without ataxia show strong association with anti-GQ1b antibodies (Lee et al., 2008). Acute ataxic neuropathy without ophthalmoplegia frequently displays anti-GD1b reactivity (Ito, Matsuno, Sakumoto, Hirata, & Yuki, 2011).

Bickerstaff brainstem encephalitis (BBE): a condition that presents similarly to MFS with ataxia, ophthalmoplegia, and areflexia but shows prominent CNS involvement, manifested in disturbances of consciousness and upper motor neuron signs. BBE shares many other features of MFS, including anti-GQ1b antibodies (Bourque et al., 2015).

Pharyngeal-brachial variant of GBS: associated with antibodies against GT1a and GQ1b gangliosides (Bourque et al., 2015). It is an unusual variant in which the paresis is restricted to the upper extremities but may progress to involve the lower extremities as shown by sensory signs, depressed or absent reflexes, or electrophysiological changes in these nerves (van den Berg, Fokke, et al., 2014).

Acute pure sensory ataxic GBS: a variant that is thought to involve the dorsal roots and ganglia. Ataxia is typically a characteristic sensory ataxia, although rarely, a cerebellar-type ataxia may be present. Spinocerebellar 1a afferent fibers have been implicated in the ataxia in this condition, and cerebellar lesions have not been documented. Some of these patients also have immunoglobulin G (IgG) antibodies to GQ1b or GD1b ganglioside. This condition may represent overlap with the acute ataxic neuropathy without ophthalmoplegia variant of MFS, which is also noted for a sensory ataxia and dorsal root ganglia involvement (Dalakas, 2011b, 2013b; Kusunoki & Kaida, 2011; Willison & Yuki, 2002).

Acute pandysautonomic neuropathy: In this variant, the target antigen is in the sympathetic ganglionic neurons (Dalakas, 2011b, 2013b). Symptoms include orthostatic changes, gastrointestinal and urinary dysfunction, dry mouth or eyes, and photophobia due to mydriasis. There is a strong association with ganglionic (nicotinic) acetylcholine receptor antibodies, with up to half testing positive for Acetylcholine Receptor antibodies. Nerve biopsies have shown loss of unmyelinated fibers. There may be pain or dysesthesia without true sensory loss (Koike, Watanabe, & Sobue, 2013).

PATHOGENESIS

GBS is a typical postinfectious disorder. Molecular mimicry occurs when glycoconjugate epitopes are shared between certain viral or bacterial proteins and myelin (Dalakas, 2011b; Gondim et al., 2015) or nerve axolemma (Susuki et al., 2012; Willison, 2012; Willison & Goodyear, 2013) proteins (Fig. 15.2). Thus, an antecedent infection can break tolerance and trigger an autoimmune attack (Hughes & Cornblath, 2005; van den Berg, Walgaard, et al., 2014). GBS typically follows a rapidly progressive, monophasic course (<1 month) shortly after infection, usually without relapse. Two-thirds of adult patients report preceding symptoms of a respiratory or gastrointestinal tract infection within 4 weeks of onset of weakness (Jacobs et al., 1998). Recent literature described cases of GBS following the use of tumor necrosis factor inhibitors (TNF inh) infliximab or adalimumab (Mohan et al., 2001). Potential mechanism may be explained by systemic TNF inh resulting in decreased apoptosis of autoreactive T cells, which may enhance autoimmune responses (Robinson, Genovese, & Moreland, 2001). Another hypothesis is an increased susceptibility to infections. Treatment is by cessation of TNF inh therapy.

In AIDP, there is perivascular and endoneural inflammatory infiltrates throughout the nerves, roots, or plexuses along with segmental demyelination mediated by macrophages (Dalakas, 2011b, 2013b; Hughes & Cornblath, 2005; Yuki & Hartung, 2012). The macrophages break through the basement membrane of healthy Schwann cells and make direct contact with the outermost myelin lamellae, leading to destruction of the superficial myelin sheath (Dalakas, 2011b, 2013b; Hughes & Cornblath, 2005; Yuki & Hartung, 2012; Winer, 2011). Released cytokines and chemokines facilitate ongoing T-cell activation (Yuki & Hartung, 2012). There are deposits of complement-fixing antibodies, IgG, IgM, and MAC against myelinated fibers and against glycolipids that contain carbohydrate (glycocongugate) epitopes (Kusunoki & Kaida, 2011; Willison & Yuki, 2002; Yuki et al., 2004) on peripheral nerves. The glycolipids bear one or more sialic acid molecules (such as ganglioside GM1, GD1a, GT1a, GQ1b), exposed at the extracellular surface (Dalakas, 2011b, 2013b; Dalakas & Quarles, 1996; Yuki et al., 2004).

Viruses, such as cytomegalovirus, EBV, herpes, hepatitis A and E, or HIV, and bacteria, such as *Haemophilus influenzae*,

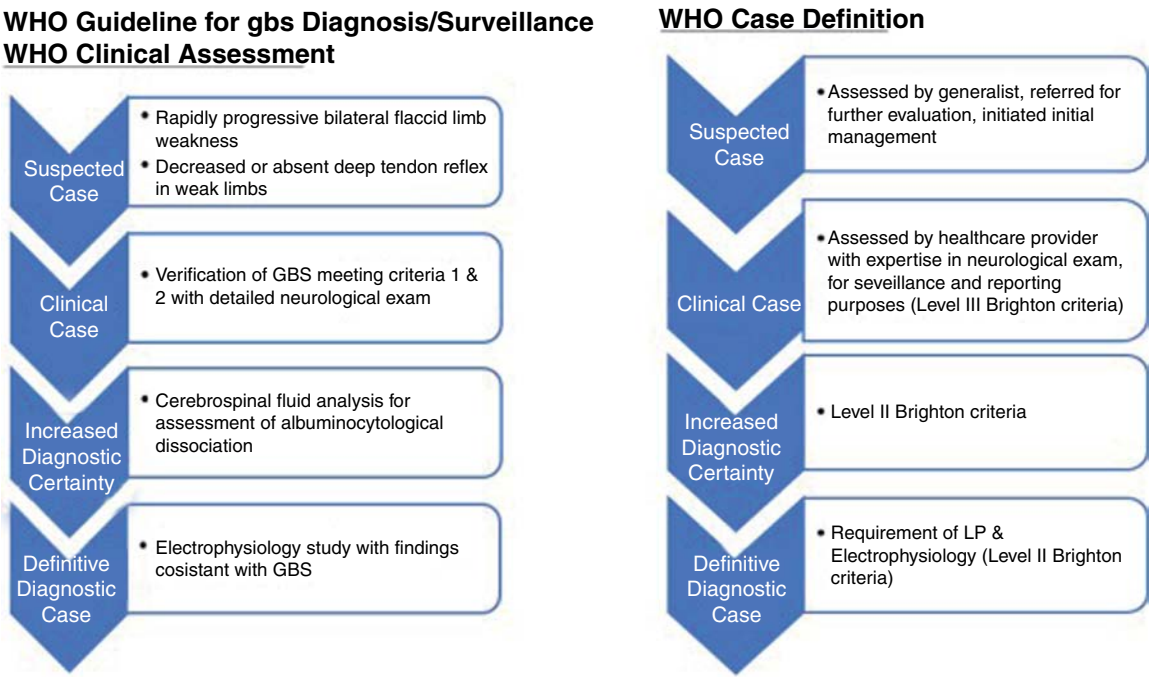


Fig. 15.4 World Health Organization (*WHO*) guideline for Guillain-Barré syndrome (*GBS*) diagnosis/surveillance. *LP*, Lumbar puncture.

Mycoplasma pneumoniae, and *C. jejuni* (Islam et al., 2010; Rees, Soudain, Gregson, & Hughes, 1995), are most commonly implicated. In endemic areas of infection, dengue virus and Zika virus have been associated with the development of GBS, which is usually of the AIDP variety. Most of the antibodies associated with GBS are of the IgG subclass.

Infection by *C. jejuni* carrying GM1-like or GD1a-like lipo-oligosaccharide induces IgG or IgM antibodies to GM1 or GD1a expressed in motor nerves, resulting clinically in AMAN in 80% of patients (Dalakas, 2013b; Kusunoki & Kaida, 2011; Yuki & Hartung, 2012; Willison & Yuki, 2002). IgM anti-GQ1b antibodies are also found in some patients with chronic IgM paraproteinemic polyneuropathies (Dalakas, 2011b, 2013b; Dalakas & Quarles, 1996; Kanjwal, Karabin, Kanjwal, & Grubb, 2010; Schofield & Chemali, 2019). Hemophilus influenzae carries GM1 and GQ1b epitopes and may cross-react with the corresponding myelin antigens. *Mycoplasma pneumoniae* stimulates antibodies against peripheral nerve galactocerebroside (Ang, Jacobs, & Laman, 2004; Dalakas, 2011b, 2013b; Yuki & Hartung, 2012). GBS triggered by CMV infection has been also associated with the presence of IgM anti-GM2 antibodies (Dalakas, 2011b, 2013b). Although probably relevant, genetic and environmental factors that affect an individual's susceptibility to develop the disease are unknown (Blum & McCombe, 2014).

ELECTROPHYSIOLOGY

NCSs can support the diagnosis, differentiate between axonal and demyelinating subtypes (Ho et al., 1995), and provide prognostic insight. Early on, the nerves are so severely affected that they are inexcitable. Abnormalities are most pronounced 2 to 4 weeks after the start of weakness (Hadden et al., 1998). F-wave prolonged latency or absent response is used in GBS diagnosis. The H-reflex stimulates directly the Ia fibers, bypassing the muscle spindle organs, and is absent in GBS. NCSs in AIDP show features of demyelination that include increased distal motor latencies, decreased nerve conduction velocities, absence or decreased persistence of F-waves and H-reflexes, increased temporal dispersion, and CBs. The sural sensory potential is often preserved (Blum & McCombe, 2014), and this electrophysiological feature helps to distinguish GBS from other varieties of polyneuropathy. Features of axonal GBS (AMAN or AMSAN) are decreased sensory nerve action potential (SNAP) amplitudes, decreased CMAP amplitudes, or both. Reversible conduction failure or transient CB may be secondary to inflammatory injury of either glial or axonal membranes (or both simultaneously), caused by antiganglioside antibodies (Umapathi, Tan, Kokubun, Verma, & Yuki, 2012; Uncini, 2012) at the node of Ranvier. Nodal CB can arise quickly, but functionality can be restored in equally short time. Most often, nodal CB occurs in the AMAN variant of GBS (Kokubun et al., 2010; Kokubun, Shahrizaila, Hirata, & Yuki, 2013).

AMAN can either improve very slowly and incompletely or recover rapidly, probably because of restoration of transient CBs. GBS with features of demyelination and secondary axonal loss seen as low CMAP are predictive of poor outcome. Severe demyelination reflects a more diffuse neurological injury or an impaired process of nerve recovery that may affect phrenic nerves as well (Fourrier, Robriquet, Hurtevent, & Spagnolo, 2011).

DIAGNOSIS

GBS is a clinical diagnosis. Examination of the CSF usually shows albumino-cytological dissociation, which is defined as the combination of a normal cell count and increased protein level. A normal protein level (especially in the first week) does not rule out the diagnosis (Lichtenstein et al., 2018). Additionally, 15% of patients

Table 15.2 Differential Diagnosis of Guillain-Barré Syndrome

Central nervous system conditions	Brainstem: stroke (asymmetric limb paresis), infection. Spinal cord: compression (asymmetric), poliomyelitis (purely motor disorder with meningitis), transverse myelitis (abrupt bilateral leg weakness, ascending sensory).
Muscle conditions	Metabolic: hypokalemia, hypophosphatemia (irritable, apprehensive, hyperventilation, normal cerebrospinal fluid). Myopathy: infectious, inflammatory polymyositis (chronic, affects proximal limb muscles), toxic. Rhabdomyolysis, periodic paralysis.
Neuromuscular junction conditions	Myasthenia gravis (weakness and fatigue that improves with rest), toxins.
Polyneuropathies	CIDP. Critical illness. infection (Lyme disease, HIV). Metabolic: diabetes mellitus, porphyria, uremia. Vasculitic neuropathies (mononeuropathy). Toxicity: diphtheria, botulism (descending paralysis), heavy metals (arsenic) (slowly progressive confusion, psychosis, organic brain syndrome), substance abuse (n-hexane exposure from glue sniffing).

Diagnosis of GBS, Miller Fisher syndrome, and their subtypes can be challenging in early disease, but many differentials can be excluded based on history and examination alone.
CIDP, Chronic inflammatory demyelinating polyneuropathy; *GBS*, Guillain-Barré syndrome.

with the disease have a mild increase in CSF cell count (5–50 cells per μL) (Borman, Gokoglu, Kocaoglu, & Yorgancioglu, 2008) (Fig. 15.4)

Differential Diagnosis

The differential diagnosis can be broad with all the variants of GBS (Table 15.2). Vasculitic neuropathy is characterized by painful asymmetric weakness that is progressive over months. The etiologies include cryoglobulinemia, hepatitis, HIV and Lyme, cancers (lymphomas), and connective tissue diseases (Mendell, Cornblath, & Kissel, 2001). Diphtheria is a rapidly progressive demyelinating polyneuropathy that can also affect the cranial nerves (Levin, 2004). Polio is purely motor (Dumitru, Amato, & Zwarts, 2002; Levin, 2004). West Nile virus can cause mild sensory polyneuropathy, weakness, and encephalitis (Govoni & Granieri, 2001). Botulism causes descending weakness that starts as cranial neuropathies, similar to Miller Fisher, and is complicated by severe autonomic symptoms. HIV infection increases the incidence of GBS. Lumbar puncture shows increased nucleated cells. Acute intermittent porphyria causes multifocal neuropathy with motor much worse than sensory involvement with autonomic dysfunction (Dumitru et al., 2002; Govoni & Granieri, 2001). Tick paralysis causes paresthesias, followed rapidly by gait ataxia, cranial neuropathy leading to blurry and double vision, dysarthria, and respiratory failure (Levin, 2004). Lead and mercury cause slowly progressive weakness (Dumitru et al., 2002). Arsenic neuropathy begins after weeks of exposure with paresthesias followed by progressive weakness, sensory loss, ataxia, and autonomic dysfunction. Glue Sniffer neuropathy caused by hexacarbons leads to initial paresthesias, followed by progressive weakness secondary to sensory and motor axonal neuropathies (Towfighi, Gonatas, Pleasure, Cooper, & McCree, 1976). Amiodarone causes chronic sensorimotor demyelinating polyneuropathy and, rarely, acute polyneuropathy, virtually indistinguishable from AIDP (Dumitru et al., 2002; Mendell et al., 2001). Nitrous oxide in the setting of B_{12} deficiency can lead to acute neuropathy and subacute combined degeneration. Cytosine arabinoside rarely causes acute progressive demyelinating polynuropathy. Increased CSF protein is apparent (Leikin & Paloucek, 2008; Levin, 2004). Critical illness myopathy is typically a generalized, more proximal weakness, including neck and facial strength. The time course and progression of illness and facial weakness may help differentiate from GBS (Dumitru et al., 2002). Subacute or acute cervical myelopathy has a similar appearance to GBS (Levin, 2004). CIDP is separated from GBS by the timing and course of illness (Aminoff, 1998; Dumitru et al., 2002; Mendell et al., 2001).

TREATMENT

GBS is a potentially life-threatening disease (Benamer & Bredan, 2014; Netto, Taly, Kulkarni, Rao, & Rao, 2011; van den Berg, Bunschoten, van Doorn, & Jacobs, 2013). The severity and duration can range from mild weakness that recovers spontaneously to quadriplegia and ventilation dependence or severe, permanent disability.

Supportive care is necessary and encompasses monitoring respiratory function by frequent measurement of forced vital capacity or negative inspiratory force. The Erasmus GBS Respiratory Insufficiency Score determines the chance a patient will need artificial ventilation (Walgaard et al., 2010). Cardiac and hemodynamic monitoring for autonomic dysfunction and timely transfer to ICU when needed are crucial (Hughes et al., 2005; van den Berg, Walgaard, et al., 2014). Additional and important management issues include prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, early initiation of physiotherapy and rehabilitation, and psychosocial support.

IVIg (0.4 gm/kg body weight daily for 5 days) and large volume PE (200–250 mL plasma/kg body weight in five sessions) are equally effective treatments for GBS (Hughes et al., 2007; Raphaël, Chevret, Hughes, & Annane, 2012; Verboon, van Doorn, & Jacobs, 2017). IVIg is no better than PE, and the combination of both treatments is no better than one treatment alone. IVIg is usually the treatment of choice as it is easier to administer and more available (Branch, Porter, Paidas, Belfort, & Gonik, 2001; Tomimatsu et al., 2016). Randomized controlled trials (RCTs) on the efficacy of

corticosteroids showed no significant benefit; oral corticosteroids in fact have been shown to have a negative effect on outcome (Hughes et al., 2007; Hughes & van Doorn, 2012). An RCT of the humanized monoclonal antibody eculizumab (Fitzpatrick et al., 2011; Halstead et al., 2008) is being performed (Fokkink et al., 2017; Yamaguchi et al., 2016).

Pain that is moderate to severe is a common symptom in GBS. It may present during the acute stage or may be reported a year after GBS onset. Pain intensity was shown to be associated with the level of weakness, fatigue, and functional disability during the later stages of GBS (Ruts et al., 2010). Multiple types of pain (back and sciatic pain, meningeal signs, dysaesthesia and paraesthesia, muscle pain, arthralgia, visceral pain, etc.) suggest nociceptive and neuropathic origin (Pentland & Donald, 1994). Radicular pain, linked to inflammation of nerve roots (Ruts, van Koningsveld, Jacobs, & van Doorn, 2007), and muscle pain are the most common types during the acute phase (Tripathi & Kaushik, 2000). Carbamazepine (Yao et al., 2018) and gabapentin (Pandey et al., 2002), as well as opioids (Genis et al., 1989), are used as pain management in patients with GBS.

MFS is a self-limiting condition with gradual spontaneous improvement of symptoms and eventual recovery. Ataxia and ophthalmoplegia typically resolve within 1 to 3 months after onset, and near-complete recovery is expected within 6 months (Mori et al., 2001). Immunomodulatory therapies including IVIg and PE are used to hasten recovery and decrease the likelihood of progression to a more severe GBS (Overell & Willison, 2005).

The severity of the disease course of BBE justifies treatment with IVIg or PE, although evidence of efficacy is limited (Odaka et al., 2003; Overell, Hsieh, Odaka, Yuki, & Willison, 2007). Neither IVIg nor PE is contraindicated during pregnancy. IVIg might be preferred due to convenience of administration (Branch et al., 2001; Tomimatsu et al., 2016).

Treatment-related fluctuation: occurs within the first 8 weeks of treatment with IVIg or PE in about 10% of patients (Kleyweg & Van der Meche, 1991; Sala et al., 2018). It is explained by prolonged and sustained nerve damage or functional blockade (Willison et al., 2016) and implies that progression might have been worse without therapy (Hughes et al., 2007; Verboon et al., 2017; Willison et al., 2016). Repeating treatment was shown to have no effect on the outcome (Farcas, Avnun, Frisher, Herishanu, & Wirguin, 1997; Oczko-Walker, Manousakis, Wang, Malter, & Waclawik, 2010). When there is a new deterioration after 8 weeks, the diagnosis of CIDP should be suspected and occurs in about 5% of patients (Dionne, Nicolle, & Hahn, 2010; Halstead et al., 2008; Hughes et al., 2008).

Predictors of outcome: The Erasmus GBS Outcome Scale is based on age, worse at 40 years and over, preceding diarrheal infection in the past 4 weeks, and high disability at nadir with greater weakness, facial/bulbar weakness, and mechanical ventilation, to predict the ability to walk at 6 months (Van Koningsveld et al., 2007). Electrodiagnostically, demyelination and low CMAP amplitudes are associated with a worse prognosis. Low serum albumin (<3.5 g/dL) at baseline, but especially 2 weeks after IVIg treatment, is associated with a worse outcome (Fokkink et al., 2017).

GBS as a neurologic complication of SARS-CoV-2, COVID-19:

A systematic review aimed to identify predominant clinical, laboratory, and neurophysiological patterns of neurologic complications in association with COVID-19 infection showed that neurological symptoms arise with a median latency of 14 days. A higher prevalence of GBS in patients with COVID-19 was seen in males compared to females [1] with a worse clinical outcome compared to the females [2,3] and Pediatric cases have been increasingly reported in the literature [4,5,6,7]. Similar to classic GBS risk factors for unfavorable outcome in COVID-19 associated GBS include older age, preceding diarrhea and past or concurrent COVID-19 pneumonia [8,9]. Nevertheless, GBS may also develop in the context of a paucisymptomatic or asymptomatic COVID-19 (10)

The pathophysiologic basis is that abnormal immune-mediated response of cytokine overproduction e.g., CRP, IL-6, TNF-α, IL-1, etc. leads to systemic inflammatory storm that manifest as myelitis, encephalitis, GBS or hypercoagulable state and cerebrovascular events [11,12]. A postinfectious mechanism for GBS is that of molecular mimicry between the viral protein associated gangliosides, the angiotensin-converting enzyme 2 and the gangliosides containing sialic acid residues including the GalNAc residue of GM1, and peripheral nerve gangliosides.54–56 thus resulting in delayed immune-mediated damage to peripheral nerve (13). This is supported by absence of SARS-CoV-2 RNA in CSF and the response to IVIG.

Clinical manifestation of GBS in patients with COVID-19 is symmetrical and generalized weakness and sensory disturbances. Weakness in the limbs and acute flaccid quadriparesis were observed in most cases (14) All of the major GBS electrodiagnostic patterns have been reported in association with COVID-19. As in classic GBS, the demyelinating pattern, acute inflammatory demyelinating polyneuropathy (AIDP) was the most common pattern (15), and to a lesser extent AMSAN and AMAN [16]. In analogy to classic GBS, approximately one-fifth of COVID-19-associated GBS subjects required mechanical ventilation during hospitalization [17]. The workup frequently reveals negative nasopharyngeal swab at GBS onset [18,19, 20,21]. CSF from COVID-19 associated GBS patients, similar to classic GBS, shows elevated protein levels, normal cell counts and absent the anti-ganglioside antibodies. CSF has been negative for SARS-CoV-2 by RT-PCR. Post-mortem brain tissues from COVID-19 patients did not show evidence for viral infection by immunohistochemical analysis (22).

COVID-19- induced cytokine storm associated with GBS responds well to IVIG therapy, based on direct removal of cytokines and the shift towards a more favorable anti-inflammatory cellular and cytokine profile (23-25). Plasma exchange is not preferred to treat COVID-19 associated GBS at present, as it challenges the tenuous hemodynamic state of critically ill patients and exposes more health care workers for longer periods of time to infected patients (23-25). The potential GBS risk from the vaccine should be weighed against the considerable morbidity and mortality of the infection (26).

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CHRONIC AUTOIMMUNE PERIPHERAL NEUROPATHIES

CIDP typically presents with motor and sensory symptoms leading to relatively symmetrical, proximal, and distal weakness. By definition, CIDP should progress or relapse for a period greater than 8 weeks. CIDP is the most common acquired autoimmune-mediated neuropathy, with a prevalence of 8–9/100,000 (Dalakas, 2011a, 2013b; Lunn, Manji, Choudhary, Hughes, & Thomas, 1999). The mean age of onset is around 50 years, with a slightly lower prevalence in children and women (McLeod et al., 1999). There are variable clinical phenotypes with variable clinical course and differing responses to immunotherapy (Dalakas, 2011a; Renaud et al., 2005; Lee, Xiang, Brannagan, Chin, & Latov, 2010; Querol et al., 2013).

PATHOLOGY

The neuropathy is inflammatory, with perivascular and endoneural lymphoid cell infiltrates throughout the nerves, roots, or plexuses, and demyelinating with signs of segmental demyelination. Pathological findings could be patchy and thus missed on biopsy. Demyelination is induced by complement-fixing antibodies and macrophages as the final effector cells (Dalakas, 2011b, 2013b; Hughes & Cornblath, 2005; Yuki & Hartung, 2012), such as the nodal/paranodal antibodies.

CLASSIFICATION

The Joint Task Force of the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) divided CIDP into two clinical subtypes: "typical CIDP (t-CIDP)" and "atypical CIDP," which includes multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), distal acquired demyelinating sensorimotor neuropathy (DADS), pure sensory form, each comprising 15% of the whole CIDP population, and the less common pure motor form and focal CIDP (Dalakas, 2011b, 2013b; Hughes, Allen, Makowska, & Gregson, 2006; Köller, Kieseier, Jander, & Hartung, 2005; Kuwabara & Misawa, 2011; Querol et al., 2018) (Table 15.3). The different clinical presentations and response to therapy among the different atypical CIDP types might be associated with different underlying immunological abnormalities, as was reported for patients with antibodies to nodal-paranodal proteins neurofascin 155 and contactin 1 (Illa, 2017; Vural, Doppler, & Meinl, 2018). The EFNS/PNS criteria exclude multifocal motor neuropathy (MMN) and anti-myelin associated glycoprotein (anti-MAG) neuropathy from CIDP, mainly because of different treatment responses.

Table 15.3 Notable Features of Key Variants of CIDP

Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy)	Motor and sensory deficits, asymmetrical presentation of symptoms, often start from upper limbs, conduction block found in the affected nerves, usually good response to steroids.
Distal acquired demyelinating symmetric neuropathy	Predominantly distal sensory loss, mild distal weakness, and unsteady gait. When no monoclonal protein is found, response to therapy seems similar to that of typical CIDP.
Pure motor form	Symmetrical and selective involvement of motor fibers; conduction blocks; more responsive to IVIg than it is to steroids.
Sensory CIDP or chronic sensory demyelinating neuropathy	Numbness in the extremities is frequent; ataxia can be prominent; nerve conduction studies show motor abnormalities typical of CIDP; significant weakness can appear at follow-up.
Chronic immune sensory polyradiculopathy, sensory ataxia form	Sensory ataxia and large fiber sensory loss; nerve conduction studies are normal, histological pattern of rootlet biopsy is similar to that of CIDP.

CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; *IVIg*, intravenous immunoglobulin.

MAIN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY VARIANTS BASED ON PATTERNS OF SYMPTOMS AND SIGNS

PATHOGENESIS

In contrast to GBS, there is little evidence that viral or bacterial infections are antecedent events in CIDP. The role of autoimmunity is becoming increasingly compelling (Dalakas, 2011b, 2013b, 2015).

In typical CIDP, there is deranged homeostasis in the neural milieu through invasion of immune cells where the BNB is dysfunctional at the proximal and distal nerve segments (i.e., nerve roots and neuromuscular junction) (Kanda, 2013; Kanda, Numata, & Mizusawa, 2004; Shimizu et al., 2014a, 2014b). Autoantibodies against myelin components and inflammatory cytokines (Furukawa et al., 2014, 2015; Mahad, Howell, & Woodroofe, 2002; Maimone, Annunziata, Simone, Livrea, & Guazzi, 1993; Mei et al., 2005; Misawa et al., 2001; Press, Pashenkov, Jin, & Link, 2003; Terenghi, Allaria, & Nobile-Orazio, 2006) enter at these sites and play the primary role in the mechanisms of neuropathy (Shimizu et al., 2014a). Electrophysiologic markers at disease onset (delayed F-waves and absent H-responses) suggest that the process begins as a proximal polyradiculopathy that subsequently extends distally.

The predominant lymphoid cells consist of macrophages (Dalakas, 1999, 2013b; Prineas & McLeod, 1976; Sommer et al., 2005; Vallat, Sommer, & Magy, 2010; Vital et al., 2000), which are activated by cytokines released by autoreactive T cells (Dalakas, 2011a, 2013b; Hu et al., 2007; Hughes et al., 2006; Kiefer et al., 2000; Kieseier et al., 2002; Köller et al., 2005; Lunn et al., 1999; Murata & Dalakas, 2000; Sommer et al., 2005; Vallat et al., 2010; Vital et al., 2000) and constitute the final effector cells associated with demyelination. Macrophages at the basement membrane of the Schwann cell displace the cytoplasm, split the myelin lamellae, and result in focal destruction of the myelin sheath (macrophage-mediated demyelination).

Some immune neuropathies, including CIDP, may be mediated directly by systemic B-cell production of autoreactive antibodies that are able to traverse a leaky BNB. At the endoneurial level, antibodies may produce a direct humoral, complement-mediated attack or recruit macrophages expressing Fc receptors. T cells may directly execute the cytotoxic attack or recruit local macrophages through the production of cytokines and chemokines (Bourque et al., 2015). Humoral factors' role is indicated by the fast effect of PE that removes a circulating factor, probably an antibody, responsible for demyelination and CB (Dalakas, 2011a, 2011b, 2013b), the presence of complement fixing IgG and IgM deposits on the myelin sheath (Dalakas & Engel, 1980), and IgG in the CSF (Dalakas, Houff, Engel, Madden, & Sever, 1980). Humoral factors cause more severe BNB damage in t-CIDP than in atypical CIDP and more severe damage in patients with MMN than in those with MADSAM (Dalakas, 2015; Shimizu et al., 2014b). There is dysfunction of immunoregulatory T cells (Chi et al., 2010; Chi, Wang, & Wang, 2008; Dalakas, 2011a, 2013b, 2014; Sanvito, Makowska, Gregson, Nemni, & Hughes, 2009) and increased serum interleukin-17 and Th17-positive cells in blood and CSF, all of which enhance the immune process (Chi et al., 2010).

The anaphylatoxins C3a and C5a, together with other complement components, orchestrate inflammation toward direct cellular damage by the MAC (Morgan, Boyd, & Bubeck, 2017). In both GBS and CIDP, MAC deposits on Schwann cells and compact myelin (Dalakas & Engel, 1980; Hafer-Macko et al., 1996; Hays, Lee, & Latov, 1988; Koski et al., 1987) and levels decline with clinical improvement (Koski et al., 1987). Increased serum levels of MAC components are reported to correlate with clinical disease (Quast, Keller, Hiepe, Tackenberg, & Lünemann, 2016).

Recent studies have shown yet another mechanism that results in nerve conduction abnormalities in patients with autoantibodies against paranodal junction proteins, such as neurofascin-55 and contactin-1 (Doppler et al., 2015; Koike et al., 2017; Ogata et al., 2015). Biopsies show paranodal dissection, which leads to focal disruption of the BNB that is distinct from classical macrophage-induced demyelination in antibody-negative cases (Koike et al., 2017, 2018). These focal lesions present in the nerve trunk in patients with MADSAM. As focal lesions are also found in patients with DADS and pure sensory type, these subtypes may share their mechanisms of neuropathy with MADSAM rather than typical CIDP.

ELECTROPHYSIOLOGY

Features of demyelination in motor and sensory fibers are decreased conduction velocities, temporal dispersion of CMAP, CB, increased distal motor or sensory latencies, and increased F wave latencies (Adler, Russell, Hummers, & McMahan, 2018; Bourque et al., 2015; Hughes et al., 2006; Köller et al., 2005; Sommer et al., 2005; Vallat et al., 2010; Vital et al., 2000). In t-CIDP, there is often demyelination in the nerve roots, reflected by increased F wave latencies and slowing of motor nerve conduction velocity, as well as in the distal nerve terminals, reflected by prolongation of distal motor latency (DML) and the slowing of sensory nerve conduction velocity (Benjamin et al., 2018; Ikeda et al., 2019; Koopman et al., 2016; Kuwabara & Misawa, 2011; Kuwabara, Ogawara, Misawa, Mori, & Hattori, 2002; Kuwabara et al., 2015; Liu, Treister, Lang, & Oaklander, 2018; Olsson, 1968, 1990). Median sensory nerve conduction studies assess the most distal part of the nerve, whereas the intermediate portion is examined in sural nerve studies. The typical pattern of sensory nerve involvement is distal demyelination in the median sensory response while the sural response remains normal (Bromberg & Albers, 1993; Kuwabara, 2007). Similarly, ulnar sensory responses are abnormal, with intact superficial radial sensory responses (Kuwabara et al., 2015). Normal SNAPs are explained by pathology being in nerve roots.

Electrophysiologic studies of MADSAM show multifocal nerve CB in the intermediate nerve trunks (Kuwabara & Misawa, 2011; Magda et al., 2005; Mahad et al., 2002; Shimizu et al., 2014a, 2014b). In DADS, there is preferential demyelination in the distal nerve terminals as indicated by disproportionately increased distal latencies (Shimizu et al., 2014b).

SUBTYPES OF CIDP

1. **Typical CIDP:** There is relatively uniform, chronic progressive or recurrent proximal and distal weakness and sensory dysfunction developing over at least 2 months (American Academy of Neurology AIDS Task Force, 1991; Barohn, Kissel, Warmolts, & Mendell, 1989; Van den Bergh et al., 2010). It is characterized by multiple mononeuropathy, which is involved in multifocal nerve CB on nerve conduction studies (Saperstein et al., 1999; Viala et al., 2004). Typical CIDP can have Monoclonal Gammopathy of Undetermined Significance and the treatment approach is similar.
2. **Atypical CIDP:** The frequency of the CIDP variants as a group (including MADSAM, DADS, pure motor, and pure sensory types) ranges between 1% and 49% (Lefter, Hardiman, & Ryan, 2017; Mathey et al., 2015). MADSAM, DADS, and pure sensory types each comprise approximately 15% of the entire population with CIDP (Kuwabara et al., 2015). A study of an Italian cohort suggests that some of the patients with atypical CIDP evolve into typical CIDP (Dalakas, 2011c; Doneddu et al., 2019) in 20%–71% (Berger, Herskovitz, & Kaplan, 1995; Doneddu et al., 2019; van Dijk, Notermans, Franssen, & Wokke, 1999; Viala et al., 2004).

ATYPICAL CIDP SUBTYPES

2a. **MADSAM neuropathy (Lewis Sumner syndrome).** This is characterized by an asymmetrical multifocal pattern of motor and sensory impairment circumscribed to multiple individual nerve territories (i.e., mononeuropathy multiplex) (Saperstein et al., 1999; Viala et al., 2004). The distal portion of the upper limbs is initially affected, with pure sensory, pure motor (Rajabally & Chavada, 2009; Verschueren et al., 2005), or sensory-motor involvement affecting the median and/or ulnar nerves. Proximal involvement is common (Fargeot et al., 2019), mainly in the upper limbs. Patients tend to show frequent muscle atrophy. Root and plexus abnormalities are also frequently seen on MRI (Mathey et al., 2015). Focal demyelinating lesions secondary to disrupted axon-Schwann cell interaction (Ikeda et al., 2019) and demonstrable by NCSs are found in the intermediate portions of the nerves (Katz & Saperstein, 2001; Nobile-Orazio, 2001; Oh, LaGanke, et al., 2005). Sensory involvement is often extensive, spreading beyond nerves with CB. Spread to other limbs, generalized areflexia, and ataxia have been reported in 13%–39% of patients (Attarian et al., 2011; Oh, Claussen, & Kim, 1997; Parry, 1999; Van den Berg-Vos et al., 2000; Viala et al., 2004). CSF protein levels are often normal. Electrophysiologically, there is usually decreased conduction velocity and focal CB in multiple nerves. Regions of CB with retained conduction velocity early in the course of the disease may be explained by yet undiscovered antibodies to an axonal or nodal/paranodal protein (Li et al., 2019).

2b. **Distal acquired demyelinating sensorimotor neuropathy (DADS).** Patients present with chronic, slowly progressive, large-fiber, symmetric sensory, or sensorimotor symptoms and signs starting distally in the lower limbs that manifest as sensory ataxia with or without neuropathic pain, autonomic symptoms, and tremor. Upper-limb distal sensory or sensorimotor symptoms and signs may occur after 1 year from onset (Ang et al., 2004; Dalakas, 2013b; Dalakas & Quarles, 1996; Illa et al., 1995; Katz, Saperstein, Gronseth, Amato, & Barohn, 2000; Latov, Hays, & Sherman, 1988; Saperstein, Katz, Amato, & Barohn, 2001). Electrophysiologic findings are consistent with distal demyelination.

2c. **Pure sensory CIDP/chronic immune sensory polyradiculopathy (CISP).** Pure sensory type is defined as sensory neuropathy without motor symptoms. Patients present with sensory symptoms (including ataxia), without weakness, in a symmetric or asymmetric polyneuropathic distribution and symptoms may start anywhere in the body, but not in a length-dependent pattern (Doneddu et al., 2019). There may or may not be abnormal motor nerve conduction studies. There is elevated CSF protein levels and frequent segmental demyelination (Ikeda et al., 2019).

Patients have relative preservation of functional status because of the preservation of motor functions.

CISP patients have sensory symptoms with a polyneuropathic distribution without weakness, normal motor, and sensory nerve conduction and EMG studies. MRI can show gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses. There may be elevated CSF protein level with normal cell count (Doneddu et al., 2019). All of these features

indicate that the predominant pathology is restricted to the sensory nerve roots.

2d. **Pure motor type** was defined as motor neuropathy without sensory disturbance.

2e. **Focal type** was defined as motor or sensorimotor neuropathy confined to one limb.

IgM-Monoclonal Gammopathy of Undetermined Significance neuropathy with anti-MAG antibodies: This is the best characterized paraproteinemic neuropathy with IgM antibody-mediated monoclonal gammopathy and presents with the DADS phenotype associated with distal demyelination. Sera from these patients react with glycoprotein of compact myelin, myelin-associated glycoprotein (MAG) in 50% of cases (Ang et al., 2004; Dalakas, 2013b; Dalakas & Engel, 1981; Dalakas & Quarles, 1996; Ilyas et al., 1984; Ilyas, Quarles, Dalakas, & Brady, 1985; Daune, Farrer, Dalakas, & Quarles, 1992; Latov et al., 1981, 1988; Quarles & Dalakas, 1996). The sulfoglucuronyl glycosphingolipid in the ganglioside fraction of the MAG is found exclusively in the peripheral nerve and is the antigenic epitope in IgM-MGUS patients (Dalakas & Quarles, 1996; Daune et al., 1992; Latov et al., 1988; Quarles & Dalakas, 1996). Sural nerve biopsy demonstrates diminished number of myelinated axons with a characteristic splitting of the outer myelin lamellae, linked to deposition of IgM that recognizes MAG in the same area of the split myelin (Ang et al., 2004; Dalakas, 2013b; Latov et al., 1988). Patients with anti-MAG antibodies tend to have only marginal and transient responses to conventional immunotherapies, and some are severely disabled by the sensory ataxia (Barohn et al., 1989; Chassande et al., 1998; Léger et al., 2013; Lunn & Nobile-Orazio, 2016; Mygland & Monstad, 2003; Van Den Berg et al., 1996).

Patients who also display ophthalmoplegia and have an associated M-protein have been described under the acronym CANOMAD, for chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosylantibodies (Willison et al., 2001). There is an association with IgM anti-GD1b (Attarian et al., 2010). About 70% of such patients respond at least partially to IVIg infusions (Attarian et al., 2010).

MMN is a distinct acquired chronic immune neuropathy characterized by multifocal pattern of motor impairment, focal muscle weakness, and atrophy, in the distribution of individual motor nerves (Box 15.1). Cramps and fasciculations occur in 50% of patients (Pestronk, 1998). Electrophysiologically, there is multifocal persistent CB in motor nerves with the retaining of normal sensory conduction across the nerve segments that have the motor block (Dalakas, 2011b, 2013b; Nobile-Orazio, 2001). Approximately 40% to 50% of MMN patients have elevated IgM anti-GM1 antibody titers (Dalakas, 2011b, 2013b; Nobile-Orazio, 2001). GM1 antibodies trigger direct and complement-dependent damage to axons and nodes of Ranvier (Willison & Yuki, 2002; Yuki, Watanabe, Nakajima, & Späth, 2011), causing functional CB (Beadon, Guimarães-Costa, & Léger, 2018; Garg et al., 2019; Harschnitz et al., 2014; Kiernan, Guglielmi, Kaji, Murray, & Bostock, 2002; Shimizu et al., 2019). Biopsies from the site of CB showed multifocal degeneration and a loss of nerve fibers without inflammation or lymphocyte infiltration (Taylor et al., 2004). Electrophysiologically, there is axonal membrane hyperpolarization due to the overactivation of Na+/K+ ATPase at the node of Ranvier around the sites of CB, resulting in a decrease in the persistent Na+ current. Therefore, MMN may really be a chronic nodo-paranodopathy (Beadon et al., 2018; Bourque et al., 2015; Kiernan et al., 2002). Box 15.1 summarizes the diagnostic criteria for MMN.

The polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare neuropathic syndrome resulting from an underlying plasma cell disorder, most often an osteosclerotic myeloma, or Castleman syndrome (angiofollicular hyperplasia). Hypersecretion of vascular endothelial growth factor is both a diagnostic criterion and a marker of disease progression. A small monoclonal protein is usually detected on immunofixation (85% of cases), most often comprised of a lambda light chain (95% of cases). Treatment includes eliminating clonal plasma cells, either with local radiotherapy when the disease is circumscribed or with systemic chemotherapy and

Box 15.1 Clinical Criteria for Multifocal Motor Neuropathy

Core criteria (both must be present)

- Slowly progressive or stepwise progressive, focal, asymmetric[a] limb weakness, motor involvement in motor nerve distribution of at least two nerves, for more than 1 month[b]. If symptoms and signs are present only in the distribution of one nerve, a possible diagnosis can be made.
- No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs[c].

Supportive clinical criteria

- Predominant upper limb involvement[d]
- Decreased or absent tendon reflexes in the affected limb[e]
- Absence of cranial nerve involvement[f]
- Cramps and fasciculations in the affected limb
- Response in terms of disability or muscle strength to immunomodulatory treatment

Exclusion criteria

- Upper motor neuron signs
- Marked bulbar involvement
- Sensory impairment more marked than minor vibration loss in lower limbs
- Diffused symmetric weakness during the initial weeks

[a] Asymmetric = a difference of 1 MRC grade if strength is MRC N3 and 2 MRC grades if strength is MRC ≤3.
[b] Usually more than 6 months.
[c] Sensory signs and symptoms may develop over the course of MMN.
[d] At onset, predominantly lower limb involvement accounts for nearly 10% of the cases.
[e] Slightly increased tendon reflexes, in particular in the affected arm, have been reported and do not exclude the diagnosis of MMN provided criterion 8 is met.
[f] Twelfth nerve palsy has been reported.

Source: Van Schaik, I., Léger, J. M., Nobile-Orazio, E., Cornblath, D., Hadden, R., Koski, C., et al. (2010). European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. Joint Task Force of the EFNS and the PNS. *Journal of the Peripheral Nervous System*, *15*, 295-301.

MMN, Multifocal motor neuropathy; *MRC*, Medical Research Council.

stem cell transplantation for more diffuse disease (Dispenzieri & Buadi, 2013).

NODOPATHIES

The node of Ranvier has emerged as a target in GBS, CIDP, and MMN. The term "nodo-paranodopathy" was proposed to better characterize immune-mediated neuropathies with dysfunction at the node of Ranvier and paranode ranging from transitory nerve conduction failure to axonal degeneration (Uncini et al., 2013). Antigangliosides, concentrated at the node and paranode and exposed axonal membranes at nerve terminals, are commonly associated with "axonal" forms of GBS (Goodfellow & Willison, 2016). Antinodal adhesion molecules, NF155, NF186, gliomedin, and contactin, lead to Voltage-Gated Na+ channels alteration and conduction defects, leading to neuropathies considered "demyelinating," such as CIDP and MMN (Devaux, Odaka, & Yuki, 2012).

Clinical features vary in accordance to the underlying pathomechanism such that focal demyelination can show rapid clinical recovery and return to normal. This state could progress to axonal degeneration or classical/segmental demyelination where remyelination takes a longer time frame. Alternatively, chronically demyelinated axons may subsequently degenerate.

The nodo-paranodopathy classification (Uncini et al., 2013) may explain how some acute axonal neuropathies can have reversible conduction failure or functional CB. The proposed explanation is that CB is caused by antibody binding at the nodal/paranodal regions (Uncini et al., 2013). Nodal CB is of axonal origin, can arise quickly, and is functionality restored equally quickly through local repair of injured membranes. The nodal area has a critical role in nerve action potential transmission since it is the area of the axon with a high concentration of voltage-gated sodium channels (Uncini et al., 2013) (Fig. 15.5). The CB in CIDP and in AIDP can be explained by a change in the fine structure at the nodal, paranodal, or juxtaparanodal (the Schwann cell/axonal interactions) regions, leading to blockade of saltatory conduction (Dalakas, 2011a, 2013b; Pollard & Armati, 2011). It is rich with proteins and glycolipids that can be potential antigens for an autoimmune process. Some of the putative antigenic proteins at the node are the neurofascin (NF186), gliomedin, sodium channels, ankyrin G, or spectrin; at the paranode: the neurofascin 155, contactin/Caspr 1 and connexins Cx31.3, Cx3232, Cx31.3, or 29; and at the juxtaparanode: the transient axonal glycoprotein-1/Contactin-associated protein and potassium channels (Lonigro & Devaux, 2009; Susuki, 2013).

CIDP with antibodies to cell adhesion antigens: Recently, a small subset of CIDP patients (3%–18%) have been demonstrated to have autoantibodies against cell adhesion antigens, neurofascin (NF) (Devaux et al., 2012; Kadoya et al., 2016; Ogata et al., 2015; Querol et al., 2014; Thaxton, Pillai, Pribisko, Dupree, & Bhat, 2011), CNTN1 (Davis, Lambert, & Bennett, 1996; Doppler et al., 2015; Miura et al., 2015; Querol et al., 2013), and CASPR1 (Allen, Berger, Querol, Kuitwaard, & Hadden, 2018; Burnor et al., 2018; Doppler et al., 2016; Ogata et al., 2015). These molecules are critical for the formation and maintenance of the nodes of Ranvier. NF186 and NF155 cluster sodium channels at the nodes and paranodes of Ranvier (Davis et al., 1996) in both the peripheral nervous system and CNS (Davis et al., 1996; Stathopoulos, Alexopoulos, & Dalakas, 2015). NF186 plays a role in the assembly of the nodal complex by acting as a molecular boundary to restrict the migration of paranodal loops into nodal areas (Tait et al., 2000; Thaxton et al., 2011). NF155 is expressed at the paranodal loops of oligodendrocytes in the CNS and in Schwann cells in the peripheral nervous system. It acts as the myelin ligand of the contactin-1/contactin-associated protein 1 (CNTN1/CASPR1) complexes at the paranode and is essential for saltatory conduction (Devaux et al., 2012; Kadoya et al., 2016; Kuwahara et al., 2018; Thaxton et al., 2011). Anti-NF-155 antibodies, detected in a minority of CIDP patients (Ogata et al., 2015), disturb the glial-axon integrity and lead to conduction disturbances (Koike et al., 2017; Sherman et al., 2005; Vallat et al., 2017). These antibodies are immunoglobulin G4 (IgG4) and do not activate complement. Their presence carries a specificity approaching 100% for a diagnosis of CIDP (Burnor et al., 2018; Devaux et al., 2016). Binding specifically to paranodal regions leads pathologically (Devaux et al., 2012; Koike

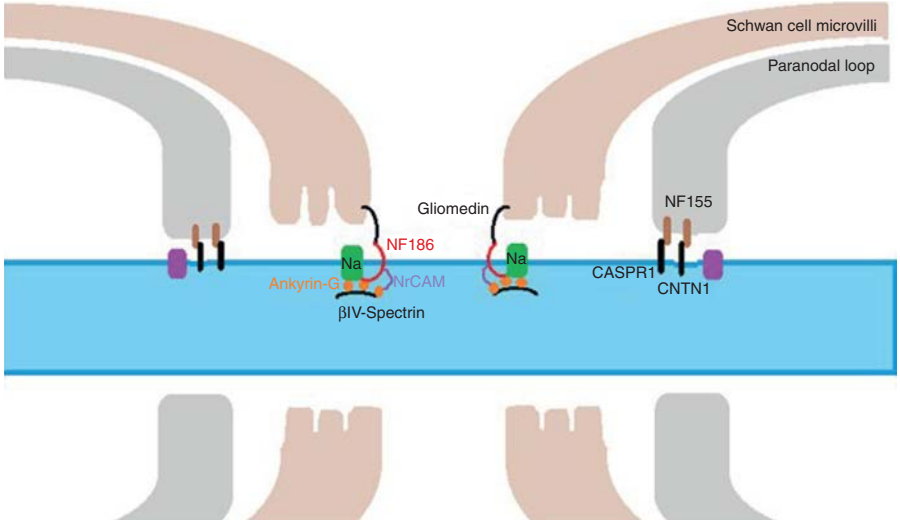


Fig. 15.5 Schematic illustration of the node of Ranvier in the PNS. *CASPR1*, Contactin-associated protein 1; *CNTN1*, contactin-1; *Kv*, potassium channel; *Na*, sodium channel; *NF*, neurofascin; *NrCAM*, neuronal cell adhesion molecule

et al., 2017; Ogata et al., 2015) to detachment of terminal Schwann cell loops from axons at the paranodes, disrupting septate-like transverse bands (Koike et al., 2017; Kuwahara et al., 2018). Clinically, patients often demonstrate an aggressive CIDP phenotype with a younger age of onset. MRI neurography has shown marked nerve root hypertrophy and may demonstrate diffuse cranial nerve hypertrophy (Fig. 15.6) (Hiwatashi et al., 2017, 2019; Ogata et al., 2015, 2016).

There is a probable favorable response to B-cell depleting therapies like rituximab (Fujita, Ogata, Yamasaki, Matsushita, & Kira, 2018) but poor response to IVIg (Miura et al., 2015; Querol et al., 2014). In fact, the finding of these IgG4 antibodies in patients with CIDP indicates a low likelihood of response to IVIg treatment. There is a concomitant reduction in antibody levels with successful treatment, suggesting that titers may be used to monitor progress over time (Devaux et al., 2016; Fujita et al., 2018).

CIDP with anti-CNTN1 antibodies: These antibodies have been found in a small subset of patients with CIDP and GBS (1% to 7%) (Delmont et al., 2017; Miura et al., 2015). CNTN1 is an axonal adhesion protein. It interacts with contactin associated protein 1 (CNTNAP1/CASPR1) on the axonal side and NF155 on the glial side to form the paranodal axo-glial junctions. Patients with anti-CNTN1 and anti-CASPR 1 seropositive CIDP often have a severe clinical phenotype. They often show advanced age at presentation (Doppler et al., 2015; Koike et al., 2017; Lin, Ho, & Chuquilin, 2018; Miura et al., 2015). Patients tend to respond well to corticosteroids and rituximab, but not to IVIg therapy (Miura et al., 2015).

CIDP with anti-NF140/186 IgG antibodies have been described, occurring in less than 2% of patients with CIDP (Delmont et al., 2017). Antibodies belong to the IgG4 subtype. NF140 is located at the nodes of Ranvier, where they help to form nodal complexes and cluster sodium channels. These patients show subacute onset, severe leg weakness at disease nadir, sensory ataxia, CB, and cranial nerve involvement. They are reported to have a good response to treatment with steroids and IVIg (Delmont et al., 2017).

CIDP with anti-CASPR1 antibodies: A case report describes a patient with a painful polyneuropathy and anti-CASPR1 antibodies (Doppler et al., 2016). The sera from this case bound not only the paranodes but also some dorsal root ganglion neurons, suggesting that anti-CASPR1 antibodies may cause painful neuropathy via impairment of small dorsal root ganglion neurons conveying pain sensation (Doppler et al., 2016).

The plethora of proteins in the nodal regions open the way to explore other candidate target antigens, especially against proteins with an extracellular domain.

Combined central and peripheral demyelination (CCPD): Based on a nationwide survey in Japan in 2016 (Kira, Yamasaki, & Ogata, 2019), CCPD was diagnosed in less than 0.52% of multiple sclerosis (MS) and 2.8% of CIDP patients. Onset with CNS symptoms occurred in about 40%; onset with peripheral nervous system manifestations, in around 40%; and onset with both CNS and peripheral nervous system manifestations, in about 20%. The mean age at onset was 32 years and the male-to-female ratio was 1:2.6. The mode of onset can be acute, subacute, or chronic. The disease course can be monophasic, relapsing-remitting, or chronic progressive.

Characteristics of these patients are young age at presentation, high frequencies of drop foot, gait disturbance, and tremor (Ogata et al., 2015). The most common symptoms/signs were sensory disturbances, followed by motor

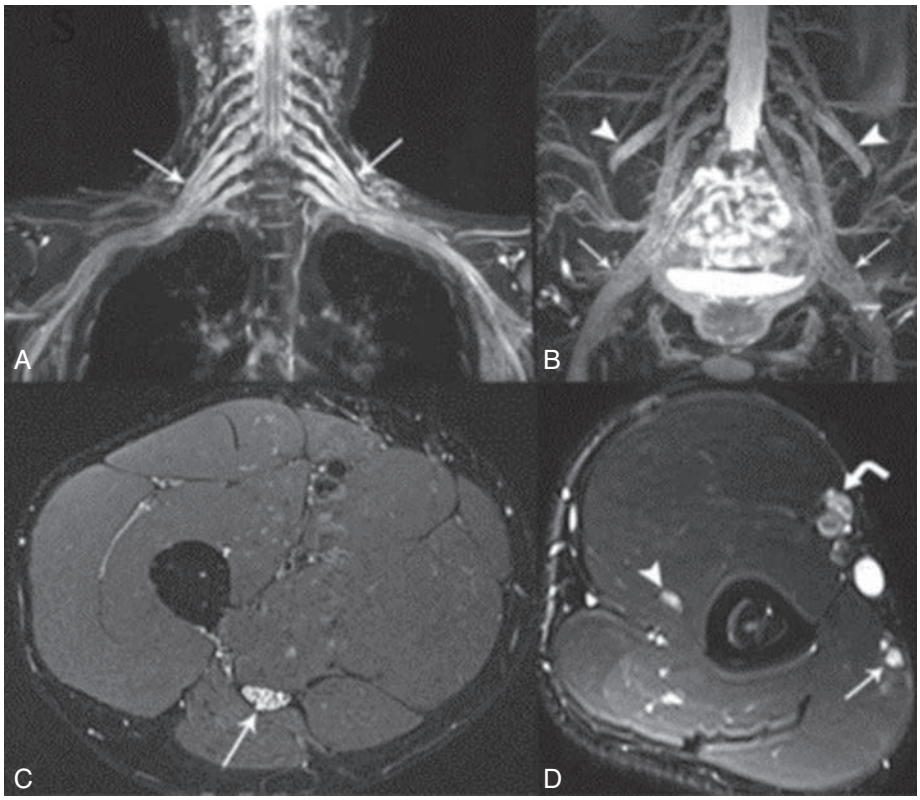


Fig. 15.6 In patients with immunoglobulin G4 (IgG4) anti-NF-155 antibodies. Three-dimensional (3D) magnetic resonance (MR) neurography revealed bilateral hypertrophy of brachial and lumbosacral plexi. 3D MR neurography of the brachial (A) and lumbosacral plexus (B), coronal views; 2D MR neurography of the right sciatic nerve at mid-thigh (C) and of the right arm at mid-humerus (D). (A) Bilateral, symmetric hypertrophy of the brachial plexus, which is predominant in the nerve roots, with gradual normalization toward the proximal limbs (*arrows*). (B) Bilateral symmetric hypertrophy of the lumbosacral plexus, involving the terminal branches, intrapelvic femoral nerves (*arrowheads*), and sciatic nerves at the sciatic notch (*arrows*). (C) Increased signal intensity and size (cross-sectional area [CSA] = 89 mm^2) of the right sciatic nerve, with diffuse fascicular hypertrophy (*arrow*). (D) Increased signal intensity and size of the right median (CSA = 16 mm^2, *curved arrow*), ulnar (CSA = 10 mm^2, *arrow*), and radial (CSA = 7.6 mm^2, *arrowhead*) nerves.

weakness and muscle atrophy, gait disturbance, and cranial nerve (most commonly optic nerve) manifestations. CNS and peripheral nervous system involvement occurs either simultaneously or sequentially (Kawamura et al., 2013; Ogata et al., 2016) (Fig. 15.7). CNS symptoms include visual disturbance, hemiplegia, and hemisensory disturbance and cerebellar ataxia. Clinically, mental disturbance, seizure, and respiratory disturbance were occasionally observed. Spinal cord lesions with Gad-enhancement can develop (Kira et al., 2019). At the illness peak, patients may be severely affected and may require artificial ventilation (Kira et al., 2019).

NCSs show features of demyelination, decreased motor nerve conduction velocities and increased F-wave latencies, decreased CMAP amplitudes, increased distal latencies, as well as CB and temporal dispersion. Sensory NCSs show decreased or absent sensory action potentials more often than decreased velocities.

CSF may show albumino-cytological dissociation and oligoclonal IgG bands with an increased IgG index.

MRI may show lesions throughout the CNS. Brain MRI may show diffuse cerebral white matter lesions (Kira et al., 2019). Spine MRI may show longitudinally extensive spinal cord lesions, extending three or more vertebral segments (Kira et al., 2019). A new MRI neurography method with three-dimensional nerve-sheath signal of spinal roots and plexuses uniformly demonstrated marked cervical and lumbar spinal root hypertrophy (Hiwatashi et al., 2017; Ogata et al., 2015). Proximal cranial nerves such as oculomotor and trigeminal nerves may show hypertrophy radiologically, called the "Moustache" sign (Franques, Chapon, Devaux, & Mathis, 2017).

Autoimmune autonomic dysfunction may be central, for example, in MS (Kanjwal et al., 2010), or it may be peripheral due to an immune-mediated small fiber polyneuropathy (SFPN). SFPN involves preferential damage to the small diameter, unmyelinated C-fibers, or thinly myelinated A-delta fibers that signal pain, tissue damage, and inflammation and regulate the body's tissues and organs (Chan & Wilder-Smith, 2016). SFPN may manifest clinically as postural tachycardia syndrome, orthostatic intolerance, orthostatic hypotension, inappropriate sinus tachycardia, gastrointestinal dysmotility, complex regional pain syndrome, and/or neurogenic bladder (Schofield & Chemali, 2019). In some patients, dysautonomia may occur in association with primary antineuronal autoimmunity, including antibodies directed against the adrenergic or muscarinic receptors, ion channels, ganglionic acetylcholine receptors, *N*-methyl-D-aspartate receptor, or N-type or P/Q-type calcium channels (Lambert-Eaton syndrome) (Vernino & Stiles, 2018). In some patients, autoimmune autonomic dysfunction may occur in the context of systemic autoimmune disease (Vernino & Stiles, 2018; Blitshteyn, 2015), such as Sjögren syndrome (Barendregt, Markusse, & Man In't Veld, 1998) or the antiphospholipid syndrome (Schofield, 2017). Dysautonomia may also occur in association with several other autoimmune diseases, such as Hashimoto thyroiditis (Blitshteyn, 2015), rheumatoid arthritis (Adlan, Lip, Paton, Kitas, & Fisher, 2014), spondyloarthropathy (Borman et al., 2008), systemic lupus erythematosus (Bortoluzzi, Silvagni, Furini, Piga, & Govoni, 2019), systemic sclerosis (Adler et al., 2018), celiac disease (Gibbons & Freeman, 2005), inflammatory bowel disease (Gondim et al., 2015), myasthenia gravis (Benjamin et al., 2018), and MS (Kanjwal et al., 2010). Indeed, it has been hypothesized that autoimmune autonomic dysregulation may be involved in the etiopathogenesis

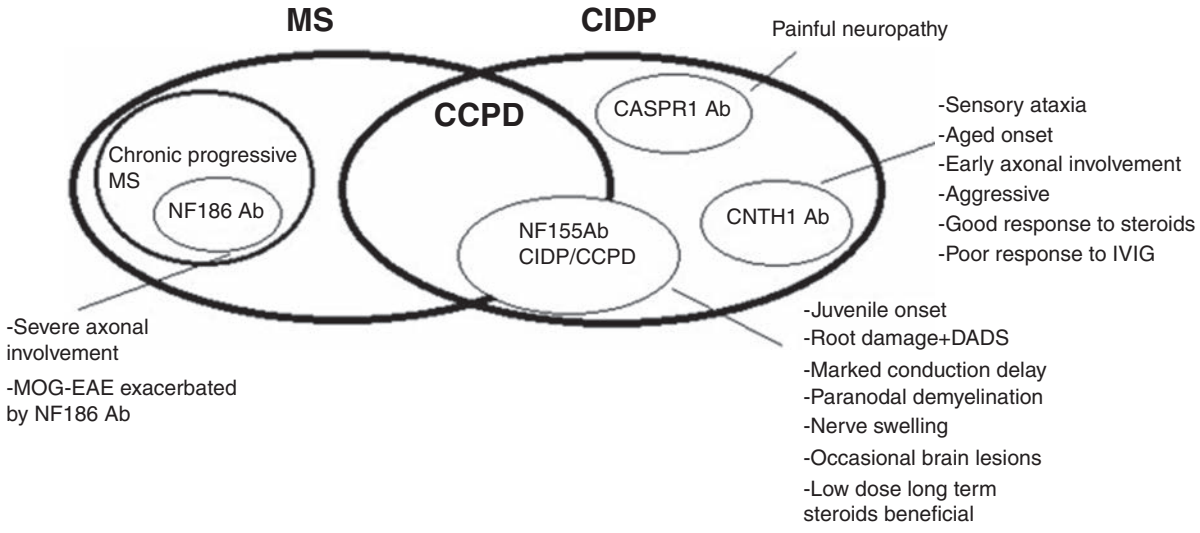


Fig. 15.7 Chronic demyelinating diseases targeting the axo-glial junction are termed nodopathy or paranodopathy. Autoantibodies against NF186, gliomedin, and contactin were reported in a minority of patients with Guillain-Barré syndrome, an acute demyelinating disease of the peripheral nervous system (Devaux et al., 2012). The disease entity and the exact positioning of combined central and peripheral demyelination (*CCPD*) in the demyelinating diseases have not been established. In our previous study on seven CCPD cases (Kawamura et al., 2013), all seven CCPD cases fulfilled the European Federation of Neurological Societies and Peripheral Nerve Society criteria for CIDP and six cases met the McDonald criteria (2011) for MS. In the first nationwide survey on CCPD (Ogata et al., 2016), 67.5% (27/40) of the CCPD patients met the McDonald criteria for MS, while 87.5% (35/40) fulfilled the European Federation of Neurological Societies and Peripheral Nerve Society definite criteria for CIDP. *Ab*., antibody; *CASPR1*, contactin-associated protein 1; *CCPD*, combined central and peripheral demyelination; *CIDP*, chronic inflammatory demyelinating polyradiculoneuropathy; *CNTN1*, contactin-1; *DADS,* distal acquired demyelinating symmetric neuropathy; *EAE*, experimental autoimmune encephalomyelitis; *IVIg*, intravenous immunoglobulin; *MOG*, myelin oligodendrocyte glycoprotein; *MS*, multiple sclerosis; *NF*, neurofascin.

of systemic autoimmunity (Koopman et al., 2016). Binding of acetylcholine, produced by the parasympathetic system to receptors on immune cells, has an immunosuppressive effect (Koopman, Schuurman, Vervoordeldonk, & Tak, 2014). Thus, autonomic dysregulation leads to disinhibition of autoimmunity (Koopman et al., 2014).

DIAGNOSIS

The diagnosis of CIDP is based on clinical and electrophysiological criteria, often supported by the finding of a raised CSF protein without significant pleocytosis (Van den Bergh et al., 2010). Rates of misdiagnosis in CIDP may exceed 40% (Devaux et al., 2016), due to the complexity of the electrodiagnostic (EDX) criteria for demyelination and the lack of a specific disease marker.

Testing for specific autoantibodies against isoforms of NF (NF155 and NF186) or against contactin-1 (CNTN1) can improve the diagnostic yield; however, they are not widely available yet.

NEUROIMAGING

By conventional MRI, plexus enlargement or T2 hyperintensity can be observed in typical and atypical CIDP variants (Lehmann, Burke, & Kuwabara, 2019) (Fig. 15.8). Magnetic resonance neurography (Hiwatashi et al., 2019; Ishikawa et al., 2017; Markvardsen, Vaeggemose, Ringgaard, & Andersen, 2016) and diffusion tensor imaging (Katz et al., 2000; Saperstein et al., 2001; Viala et al., 2004) can show enlarged cross-sectional areas and allow visualization of nerve fiber tracks and provide quantitative data on myelin sheath integrity (Gilmore et al., 2018; Katz et al., 2000; Saperstein et al., 2001; Viala et al., 2004; Zaidman, Al-Lozi, & Pestronk, 2009). An advanced MRI technique has demonstrated increased size of dorsal root ganglia and nerve roots in some patients with CIDP (Hiwatashi et al., 2017).

Nerve ultrasonography in CIDP usually shows enlarged cross-sectional areas in affected nerves, such as in the proximal median nerve and brachial plexus. These findings appear to be highly discriminative for CIDP compared to axonal neuropathies (Goedee et al., 2017). Ultrasound scores can increase diagnostic sensitivity compared with other chronic immune-mediated (Kerasnoudis, Pitarokoili, Haghikia, Gold, & Yoon, 2016), hereditary (Grimm et al., 2016), or diabetic neuropathies (Tan et al., 2018).

Muscle imaging in patients with CIDP helps assess disease severity by showing structural alterations in muscle tissue composition secondary to denervation and correlates closely with the degree of weakness (Gilmore et al., 2018).

MEASURES OF DISEASE ACTIVITY

The Inflammatory Neuropathy Cause and Treatment (INCAT) Group published various papers considering outcome measures in patients with GBS and CIDP, focusing on their scientific properties such as being simple, valid, reliable, and responsive. Among the INCAT group, the INCAT Overall Disability Sum Score was proposed to measure disability as the main level of measuring therapeutic response (Merkies & Schmitz, 2006). It relies on self-reported impairment in undertaking activities of daily living and the Medical Research Council Muscle Sum Score, which relies on examiner-based evaluation of strength in a variety of muscles (Graham & Hughes, 2006; Kleyweg, Van Der Meché, & Schmitz, 1991; Merkies & Schmitz, 2006; Merkies, Schmitz, van der Meché, Samijn, & van Doorn, 2002; Merkies, Schmitz, van der Meché, & van Doorn, 2000; van Nes et al., 2011).

DIFFERENTIAL DIAGNOSIS

Rare conditions that may fulfill the EFNS/PNS criteria for diagnosis of CIDP are transthyretin familial amyloid polyneuropathy and POEMS syndrome (Lozeron et al., 2018; Mauermann et al., 2012; Nasu et al., 2012). Symptoms of pain, dysautonomia, and small fiber sensory loss, in addition to pronounced axonal damage on nerve conduction studies (Lozeron et al., 2018), cannot always differentiate amyloidosis from CIDP. POEMS syndrome is characterized by less prolonged DML and higher terminal latency index in the

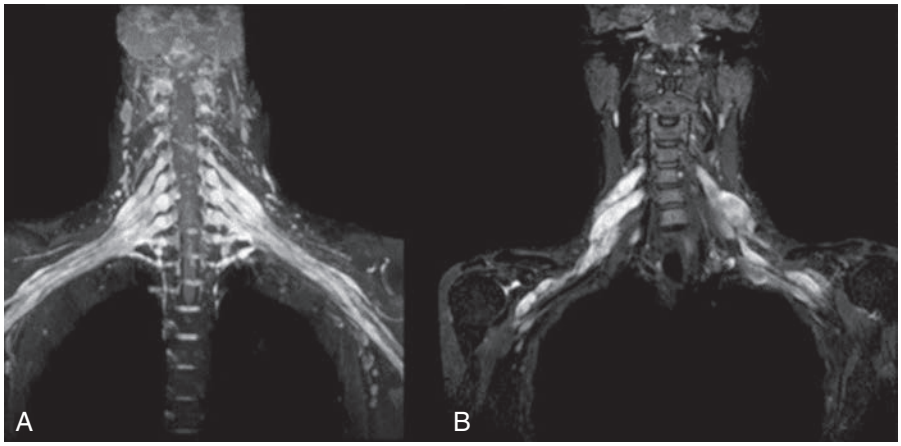


Fig. 15.8 Nerve hypertrophy in typical and atypical CIDP. (A) Coronal STIR reconstruction MRI reveals symmetrical bilaterally enlarged brachial plexus in a patient with typical CIDP. (B) Multifocal fusiform hypertrophy of the left cervical roots in a patient with MADSAM (coronal STIR weighted MRI). The symmetrical, root-dominant nerve hypertrophy in typical CIDP suggests an antibody-mediated immune attack primarily on the nerve roots, where the blood-nerve barrier is anatomically deficient, whereas the multiple sclerosis–like multifocal involvement in MADSAM could be caused by cell-mediated immunity. *CIDP,* Chronic inflammatory demyelinating polyneuropathy; *MADSAM*, multifocal acquired demyelinating sensory and motor neuropathy; *MRI*, magnetic resonance imaging; *STIR,* short tau inversion recovery

median nerves (electrophysiological parameter for identifying abnormalities in the distal segment of motor nerves) and unrecordable tibial and sural responses, suggesting demyelination predominately in the nerve trunk rather than in the distal nerve terminals, and axonal loss in the lower limb nerves (Mauermann et al., 2012). Other conditions (Table 15.4), including diabetes mellitus, can cause slowing of nerve conduction that may be misinterpreted as a primary demyelinating feature. Elevations in CSF protein and subjective improvement of symptoms subsequent to immunotherapy can lead to misdiagnosis (Devaux et al., 2016).

PITFALLS IN THE DIAGNOSIS OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

TREATMENT

Treatment of patients with CIDP requires individualized treatment strategies. First-line therapies that have been shown to be efficacious include corticosteroids, IVIg, and PE (Dalakas, 2011a; Dyck et al., 1994; Hahn et al., 1996; Hughes et al., 2008, 2010; Mahdi-Rogers, Brassington, Gunn, van Doorn, & Hughes, 2017; RMC Trial Group, 2009; Tan et al., 2018) (Table 15.4).

The first first-line treatment. In typical CIDP, the Intravenous Immunoglobulin CIDP Efficacy (ICE) trial established that IVIg is an effective first-line therapy for CIDP when given at an induction dose of 2 g/kg and a maintenance dose of 1.0 g/kg every 3 weeks (Hughes et al., 2008; Kuwabara et al., 2017). The mechanisms by which IVIg exerts a regulatory effect on the dysimmune response could be (1) neutralization of pathogenic autoantibodies, (2) inhibition of complement binding, and possibly (3) enhancement of remyelination (Dalakas, 2011c). IVIg can prevent complement-mediated tissue injury (Basta, Kirshbom, Frank, & Fries, 1989; Magee et al., 1995) and inhibits complement-mediated demyelination (Winter et al., 2016) but is not associated with terminal complement inhibition (Keller, Quast, Dalakas, & Lünemann, 2019).

There is weak Class IV evidence that IVIg is safe and effective for rigorously selected SFPN patients with apparent autoimmune causality (Liu et al., 2018). Adverse reaction: Patients with autonomic dysfunction treated with IVIg may develop aseptic meningitis or headaches due to IVIg-induced mast cell activation (Sekul, Cupler, & Dalakas, 1994).

Subcutaneous immunoglobulin (SCIg) was shown in the PATH study to be efficacious and well tolerated as maintenance treatment for CIDP (Sala et al., 2018; van Schaik et al., 2018) (Table 15.5). SCIg represents a therapeutic alternative for patients who suffer severe adverse effects, poor venous access, or wear-off phenomena with cyclic deterioration at an interval following an IVIg infusion (van Schaik et al., 2018).

The second first-line treatment is corticosteroids. Different regimens (daily oral prednisolone, pulsed oral dexamethasone, or pulsed intravenous methylprednisolone) have shown approximately 60% response rates. No significant differences in safety and efficacy have been shown among the three treatment regimens (Koike et al., 2017).

The third first-line treatment is PE. Both PE and IVIg have a high response as therapy and are reasonable therapeutic options.

Table 15.4 Interpretation of CIDP Clinical Evaluation and Workup Findings

Category	Compatible with CIDP	Pitfall	Alternative Explanation to Consider
Clinical	Widespread loss of reflexes	Only absence of ankle reflex	Length-dependent neuropathy
	Loss of vibration sense	Vibration sense not reduced	Motor neuron disease
	Treatment response assessed by objective scales	Subjective or nonspecific response to immunotherapy	Placebo effect, confounding factors as fatigue or depression
	Improvement with increasing IVIg frequency or by other immunotherapy	No response to immunotherapy considered refractory	Nonimmunotherapy, motor neuron disease
CSF	High elevation of protein >100 mg/dL	No or mild elevation of protein	Nonspecific, occurs in other conditions like spinal stenosis or diabetes mellitus
Electrophysiology	Significantly reduced conduction velocity Conduction slowing independent of compression site	Misinterpretation of conduction slowing	Conduction slowing for small potentials & compression sites
	Upper limb segmental demyelination	Abnormalities only in lower extremity nerves	Length-dependent neuropathy
	Heterogenous motor conduction slowing	Homogenous nerve conduction slowing	Hereditary neuropathy

CIDP misdiagnosis is common. Overreliance on subjective patient-reported perception of treatment benefit, liberal electrophysiologic interpretation of demyelination, and placing an overstated importance on mild or moderate cytoalbuminologic dissociation are common diagnostic errors.

CIDP, Chronic inflammatory demyelinating polyneuropathy; *CSF*, cerebrospinal fluid; *IVIg*, intravenous immunoglobulin.

Table 15.5 Therapeutic Randomized Controlled Studies in CIDP 2015–2018

Study	Intervention	Design	Patients (*n*)	Primary End Point	Result	Duration	Reference
PATH	SCIg vs placebo	Randomized, controlled, double blinded	Definite or probable CIDP, IVIg responsive, *n* = 172	Proportion with relapse or withdraw for other reason	63% on placebo, 39% on low-dose SCIg, and 33% on high-dose SCIg	24 weeks	Bril V, et al. Electrophysiological testing in chronic inflammatory demyelinating polyneuropathy patients treated with subcutaneous immunoglobulin: The Polyneuropathy And Treatment with Hizentra (PATH) study. Clin Neurophysiol 2021 Jan;132(1):226-231
FORCIDP	Fingolimod vs placebo	Randomized, controlled, double blinded	Definite or probable CIDP, *n* = 106	Time to relapse (≥1 adjusted INCAT score)	Ended for futility, fingolimod 42% vs placebo 43%	Flexible	Hughes R et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial. Lancet Neurol. 2018 Aug;17(8):689-698
Lieker et al.	IA vs PE	Randomized, controlled, NOT double blinded	CIDP, *n* = 18 of 20	Improvement in INCAT score and MRCs	IA 6/9 vs PE 4/9	Six sessions	Lieker et al. A prospective study comparing tryptophan immunoadsorption with therapeutic plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy. J Clin Apher 2017 Dec;32(6):486-493.
Danish CIDP and MMN study group	SCIg vs IVIg	Randomized, controlled, crossover, single blinded	Definite CIDP, *n* = 20	cIKS	CI KS, 7.4 (SCIg) vs 6.9 (IVIg)	10 weeks	Markvardsen et al. Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy. Randomized Controlled Trial Eur J Neurol. 2013 May;20(5):836-42.

IKS, Isokinetic muscle strength; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *FORCIDP*, Oral Fingolimod for Chronic Inflammatory Demyelinating Polyneuropathy; *IA*, Immunadsorbtion; *INCAT*, Inflammatory Neuropathy Cause and Treatment; *IVIg*, intravenous immunoglobulin; *MMN*, multifocal motor neuropathy; *MRCss*, Medical Research Council scale; *PATH*, Polyneuropathy And Treatment with Hizentra; *PE*, plasma exchange; *SCIg*, subcutaneous immunoglobulin.

PE is utilized less frequently than IVIg or corticosteroids, but it can be very effective for CIDP, especially in patients who have a relapsing disease course. The combination of plasmapheresis and IVIg is not more effective than either therapy alone. There is a similar rate of clinical improvement and adverse effects between PE and immunoadsorption therapy (Lieker, Slowinski, Harms, Hahn, & Klehmet, 2017).

Immunosuppressants may be required, particularly for patients with CIDP who are refractory to first-line treatments. Cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate are frequently used; however, high-quality evidence of effectiveness is lacking for these agents (Dalakas, 2011c; Dalakas et al., 2009).

MADSAM neuropathy: Patients with MADSAM do not respond as well to standard treatments for typical CIDP and can experience a chronic progression of the disease. These patients have a less favorable therapeutic response rate than patients with typical CIDP. IVIg treatment is often used first-line as in typical CIDP (Attarian et al., 2011; Katz & Saperstein, 2001; Rajabally & Chavada, 2009; Van den Berg-Vos et al., 2000; Verschueren et al., 2005; Viala et al., 2004). Corticosteroids are also used as in typical CIDP (Attarian et al., 2011; Kuwabara et al., 2015; Saperstein et al., 1999; Van den Berg-Vos et al., 2000; Viala et al., 2004). PE is used less frequently and is generally believed to be less effective than in typical CIDP (Attarian et al., 2011; Kuwabara et al., 2015; Li et al., 2019; Viala et al., 2004).

Anti-MAG neuropathy is refractory to most available therapies (Dalakas et al., 1996; Kanjwal et al., 2010; Rees, Soudain, et al., 1995). There is inadequate reliable evidence from trials of immunotherapies to form an evidence base supporting any particular therapy. IVIg has a statistically significant, but probably not clinically significant, benefit in the short term. A meta-analysis of two trials of rituximab in anti-MAG neuropathy demonstrated low-quality evidence of benefit (Léger et al., 2013; Dalakas 2009).

MMN: The only proven effective treatment for MMN is IVIg (Bourque et al., 2015; Mahad et al., 2002). Mechanisms independent of terminal complement inhibition contribute to IVIg-mediated treatment effects (Fitzpatrick et al., 2011). MMN may worsen with corticosteroids (Beadon et al., 2018; Furukawa et al., 2014, 2015; Shimizu et al., 2019; Taylor et al., 2004; Terenghi et al., 2006), and these are contraindicated. PE is ineffective and should not be used to treat MMN.

CIDP with anti-paranodal antigen antibodies: Corticosteroids combined with IVIg are more beneficial than IVIg alone in improving disability in this disease (Ogata et al., 2015). In fact, IVIg alone appears to show poor efficacy in the treatment of these varieties of CIDP. Whether rituximab is beneficial is uncertain because trial results are conflicting (Benedetti et al., 2011; Querol et al., 2013, 2015). For sustained improvement, long-term immunosuppression using corticosteroids or immunosuppressants is probably necessary. Anti-NF155 antibody levels change in parallel with the clinical and electrophysiological changes (Fujita et al., 2018) and thus theoretically can be used to assess response to treatment.

DADS: These patients have been reported to have a less satisfactory response to IVIg than patients with typical CIDP (Doneddu et al., 2019; Katz et al., 2000), while there were no differences in the response to steroids (Doneddu et al., 2019).

Motor CIDP: Treatment is usually with IVIg as recommended in the EFNS/PNS guidelines (Van den Bergh et al., 2010), based on reports of lack of response or even worsening after corticosteroids (Kimura et al., 2010; Sabatelli et al., 2001). A positive response to corticosteroids has since been reported (Busby & Donaghy, 2003) in patients with concomitant sensory electrophysiological impairment (Doneddu et al., 2019).

Sensory CIDP shows a favorable response to both IVIg and corticosteroids (Busby & Donaghy, 2003; Chin et al., 2004; Oh, Joy, & Kuruoglu, 1992; Van Dijk, Notermans, Franssen, Oey, & Wokke, 1996).

A cross-sectional quantitative survey of neurologists in the United States showed that only 13% cited using the EFNS/PNS guidelines for the diagnosis and treatment of CIDP. Additionally, neurologists reported tremendous variability in treatment approaches, outcome measures, and protocols for weaning therapy. These results clearly indicate that there is a need for more clinically focused guidelines combined with more education on diagnosis and treatment of CIDP (Gelinas, Katz, Nisbet, & England, 2019).

EMERGING THERAPIES

There is a pressing need for more effective treatment in the population of APN patients who do not adequately respond to current therapies. There is a special need for more specific therapies to compliment or replace treatment with IVIg, corticosteroids, and PE. Emerging therapies that are being studied use agents that target the immunopathology from the early T- and B-cell activation to the final induction of cytotoxicity through cytokines, complement, and adhesion or transmigration molecules (Dalakas, 2011a, 2012, 2013a, 2013b)

Fc-gamma receptors (FcγRs) provide an important link between the humoral and cellular immune systems to generate inflammation in the APNs (Asbury, Arnason, & Adams, 1969; Dong et al., 2017; Feasby et al., 1986; Griffin et al., 1996; Prineas, 1981; Waksman & Adams, 1955; Zhang et al., 2014). Humoral immunity can induce tissue damage via the binding of immune complexes to cellular FcγRs expressed on macrophages and monocytes (Hogarth, 2002; Takai, 2002; Nimmerjahn & Ravetch, 2008). Agents that modulate FcγRs (Ortiz et al., 2016; Spirig et al., 2018) have the potential to limit inflammatory nerve injury and are potential therapeutic modalities for treating inflammatory demyelinating neuropathies.

B cells and B-cell trophic factors: Belimumab is a monoclonal antibody against B-lymphocyte stimulator and has been approved for the treatment of systemic lupus erythematosis. Rituximab and obinutuzumab are monoclonal antibodies against CD20 that cause B-cell depletion. They have been used to treat patients with anti-MAG neuropathy (Dalakas et al., 2009; Léger et al., 2013) and chronic lymphocytic leukemia (Dalakas, 2008).

Complement inhibiting agents such as eculizumab are increasingly being studied in several diseases where complement fixation is part of the disease process. Eculizumab is a monoclonal antibody that binds to C5 and inhibits the formation of terminal complement components. By binding to C5, the C5 convertase-mediated cleavage of C5 into C5a and C5b is inhibited, and this prevents the downstream terminal formation of MAC (Howard et al., 2013; Rother, Rollins, Mojcik, Brodsky, & Bell, 2007). This agent is of interest for the treatment of both CIDP and GBS. It has shown promise in a small uncontrolled trial in MMN patients (Howard et al., 2013). Whether this drug will be useful in combination therapy with IVIg or corticosteroids in CIDP is unknown (Fitzpatrick et al., 2011; Yamaguchi et al., 2016).

A retrospective case series reported beneficial effects of treatment with the proteasome inhibitor bortezomib subcutaneously in a group of severely affected (INCAT score 6 or 7) treatment-refractory patients with CIDP (Pitarokoili et al., 2017).

DISEASE FOLLOW-UP

The best way to assess disease course and response or lack of response to therapy is by serial focused clinical neurological exams, especially formal measures of strength and functional disability such as the Inflammatory Rasch-built Overall Disability Scale and the vigorimeter (Draak et al., 2016; Gelinas et al., 2019; Vanhoutte, Faber, & Merkies, 2013). Subjective patient reports are inadequate and misleading measures of disease status and response to therapy.

Serial nerve conduction studies correlate poorly with clinical progression of CIDP (Rabin et al., 2014). In the ICE extension study, it was shown that F-wave latency and distal CMAP duration may be biomarkers for predicting relapse following treatment withdrawal (Chin et al., 2015). Nerve ultrasound longitudinal changes appear to correlate well with clinical status, and amelioration of nerve enlargement during treatment with IVIg has been shown to be concordant with clinical improvement (Härtig et al., 2018). The accumulation of an electrophysiologic burden of disease may predict treatment dependency (Chin et al., 2015). Since as many as 21% of patients with CIDP are refractory to current therapies, there is an obvious need for new and effective

treatment modalities in this and other autoimmune neuropathies (Kuwabara et al., 2006; Simmons, Albers, Bromberg, & Feldman, 1995; Viala et al., 2010).

VASCULITIC NEUROPATHIES AND CRYOGLOBULINEMIA

The vasculitic neuropathies are a heterogenous group of disorders that result in inflammation targeting the vasa nervorum of peripheral nerves. In primary systemic vasculitides, there is involvement of multiple organ systems with no clear causative entity. Examples are polyarteritis nodosa, microscopic polyangiitis, Churg-Strauss syndrome, hepatitis C infection, granulomatosis with polyangiitis, hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell arteritis, or Takayasu arteritis. The primary systemic vasculitides are subdivided into predominantly large vessel vasculitis, predominantly medium vessel vasculitis, and predominantly small vessel vasculitis (Jennette et al., 2013). The International Chapel Hill Consensus Conference guidelines of 2012 further subdivide the small vessel primary systemic vasculitides into those associated with vessel wall immune globulin deposition and those without (antineutrophilic cytoplasmic antibody [ANCA] associated) (Jennette et al., 2013).

Vasculitic neuropathy characteristically presents as acute or subacute onset of multiple, painful sensory or sensorimotor mononeuropathies. All sensory modalities are typically involved and may crescendo over weeks and overlap (Bennett et al., 2008). Infarction often affects the proximal nerve. Distal extremity nerves are less commonly affected (Dyck, Conn, & Okazaki, 1972). Cranial neuropathies are occasionally encountered in ANCA-associated vasculitis (André et al., 2017; Lee, Park, Choi, & Park, 2018). Progression is stepwise in two-thirds of cases and slowly progressive in the remaining third (Bennett et al., 2008).

There are a wide variety of secondary vasculitides due to connective tissue diseases, infections, malignancy, drugs, or other systemic inflammatory conditions. These vasculitides are felt to be immune mediated (Collins, Dyck, et al., 2010; Langford, 2010).

Nonsystemic vasculitic neuropathy (NSVN) comprises about 26% of vasculitic neuropathies and involves the peripheral nervous system, with systemic symptoms mostly absent (Dyck et al., 1987). Subtypes include Wartenberg migratory sensory neuropathy, nondiabetic lumbosacral radiculoplexus neuropathies, and postsurgical inflammatory neuropathies. Other localized vasculitides such as diabetic lumbosacral radiculoplexus neuropathy (LSRPN) and parsonage Turner syndrome (i.e., neuralgic amyotrophy [NA]) are considered variants of the NSVN category (Collins & Hadden, 2017). Treatment consists of corticosteroids.

Recently, serum neurofilament light chains (Bischof et al., 2018) have been shown to predict vasculitic neuropathy with a sensitivity of 82% and specificity of 100% and appeared to correlate with disease activity (Bischof et al., 2018).

EDX patterns are multiple mononeuropathy, followed by asymmetric axonal sensorimotor polyneuropathy (Živković, Ascherman, & Lacomis, 2007). The approach includes a wide sampling of distal and proximal nerves with side-to-side comparisons looking for asymmetry.

Biopsy of nerve in both systemic vasculitic neuropathy and NSVN shows axonopathy with Wallerian degeneration, hemosiderin-laden macrophages, perineurial thickening, neovascularization, immune deposits of IgM, complement proteins, and fibrinogen in epineurial vessel walls (Benstead, Dyck, & Sangalang, 1989; Collins, Dyke, et al., 2010; Collins, Periquet-Collins, Sahenk, & Kissel, 2010; Dyck et al., 1972; Nukada & Dyck, 1984; Nukada, Dyck, & Karnes, 1985; Tracy, Engelstad, & Dyck, 2009). Adjunctive muscle biopsy, such as peroneus brevis, improves diagnostic yield (Agadi, Raghav, Mahadevan, & Shankar, 2012; Collins & Kissel, 2005; Lacomis & Živkovic, 2007; Said & Lacroix, 2005; Vital et al., 2006; Vrancken, Gathier, Cats, Notermans, & Collins, 2011).

Induction therapy is with corticosteroids with a prednisone dose of 1 mg/kg per day. For severe symptoms, methylprednisolone is given over 3 to 5 days followed by daily oral therapy (Agadi et al., 2012; Said & Lacroix, 2005) and high doses are continued for 6 to 8 weeks, then tapered (Collins & Kissel, 2005; Said & Lacroix, 2005). Cyclophosphamide for 3 to 12 months is used for severe cases, usually of granulomatosis with polyangiitis and microscopic polyangiitis (Collins & Kissel, 2005; Gorson, 2006), then switched to maintenance therapy (Collins & Kissel, 2005; Gold, Fontana, & Zierz, 2003; Langford, 2010). Rituximab was shown to be as effective as cyclophosphamide (Fanouriakis et al., 2015; Jones et al., 2010; Pagnoux, Guillevin, & French Vasculitis Study Group, MAINRITSAN Investigators, 2015). Methotrexate is another option for induction in patients with milder symptoms from Granulomatosis With Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) (Fanouriakis et al., 2015; Gold et al., 2003; Hoffman et al., 1992; Jones et al., 2010; Langford, 2010; Pagnoux et al., 2015). Maintenance therapy involves substituting cyclophosphamide for azathioprine or methotrexate (Collins & Kissel, 2005; Jayne et al., 2003; Langford, 2010) and is continued at a standard dose for 18 to 24 months before tapering is attempted (Collins & Kissel, 2005; Langford, 2010). Other options for refractory symptoms or progression of disease include PE and IVIg infusions (Jayne et al., 2000; Levy et al., 2005; Martinez et al., 2008; Tsurikisawa et al., 2004).

NSVN can persist without the development of a systemic vasculopathy and can be diagnosed when vasculitis is noted on nerve biopsy after systemic vasculitis is ruled out by appropriate laboratory testing, according to Peripheral Nerve Society guidelines. First-line treatment is with corticosteroids; however, combination therapy is more effective than corticosteroids alone (Davies, Spies, Pollard, & McLeod, 1996; Gorson, 2006), especially in rapidly progressive NSVN. Cyclophosphamide, methotrexate, and azathioprine are the second-line agents. Alemtuzumab (Schneider et al., 2017) is a potential future treatment target, as CD52 was found to be expressed in some nerve biopsies of patients with NSVN.

Cryoglobulins are circulating immunoglobulin proteins that precipitate at temperatures below 37°C. They can be essential or secondary to a connective tissue disease, lymphoproliferative disorder, or chronic infection. In chronic hepatitis C viral infection, cryoglobulinemia is found in 50% of patients, with 15% developing a secondary vasculitis; of those with vasculitis, neuropathy is noted clinically in 65% and electrodiagnostically in 80%. The neuropathy tends to be distal, progressive, and sensory or sensorimotor, although asymmetric and multifocal and small fiber forms

are noted. Nerve biopsies most consistently implicate an epineurial vasculitic process (Collins, 2012).

Antidisialosyl ganglioside reactivity has been reported with predominantly sensory neuropathy and ophtalmoplegia (Noguchi et al., 2003; Sidana et al., 2017) and anti-GM1 reactivity with MMN (Choudhry, Rao, & Juneja, 2012; Tomita et al., 2013).

Predominantly distal sensory axonal neuropathy characterizes cryoglobulinemia (Vallat et al., 1980). Nerve biopsy shows necrotizing vasculitis or a perivascular lymphocytic reaction and endoneurial deposits of the monoclonal component (Vallat et al., 1980).

Neuralgic amyotrophy (NA) is also known as Parsonage-Turner syndrome or brachial neuritis. The latter naming typically demonstrates the clinical phenomenon of the focal mononeuropathy presentations of NA (England, 1999; England & Sumner, 1987; Malamut, Marques, England, & Sumner, 1994). It presents with onset of severe refractory upper extremity pain over the course of hours, weakness that presents over the course of days, and resolution over the course of months. Estimates of incidence vary widely from 1:1,000 to 1:100,000. Classically, the disease is self-limited and affects the long thoracic, suprascapular, and anterior interosseous nerves, resulting in scapular winging, arm external rotation, thumb flexor weakness, and sensory symptoms on the lateral shoulder and arm. In one third of patients, other nerves and roots are affected; these can include the lower brachial plexus, affecting the distal upper extremity, phrenic nerve affecting breathing, the sympathetic system resembling complex regional pain syndrome, or the lumbosacral plexus resembling radiculopathy. The lumbosacral variant is also known as LSRPN and typically but not exclusively occurs in type II diabetics; in these cases, this condition is also referred to as diabetic amyotrophy (Sierra et al., 1991; Van Eijk, Groothuis, & Van Alfen, 2016).

Pathologically LSRPN and postsurgical idiopathic plexopathies have been shown to be microvasculitic in etiology. It is thought that these are immune-mediated attacks, given the high rate of antecedent infections, particularly hepatitis E, as well as other antecedent physiologic stresses such as surgery or childbirth. A limited number of biopsies in subacute cases have shown epineural perivascular mononuclear T-cell infiltration, active multifocal axonal degeneration without vessel wall inflammation or necrosis, and perineural thickening (Van Eijk et al., 2016). It has been shown that lymphocytes from patients with NA will react to extract from brachial plexus but not lumbar plexus. This suggests a tissue-specific immune response underpins these cases (Sierra et al., 1991).

There is no confirmatory testing and no known antibody. In patients with specific risk factors, testing for hepatitis E virus, *Borrelia burgdorferi*, *Bartonella henselae*, or HIV is indicated. While the nerve conduction study will show decreased CMAP amplitudes, these can be normalized with reinnervation. Electromyography may demonstrate evidence of denervation and reinnervation, but the patchy nature of the disease makes sampling error and falsely normal testing a notable concern. There are reports of NA with paraspinal involvement, which limits the ability of electromyography to distinguish it from radiculopathy. Peripheral nerve ultrasound demonstrates findings similar to other inflammatory neuropathies (Sierra et al., 1991).

At onset, pain is severe and typically lasts for 3 weeks in duration. Nonsteroidal anti-inflammatory drugs, in combination with long-acting opioids, are typically effective over the short duration. There is only limited evidence that immunotherapy can shorten duration to recovery. Physical and occupational therapy can help with strengthening recovering and adjacent muscles and forming adaptive movement strategies (Van Eijk et al., 2016).

Celiac disease (CD) is an autoimmune disease. The primary immunologic response targets autoantigen (transglutaminases 6) in neurologic manifestations, and mutations of the TGM6 gene have been linked to ataxia (Wang et al., 2010; Tripathy et al., 2017). TG6 is expressed in the cerebellar cortex (Purkinje cells) and cerebellar nuclei, and in the thalamus (Liu et al., 2013; Thomas et al., 2013), potentially affecting GABA-ergic inhibitory pathways. There is cortical excitability (Hadjivassiliou et al., 2001; Lebwohl, Roy, Alaedini, Green, & Ludvigsson, 2016; Zis, Julian, & Hadjivassiliou, 2018). Gluten encephalopathy comprises headaches and white matter abnormalities on MRI. The high prevalence of white matter abnormalities potentially contributes to an increased risk of vascular dementia in patients with CD.

In distal symmetric polyneuropathy, the incidence of CD is 2.5%–8% vs 1% in the general population. Patients with CD showed a 2.5-fold increased risk for peripheral neuropathy. Sensory neuropathy is more common than sensorimotor neuropathy. Large (Zis, Sarrigiannis, Rao, & Hadjivassiliou, 2018) and painful small (Brannagan et al., 2005) fiber sensory neuropathies occur in length-dependent as well as non-length-dependent patterns (Thawani, Brannagan, Lebwohl, Green, & Ludvigsson, 2015; Zis et al., 2018). Exclusive painful SFN can occur (Brannagan et al., 2005). Biopsies of the sural nerve show axonal loss (Thawani et al., 2015).

Paraneoplastic sensory neuropathies are a consequence of cross-reactivity between tumor and host antigens. Subacute sensory neuropathy (SSN) (a.k.a. sensory ganglionopathy) is the most frequent paraneoplastic neurological syndrome (Giometto et al., 2010). It is T-cell mediated and targets sensory neurons in dorsal root ganglia (Antoine et al., 2016; Giometto, Grisold, & Grisold, 2016). There is subacute onset or rapidly progressive (Graus et al., 2001) course with marked numbness with a multifocal, asymmetric pattern in the face, chest, trunk, and the limbs in a non-length-dependent distribution (Gwathmey, 2016) and significant proprioceptive loss with associated ataxia. Pain is predominant in 80% of sensory neuropathies (Camdessanché et al., 2002), and patients can present with prominent pain and a milder or absent ataxia, more suggestive of a small fiber neuropathy (SFN). Large and small sensory neurons can also be simultaneously affected (Oki et al., 2007).

The EDX hallmark is a severe and diffuse absence of SNAPs. Motor conduction velocity is classically but not exclusively normal (Camdessanché et al., 2002; Oh, Gürtekin, Dropcho, King, & Claussen, 2005). CSF usually shows elevated protein concentration, pleocytosis, and oligoclonal bands. Pathologically, the most common findings are marked loss of large sensory neurons in the dorsal root ganglion with associated lymphocytic infiltration (Koike & Sobue, 2013). Sural nerve biopsy shows axonal degeneration and inflammatory cells in 43% of cases (Antoine et al., 1999). In 70%–80% of cases, SSN occurs with small cell lung cancer (SCLC) and most patients have anti-Hu Abs. Anti-Hu

antibodies are associated with sensorimotor peripheral neuropathy and dysautonomia.

SCLC is associated with 70% to 80% of cases. In addition to SCLC, other associated malignancies include adenocarcinomas, lymphomas, thymomas, breast cancer, and gastrointestinal cancers (Giometto et al., 2016).

The mainstay of therapy is identifying and treating the underlying malignancy (Graus et al., 2001). The second principle of management is immunomodulatory treatment: corticosteroid therapy (intravenously administered methylprednisolone) or IVIg therapy while the malignancy is being evaluated. There is a limited window of opportunity for disease stabilization before irreversible neuronal damage sets in, at which point therapeutic intervention is likely futile (Antoine et al., 2016; Antoine & Camdessanché, 2013).

Neuropathy occurs in 57% of patients with anti-CV2/CRMP5 Abs. These patients frequently present with cerebellar ataxia, limbic encephalitis, ocular involvement, or Lambert-Eaton myasthenic syndrome (Honnorat et al., 2009), and SCLC and thymoma are the usual tumors (Antoine et al., 2001). The neuropathy is mostly sensory or sensory-motor. EDX studies show an axonal or mixed axonal and demyelinating pattern (Camdessanché et al., 2012; Samarasekera & Rajabally, 2011) as CRMP5 is expressed in Schwann cells (Taieb et al., 2012).

Anecdotal cases of sensory neuropathy have been reported with anti-Yo Abs (Ayrignac et al., 2008), mononeuritis multiplex with Ma2 Abs (Coppens et al., 2006), and sensorimotor neuropathy with antiamphiphysin Abs (Forsyth et al., 1997).

Pure lower motor neuron disease is very rare with onconeural antibodies. It has been reported with anti-Hu Abs and anti-Ma2 Abs (Distad & Weiss, 2010; Waragai et al., 2006).

Paraneoplastic syndromes can also present in the absence of an identifiable antibody. The most common associated paraneoplastic antibody is anti-Hu (a.k.a. anti-ANNA-1) followed by anti-CV2 (a.k.a. anti-CRMP-2). Other antibodies, however, have been and continue to be identified and associated with Peripheral neuropathy, including anti-Yo, anti-Ri, and antiamphiphysin (Giometto, Vitaliani, Lindeck-Pozza, Grisold, & Vedeler, 2012; Neal, Qian, Clinch, & Le, 2014; Samarasekera & Rajabally, 2011).

Aside from treatment of the underlying malignancy, more specific guidance on treatment for PN is limited (Graus & Dalmau, 2013; Huijbers et al., 2015).

Peripheral nerve hyperexcitablity (PNH) syndromes: Isaacs syndrome (Hart, Maddison, Newsom-Davis, Vincent, & Mills, 2002) and Morvan syndrome (Maddison, Mills, & Newsom-Davis, 2006) are disorders marked by abnormal muscle activities with cramps, stiffness, twitching, spasms, and abnormal relaxation and can be neurologic paraneoplastic manifestations. Diagnosis relies on recording of fibrillation and fasciculation potentials, myokimia, neuromyotonic, and posteffort or poststimulation discharges (Joubert et al., 2016). Morvan syndrome occurs with thymoma, thus the increased incidence of myasthenia gravis in this context (Laurencin et al., 2015; Torres-Vega et al., 2017) and, rarely, with SCLC or lymphoma (Lancaster et al., 2011). Some patients with Morvan syndrome develop SFN (Kobayashi, Kato, Funakoshi, Watanabe, & Toyoshima, 2005). Caspr2, a membrane protein of the juxta-paranodal region, is the target of Abs in Morvan syndrome (Willison et al., 2001). Caspr2 Abs also occurs with limbic encephalitis, and PNH occurred in 11% of these cases (Vallat et al., 1995). Netrin 1 receptor antibodies have been identified as predictive of thymoma in patients with PNH and myasthenia gravis, frequently in association with Caspr2 Abs (Laurencin et al., 2015). This is also discussed in detail in Chapter 18.

Connective tissue diseases are a heterogeneous group of autoimmune disorders where there are autoantibody production and organ inflammation. The central and peripheral nervous systems can be affected by vasculitis and immune complex deposition (Jin & Shin, 2019).

Systemic lupus erythematous can affect virtually every organ in the body with numerous neurologic presentations. The most common manifestation of PN is asymmetric pure sensory or sensorimotor polyneuropathy manifesting late in the disease course (Jin & Shin, 2019), axonal more than demyelinating (Florica et al., 2011). Sural, peroneal, and median nerves were most frequently involved (Florica et al., 2011). Other manifestations included length-dependent axonal polyneuropathy, cranial neuropathy, and mononeuritis multiplex. With neuropathy, there is a higher chance of CNS involvement (Jin & Shin, 2019).

Sjögren syndrome can affect any portion of the peripheral nervous system. The most common manifestations are pure sensory neuropathies, which present with distal symmetric sensory loss due to axonal degeneration of sensory fibers; sensory ataxia due to loss of proprioceptive large fibers (ganglionopathy); or painful dysethesias (small fiber sensory neuropathy) due to degeneration of cutaneous axons. The latter appears to be the most common neuropathy in Sjögren syndrome and requires skin biopsy for diagnosis to document loss or reduction of nerve fiber density. Another type of neuropathies seen in Sjögren syndrome is sensorimotor polyneuropathy affecting sensory and motor axons, often associated with severe systemic or prolymhomatous manifestations, such as palpable purpura and cryoglobulinemia. Rare peripheral neuropathic manifestations include autoimmune demyelinating neuropathy, mononeuropathy, mononeuropathy multiplex, and autonomic neuropathy (Dimberg, 2017; Pavlakis et al., 2012). Treatment is symptomatic with neuropathic pain agents. Small trials showed benefit in treating the SFN IVIg (Morozumi et al., 2009). Sjögren syndrome can also manifest as a sensorimotor axonal polyneuropathy, with accompanying distal symmetric weakness.

Rheumatoid arthritis: Neuropathy with rheumatoid arthritis is largely subclinical and affects 65% to 85% of patients, with only 25% of patients manifesting clinically (Agarwal et al., 2008; Dimberg, 2017; Good, Christopher, Koepke, Bender, & Tarter, 1965; Puéchal et al., 1995). Joint inflammation and deformity can result in entrapment neuropathies, like carpal tunnel syndrome. Nonentrapment neuropathies are attributed to necrotizing vasculitis and can lead to mononeuritis multiplex or a length-dependent sensory or sensorimotor polyneuropathy (Agarwal et al., 2008; Dimberg, 2017; Good et al., 1965; Puéchal et al., 1995). Electrophysiologic testing demonstrates a sensorimotor axonopathy (Agarwal et al., 2008; Dimberg, 2017; Good et al., 1965; Puéchal et al., 1995).

Sarcoidosis can affect any part of the nervous system. The most common manifestation of sarcoidosis is SFN in 40% of patients. Frequently, symptoms start in the feet and then spread in a patchy and non-length-dependent distribution. Sensory disturbance in the face and trunk is common.

Autonomic disturbance has also been described (Tavee & Stern, 2014). The symptoms of SFN are generally unresponsive to standard immunosuppressant treatments of sarcoidosis, including corticosteroids and methotrexate. IVIg and antitumor necrosis factor-α agents have been shown to be effective (Parambil, Tavee, Zhou, Pearson, & Culver, 2011; Tavee & Culver, 2011; Tavee et al., 2017). ARA290, an erythropoietin derivative, is undergoing investigation as a treatment of SFN in sarcoidosis (and other causes) and has demonstrated early positive results (Brines et al., 2014; Dahan et al., 2013; Heij et al., 2012). Large-fiber PN is much less common and presents with non-length-dependent polyneuropathy or polyradiculoneuropathy. Electrophysiologic studies most frequently demonstrate a sensorimotor multifocal axonopathy (Said et al., 2002). Atypical presentations include mononeuritis multiplex, plexopathy, acute inflammatory demyelinating polyradiculoneuropathy, and symmetric sensorimotor neuropathy (Zuniga, Ropper, & Frank, 1991).

Monoclonal gammopathies are associated with peripheral neuropathies due to the cross-reaction of M protein with neural antigens, deposition of paraprotein in nerve myelin, and/or neurotoxic effects of the paraproteins (Ramchandren & Lewis, 2012). Patients with MGUS have a 4-fold increase in risk for PN (greater than that of diabetes) (Rögnvaldsson et al., 2017). MGUS IgM kappa gammopathy presents as a distal acquired demyelinating symmetric neuropathy (a.k.a. DADS), which predominantly affects large fiber sensory nerves with occasional motor involvement. Anti-MAG antibody is present in 50% of these patients. Patients with MGUS IgA and IgG kappa present with a broad spectrum of PN with sensory, motor, or mixed features, and electrophysiologic findings of demyelination and/or axonal neuropathy.

Waldenstrom macroglobulinemia occurs with a large spectrum of neuropathy. In 50% of cases it is associated with anti-MAG antibodies of the IgM subclass. This presentation is similar to MGUS neuropathy with anti-MAG positive antibodies, where both disorders display a DADS phenotype with distal demyelinating pattern on EDX. (Attarian, Azulay, Boucraut, Escande, & Pouget, 2001). Up to 30% of patients with IgM MGUS evolve to Waldenstrom disease (Nobile-Orazio et al., 1989).

In multiple myeloma, PN is associated with IgG and presents with a length-dependent sensory greater than motor neuropathy with electrophysiologic findings of either axonopathy or demyelination (Chaudhry, Mauermann, & Rajkumar, 2017; Mauermann, 2017; Ramchandren & Lewis, 2012).

Amyloid light-chain (AL) amyloidosis is the most common acquired form of amyloidosis. Systemic disease triggers the excess secretion of light chains from normal plasma cells. It is a characteristically painful, length-dependent sensory or sensorimotor neuropathy with additional prominent involvement of autonomic nerves (Kaku & Berk, 2019; Jin & Shin, 2019). Neuropathy is reported to affect 15% to 20% of patients with amyloidosis and frequently precedes the diagnosis (Jin & Shin, 2019). Electrophysiologic studies generally demonstrate sensory greater than motor axonopathy (Chaudhry et al., 2017; Mauermann, 2017). Entrapment neuropathies are common, and the neuropathy is more likely to be progressive and lead to disability.

POEMS (Dispenzieri, 2011) can present with severe sensory and motor findings with electrophysiologic findings of demyelination with early secondary axonopathy (Cui, Huang, Liu, Chen, & Pu, 2012) and is associated with lambda light chain (Campagnolo et al., 2017; Joint Task Force of the EFNS and the PNS, 2010). Serum immunofixation provides the highest sensitivity over serum and urine protein electrophoresis for paraproteinemia and can verify the monoclonal nature of a paraprotein. If amyloidosis or POEMS is suspected, further confirmatory testing with a bone marrow biopsy (and/or fat pad biopsy in the case of amyloidosis) should be performed (Joint Task Force of the EFNS and the PNS, 2010; Mauermann, 2017).

Treatment of the underlying gammopathy does not reverse the symptoms of neuropathy. The use of IVIg and PE in the treatment of MGUS neuropathy has shown mixed results (Chaudhry et al., 2017). Small series have demonstrated the benefit of rituximab in the treatment of MGUS anti-MAG-related neuropathy (Campagnolo et al., 2017).

Antidisialosyl gangliosides reactivity has been reported with predominantly sensory neuropathy and ophtalmoplegia (Kobayashi et al., 2005; Willison et al., 2001) and anti-GM1 reactivity with MMN (Noguchi et al., 2003; Vallat et al., 1995).

Monoclonal antibodies: APNs have also been encountered secondary to monoclonal antibody use in treatment of other systemic disease. The anti-TNF-alpha antibodies (adalimumab and infliximab) are used to treat Crohn disease, rheumatoid arthritis, psoriasis, and other conditions (Lee, Park, & Park, 2018;Patwala, Crump, & De Cruz, 2017). They have been shown to induce a variety of neuropathies, as well as a MS-like condition (Patwala et al., 2017). The proposed mechanisms include decreased apoptosis of T cells, increased cytokine milieu, as well as increased susceptibility to potentially antecedent infections (Kao et al., 2017). The anti-DP1 antibodies (pembrolizumab and novolumab) are being used increasingly in the treatment of solid tumors of varied origins. They can induce varied neuropathies as well, in addition to myopathies, retinopathy, and brainstem syndromes. With these agents, disinhibition of T cells leads to increased autoimmunity (Kao et al., 2017).

Small fiber neuropathy: The term "small fiber neuropathy" refers to a group of neuropathies characterized by a selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibers and unmyelinated C-fibers leading to excruciating sensory positive or negative symptoms, in the setting of normal nerve conduction studies and electromyography (Themistocleous et al., 2016).

SFN cases present with a length-dependent distribution, as mononeuropathy, multifocal neuropathy, or as ganglionopathy with a non-length-dependent pattern (Gemignani et al., 2010; Gorson et al., 2008; Khan & Zhou, 2012; Khoshnoodi et al., 2016) (Fig. 15.9). It is associated with multiple diseases, which can be immunological conditions, genetic causes (Cazzato & Lauria, 2017; Lauria, Merkies, & Faber, 2012), sodium channel gene variants, metabolic such as in diabetes mellitus, vitamin B_{12} deficiency, alcohol abuse, exposure to drugs and toxins such as chemotherapy, MGUS, haemo-chromatosis, and transthyretin mutations (Masuda et al., 2017). The diagnostic workup in 921 with SFN showed immunological conditions as the most common etiological factor (de Greef et al., 2018). In patients with otherwise cryptogenic SFN, one study demonstrated that 48% had IgM antibodies to trisulfated disaccharide IdoA2S-GlcNS-6S (TS-HDS) (IgM) (Pestronk, Choksi, Logigian, & Al-Lozi, 2003; Pestronk, Schmidt,

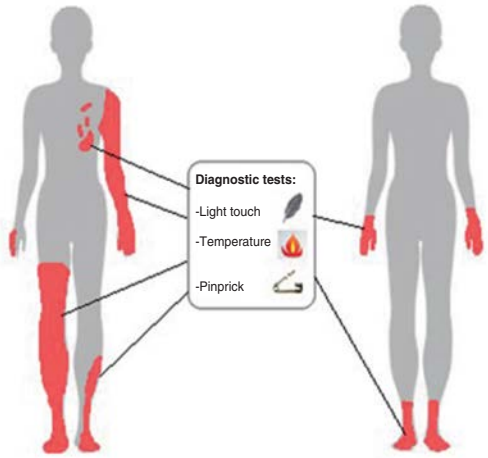


Fig. 15.9 Small fiber neuropathy (*SFN*) distribution. (A) Pain, sensory loss, or increased sensitivity to soft touch, pin prick, and temperature, in a single nerve or patchy distribution. Proprioception, vibration, and deep tendon reflexes are preserved. (B) Similar presentation as in A, but in a glove and stock distribution.

Choksi, Sommerville, & Al-Lozi, 2012) or IgG antibodies binding to fibroblast growth factor receptor 3 (FGFR-3) (Kafaie, Al Balushi, Kim, & Pestronk, 2017). IgM binding to TS-HDS was found to be associated with subgroups of SFN of acute-onset, female, and non-length-dependent pathology. A non-length-dependent neuropathy pattern suggests cell-body disorders (ganglionopathies) (Khan & Zhou, 2012), which may be treatment-refractory even with effective immunosuppression, similar to IgM types of autoantibodies in motor syndromes and MAG antibody–associated neuropathy that respond poorly to many therapeutic modalities (Levine et al., 2020). FGFR-3 antibodies in SFN occurred in 15% of patients and were significantly associated with non-length-dependent syndromes (Levine et al., 2020).

The primary goals of the management of neuropathic pain in SFN are to detect underlying causes and to manage the pain. At present, therapeutic strategies are largely symptomatic using antidepressants, antiepileptics, and opioids (Finnerup et al., 2015).

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Treatment and Management of Infectious, Granulomatous, and Toxic Neuromuscular Disorders

16

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The disorders that fall under infectious, granulomatous, and toxic neuromuscular disorders are too numerous and broad to be covered comprehensively in a single chapter. To achieve the objectives of this book, we focus on conditions that are seen more frequently and concentrate on the most important and relevant aspects of their management and treatment.

INFECTIONS OF NERVE AND MUSCLE

HUMAN IMMUNODEFICIENCY VIRUS NEUROPATHIES AND MYOPATHIES

The advancements made in the treatment of human immunodeficiency virus (HIV) infection have resulted in marked changes in the neurologic complications associated with HIV infection; as a result, the disease has turned into a chronic illness, with less immunosuppression, resulting in patients living longer with prolonged exposure to multiple medications, but with reduced utilization of neurotoxic medications. The confluence of these factors has resulted in an overall reduction of the incidence and prevalence of the known HIV-associated neurologic complications, compared to before the combination antiretroviral treatment (cART) era (Centner et al., 2018; Pillay, Wadley, Cherry, Karstaedt, & Kamerman, 2019; Vecchio et al., 2020). In spite of these changes, peripheral neuropathies continue to be the most common neurologic complications of HIV infection and can result in significant impairment (Dudley, Borkum, Basera, Wearne, & Heckmann, 2019). The most common pattern of neuropathy is a distal symmetrical sensory polyneuropathy (HIV distal sensory polyneuropathy, or HIV-DSP), which can be symptomatic and painful or asymptomatic. It can be associated with viral or immune mechanisms or with toxicity from antiretroviral agents (antiretroviral toxic neuropathy, or ATN), and they can coexist. Other types of neuropathies that can be observed are acute and chronic forms of inflammatory demyelinating polyneuropathies (Guillain-Barré syndrome [GBS] or acute inflammatory demyelinating polyneuropathy [AIDP] and chronic inflammatory demyelinating polyneuropathy [CIDP]), multiple mononeuropathies (mononeuritis multiplex), diffuse infiltrative lymphocytosis syndrome (DILS) neuropathy, and progressive polyradiculopathy (Aziz-Donnelly & Harrison, 2017; Centner, Bateman, & Heckmann, 2013; Prior, Song, & Cohen, 2018) (Table 16.1). The precise underlying mechanisms for these neuropathies are not well understood but include immune dysregulation from infection of macrophages and T cells with abnormal production of inflammatory cytokines and chemokines, neurotoxicity from viral proteins, antiretroviral medications, and, in some cases, infectious opportunistic agents.

Involvement of skeletal muscle can also be observed in HIV-seropositive patients at the onset, or as the presenting symptom, or more advanced stages of infection and at different stages of immunosuppression, and it can vary in its clinical and pathologic features (Hiniker, Daniels, & Margeta, 2016; Lloyd et al., 2017). Similar to the HIV neuropathies, the HIV-associated myopathies can be associated with toxicity from antiretroviral medications, as is the case with zidovudine (AZT), from immune restoration, or from alterations induced by the HIV infection per se. The principal types of nontoxic myopathies have been grouped as variants of HIV-associated myopathy or myositis: HIV-polymyositis (HIV-PM), which can be sporadic or associated with the immune reconstitution inflammatory syndrome (IRIS); diffuse infiltrative inflammatory syndrome (DILS)-associated myositis; HIV-associated inclusion body myositis (HIV-IBM); and HIV-associated sporadic late-onset nemaline/rod myopathy (HIV-SLONM) (Authier, Chariot, & Gherardi, 2005; Prior et al., 2018) (Table 16.2). They are primarily distinguished by their pathologic features, and it is not clear if they represent a spectrum of the same complication or have different pathophysiologic mechanisms. Other forms of myopathy are the toxic myopathies (AZT myopathy) and HIV-associated rhabdomyolysis. With the advent of cART and better immunocompetence, some of these forms are now seen less frequently.

DIAGNOSIS AND EVALUATION

As is the case in most neuromuscular diseases, the diagnosis of the various types of neuropathy and myopathies in HIV infection relies on a careful history and physical examination. It is important to have a basic understanding of some pertinent historical aspects of the various types of HIV-associated neuropathies. First, with the advent of cART, markers of more advanced immunosuppression, like CD4 counts, and more active infection, like viral loads, are no longer associated with HIV neuropathy and some predictors for the development of neuropathy are older age, increased height, prior exposure to antiretrovirals, substance use, hypertriglyceridemia, and diabetes (Kaku & Simpson, 2014). This implies that a comprehensive evaluation for comorbid

Table 16.1 HIV-Associated Neuropathies

Neuropathy Type	Distinguishing Features	Management/Treatment
Acute inflammatory demyelinating polyneuropathy (AIDP, Guillain-Bar<acute accent> syndrome)	>More common in early stages of HIV infection >CSF pleocytosis >Can be associated with IRIS >More rapid presentation and evolution than non-HIV	>IVIg at 0.4 gm/kg for 5 days >Plasmapheresis
Chronic inflammatory demyelinating polyneuropathy	>More common in moderately advanced disease >More common than AIDP >Younger age than non-HIV >Highly steroid responsive	>Prednisone 60 mg daily for 8 weeks with gradual taper >IVIg at 0.4 gm/kg for 5 days >Plasmapheresis
Distal symmetric polyneuropathy	>Present in all stages >Clinically indistinguishable from antiretroviral toxic neuropathy	>Early initiation of cART >Avoid neurotoxic antiretrovirals >Topical high-concentration (8%) capsaicin >? Medicinal cannabis
Mononeuritis or mononeuritis multiplex	>Unilateral or bilateral facial neuropathy more common >In early infection: dysimmune or vasculitic >In advanced disease: Cytomegalovirus (CMV)	>Hepatitis B, hepatitis C serology >Cryoglobulin testing >CSF PCR for CMV >Ganciclovir or foscarnet if CMV
Diffuse infiltrative lymphocytosis syndrome (DILS) neuropathy	>Acute/subacute painful sensorimotor polyneuropathy >Parotid enlargement >Multiorgan infiltration	>Check CD4/CD8 ratio >Extractable nuclear antigen antibodies (anti-SSA-anti-SSB), cryoglobulins, exclude HTLV-1 and EBV >TX: Antiretroviral treatment Steroids
Progressive lumbosacral polyradiculopathy	>Advanced HIV with low CD4+ cell counts >Cauda-equina-like syndrome >CMV most common	>Ganciclovir or foscarnet >CSF PCR for CMV, zoster and HSV >Monitor CSF pleocytosis as response to treatment >Maintenance treatment may be stopped with CD4 counts >200 cells/L and viral suppression
Antiretroviral toxic neuropathy (ATN)	>Onset shortly after starting or increasing dose of antiretroviral >Coasting observed	>Lamotrigine: start 25 mg with slow increase to target dose of 200 mg twice a day

cART, Combination antiretroviral therapy; *CSF*, cerebrospinal fluid; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *HTLV-1*, human T-lymphotrophic virus type 1; *IRIS*, immune reconstitution inflammatory syndrome; *IVIg*, intravenous immunoglobulin; *PCR*, polymerase chain reaction.

conditions, prior medications, or substance exposure or abuse is equally important. The HIV myopathies are less common than the neuropathies and the typical HIV myositis can occur at any stage of infection. The demyelinating polyneuropathies, and in particular the AIDP form of GBS, tend to occur at the time of seroconversion or during the early stages of HIV infection while the chronic type, CIDP, occurs more frequently in moderately advanced disease and is more common than AIDP in HIV infection (Centner et al., 2013). Since the introduction of cART, GBS has been seen in association with IRIS (Piliero et al., 2003; Teo, Azwra, Jones, Gazzard, & Nelson, 2007). The mononeuropathies and mononeuritis multiplex are less common and present more frequently as lesions of the facial nerve, lateral femoral cutaneous nerve of the thigh, median nerve at the wrist, or peroneal nerves. Facial neuropathies, unilateral or bilateral, are probably one of the more common presentations, again sometimes occurring during seroconversion. If the mononeuritis multiplex is present during the early stages of HIV infection, with less immunosuppression, it is associated with dysimmune processes or vasculitis, but if present with advanced immunosuppression, it can be associated with cytomegalovirus (CMV) infection (Ferrari et al., 2006).

The most common symptoms with predominantly sensory neuropathies (HIV-DSP/ATN) are symmetrical distal painful dysesthesias, paresthesias, and numbness in the feet and toes that extend proximally as the neuropathy advances. Patients complain of tingling, burning, and aching pain in the toes and soles, but any nonspecific discomfort in the feet and toes should trigger the suspicion in the clinician. The distinction between viral-associated neuropathy and ATN is difficult because, clinically, they are indistinguishable and

Table 16.2 HIV-Associated Myopathies

Myopathy Type	Distinguishing Features	Management/Treatment
HIV polymyositis	>Sporadic or associated with immune reconstitution inflammatory syndrome (IRIS) >Can occur at any stage of infection	>Prednisone 60 mg daily for 4 weeks with slow taper >IVIg at 0.4 gm/kg for 5 days
DILS-associated myositis	>Parotid gland enlargement >Multiorgan infiltration >increased peripheral CD8+ lymphocytes	>Check CD4/CD8 ratio >Extractable nuclear antigen antibodies (anti-SSA-anti-SSB), cryoglobulins, exclude HTLV-1 and EBV >TX: antiretroviral treatment Steroids
HIV-associated inclusion body myositis	>Younger age and higher CK than non-HIV >TDP-43 and p62 positive staining in biopsy >Coexistent hepatitis C infection	>Hepatitis C serology >Trial of steroids or IVIg early in course if proximal weakness
HIV-sporadic late-onset nemaline/rod myopathy (HIV-SLONM)	>May be associated with monoclonal gammopathy >Nemaline rods on muscle biopsy	>Prednisone 60 mg daily for 4 weeks with slow taper >IVIg at 0.4 gm/kg for 5 days
Zidovudine (AZT)-associated myopathy	>Features of mitochondrial dysfunction	>Discontinue or substitute zidovudine >Trial of steroids or IVIg if no improvement
HIV-associated rhabdomyolysis	>Multifactorial: could be from concurrent infections medications or toxins	>Prevention and treatment of acute kidney injury

CK, Creatinine kinase; *DILS*, diffuse infiltrative lymphocytosis syndrome; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *HTLV-1*, human T-lymphotrophic virus type 1; *IRIS*, immune reconstitution inflammatory syndrome; *IVIg*, intravenous immunoglobulin.

they may often coexist. Suspicion for ATN should arise if the symptoms start shortly (within weeks) after starting or increasing the dose of one of the suspect medications and if the symptoms improve or disappear after reducing the dose or discontinuing the suspect medication (Arenas-Pinto, Bhaskaran, Dunn, & Weller, 2008). On the clinical examination, the most common findings are impaired distal sensation and reduced deep tendon reflexes, more prominently the Achilles tendon reflex. The latter reflex may appear normal but be relatively reduced when compared with the patellar reflex. Although patients may exhibit reduced pinprick sensation, in our experience and that of others (Cherry et al., 2006), decreased vibratory sensation at the toes is a more sensitive sign. Joint position sense is usually normal, and weakness, if present, is limited to the distal foot muscles and is mild. In addition, patients may exhibit allodynia or hyperalgesia in the distal feet.

The clinical presentation of the acute and chronic demyelinating polyneuropathies may be slightly different from the presentations seen in HIV seronegative patients. HIV patients with GBS will have a more rapid presentation and evolution than non-HIV patients (Centner et al., 2013). HIV-infected patients with CIDP are younger and more commonly display a monophasic progressive course than non-HIV patients (Moodley, Bill, & Patel, 2017). They are characterized by acute or progressive weakness, with or without prominent sensory symptoms, and reduced or absent reflexes. The mononeuropathies or mononeuritis multiplex cases usually present with a stepwise progression with multiple, often painful, mononeuropathies. A lumbosacral polyradiculopathy presenting as a cauda equina-like syndrome is usually seen in advanced immunosuppression with low CD4+ T-cell count. Clinically, it presents with lower back and radiating radicular pain, saddle anesthesia, and rapidly progressive weakness in the lower limbs with bladder and bowel dysfunction. It evolves in an acute or subacute fashion and is often caused by CMV or less commonly by herpes simplex virus (HSV), varicella zoster virus, syphilis, or tuberculous meningitis (Centner et al., 2013).

Muscle involvement in HIV infection has a wide spectrum of presentations, most of which are in the inflammatory spectrum (Table 16.2). T-cell-mediated inflammatory myopathies include features indicative of polymyositis (HIV-PM) and inclusion body myositis (HIV-IBM), and some authors have also described a nonspecific myositis (Landon-Cardinal et al., 2019). HIV-PM is usually associated with subacute and symmetrical proximal muscle weakness, with involvement of the legs and, less often, the arms. Patients may complain of difficulty rising from a chair or climbing stairs and may indicate myalgias and decreased stamina.

Two of the variants have some distinctive clinical features: myositis associated with DILS (DILS myositis) is associated with enlargement of the salivary glands and increased peripheral CD8+ lymphocytes, and HIV-IBM, which may be clinically indistinguishable from sporadic IBM, with involvement of quadriceps and forearm muscles, except sometimes it is seen in younger patients and the creatinine kinase (CK) levels are higher (Cupler et al., 1996; Lloyd et al., 2017). Some studies have described overlapping features of HIV-PM and HIV-IBM initially, with evolution of HIV-PM over time to an inclusion body myositis phenotype, proven by biopsy (Landon-Cardinal et al., 2019; Lloyd et al., 2017).

An important part of establishing the diagnosis of HIV-DSP/ATN relies on the exclusion of other causes or modifying factors for neuropathy. We usually order a comprehensive metabolic panel with fasting blood sugar to check for

diabetes and liver or renal impairment. We also check vitamin B_{12} levels, pyridoxine (vitamin B_6) levels, and thiamine levels in whole blood; perform thyroid function tests; carry out lipid panel to check for hypertriglyceridemia; test for hepatitis B or C coinfection; and perform serum and urine immunofixation. Careful assessment for alcohol and substance consumption is also important given the high prevalence of their use in people with HIV and the increased risk for neuropathy (Robinson-Papp et al., 2012). For a clinical presentation of acute or subacute painful sensorimotor polyneuropathy, CD8+ cell counts to identify DILS is necessary, even in the absence of other clinical features. Nerve conduction studies (NCSs) are helpful in establishing the diagnosis of HIV-DSP/ATN and in detecting neuropathy in patients with nonspecific symptoms in the feet. The typical pattern shows a predominantly sensory axonal polyneuropathy, although the study may be normal even in the presence of pain, given the possibility of predominant involvement of small sensory fibers. An inflammatory demyelinating polyneuropathy (AIDP or CIDP) will be suspected if motor weakness is a prominent feature. NCSs and needle electromyography (EMG) are an important part in the evaluation of these patients, because they provide objective information about axonal loss and demyelination. AIDP usually occurs in patients with preserved CD4+ cell counts, but if seen in a patient with profound immunosuppression, the possibility of infection with CMV should be considered and treated accordingly (Brannagan & Zhou, 2003). In HIV-DSP, the typical features would be those of a length-dependent predominantly sensory polyneuropathy with loss of sensory axons in the distal lower extremities, resulting in reduced-amplitude sensory responses. Up to 25% of patients may have abnormal electrophysiologic findings without symptoms, and approximately 20% of patients with HIV-DSP have normal NCSs due to preferential involvement of small fibers (Tagliati, Grinnell, Godbold, & Simpson, 1999). We have also examined the value of the ratio of the superficial radial sensory amplitude to the sural sensory amplitude but have not found that this increases the detection of neuropathy.

In addition to the clinical features, laboratory studies like serum creatine kinase (CK) and aldolase, the EMG examination, and the muscle biopsy are important tools in the evaluation of a patients suspected of having HIV-associated muscle involvement. In the HIV-inflammatory myopathies (HIV-PM, HIV-IBM), the serum CK level can be markedly increased, up to 10 times the upper limit of normal (ULN), although it can also be elevated in AZT myopathy. The needle EMG typically shows increased spontaneous activity with fibrillation potentials and positive waves, as well as increased numbers of small-amplitude, short-duration polyphasic motor unit potentials, and this can be observed in the toxic and HIV-associated types. Not uncommonly, myositis and distal sensory neuropathy coexist, as both are more common in the advanced stages. A muscle biopsy can be important in differentiating toxic myopathy from the nontoxic subtypes. In zidovudine-associated myopathy, features of mitochondrial dysfunction are prominent, with numerous "ragged red" fibers, subsarcolemmal accumulation of red granular material, sparse, if any, endomysial inflammation, lipid accumulation, and paracrystalline mitochondrial inclusions on electron microscopy (Dalakas et al., 1990). The typical biopsy in the patient with HIV-PM will show more prominent perimysial, endomysial, perivascular, and primary inflammation of nonnecrotic fibers, with varying degrees of necrosis, phagocytosis, and degeneration of muscle fibers (Landon-Cardinal et al., 2019; Lloyd et al., 2017). Biopsies from patients with HIV-IBM will show primary inflammation but will also show rimmed vacuoles and amyloid deposition with Congo red staining. Immunostaining for aggregated proteins, i.e., TDP-43 and p62, and electron microscopy for inclusions can also help in differentiating from HIV-PM or other myopathies with inflammation (Hiniker et al., 2016). An additional test in HIV-IBM can be the presence of antibodies against cytosolic 5' nucleotidase (anti-CN1A ab), which is uncommon in HIV-PM (Lloyd et al., 2017). In some patients, abundant nemaline (rod) bodies can be observed and may be a predominant feature without inflammation, a finding used to define the nemaline subtype of HIV-associated myopathy, HIV-SLONM. This observation has led to the suggestion that adult patients with nemaline myopathy on muscle biopsy should be tested for HIV infection. Additionally, serum and urine electrophoresis are performed since SLONM can be associated with a monoclonal gammopathy. In DILS-associated myositis, typically there is a prominent CD8+ inflammatory infiltrate, and the diagnosis can be determined by measuring CD4 and CD8 T cells in blood and determining the CD4/CD8 ratio as well as excluding other confounders such as other autoimmune or infectious diseases. The muscle biopsy can show CD8+ T cell infiltration consistent with the diagnosis. Tests should also be sent for antibodies against extractable nuclear antigens (anti-SSA, anti-SSB), cryoglobulins, human T-lymphotrophic virus type 1 (HTLV-1), and EBV. Biopsy of salivary gland is often needed for definitive diagnosis (Ghrenassia et al., 2015).

Because of the predominant involvement of small unmyelinated and myelinated fibers, the use of skin biopsies to study epidermal nerve fibers has been shown to be an important tool in the study of neuropathy in these patients. Skin biopsies are usually obtained in the lateral aspect of the distal leg and thigh. Studies examining epidermal innervation in adult HIV patients have shown that the density in epidermal nerve fibers is reduced in HIV patients compared to control subjects regardless of neuropathy status and is more reduced in patients with HIV-DSP (Polydefkis et al., 2002). However, in children and adolescent patients, the epidermal nerve fiber density may be paradoxically increased (Luciano et al., 2006). Additional studies have shown that reduced epidermal nerve fiber densities in asymptomatic HIV patients may be a predictive factor for the development of neuropathy within 1 year (Herrmann et al., 2006). Nerve biopsies are usually not necessary for the diagnosis of neuropathy in these patients, unless the patient has an asymmetrical or multifocal pattern that may suggest a vasculitic component.

Lumbar puncture with cerebrospinal fluid examination would be necessary in the context of a demyelinating polyneuropathy or a polyradiculopathy. Both acute and chronic demyelinating polyneuropathies show increased protein levels in the cerebrospinal fluid (CSF), but unlike the non-HIV demyelinating neuropathies, this is often, but not always, associated with a mild pleocytosis (Brannagan & Zhou, 2003).

The diagnosis of the acute or subacute progressive lumbosacral polyradiculopathy will require a lumbar puncture,

electrodiagnostic testing, and a contrast-enhanced magnetic resonance imaging (MRI) of the lumbosacral roots. The CSF may show a polymorphonuclear pleocytosis, with increased protein and reduced CSF glucose (Centner et al., 2013). In these cases, polymerase chain reaction (PCR) testing of the CSF for CMV, and if negative, PCR for HSV, varicella zoster, is necessary. The EMG will confirm the clinical suspicion and demonstrate acute denervation in the paraspinal muscles, and the MRI may show enhancement of the lumbosacral roots.

TREATMENT AND MANAGEMENT

The basic principles for treatment of HIV neuropathies are mainly based on preventive strategies and symptomatic or immunomodulating treatment. As with other toxic neuropathies and myopathies, removal of the offending agent is a critical and important step for improvement or reversal of symptoms. Treatment of HIV-DSP is important because the associated neuropathic pain can result in impairment, reduced quality of life, and unemployment (Dudley et al., 2019; Galantino et al., 2014). In the case of ATN, however, in a phenomenon called *coasting*, symptoms may increase temporarily for 6 to 8 weeks after stopping the offending medication. This should not be confused with progression of the neuropathy. Also, because ATN often coexists with HIV-DSP, the symptoms may improve but may not disappear completely. The reduced incidence of HIV-DSP since the introduction of cART supports the notion that proper treatment of the HIV infection, with reduction in viral loads and increased CD4 counts and avoidance of neurotoxic antiretrovirals, can also result in improvement of the neuropathy. Early initiation of cART has been shown to reduce the incidence of DSP (Vecchio et al., 2020) and the prevalence of painful symptoms in patients with symptomatic painful sensory neuropathy, and should be an integral part of treating or preventing HIV-DSP (Centner et al., 2018). Careful follow-up by an HIV specialist is an integral part of the management of these patients.

There are no Food and Drug Administration (FDA)–approved drugs for the symptomatic treatment of HIV-DSP, and many of the medications used in the management of painful dysesthesias and paresthesias in other neuropathies such as diabetic neuropathy have been proven ineffective. These include gabapentin, pregabalin, duloxetine, amitriptyline, 5% topical lidocaine gel, 0.075% topical capsaicin cream, Peptide T, and mexiletine (Aziz-Donnelly & Harrison, 2017; Kaku & Simpson, 2014). The only treatments that have proven effective in randomized controlled trials have been topical high concentration (8%) capsaicin, smoked cannabis, and recombinant human nerve growth factor (Amaniti et al., 2019; Phillips, Cherry, Cox, Marshall, & Rice, 2010). The topical high-concentration (8%) capsaicin dermal patch is applied after pretreatment with a topical mixture of local anesthetics (EMLA cream) to limit pain and discomfort (Simpson, Brown, Tobias, & NGX-4010 C107 Study Group, 2008). Smoked cannabis is limited to states or countries where this therapy is legal and presents the additional potential for respiratory side effects. Acupuncture/moxibustion (burning of mugwort leaf) has shown some efficacy as a nonpharmacologic therapy in a small study, but larger studies are necessary before proving this an effective (Anastasi, Capili, McMahon, & Scully, 2013). Lamotrigine has been used, but published reports have shown efficacy only in a small study and in subsequent analysis in the subgroup with ATN and not in HIV-associated neuropathy as a separate entity (Simpson et al., 2003). The clinician must always also be aware of the potential interactions with the antiretroviral medications and the multitude of other medications that HIV patients must take.

Although controlled studies specific for HIV-associated acute or chronic demyelinating polyneuropathies have not been performed, it is generally accepted that response to treatment is similar to non-HIV AIDP and CIDP.

Preferred treatment options for HIV-AIDP include intravenous (IV) gamma globulin at a dose of 0.4 g/kg/day for 5 days. Plasmapheresis is an alternative, but IV immunoglobulin (IVIg) is generally more accessible and does not require special expertise. For HIV-CIDP, comparison with non-HIV-CIDP patients has shown that patients with HIV-CIDP are highly steroid responsive and many go into remission within 12 months of treatment, implying the effectiveness of a limited course of steroid treatment and negligible risk of complications due to coexistent HIV immunosuppresion (Moodley et al., 2017). One strategy that we often use is an induction dose of 60 mg of daily prednisone for approximately 8 weeks, followed by a slow tapering course and change to alternate day treatment. Other treatment alternatives would also be regular courses of IVIg or plasmapheresis.

Progressive polyradiculopathy is now rarely encountered since the introduction of cART. Treatment is based on anti-CMV therapy and the initiation or optimization of highly active antiretroviral therapy (HAART). The current therapies available are ganciclovir, valganciclovir, foscarnet, cidofovir, and fomivirsen. If CMV infection is suspected, the initial recommendations are for IV infusions of ganciclovir or foscarnet, twice daily as induction therapy, followed by IV maintenance therapy. In patients with severe disease, the use of two medications concomitantly is indicated (Ferrari et al., 2006). Patients may worsen during the first 2 weeks of therapy, but this does not indicate treatment failure (Brew, 2003). Monitoring of CSF pleocytosis may be used as a marker of response to therapy. Maintenance therapy may be stopped once the CD4 counts have remained above 200 cells/μL and the viral loads have been reasonably suppressed for several months (Brew, 2003).

Because of their relative rarity, there are no controlled studies of treatment for the HIV-associated myopathies. Treatment recommendations are based on anecdotal experience and from small case series and isolated case reports. The basic assumption for the nontoxic myopathies is that the manifestations are related to immune-mediated mechanisms associated with immune dysregulation in HIV infection. Based on this, investigators have used standard immunosuppressants with overall positive results (Lloyd et al., 2017; Johnson, Williams, Kazi, Dimachkie, & Reveille, 2003; Robinson-Papp & Simpson, 2009). HIV myositis can be treated with a short course of prednisone at a dose anywhere from 40 to 60 mg/day, as well as IVIg at dose of 2 g/kg given over 5 days. This should be given in conjunction with antiretroviral therapy to ensure adequate viral suppression. In HIV-associated nemaline rod myopathy (HIV-SLONM), steroids, IVIg, and plasmapheresis have also been used, with some success in a few cases (de Sanctis, Cumbo-Nacheli,

Dobbie, & Baumgartner, 2008; Dwyer, Mayer, & Lee, 1992; Silva et al., 2017).

In the case of AZT-myopathy, discontinuing or reducing the dose of zidovudine and substituting with a nonmyotoxic antiretroviral agent usually results in improvement. The rapidity and degree of improvement depend on the severity of the myopathy at the time of discontinuation, but strength is usually improved within 4 to 6 weeks (Dalakas, 2009; Dalakas et al., 1990). If strength does not improve, the possibility of a coexisting inflammatory component should be considered and a trial of steroids or IVIg may be of benefit.

WEST NILE VIRUS NEUROINVASIVE DISEASE

West Nile virus (WNV) is a mosquito-borne RNA flavivirus that has been identified as an important infectious agent associated with encephalitis and with involvement of the neuromuscular apparatus (Sejvar, 2016). Since it was first identified in the West Nile region of Uganda in 1937, it spread to the Middle East and Eastern Europe and has now been identified in all the major continents. It was first identified in the United States in 1999 (Nash et al., 2001) and has now become endemic and the leading cause of domestically acquired arboviral disease in the continental United States with neurological manifestations (McDonald et al., 2019). Although generally transmitted through a mosquito bite, it can be transmitted through contaminated blood transfusion or solid organ transplantation.

The majority of cases of human infection are subclinical or, when symptomatic, can present as a febrile illness with malaise, myalgias, headaches, lymphadenopathy, gastrointestinal symptoms, and sometimes an associated maculopapular rash (Hayes et al., 2005). The incubation period after inoculation in most cases is 2 to 14 days, and older adults and immunosuppressed patients are at higher risk of having a more severe and complicated illness. Contrary to West Nile's clinical manifestations in the areas where it was originally described, where it usually results in a mild uncomplicated febrile illness (West Nile fever [WNF]), the epidemics in the United States, Israel, and Eastern Europe have been associated with more prominent involvement of the nervous system, termed "neuroinvasive disease." Only a minority of all infected patients (<1%) develop neuroinvasive disease, although this disease can have a major impact on morbidity and mortality rates (Hawkes, Carabenciov, Wijdicks, & Rabinstein, 2018; Sejvar, 2016). Clinically apparent WNV neuroinvasive disease can be categorized in three distinctive groups: WNV meningitis, WNV encephalitis, and WNV acute flaccid paralysis (WNV-AFP) (Debiasi & Tyler, 2006; Kramer, Li, & Shi, 2007). There can be substantial overlap between these presentations so that they can coexist. Patients with WNV meningitis will present with fever, stiff neck, and photophobia, classic signs of meningeal irritation. In addition, cranial nerve abnormalities, in particular unilateral or bilateral facial neuropathies, can be a frequent accompanying abnormality. Those with WNV encephalitis, in addition to signs of meningeal irritation, will present with altered level of consciousness, disorientation and confusion, and more focal signs of central nervous system (CNS) involvement such as seizures, ataxia, myoclonus, postural or kinetic tremors, and parkinsonism. These are less common features of other viral encephalitides and are seen more often in older (>50 years) patients (Debiasi & Tyler, 2006).

Patients with WNV-AFP develop a rapid (24 to 48 hours) and progressive, usually asymmetrical, paralysis caused by destruction of motor neurons in the anterior horn of the spinal cord, a poliomyelitis syndrome. Although it is more commonly seen in patients in the context of WNV-meningoencephalitis, it may also present in the absence of fever or viral symptoms, as an isolated clinical presentation (Leis, Stokic, Webb, Slavinski, & Fratkin, 2003; Li et al., 2003). The deep tendon reflexes are usually reduced or absent in the affected limb; a normal sensory examination points to an abnormality in the anterior horn cells. Although the pattern of weakness is usually asymmetrical, it can range from subjective weakness and disabling fatigue without objective weakness on examination to a monoparesis or a rapidly ascending flaccid quadriparesis with respiratory failure, clinically very similar to GBS. Indeed, some cases of WNV infection have been associated with GBS, although this is a less common complication (Leis & Stokic, 2012). Dysarthria and dysphagia could be predictive of progression to respiratory failure. Loss of bladder function can be observed. On a long-term basis, the weakness usually persists, although the degree of improvement may vary depending on the severity of loss of motor neurons. Greater degrees of strength improvement are usually seen within the first 4 months after the infection and most recovery occurs within the first 6 to 8 months after the acute illness (Sejvar, 2016). Motor unit estimation may be useful in determining prognosis for recovery of strength in AFP (Cao, Ranganathan, Kupsky, & Li, 2005). In some instances, muscle weakness is rapidly reversible, implying that damage to the motor neurons may not necessarily be irreversible and that damage may occur in other segments of the motor unit such as the distal motor axons.

WNV-AFP can usually be distinguished clinically from typical GBS by the development of flaccid weakness during the symptomatic febrile stage of viral infection, in contrast to GBS, in which symptoms typically develop 2 to 8 weeks after the viral infection. In addition, the presence of CSF pleocytosis, the meningoencephalitic symptoms, and the absence of sensory symptoms can be helpful distinguishing clinical features. EMG-NCS can provide further evidence with the absence of demyelinating features.

DIAGNOSIS AND EVALUATION

The diagnosis of WNV infection should be suspected in any patient with onset of asymmetric paralysis in the context of a febrile illness, and more so if there are features of meningitis or meningoencephalitis. The diagnosis can be made by the detection of WNV-specific immunoglobulin M (IgM) from serum or CSF preferably between 8 and 21 days after onset; before 8 days, WNV-IgM may not be detected (Table 16.3). Because WNV-specific IgM may be detected in serum for up to 3 years, and in CSF at 3 to 6 months after the acute illness, a positive result may reflect past infection (Sejvar, 2016). In cases where doubt exists, to confirm recent WNV infection, it is usually required that a four-fold or higher increase in acute and convalescent antibody titers 2 to 3 weeks apart be detected. Because there can be cross-reaction with antibodies against other flaviviruses, determination of neutralizing antibody titers (plaque reduction neutralization test) is usually required when only serum specimens are available

Table 16.3 Infectious Neuronopathies, Neuropathies, and Polyradiculopathies

Neuropathy Type	Diagnosis/Management	Treatment
West Nile virus (WNV) neuroinvasive disease	>WNV-specific IgM in serum or CSF 8–21 days after onset of symptoms >MRI of spinal cord >EMG to establish anterior horn cell pattern	Prevention: protection during outdoor activities >Monitor for dysautonomia and respiratory failure >? High-dose steroids?
Lyme neuroborreliosis	>Establish appropriate geographic location, seasonal preference, and typical manifestations >Two-tier testing: Borrelia-specific IgM and IgG ELISA or C6 peptide ELISA followed by Western blotting or C6 peptide ELISA	>Uncomplicated facial neuropathy or radiculitis: doxycycline 100 mg twice daily for 14 days >Complicated with CNS involvement: IV ceftriaxone or cefotaxime or penicillin G for 20 to 21 days
Leprous neuropathy	>Anesthetic skin lesions, enlarged nerves evidence of acid-fast bacilli on skin or nerve biopsy >PGL-1 serology	>Paubacillary: rifampicin, 600 mg/day and dapsone 100 mg/day for 12 months >Multibacillary: clofazimine 50 mg/day added to dapsone and rifampicin for 24 months

CNS, Central nervous system; *CSF*, cerebrospinal fluid; *ELISA*, enzyme-linked immunosorbent assay; *EMG*, electromyography; *IgM,* immunoglobulin M; *MRI*, magnetic resonance imaging; *PGL-1*, phenolic glycolipid-1.

(Hayes et al., 2005; Sejvar, 2016). Alternatively, PCR of CSF for viral RNA can be performed, although the sensitivity is lower. Other ancillary studies include CSF analysis, MRI, and EMG/NCS. CSF analysis in WNV is notable for a modest pleocytosis (<500 cells/mm^3), with initial and often prolonged (>48 hours) predominance of polymorphonuclear neutrophils, changing later to a lymphocytic predominance, which is unusual for viral meningoencephalitides. The CSF protein is increased but the CSF glucose remains normal (Tyler, Pape, Goody, Corkill, & Kleinschmidt-DeMasters, 2006). This pleocytosis differentiates WNV-AFP from GBS. The MRI is most often unremarkable, although in patients with WNV encephalitis, abnormally increased signal can be observed on T2-weighted, diffusion-weighted, and fluid-attenuated inversion recovery images in cerebral white matter, in the deep gray matter nuclei such as thalamus and basal ganglia, and in the brain stem. In patients with AFP, there can also be increased signal in the anterior horns of the spinal cord in the T2-weighted images, an important finding indicating focal involvement of the motor neurons (Petropoulou, Gordon, Prayson, & Ruggierri, 2005; Sejvar, 2016). EMG and NCS are an important component in the assessment of suspected WNV-AFP. These most often show decreased compound muscle action potential (CMAP) amplitudes with preserved motor conduction velocities and normal sensory NCSs. This picture is in the context of widespread denervation in weak limbs and paraspinal muscles, consistent with an anterior horn cell disorder (Leis & Stokic, 2012).

TREATMENT AND MANAGEMENT

There is no specific antiviral treatment for infection with WNV at the present time, so a lot of the efforts have focused on prevention; information campaigns educating the public about protection measures during outdoor activities in the high-risk season and the development of potential vaccines. Patients with documented WNV infection and risk factors for worse outcomes, the elderly, or the immunosuppressed should be hospitalized for observation and detection of progression to neuroinvasive disease. Support treatment includes management of fever, hydration, pain control for headache, and management of nausea and vomiting. In patients with encephalitis, management of seizures and increased intracranial pressure may be required. Since some patients develop signs of dysautonomia (labile blood pressure, dysrhythmias, gastrointestinal symptoms) (Bai, Thompson, Vig, & Leis, 2019), this should be monitored and managed. Patients with WNV-AFP who develop early dysarthria and dysphagia may be at increased risk for respiratory failure and should be monitored accordingly (Sejvar et al., 2005). Based on the experience with polio virus poliomyelitis, aggressive physical activity during the acute febrile illness, or initial 48 to 72 hours of weakness, should be avoided (Sejvar, 2016). With respect to specific therapies, most reports at present are anecdotal, and clinical trials have shown no efficacy or inconclusive results due to difficulties in recruiting an appropriate sample size. A study of anti-WNV antibodies using an IVIg preparation made with pooled blood from donors with high titers of anti-WNV antibodies (Omr-IgG-am, Omrix Biopharmaceuticals) and compared to United States–produced IVIg was inconclusive because of difficulties enrolling an appropriate number of patients. Additional anecdotal reports or open-label studies have shown no effectiveness for ribavirin and interferon α. Some investigators have proposed a role for high-dose steroids, based on a few cases and anecdotal reports in patients with particular clinical features, but this remains to be proved (Bai et al., 2019; Leis & Stokic, 2012).

The information available about the long-term outcome of infection with WNV suggests that there is a wide range of residual symptoms and deficits and that these, in general, do not necessarily correlate with the severity of the initial infection (Hawkes et al., 2018; Sejvar, 2014, 2016). Patients with WNF and WNV meningitis have a more favorable outcome than those with encephalitis or AFP. Many patients report residual functional and cognitive changes such as difficulty with concentration and memory, suggestive of a subcortical type dysfunction, which impacts their ability to return to work (Hawkes et al., 2018; Sejvar, 2014, 2016). However, some patients, particularly if in good health prior to the

illness, still recover to their premorbid level of functioning. Patients with WNV-AFP appear to have the worse long-term outcome, with more prominent morbidity and mortality rates. As a group, worse outcome and increased mortality rates are seen in patients who develop respiratory failure, have more extensive weakness due to loss of motor neurons, and are older. Mortality rates in patients with more severe involvement and in particular those with respiratory failure can range from 6% to 25%. Some studies have shown limited or absent recovery in very weak limbs, as one would expect with severe loss of motor neurons. In general, the outcome data to this date have shown that there is a spectrum of functional outcomes and that recovery is highly variable and that intensive support and effective rehabilitation strategies at the appropriate time, after hospital discharge, can result in good functional recovery (Hawkes et al., 2018; Sejvar, 2014, 2016).

SARS-COV-2 INFECTION (COVID-19)

Coronavirus disease 2019 (COVID-19) is a severe disorder caused by a novel coronavirus, SARS-CoV-2, that involves many organs, primarily affecting respiratory and cardiac function. Various neuromuscular complications have been described to date (Ahmad & Rathore, 2020; Guidon & Amato, 2020; Romoli et al., 2020). The neuromuscular complications described are critical illness neuropathy, myopathy, myositis, rhabdomyolysis, and GBS including the Miller-Fisher variant (Dalakas, 2020; Guidon & Amato, 2020; Reyes-Bueno et al., 2020; Toscano et al., 2020). These can occur not only after the onset of systemic symptoms but also during or even preceding systemic symptoms, although anosmia and ageusia are often present prior to the development of neurologic symptoms. Some of these complications may be caused by worsening of preexisting diseases and others, possibly caused by the associated exaggerated immune response in some patients. Anywhere from 19% to 35% of patients with COVID-19 infection suffer from myalgias and high CPKs (Li et al., 2020; Mao et al., 2020), and some have developed COVID-19-related myositis or rhabdomylysis, suggesting that SARS-CoV-2 may cause a viral myositis. In at least one patient with myopathy and COVID-19 disease, there was evidence of a virus-induced type I interferonopathy (Manzano, Woods, & Amato, 2020).

DIAGNOSIS AND EVALUATION

It has been stated that in the COVID-19 pandemic, any patient who presents with an acute paralytic illness should be tested for SARS-CoV-2 infection (Dalakas, 2020). The concomitant presence of anosmia, ageusia, lymphopenia, or thrombocytopenia should prompt immediate suspicion for the diagnosis in patients presenting with neuromuscular symptoms. Diagnostic tests for COVID-19–associated neuromuscular symptoms are no different from those routinely used for diseases of the muscle, neuromuscular transmission, or peripheral nerve. Given the concern of potential contagion, telemedicine and teleconsultations have become the preferred method of routine follow-up of patients with known and stable neuromuscular diseases. In-person visits are being limited to new patients who have not been examined with concerns of a potentially complicated neuromuscular condition with serious complications and those in which appropriate evaluation and diagnosis will be crucial for treatment and management decisions. Emphasis is made in evaluating only patients with acute presentations or with life-threatening symptoms or rapid progression without an established diagnosis.

The American Association of Neuromuscular and Electrodiagnostic Medicine has also published guidelines for the performance of electrodiagnostic studies during the COVID-19 pandemic, emphasizing prescreening, coordinated scheduling, the critical need for the study and potential for changing management, and the use of protective equipment (Desai et al., 2020).

TREATMENT AND MANAGEMENT

Management of neuromuscular patients in the COVID must take into account the preexisting respiratory and cardiac involvement and their immunocompetence status. Patients with neuromuscular disorders are at increased risk for complications due to the impaired respiratory capacity, as well as preexisting cardiomyopathy. Those on immunosuppressants are also at increased risk, in spite of the fact that some have suggested that the use of some immunotherapeutic drugs may decrease the exaggerated immune reaction caused by SARS-CoV-2 and be beneficial to patients (Safavi & Nath, 2020).

Published guidelines and recommendations for patients with neuromuscular diseases in the COVID-19 era agree on avoiding unnecessary hospital or outpatient visits and procedures, and considering teleconsultation strategies. Particular consideration should be given for increased risks of infections during hospital visits for necessary treatment, such as intrathecal nusinersen, and from complications of therapies such as those that may predisposed to arrhythmias as well as those that may worsen respiratory dysfunction. Patients with disorders of neuromuscular transmission may be at risk of deterioration by using drugs that may affect neuromuscular transmission. Guidance for care of these patients during COVID-19 infection has been published and should be considered by those caring for these patients (Dubbioso et al., 2020; International MG/COVID-19 Working Group et al., 2020; Solé et al., 2020).

NERVOUS SYSTEM LYME DISEASE (*LYME NEUROBORRELIOSIS*)

Lyme disease is the most commonly reported vector-borne disease in the United States (Mead, 2015). It is a multisystemic disease caused by infection with the spirochete *Borrelia burgdorferi sensu stricto* in the United States and *Borrelia afzelii* and *Borrelia garinii* in most cases in Europe (Halperin, 2018). It is acquired through the bite of hard-shelled ticks of the *Ixodes* complex (*I. scapularis* in the northeastern United States and *I. ricinus* in Europe). The clinical condition was described originally in Europe and afterward was identified in the United States, where the spirochete causing the symptoms was first identified. The more common clinical presentations may be somewhat different in Europe and in the United States, and this has been associated with differences in the strains of *Borrelia* that predominate in each region (Pachner & Steiner, 2007). The infection has preferential involvement of the skin, heart, joints, and nervous system, hence its common symptomatic manifestations of skin rash, carditis and cardiac conduction defects, arthralgias or frank

arthritis, and meningoradiculoneuritis. When it involves the nervous system (Lyme neuroborreliosis), it primarily causes meningeal inflammation with a wide variety of manifestations affecting both the CNS and the peripheral nervous system. The characteristic triad of neuroborreliosis consists of meningitis, cranial neuropathies, and radiculitis or radiculoneuritis, although peripheral neuropathy (mononeuritis multiplex) and, more rarely, myositis can also be observed (Halperin, 2018; Pachner & Steere, 1985). We will focus our discussion around the more common manifestations.

DIAGNOSIS AND EVALUATION

The diagnosis of Lyme neuroborreliosis is initially and foremost a clinical diagnosis, based on a precise history, a careful physical examination, and supportive laboratory tests (Table 16.3). The history will be important to establish the appropriate geographic location, the seasonal preference, and the typical systemic and neurologic manifestations. In North America, the majority of Lyme disease cases occur in the Northeast, mid-Atlantic, and upper Midwest regions of the United States (Schwartz, Hinckley, Mead, Hook, & Kugeler, 2017). The infection is also prevalent in middle Europe and Scandinavia, and it occurs in Russia, China, and Japan. Thus, it will be critical to determine if the patient resides or has traveled to an area where the disease is endemic. The seasonal aspect should be explored: Most infections occur from spring to autumn and are unlikely to happen during the winter months, when the tick is not active. Although most patients will not recall a tick bite, in a large proportion of patients it will be possible to establish the recent occurrence of a skin rash. This rash, the hallmark of Lyme disease in the United States, is a slowly expanding erythematous annular lesion, resembling a bull's-eye or a target, known as *erythema migrans*, occurring within a few days to the first few weeks after infection. The lesion is described as being at least 5 cm in diameter, and in the United States it could be multifocal. It is an early manifestation of the infection and in the context of systemic symptoms, such as fever, arthralgias, headache, chills, and malaise, would be strongly indicative of recent infection with *Borrelia* (stage 2). In Europe, erythema migrans is less common and more indolent, with milder systemic manifestations. European patients may present later in the course of the disease with another dermatologic manifestation, *acrodermatitis chronica atrophica* (Mullegger & Glatz, 2008). After the development of the erythema migrans, between 3% and 15% of patients with untreated Lyme borreliosis will develop neurologic symptoms, neuroborreliosis, which can result from central or peripheral nervous system involvement. The clinical consensus divides the infection into an acute localized stage (erythema migrans) and a disseminated stage, further divided into early and late phases (Garcia-Monco & Benach, 2019; Logigian, Kaplan, & Steere, 1990). The most common early presentation in the United States is a lymphocytic meningitis, with headache and mild meningismus, often with involvement of one or more of the cranial nerves, within a few weeks to a few months following the initial infection or the erythema migrans. The other major presentation, which is more common in Europe, is a painful radiculitis (Garin-Bujadoux-Bannwarth syndrome) with a lymphocytic pleocytosis on CSF analysis. Cranial neuropathies are the most common focal neuropathies and can be observed in 40% to 70% of patients with early neuroborreliosis. The most common cranial neuropathy is a facial (seventh cranial nerve) neuropathy, which accounts for about 70% to 80% of all cases (Halperin, 2003a, 2003b). The facial neuropathy is most commonly unilateral but can be bilateral in one third of the cases, as in sarcoidosis and GBS. Although it is usually accompanied by meningeal inflammation, half of the patients with facial neuropathy may not have a lymphocytic pleocytosis, indicating that the nerve can be involved distal to the subarachnoid space. Other cranial neuropathies that have been described are neuropathies of the third (oculomotor), sixth (abducens), and eighth (vestibuloauditory) cranial nerves (Halperin, 2003b).

The earliest neurologic manifestations typically occur within a few weeks of erythema migrans. The painful radiculitis can present in up to 80% of patients with European neuroborreliosis. This is an acute painful radiculitis, worse at night, with painful dysesthesias, often described as lancinating in a dermatomal distribution (Halperin, 2003b; Pachner & Steere, 1985). The radiculitis can be in the cervical, thoracic, or lumbosacral distribution, may or not be associated with meningeal inflammation, and can be focal or multifocal and asymmetrical. Within days or weeks after the onset of the painful dysesthesias, patients may develop motor weakness in the affected root distribution, which if thoracoabdominal may be associated with abdominal protrusion. Rarely, the radiculitis has been associated with spinal cord inflammation around the same segment, resulting in long tract signs, a sensory level, and sphincter abnormalities below the level of the involved segment. Brachial and lumbosacral plexopathies, mononeuritis multiplex, and a confluent mild distal axonal polyneuropathy have also been described, although they are less common. Patients with untreated Lyme disease may present with a mild indolent chronic distal axonal polyneuropathy or polyradiculoneuropathy months to years after onset of disease (Logigian et al., 1990; Logigian & Steere, 1992). This is characterized primarily by symmetrical nonpainful paresthesias in a distal lower limb distribution or asymmetrical radicular pain. The most common finding is multimodal sensory loss, but only 60% of the patients will have objective abnormalities in the neurologic examination. Contrary to acute radiculoneuritis, this finding is not associated with cranial neuropathy, and a lymphocytic pleocytosis on CSF is usually absent. This neuropathy is usually mild and often requires electrophysiologic studies for detection. In European patients, chronic Lyme polyneuropathy is usually associated with acrodermatitis chronica atrophica. The neuropathy preferentially affects the limb with the chronic skin changes and appears to be more painful and to affect motor fibers more commonly than the North American variety.

Laboratory diagnosis for neuroborreliosis relies on the detection of anti-*Borrelia* antibodies because the spirochete, if present in blood or CSF, is only present in low numbers and for a short time, it is difficult to isolate and culture, and the yield of PCR in CSF is low. In early localized stage (stage 1) disease, with a single erythema migrans lesion and local lymphadenopathy, serologic testing is not recommended, because it will be too early for antibody production (John & Taege, 2019). Thus, if the patient has the characteristic *erythema migrans* lesion, treatment should be instituted in spite of the negative serologic test. Convalescent serum samples

2 weeks after the onset of symptoms may help confirm the diagnosis, although patients treated very early may never develop antibodies. For early disseminated disease (stage 2) with lymphocytic meningitis, facial nerve paralysis or radiculoneuropathy, or late Lyme disease (stage 3, Lyme arthritis), current recommendations are for the use of a two-tier (two-step) approach, checking for *Borrelia*-specific antibodies using IgM and IgG enzyme-linked immunosorbent assay (ELISA), and if the ELISA is positive, followed by Western blotting (John & Taege, 2019; Centers for Disease Control and Prevention [CDC], 1995). Western blots should not be performed in patients with a negative ELISA. Newer ELISAs that use recombinant proteins, and in particular against the C6 peptide, have shown comparable or higher sensitivity but higher specificity during early infection (Branda et al., 2018). Based on these new enzyme immunoassays, the CDC has updated its recommendations and now includes a two-tier format using two sequential enzyme immunoassays as an alternative to serologic diagnosis of Lyme disease (Mead, Petersen, & Hinckley, 2019).

With suspected involvement of the CNS, testing for intrathecal production of Lyme-specific antibodies is important in establishing the diagnosis. The demonstration of anti-*Borrelia* antibodies in serum or CSF alone does not constitute evidence of neuroborreliosis, because they may originate by passive transfer from blood, and many individuals from endemic areas have positive IgG and IgM antibodies in the absence of borreliosis or neuroborreliosis. To establish the presence of intrathecal synthesis of anti-*Borrelia* antibodies, and the diagnosis of neuroborreliosis, the use of an antibody index comparing proportions of CSF to serum antibodies has been recommended (Blanc et al., 2007; Mygland et al., 2010). The index is defined as the ratio of *B. burgdorferi*–specific IgG in the CSF to *B. burgdorferi*–specific IgG in serum, in relation to the total IgG in CSF and total IgG in serum. In a group of established cases of neuroborreliosis, the index had a diagnostic sensitivity of 75% with a specificity of 97%. A limitation of this assessment is the fact that it has a low sensitivity early in the disease, and an elevated CSF-to-serum ratio can persist for years after treatment (Hammers-Berggren, Hansen, Lebech, & Karlsson, 1993). In addition, patients with pure peripheral nerve syndromes may not have an increased intrathecal production of antibody. More recently, the CSF concentration of CXCL-13, a B-cell attracting chemokine, has been proposed as a potential test for neuroborreliosis (Picha, Moravcova, & Smiskova, 2016; Senel et al., 2010).

Lumbar puncture for CSF analysis provides additional evidence of CNS involvement with meningeal inflammation. This typically shows a mild or moderate lymphocytic pleocytosis with a mildly increased protein concentration and normal glucose levels (Halperin, 2018; Pachner & Steere, 1985). An increased IgG index and oligoclonal bands can also be observed. These findings could help differentiate other conditions with similar symptoms but without meningeal inflammation and may suggest the diagnosis of neuroborreliosis in patients with facial nerve palsies or painful radiculitis. As previously mentioned, some patients with strictly peripheral nervous system involvement may not have an associated pleocytosis or meningeal inflammation (Halperin, 2003b).

EMG and NCS will help establish a radicular pattern of involvement and the presence of a mononeuritis multiplex or axonal polyneuropathy. Among the findings described in studies, there can be reduced-amplitude motor and sensory responses with preserved conduction velocities, consistent with an axonal polyneuropathy, and denervation in limb muscles extending to the paraspinal muscles consistent with a radicular lesion (Halperin, 2003b; Logigian & Steere, 1992; Vallat et al., 1987). These findings may coexist.

MRI findings are not specific for neuroborreliosis, and its role may be more to exclude alternative diagnoses or to establish parenchymal CNS involvement. MRI of peripheral neuroborreliosis may provide indirect confirmatory evidence of inflammation by showing enhancement of cranial nerves in patients with cranial neuropathies or enhancement of lumbosacral roots in patients with lumbosacral radiculitis (Bannwarth syndrome) (Hildenbrand, Craven, Jones, & Nemeskal, 2009).

TREATMENT AND MANAGEMENT

Patients with Lyme neuroborreliosis should be treated as soon as diagnosed to prevent potential dissemination and sequelae. Current recommended regimens appear to be highly effective. An evidence-based review published by the American Academy of Neurology has shown that parenteral regimens with ceftriaxone and oral regimens with doxycycline are highly effective in both adult and pediatric neuroborreliosis (Halperin et al., 2007). Alternative parenteral choices can be cefotaxime or penicillin. Oral doxycycline has been shown to be as effective as parenteral ceftriaxone and has been used in Europe with success (Ljøstad et al., 2008). Doxycycline (100 mg orally twice daily in adults and in children 2.2 mg/kg twice daily to a maximum of 100 mg per dose) is considered the preferred choice for uncomplicated cases with facial neuropathies or radiculitis. Published studies have used treatment courses of 10 to 28 days, although the current recommendations are for a 14-day course; there appears to be no significant difference in the outcome. Oral doxycycline can be used for facial nerve palsy, even in the context of abnormal CSF findings (pleocytosis), and for radiculoneuritis or uncomplicated Lyme meningitis. Doxycycline is contraindicated in children younger than 8 years and in pregnant women. In these cases, amoxicillin or cefuroxime axetil are considered alternate choices. In the context of CNS parenchymal involvement (encephalitis or encephalomyelitis, which is rare), IV treatment is recommended. Recommended regimens include (1) ceftriaxone 2 g IV once daily in adults, and in children, 50 to 75 mg/kg IV once daily to a maximum of 2 g; (2) cefotaxime 2 g IV every 8 hours in adults, and in children, 150 to 200 mg/kg IV in three divided doses per day to a maximum of 6 g per day; and (3) penicillin G, 18 to 24 million units per day IV divided in six doses, and in children, 200,000 to 400,000 units/kg per day divided in six doses to a maximum of 18 to 24 million units per day. The duration of treatment will vary with severity; a 14-day course appears adequate in patients with uncomplicated disease, or up to 21 to 28 days in more complicated cases.

No benefit has been shown for prolonged treatment with antibiotics beyond 4 weeks or for the treatment of "post-treatment Lyme disease syndrome" and so it is not recommended (Berende et al., 2016; Halperin et al., 2007). Clinicians should be aware that improvement after antibiotic therapy is slow and continues after completion of therapy. This

pattern should not be confused with failure of treatment, which would be suspected only if new deficits or symptoms arise. Treatment failures with ceftriaxone and doxycycline may be seen, and alternative antibiotics may be considered in those instances. Nonsteroidal anti-inflammatory agents may be helpful for treating the myalgias, arthralgias, and headache associated with the systemic disease (Pachner & Steiner, 2007). The use of steroids as part of the treatment, in particular for facial neuropathy, has not been shown to be either beneficial or detrimental and at the present time is not recommended.

LEPROUS NEUROPATHY

Leprosy continues to be one of the leading causes of peripheral neuropathy in the world, in spite of continuing decline in the number of cases of leprosy globally in recent years. Peripheral nerve damage is the result of chronic granulomatous inflammation resulting from infection by *Mycobacterium leprae* and *Mycobacterium Lepromatosis* or from immunologically mediated reactions in the peripheral nerves (Han et al., 2009; Scollard, Truman, & Ebenezer, 2015).

The principal goal in the management of leprosy neuropathy is to prevent disability by early detection and treatment of peripheral nerve involvement. Detection of leprosy in the early stages is critical to prevent irreversible damage and long-standing disability. The onset of the disease is insidious, with an incubation period of 7 years on average, although it can range from 3 months to 40 years. The disease is classified into three major clinical subtypes, based on the aggressiveness of the infection, which is a function of the host's cell-mediated immunity. The more restricted presentation is classified as tuberculoid (paucibacillar) leprosy and the more widespread and systemic form is classified as lepromatous (multibacillar) leprosy; borderline leprosy manifests between tuberculoid and lepromatous. It is also classified according to the extent of skin involvement as multibacillary or paucibacillary leprosy.

The large majority of patients will exhibit both skin and peripheral nervous system abnormalities, although, less commonly, patients may present with a pure neural form that will require a high degree of suspicion and confirmatory tests for diagnosis (pure neuritic leprosy). The three cardinal signs in leprosy neuropathy are (1) an anesthetic skin lesion, (2) enlarged nerves, and (3) evidence of acid-fast bacilli on skin biopsy or smears (Table 16.3) (Eichelmann, Gonzalez Gonzalez, Salas-Alanis, & Ocampo-Candiani, 2013).

The skin lesions are described as macules or plaques, with a raised border and hypopigmentation and with decreased sensation or anesthesia in the central portion. These lesions tend to be found more frequently on the trunk or abdomen but may occur in other locations. One must be aware, however, that up to 30% of skin lesions in leprosy do not exhibit sensory abnormalities (Wilder-Smith & Van Brakel, 2008). Granulomatous inflammation results in palpable enlargement of the nerves; thus, enlarged nerves must be sought in the physical examination.

Involvement of peripheral nerves is different among the various forms of leprosy. In tuberculoid and borderline leprosy, the most common pattern of neuropathy is a mononeuritis multiplex. A skin lesion overlying a nerve is frequently associated with involvement of that nerve. The nerves that are commonly affected are the ulnar, radial, median, fibular (peroneal), tibial, facial, and trigeminal. In lepromatous leprosy, nerve involvement is more widespread; a distal, symmetrical polyneuropathy pattern is more common, in the early stages predominantly affecting small myelinated and unmyelinated fibers. Because the bacterium favors cooler areas of the body, sensory loss may be observed in the chin, malar areas of the face, earlobes, buttocks, knees, and distal extremities (Sabin, 1969). Negative sensory symptoms (numbness, anesthesia) are more common than positive sensory symptoms (paresthesias, pain).

DIAGNOSIS AND EVALUATION

Early diagnosis is critical because lack or delayed treatment of neuropathy in leprosy will lead to irreversible atrophy and weakness, profound sensory loss, and anesthesia, with damage and mutilation from repeated injuries and trauma. The diagnosis can be made by demonstrating organisms in skin or nerve biopsy (Fig. 16.1) and the presence of serologic markers such as phenolic glycolipid-1 and polymerase chain reaction in tissue.

Nerve biopsy of an affected sensory cutaneous nerve is an important diagnostic tool, in particular in patients without

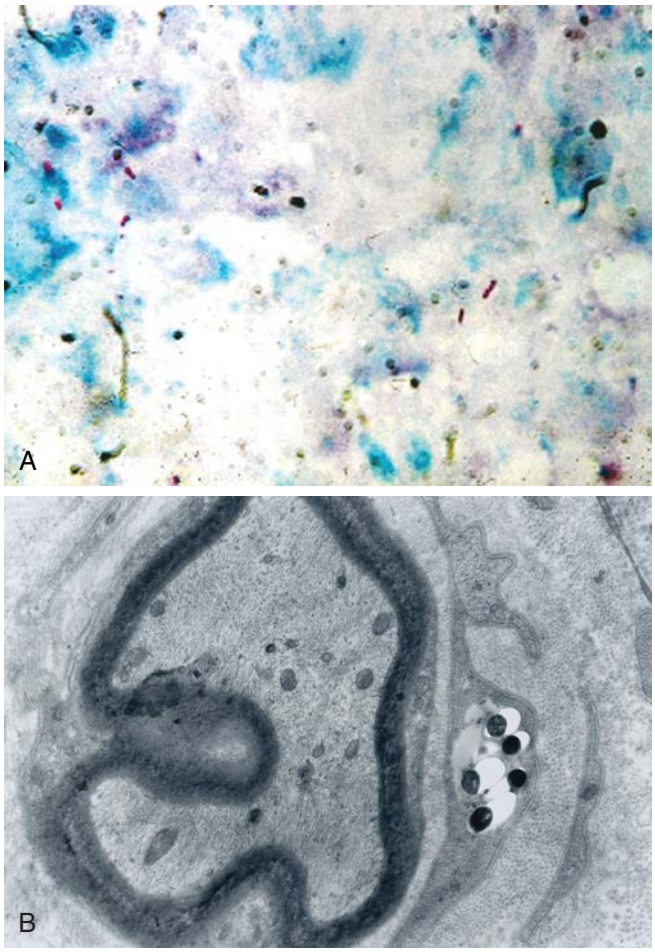


Fig. 16.1 (A) Leprosy in nerve. Acid-fast bacilli of leprosy (Ziehl-Neelsen Au20 stain, "400). (B) Leprosy in nerve. Lepra bacilli in Schwann cell cytoplasm on electron microscopy ("9,000). (A, Courtesy of Dr. Adriana Ciudad, Lima, Peru. B, Courtesy of Shankar, National Institute of Mental Health and Neurosciences, Bangalore, India.)

skin lesions with pure neuritic leprosy. The biopsy findings vary between the different subtypes of leprosy. In tuberculoid leprosy, the nerve biopsy shows marked nerve destruction, with abundant inflammatory infiltrates in the epineurium, endoneurium, and perineurium, with prominent granuloma formation, differential fascicular loss of axons with involved fascicles adjacent to normal ones, and with few or no organisms seen. In lepromatous leprosy, there is axonal loss, more prominent of unmyelinated fibers, with variable degrees of inflammation, presence of foamy cells (macrophages and Schwann cells), and numerous bacilli (Pedley, Harman, Waudby, & McDougall, 1980; Said, 2007). There can be discrepancy between the classification based on clinical features and the histologic classification based on nerve biopsy, leading some authors to recommend including the nerve biopsy findings in the classification and selection of therapy (Kulshreshtha et al., 2018).

NCSs are more sensitive at detecting peripheral nerve involvement than the clinical examination. Among the electrodiagnostic tests, sensory NCSs and, in particular, sensory amplitudes and sensory conduction velocities, as well as warm perception thresholds, are among the earliest abnormalities observed and are the most sensitive measures, even in the subclinical stages (Kumar et al., 2016; van Brakel et al., 2008). Motor nerve conductions can also be abnormal, even before clinical signs are apparent. Based on the frequency of involvement, NCSs should be performed in the ulnar, median, and superficial radial nerve in the upper limbs and the peroneal, posterior tibial, and sural nerves in the lower limbs. The trigeminal and facial nerves should also be tested. Nerve ultrasound presents another complementary strategy to detect nerve abnormalities such as abnormal thickening and asymmetry in patients with leprosy. In some instances, it can show abnormalities when neurophysiological parameters are still normal and can provide evidence of worsening of the neuropathy after treatment.

TREATMENT AND MANAGEMENT

Management of leprosy neuropathy involves managing the neurologic and physical deficits resulting from the nerve damage. Management of decreased sensation in hands and feet requires prevention of injuries, frequent evaluation for painless lesions and immediate treatment. Patients should be instructed to inspect the areas at risk on a daily basis, including the soles with the help of a mirror. Special footwear for prevention of plantar ulcers can be used. Gloves should be used for tasks that may result in skin damage. Assessment for incomplete eye closure and corneal exposure requires protective measures and may require corrective surgery.

Delayed treatment or no treatment of leprosy neuropathy is a major cause of disability, deformity, morbidity, and social isolation in these patients. Treatment of leprosy and leprosy neuropathy involves both antibacterial therapy and strategies to limit inflammatory reactions. Current antibacterial treatment involves multidrug therapy (MDT) to prevent resistance and varies between patients with paucibacillary or multibacillary disease. The first-line medications include dapsone, rifampin, and clofazimine for lepromatous disease. These medications are effective against both infectious agents, *M. leprae* and *M. lepromatosis*. Treatment recommendations, primarily duration of treatment, differ between the National Hansen's Disease Program (NHDP) and the World Health Organization. The NHDP current treatment recommendation for tuberculoid leprosy (paucibacillary disease) consists of 12 months of rifampicin (600 mg/day) and daily dapsone (100 mg). For lepromatous (multibacillary) leprosy, a recommended treatment is clofazimine (50 mg/day), added to dapsone and rifampicin and given for 24 months. Clofazimine is available in the United States only by registering as an investigator under the NHDP investigational new drug application (www.hrsa.gov/hansens-disease). Patients are rendered noninfectious within 72 hours of treatment.

Treatment of leprosy may result in inflammatory reactions termed *type 1* and *type 2 (reversal) reactions*. These immunologically mediated reactions may result in increased nerve damage and increased disability. With type 1 reactions, patients may observe enlargement of a preexisting skin lesion or the development of acute, painful nerve palsies. This reaction requires immediate treatment with prednisone at initial doses of 40 to 60 mg (1 mg/kg) lasting for 4 to 6 months and a higher dose if there is no improvement within 48 hours. Patients who have not responded to steroids after 6 weeks may be referred for surgical decompression (neurolysis). Patients with multiple or large lesions on the face may benefit from prophylactic steroids for 4 months at the start of MDT. Methotrexate and cyclosporine have been proposed as alternatives or second-line treatments for type 1 reactions. Type 2 reactions (erythema nodosum leprosum) are mostly seen in lepromatous leprosy and will present with painful erythematous papules and systemic symptoms such as fever, uveitis, fatigue, and lymphadenopathy. They will also require prompt intervention with steroids at high doses and often with repeated treatments. Prednisone (40 to 60 mg/day) should be started promptly to avoid permanent nerve damage, and quickly tapered over a 2-week period? Thalidomide has also been recommended for the management of type 2 reactions, although this therapy may be complicated by the development of drug-induced neuropathy and must be used with caution. Only prescribers under a US FDA restricted distribution program (Risk Evaluation and Management Program) are allowed to prescribe thalidomide.

OTHER INFECTIOUS NEUROPATHIES AND MYOPATHIES

Human T-Lymphotrophic Virus

HTLV-I and, less commonly, HTLV-II are most commonly associated with a progressive spinal cord disorder and as the causative agents of HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), as well as adult T-cell leukemia. The diagnosis of HTLV-I/HTLV-II is made through ELISA-based antibody detection in serum and confirmed with Western blot or PCR for pro-viral DNA in peripheral blood mononuclear cells.

Although the most common neurologic presentation is the chronic progressive myelitis, it is known that patients may exhibit coexistent or isolated neuromuscular complications such as a sensory or sensorimotor peripheral neuropathy (Araujo & Wedemann, 2019; Leite et al., 2004; Saeidi, Sasannejad, Foroughipour, Shahami, & Shoeibi, 2011), polymyositis and inclusion body myositis (Desdouits et al., 2013; Gilbert, Morgan, Smikle, Simeon, & Barton, 2001;

Leon-Monzon, Illa, & Dalakas, 1994; Martin, Taylor, & Jacobson, 2014; Morgan, Rodgers-Johnson, Mora, & Char, 1989), and an amyotrophic lateral sclerosis (ALS)–like syndrome (Silva et al., 2005). The neuropathy may be present in up to a third of patients with HAM/TSP but can be detected in about 6% of asymptomatic, HTLV-I-seropositive individuals (Leite et al., 2004; Saeidi et al., 2011). Clinically, patients with neuropathy present primarily with paresthesias or dysesthesias in the distal lower extremities, impaired vibration in the toes, and reduced (relative in the presence of hyperreflexia) or absent ankle reflexes, consistent with a DSP. Electrophysiologic studies mostly have shown a mixed or predominantly axonal, sensorimotor polyneuropathy (Leite et al., 2004; Saeidi et al., 2011), although demyelinating neuropathies have also been reported (Sawa et al., 2005). Sural nerve biopsies have shown inflammatory infiltrates and axonal degeneration and segmental demyelination, consistent with an inflammatory, immune-mediated mechanism (Kiwaki et al., 2003; Leite et al., 2004). There are no studies addressing treatment for the peripheral neuropathy in HTLV-I infection; the current treatment is primarily symptomatic.

Patients with HTLV-1-associated polymyositis will show prominent proximal muscle weakness and elevated serum CK levels. In endemic regions, small case series have shown HTLV-1 seropositivity in 30% to 85% of patients with polymyositis (Martin et al., 2014), suggesting the need for testing all patients from endemic regions presenting with polymyositis or inclusion body myositis for concomitant HTLV-1 infection. Muscle biopsies have shown predominant infiltration by CD8+, CD4+ T cells, and macrophage and ubiquitous major histocompatibility complex class 1 (MHC-1) expression (Leon-Monzon et al., 1994). There is limited information about treatment for HTLV-1 polymyositis. HTLV-I-associated myositis has been treated with prednisone at 1 mg/kg/day and oral immunosuppressants such as azathioprine, although compared to seronegative polymyositis, patients appear to have a less optimal response (Gilbert et al., 2001).

The HTLV-1 ALS-like syndrome has been described in at least 35 patients with upper motor neuron signs such as those seen in HAM/TSP, but with lower motor neuron features in at least two limbs. However, it differs from typical ALS by the presence of sensory and autonomic symptoms, bladder dysfunction, prolonged survival of 10.6 years on average, and response to steroids in some cases (Alfahad & Nath, 2013; Silva et al., 2005).

Other Viral Myopathies

Muscle involvement in the form of myalgias, myositis, or, in more severe cases, rhabdomyolysis can be seen in a variety of other viral infections, in addition to HIV and HTLV-I viral infections. Viral myositis has been reported with influenza A and B, coxsackievirus, Epstein-Barr virus, HSV, parainfluenza virus, adenovirus, echovirus, CMV, measles virus, varicella-zoster virus, and dengue virus. The most common causes of viral myositis in the United States are the influenza A and B viruses; myositis is more common with type B than with A (Crum-Cianflone, 2008). In children, this is commonly identified as "benign acute childhood myositis." Influenza infections are a seasonal problem most commonly presenting with signs and symptoms of an upper respiratory tract infection with systemic symptoms such as fever, headaches, and myalgias of varying severities that may appear before or at the same time as the systemic symptoms. In contrast to the typical myalgias, the myositis appears after the onset of fever and systemic symptoms (within a few days), is more restricted in distribution, and results in more severe pain. Clinically, it affects the calf muscles more frequently and prominently, causing pain, tenderness, and difficulty with ambulation. Myositis is more commonly seen in children than in adults and it tends to affect boys more often than girls (Agyeman, Duppenthaler, Heininger, & Aebi, 2004). When present in adults, it is more severe. The diagnosis is based on the identification of influenza A or B infection and the suggestive clinical picture. CK levels are usually elevated, more in adults than in children. Muscle biopsy, although not usually performed, may reveal features of an acute necrotizing myositis. Treatment is mainly symptomatic, for the myositis usually appears after the infection is established and there is no evidence that antiviral agents or immunotherapy are beneficial for the myositis. For the treatment of the underlying influenza, the use of neuraminidase inhibitors (oseltamivir, zanamivir, or peramivir) or baloxavir is the recommended treatment (Uyeki et al., 2019). Although infrequent, rhabdomyolysis can also be seen with influenza infection and is more common with influenza A than B and in boys more than girls (Agyeman et al., 2004).

The clinical evolution of acute viral myositis with rhabdomyolysis can vary between individuals, with secondary complications that include renal failure, fluid and electrolyte disturbances, cardiac arrhythmias, and metabolic encephalopathy. Elevation of CK has been associated with worse outcomes in patients with H1N1 influenza A infection (Borgatta et al., 2012). Because of the danger of renal damage, rhabdomyolysis must be aggressively treated. Admission to the hospital for hydration and monitoring of renal function is required.

Parasitic Myositis

The most common parasitic infections of muscles include trichinosis, cysticercosis, and toxoplasmosis.

Trichinosis or *trichinellosis* occurs from ingestion of improperly cooked meat contaminated with nematodes of the *Trichinella* genus, most commonly *Trichinella spiralis* and *Trichinella britovi*. Although it is most commonly associated with ingestion of pork meat, more recently it has been associated with the ingestion of meat from horses and wild animals, including bear, walrus, seal, cougar, and wild boar (Crum-Cianflone, 2008; Springer et al., 2017; Troiano & Nante, 2019; Wilson, Hall, Montgomery, & Jones, 2015). The clinical presentation includes a prodrome with gastrointestinal symptoms such as abdominal cramps, diarrhea, and vomiting (intestinal stage), followed by fever, muscle soreness and tenderness, edema of the eyelids, subungual splinter hemorrhages, subconjunctival hemorrhages, and eye pain (muscle stage). Examination can reveal muscle weakness that may include the intercostal muscles and diaphragm. Myocarditis may accompany the clinical picture, with persistent tachycardia, cardiac failure, and striking electrocardiographic changes, and can be a cause of death in trichinellosis (Neghina, Neghina, & Marincu, 2011). CNS manifestations can also occur. Laboratory testing shows eosinophilia, which may be as high as 50%, and elevation of serum CK, particularly in the acute stages of the disease. The EMG shows features of an inflammatory myopathy with fibrillations and myopathic changes. A muscle biopsy in affected

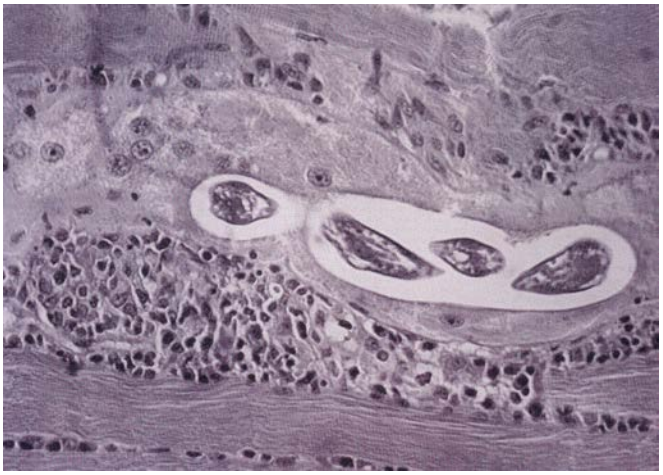


Fig. 16.2 Trichinosis in muscle. Muscle fiber showing a parasite cyst in a case of trichinosis (hematoxylin and eosin, "200). (Reprinted with permission from Bertorini, T. E. (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Woburn, MA: Butterworth-Heinemann.)

muscles may help establish the diagnosis in the early clinical stages, when the serologic test is still negative. Findings in the muscle biopsy vary depending on the stage of infection and may show motile larvae, encapsulated calcified cysts, and inflammatory infiltrates with muscle fiber necrosis (Fig. 16.2) (Banker, 2004). The diagnosis may be confirmed, establishing the presence of antibodies in serum, with ELISA, fluorescent antibody test, or the bentonite flocculation assay (Crum-Cianflone, 2008; Gottstein, Pozio, & Nockler, 2009). In patients with mild infection, the recommended treatment is usually a combination of bed rest, analgesics, and antipyretics. Albendazole (400 mg twice a day for 10 to 14 days) or, alternatively, mebendazole (200 to 400 mg daily for 3 days and then 400 to 500 mg three times daily for 10 days) may be used in the acute enteric stages of the disease to prevent further larval migration to the muscles. The drugs, however, are ineffective in treating the muscle infection. With more severe infections or myocarditis, corticosteroids (prednisone) are given in combination with the anthelmintic medications. Prevention by cooking meat properly and realizing that freezing does not kill all the trichina species are important parts in the management of this infection.

Cysticercosis is the systemic infection that results from the ingestion of undercooked pork meat contaminated with eggs from *Taenia solium*, the pork tapeworm. This is an important health problem in the developing world and is also seen in developed countries, particularly in immigrants from areas in which it is endemic. The larvae infect the CNS, muscle, eye, and subcutaneous tissue. The disease is often asymptomatic and is detected when cysticerci degenerate and cause inflammation in the CNS, resulting in seizures, or when it is detected incidentally on radiographs showing calcified cysts in muscle or CNS. Occasionally, patients may present with diffuse myalgias and lower extremity weakness after treatment (Takayanagui, & Chimelli, 1998). There is a rare form of muscle involvement termed *pseudohypertrophic myopathy* that shows symmetrical enlargement and weakness of involved muscles that especially affects the calves (Crum-Cianflone, 2008).

In addition to detecting the appropriate clinical picture and risk factors, the diagnosis is made on the basis of detection of the calcified cysts, for which computed tomography (CT), MRI, and ultrasound are often used. Biopsy of subcutaneous nodules can also be helpful in establishing the diagnosis. Confirmation of the diagnosis can be made using serologic tests, of which the ELISA is most helpful with CSF samples. The newer enzyme-linked immunoelectrotransfer blot is preferred to ELISA because of its higher sensitivity and specificity, although it may be negative in patients with inactive lesions (Arroyo et al., 2018). Stool sampling for ova and parasites is not very sensitive. Treatment recommendations are based on the number of viable cysts (White et al., 2018). For low burden (one to two viable parenchymal cysts), the current preferred treatment is albendazole, at 15 mg/kg/day in two divided doses up to 1200 mg per day, for 10–14 days with food. With a high burden (more than two viable cysts), combined treatment with albendazole (15 mg/kg/day) and praziquantel (50 mg/kg/day in three divided doses) for 10–14 days is the recommended therapy. Prior to initiation of therapy, all patients should be evaluated to exclude ocular cysticercosis, since inflammation from degenerating cysts can cause loss of vision. Corticosteroids are commonly given concomitantly prior to and during antiparasitic therapy to control inflammatory responses produced by the dying cysts.

Toxoplasmosis is the infection caused by the ingestion of cysts of *Toxoplasma gondii*, in undercooked infected meat (most often pork or lamb), by consuming food items contaminated with sporocysts derived from cat feces, and transplacentally. In immunocompetent persons, the disease is usually asymptomatic or may present with a "mononucleosis-like" illness with fever, cervical adenopathy, myalgias, and malaise (Crum-Cianflone, 2008). A polymyositis-like picture and myocarditis can develop in immunocompetent patients, although most symptomatic infections appear in individuals who are immunosuppressed, such as those with HIV infection or idiopathic CD4 lymphocytopenia. The disease may develop from primary infection or reactivation. Additional features that are sometimes seen are lymphadenopathy, hepatosplenomegaly, pneumonia, uveitis, chorioretinitis, and meningoencephalitis.

When there is muscle involvement, laboratory testing shows increased serum CK and EMG changes consistent with an inflammatory myopathy.

The diagnosis of toxoplasmosis can be made by serologic tests, by PCR, by demonstration of the organism histologically, or by isolation of the organism. The main challenge in the diagnosis is to determine if the infection has occurred recently or in the past. To differentiate between the two possibilities, clinicians most commonly order ELISAs targeting IgM or IgG antibodies (Montoya, 2002). Alternatively, patients may undergo the Sabin-Feldman dye test, which tests for IgG antibodies.

In mild cases, treatment is not indicated because the disease is self-limited. In more severe cases, including those with myositis or who are immunosuppressed, treatment is indicated with a combination of pyrimethamine and sulfadiazine, or trisulfapyrimidines (Rajapakse, Chrishan Shivanthan, Samaranayake, Rodrigo, & Deepika Fernando, 2013). Since pyrimethamine is an antagonist of folic acid, folic acid supplementation should be given during treatment.

GRANULOMATOUS DISEASES OF NERVE AND MUSCLE

SARCOID NEUROPATHY AND MYOPATHY

Sarcoidosis is a systemic disease of unknown etiology that is characterized by granulomatous involvement of many organs, including the central and peripheral nervous system. It is slightly more common in women and is more prevalent in North Americans of African ancestry and northern Europeans than in other groups (Arkema & Cozier, 2018). Neurologic complications are infrequent; prevalence is between 5% and 10% of symptomatic neurologic involvement in patients with known sarcoidosis (Burns, 2003; Tana et al., 2015). The most common neurologic manifestations of sarcoidosis are cranial neuropathies, leptomeningitis, granulomatous lesions in the brain or spinal cord with hypothalamic and pituitary dysfunction, and less commonly myopathy and radiculoneuropathies. Cranial neuropathies are seen in 50% to 80% of patients with neurosarcoidosis; facial nerve palsy is the most common and is present in 23% to 50% of patients (Stern, Krumholz, Johns, Scott, & Nissim, 1985; Voortman, Drent, & Baughman, 2019). Other cranial nerves, such as the optic nerve or the vestibuloauditory nerve, can also be affected.

Neuromuscular manifestations, besides facial neuropathies, are less common. Peripheral nerve involvement, including radiculopathies and radiculoneuropathies, occurs in approximately only 1% of patients with sarcoidosis (Burns, 2003; Hoitsma, Faber, Drent, & Sharma, 2004; Stern et al., 2018.) There is a wide spectrum of presentations of peripheral nerve disease; polyradiculoneuropathies and axonal sensorimotor polyneuropathies are the most common (Burns, Dyck, Aksamit, & Dyck, 2006; Voortman et al., 2019). Other presentations include a vasculitic mononeuritis multiplex, small fiber neuropathy, and a host of demyelinating neuropathies such as multifocal motor neuropathy and GBS. Contrary to sarcoidosis in general, peripheral nervous system sarcoidosis is more common in Caucasians than African-Americans (Tana et al., 2015).

Muscle manifestations, including asymptomatic involvement, are more common than peripheral nerve or radicular symptoms. Asymptomatic muscle sarcoidosis can be seen in up to 50% to 80% of patients with sarcoidosis, although symptomatic muscle involvement is much rarer and usually seen in 1% to 2% of patients with sarcoidosis (Maeshima et al., 2015; Silverstein & Siltzbach, 1968). Symptomatic muscle involvement is further classified as nodular, acute, or chronic myopathy (Silverstein & Siltzbach, 1968).

DIAGNOSIS AND EVALUATION

The diagnosis of neuromuscular sarcoidosis can be a dilemma due to the multitude of manifestations and the fact that they can occur in the absence of systemic sarcoidosis. Typically, the diagnosis will rely on the clinical and radiologic features, laboratory testing with tissue pathology revealing the non-caseating granulomas associated with sarcoidosis, and the absence of an alternative diagnosis.

When neurologic symptoms appear in a patient with biopsy-proven sarcoidosis, the diagnosis can be made with more certainty, but symptoms that are initial manifestations or that develop in patients with inactive sarcoidosis represent a bigger challenge. It is important to be familiar with the potential presentations of neuromuscular sarcoidosis and to consider the possibility when other systemic symptoms and signs are present. The diagnosis is based on the detection of systemic manifestations, the suspicion from known patterns of involvement of the peripheral and CNS, and the detection of involvement in other tissues, preferably with tissue diagnosis.

Sarcoid myopathy usually presents in advanced stages of the disease and can manifest in three different forms: (1) acute myositis, (2) chronic myositis, and (3) nodular myositis (Maeshima et al., 2015; Silverstein & Siltzbach, 1968). The most common form is chronic myositis; acute myositis and nodular myositis are less common and limited to isolated case reports in the literature. The chronic form usually presents in female patients older than 50 years with slowly progressive proximal weakness progressing over months to years (Maeshima et al., 2015). Myalgias appear to be frequent, and the serum CK is usually normal or only mildly increased. The nodular form may show some characteristic findings in MRI of muscle, which may be of value for diagnosis and for selecting a biopsy site (Otake, 1994). Some have suggested that predominant weakness in the gastrocnemius/soleus compared to tibialis anterior may be a useful clinical clue to the diagnosis (Maeshima et al., 2015).

A consensus group developed a set of criteria for the diagnosis of neurosarcoidosis to enhance the ability of clinicians in establishing a proper diagnosis (Stern et al., 2018). The diagnosis is categorized as probable, possible, or definite, based on the clinical and diagnostic findings. The diagnosis of sarcoid neuropathy or myopathy relies on the accurate detection of systemic involvement and pathologic confirmation in affected organs and the exclusion of other alternative diagnoses. Up to 50% of patients who present initially with neurosarcoid have systemic involvement. Evidence of systemic involvement should be sought by performing analysis to detect hypercalcemia, hypercalciuria, elevated immunoglobulins, or elevated serum or CSF levels of angiotensin-converting enzyme, although these tests are not confirmatory. Thoracic (lung, mediastinum) abnormalities are detected in 80% to 90% of patients with neurosarcoidosis, so the guidelines recommend that imaging of the thorax should be performed in all patients. Radiologic tests should include a high-resolution CT scan of the thorax; if this is negative, alternative strategies include a gallium scan or, preferably, a fluorodeoxyglucose positron emission tomography scan. This has been used to identify areas of high yield for tissue diagnosis, including muscle. An evaluation for involvement of the eye, lung, skin, or other organs potentially involved should be performed.

Pathologic evidence of sarcoidosis is usually required for diagnosis. Given the frequency of lung involvement, bronchoscopy, with the various strategies used with this technique to obtain tissue, is an important diagnostic tool and is recommended even with normal CT scans (Voortman et al., 2019). In systemic sarcodiosis, lymph nodes and skin nodules are usually targeted for biopsy.

Sarcoid muscle involvement may be established with a blind or directed muscle biopsy, and this may be abnormal, even in the absence of symptoms. The biopsy reveals

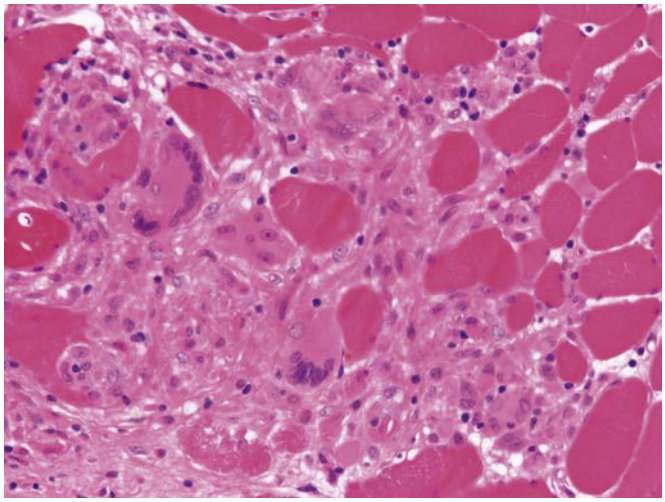


Fig. 16.3 Sarcoidosis in muscle. Granuloma in muscle with lymphocytes, f0020 epithelioid cells, and giant cells (hematoxylin and eosin, "200). (Reprinted with permission from Bertorini, T. E. (2008). *Neuromuscular case studies*. Woburn, MA: Butterworth-Heinemann.)

noncaseating granulomas predominantly in connective tissue and perivascular distribution (Silverstein & Siltzbach, 1968). These are composed of epithelioid cells, lymphocytes, and multinucleated giant cells (Fig. 16.3). Fiber necrosis is unusual or not seen. Because these are focal lesions, serial sections of the muscle biopsy are recommended. Some investigators have reported a predominant CD-4+ lymphocytic infiltration (Maeshima et al., 2015; Said et al., 2002) and diffuse staining of the sarcolemma for human leukocyte antigens-ABC (HLA-ABC), human leukocyte antigen-DR isotype (HLA-DR), and intercellular adhesion molecule 1 (ICAM-1) (Maeshima et al., 2015). More recently, some patients with overlapping features for both sarcoid myopathy and sporadic inclusion body myositis have been reported, raising the possibility of a possible connection between the two conditions and the need to differentiate between these possibilities (Alhammad & Liewluck, 2019; Dieudonné et al., 2020). Similarly, nerve biopsy can demonstrate noncaseating granulomas in the endoneurium, perineurium, or epineurium and may also show concurrent necrotizing vasculitis (Burns et al., 2006; Said et al., 2002). Skin biopsy and intraepidermal nerve fiber density may also represent an important tool in providing evidence of small fiber involvement in some cases (Bakkers et al., 2009).

There are no specific findings in NCS and EMG for neuromuscular sarcoidosis, although this is still helpful in documenting peripheral nervous system involvement. In at least one study, NCSs have shown findings consistent with a predominant proximal, multifocal process; axonal changes are more common than demyelinating changes (Burns et al., 2006). In some cases, multifocal motor conduction block has been observed in NCSs (Kono et al., 2013; Said et al., 2002). Needle EMG examination may be normal because the abnormalities are predominantly in the intervening connective tissue, or they may show myopathic changes in clinically symptomatic myopathy (Maeshima et al., 2015).

TREATMENT AND MANAGEMENT

Because neuromuscular disease in sarcoidosis is rare, there are no randomized controlled clinical trials for the treatment of these complications, and management is based on anecdotal reports or small series of cases, and experience from more general neurosarcoidosis guides the treatment. The goals of treatment are to prevent the fibrosis that may follow the chronic inflammation or the extension and progression of vascular damage when vasculitis is present. The selection of an agent will be based on the specific manifestation and the contraindications for each particular patient. Steroids are considered the first-line of treatment. Prednisone in doses of 0.5 to 1.0 mg/kg (40–60 mg/day) is usually used and has proved effective. The length of treatment varies with the severity of manifestations; a 2-week course followed by a tapering dose schedule is sufficient for a facial neuropathy, but courses of 4 weeks or longer, followed by a slow tapering course, are required for more extensive neuropathy or myopathy. As is the case in any patient being treated with steroids, evaluation for subclinical tuberculosis with purified protein derivative (PPD), or more importantly a chest radiograph, is mandatory prior to initiating therapy, as PPD could be negative even in infected cases. Prevention of osteoporosis with the use of calcium and vitamin D supplementation, or bisphosphonates in high-risk patients, should be instituted. Routine evaluations for hypertension, hyperglycemia, and cataract formation are an important part in the detection and management of side effects. In patients with refractory or relapsing disease, other immunosuppressive agents that serve as second line of treatment are methotrexate (10–25 mg once a week with folate supplementation), azathioprine (2 mg/kg), and mycophenolate mofetil (2 g per day) (Fritz, van de Beek, & Brouwer, 2016; Tana et al., 2015; Voortman et al., 2019). Hydroxychloroquine and leflunomide have been used for long-term immunomodulation in neurosarcoidosis but are not a good choice in neuromuscular sarcoidosis because they may be associated with myopathy and/or neuropathy. A new and alternative approach for patients who are steroid intolerant or unresponsive has been the use of anti–tumor necrosis factor (TNF)-α therapy. Among the various alternatives, infliximab, a chimeric monoclonal antibody against TNF-α, has been used successfully in several patients with neurosarcoidosis, including sarcoid myopathy, and is considered the main third-line option. It is typically given as an IV bolus at a dose of 3–5 mg/kg at 0, 2, and 6 weeks and then monthly for a target duration of 6 months. It can be associated with leukopenia and peripheral neuropathy, so caution and close monitoring should be performed in all patients. Because up to two thirds of patients with sarcoidosis go into spontaneous remission, it is sometimes arguable that all patients should be treated. Steroids have shown to be effective in peripheral neuropathy cases, but improvement is usually delayed and neuropathic symptoms may linger for a long time after treatment. In a large cohort of sarcoid-associated small-fiber neuropathy, patients showed symptomatic improvement with IV gamma globulin (IVIg) at a standard dose of 2 gm/kg over 5 days or infliximab using the conventional loading schedule and followed by doses of 5 mg/kg every 4 to 6 weeks (Tavee et al., 2017). For vasculitic neuropathy, corticosteroids and cytotoxic drugs have been the principal approaches for treatment.

TOXIC NEUROPATHIES AND MYOPATHIES

The expanded availability and use of medications, often in combination, have resulted in the detection of

neuromuscular toxicities that were not seen during the initial trials in a small selected population, usually without coexistent diseases. Muscle and nerve toxicities are among the more prevalent toxicities seen with many of the commonly used medications, in part because the symptoms and signs are readily recognizable. Toxicity from industrial agents has declined in some countries due to the implementation of more effective surveillance and security programs; however, this is still an important source of neurotoxicity in developing countries. What follows is a discussion of the main issues associated with muscle and nerve toxicity from some industrial toxins and medications.

TOXIC NEUROPATHIES

Although medication-induced and other toxic neuropathies represent only a minority (about 4%) of all cases of neuropathy, it is critical to identify them because they are potentially reversible and may be the only sign of a previously unidentified toxic exposure that can be eliminated. Reports of possible associations between medications or toxins and the development of neuropathy are abundant, but objective evidence to establish causation is lacking in many of these reports. It is important to understand that exposure does not equal causation. Establishing the link between exposure and the presence of a polyneuropathy is a difficult task that requires the clinician to be familiar with medications with potential for neurotoxicity and with the systemic manifestations of industrial agents or other toxins that are known to cause neuromuscular toxicity. Clinicians should also be aware that patients with coexistent peripheral neuropathies, such as diabetic, alcoholic, or inherited neuropathies, are more susceptible to toxic insults and may develop earlier and more severe neuropathy.

The following discussion concentrates on the diagnosis and management of the most important of these agents where the evidence is clear and on a few newer agents that are highly suspect, based on published reports.

Arsenic. Arsenic is a ubiquitous metal that occurs naturally, with unintentional chronic exposure resulting from the ingestion of contaminated ground water, from exposure in the metal smelting industry, pesticide manufacturing, burning of treated wood, and in non-Western traditional remedies, among others (Naujokas et al., 2013). It has also been used as a poison in suicide or homicide cases. It interferes with cellular energy metabolism and disrupts protein and enzyme activity.

The clinical presentation can vary depending on whether there is acute exposure of large amounts of arsenic or chronic low-grade exposure. In acute arsenic poisoning, patients often present initially with gastrointestinal symptoms, followed by cardiac conduction abnormalities (QTc prolongation) and encephalopathy, renal failure, and later by ascending paralysis, with a picture similar to that for GBS (Donofrio et al., 1987). This later complication may develop days to weeks after acute exposure and is often associated with a protracted and incomplete recovery. The electrodiagnostic examination initially may show features consistent with segmental demyelination later followed by a distal, dying back, predominantly axonal polyneuropathy. In chronic arsenic poisoning, the systemic manifestations are more prominent. Patients present with a gradually progressive sensorimotor polyneuropathy (Ishii, Mochizuki, Ebihara, Shiomi, & Nakazato, 2018), skin changes (palmar and plantar hyperpigmentation and hyperkeratosis), alopecia, and Mees lines. *Mees lines* are transverse lines that appear in the fingernails and toenails, although they are not specific for arsenic poisoning and may take 30 days to appear. Other clinical features are cardiomyopathy, anorexia, weight loss, bone marrow suppression, hepatomegaly, acute tubular necrosis, and encephalopathy (Ibrahim, Froberg, Wolf, & Rusyniak, 2006; London & Albers, 2007). Arsenicosis (chronic, lower-level environmental arsenic toxicity) can present obstructive pulmonary disease, bronchiectasis, distal edema, and portal hypertension.

DIAGNOSIS AND EVALUATION

The diagnosis of arsenic poisoning is made from the combinations of clinical features and the determination of potential risk factors for exposure from a thorough history and investigation. In patients in whom arsenic poisoning is suspected, urinary arsenic excretion from a 24-hour urine collection is the most specific test. Blood arsenic levels are not used because levels can drop within 2 to 4 hours after ingestion. Care must be taken to differentiate inorganic arsenic, which is the neurotoxic form, from organic arsenic, which is present in seafood and is not toxic. Patients should avoid eating seafood for at least 4 days prior to the test. Fractionation is always important to determine if elevated arsenic is organic or inorganic. Evidence of multiorgan toxicity is assessed by performing a complete blood count with smear and a comprehensive metabolic panel. Abnormalities observed include pancytopenia, basophilic stippling, elevated hepatic enzymes, and renal insufficiency (Ibrahim et al., 2006; Vahidnia, van der Voet, & de Wolff, 2007). NCS can be helpful in establishing the pattern of neuropathy. In the acute form with massive exposure, as previously mentioned, there could be a demyelinating polyneuropathy. In the chronic form, NCSs show evidence of a distal axonal sensorimotor polyneuropathy (Ishii et al., 2018). Chronic exposure can also be diagnosed from hair, nail, and skin samples.

TREATMENT AND MANAGEMENT

Treatment of arsenic toxicity starts with the elimination of the exposure and incorporates chelation and supportive measures for acute exposure. In the patient at high risk for chronic exposure, periodic urinary arsenic levels are performed to monitor for toxicity. Normal urine arsenic levels (inorganic) for a 24-hour urine are less than 50 μg/L. Chelation is indicated in patients with severe symptoms after acute ingestion and elevated in inorganic urinary arsenic levels (Kosnett, 2010, 2013). Chelation does not improve the recovery or progression of neuropathy unless given within hours of exposure. In the presence of acute neuropathy, the agents commonly used are dimercaprol (dimercaptopropanesulfonic acid), penicillamine (Ibrahim et al., 2006; Kosnett, 2013; Vahidnia et al., 2007), and succimer (dimercaptosuccinic acid [DMSA]), which, although not approved for use in arsenic poisoning, appears less toxic than the others when used for lead poisoning. Patients may experience substantial or complete neurologic recovery over months to several years depending on degree of denervation, age and underlying conditions.

Thallium

Thallium is another heavy metal used in the manufacture of lenses, semiconductors, insecticides, and rodenticides. The salts are tasteless, odorless, water soluble, and completely absorbed from the gastrointestinal tract, explaining their use as rodenticides and in intentional poisoning.

DIAGNOSIS AND EVALUATION

Clinical manifestations depend on the dose, the age of the person exposed, and whether exposure is acute or chronic. The distinctive features are a rapidly developing polyneuropathy in the context of alopecia. The neuropathy is dominated by sensory symptoms with painful dysesthesias and paresthesias that occur within a week of exposure. Alopecia and Mees lines can also be observed and are features that occur later in the course. However, they are not helpful in the diagnosis of acute poisoning. It is important to know that not all patients with thallium poisoning develop alopecia and neuropathy. Early in the course, and with mild intoxication, small fiber involvement predominates, with both painful dysesthesias and dysautonomic features. Autonomic dysfunction such as nausea, urinary retention, anhidrosis, and diarrhea may precede the onset of neuropathy. Although sensory symptoms predominate in most cases, motor manifestations can also occur (Zhao et al., 2008).

The diagnosis of thallium poisoning can be difficult given the rarity of the exposure and the nonspecific symptoms in the early stages. Hair analysis may provide early evidence of exposure. Darkening of the hair roots when examined under a microscope has been described as an early diagnostic feature (Ibrahim et al., 2006; Zhao et al., 2008). NCSs might show evidence of a sensory axonal polyneuropathy, although if small fiber involvement predominates, the studies early in the disease may be normal in spite of symptoms. The gold standard for diagnosis is the 24-hour urine collection.

TREATMENT AND MANAGEMENT

The goal of treatment and management is to stop exposure and to increase elimination. Prussian blue (potassium hexacyanoferrate) is the most effective treatment at present, forming a complex with thallium and increasing its fecal excretion. The recommended dose is 3 g orally three times per day, although others advocate 250 mg/kg divided into two doses per day (Ibrahim et al., 2006; Zhao et al., 2008). Simultaneous hemodialysis and charcoal hemoperfusion have been recommended simultaneous with Prussian blue if the ingestion occurred within the previous 24 hours.

Lead

The other prototype for heavy metal–induced neuromuscular toxicity can be absorbed through the gastrointestinal tract or inhaled and absorbed through the lungs. It is toxic in both its organic and inorganic forms. In children, it is more commonly associated with an encephalopathy, but in adults, toxic exposure is more commonly associated with a peripheral neuropathy and less commonly with features of an encephalopathy. In adults, toxic exposure has been most commonly described through occupational exposure. Among those at risk for exposure are workers in lead acid battery manufacturing plants, metal ore smelters, individuals who work in the manufacture of glazed pottery and ceramics, those working with solders, and through consumption of bootleg liquor and some folk remedies.

DIAGNOSIS AND EVALUATION

The clinical presentation of lead neuropathy in adults depends on whether there is acute exposure at high levels or chronic low-level exposure. With acute or subacute high-level exposure, patients present with an asymmetrical, predominantly motor neuropathy affecting the upper limbs more than the lower limbs with bilateral wrist drop as a typical feature (Thomson & Parry, 2006). Sensory abnormalities in this presentation are usually not present. The neuropathy is often accompanied by systemic symptoms and signs such as abdominal pain, constipation, anemia, and gingival lead lines. Nephropathy and gout can also be observed. With chronic low-level exposure, it is more common to observe a distal sensorimotor polyneuropathy (Rubens, Logina, Kravale, Eglite, & Donaghy, 2001; Thomson & Parry, 2006). Hypertension is a common clinical sign observed in workers with chronic low-level exposure. Although in animal models, the neuropathy is demyelinating, in humans, the peripheral neuropathy is more of the axonal type.

For the diagnosis of lead-associated neuropathy, it is necessary to establish exposure corresponding to the development and progression of neuropathy and to document an abnormal content of lead in fluid or tissues. The best current screening test is venous blood lead levels. Recommendations for periodic testing in workers at risk for chronic lead exposure have been published (Kosnett et al., 2007). Minor abnormalities in NCSs have been seen with lead levels of 50 μg/dL or above, but clinically apparent neuropathy is usually not seen in individuals with levels below 80 μg/dL (Windebank, 2005). The electrodiagnostic findings are still debated; most studies show mild slowing of motor conduction velocities on a group basis (exposed vs. nonexposed), but many individual values fall within the range of normal.

TREATMENT AND MANAGEMENT

Chelation therapy is usually given to adult patients who are symptomatic or have blood levels above 70 μg/dL. There is still some controversy about the optimal treatment for lead intoxication. One recommendation is to use oral succimer (DMSA) for patients with blood lead levels between 70 and 100 μg/dL. Patients with encephalopathy or levels greater than 100 μg/dL can be treated with intramuscular dimercaprol or oral succimer, followed by IV calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) (Ibrahim et al., 2006). Typically, after chelation therapy, a period of reequilibration of 10 to 14 days is allowed and blood lead concentrations are then remeasured, to account for remobilization from bone stores.

Hexacarbon Neuropathy

Peripheral neuropathy has been associated with exposure to *n*-hexane and methyl-*n*-butyl ketone. These are hexacarbons present in industrial solvents, glues, spray paints, coatings, and silicones and associated with neurotoxicity in workers in printing plants, shoe factories, and furniture factories in the United States, Europe, and Asia. Exposure in automotive technicians has also been reported (CDC, 2001). Both *n*-hexane and methyl-*n*-butyl ketone are absorbed across respiratory membranes and skin and are metabolized in the

liver to 2,5-hexanedione, which is the neurotoxic metabolite (London & Albers, 2007). In more recent times, exposure and neurotoxicity have been associated with intentional inhalation of glue by "glue sniffers" (Chaqda, El Mellakh, Kissani, & Louhab, 2019; Smith & Albers, 1997).

n-Hexane exposure results in a peripheral neuropathy with distal sensory loss, atrophy, diminished or absent deep tendon reflexes, and autonomic dysfunction. With massive acute exposure, patients can present with CNS depression, narcosis, and a clinical picture mimicking GBS, similar to acute arsenic intoxication (Smith & Albers, 1997). In these instances, motor NCSs can show partial conduction block and conduction velocities in the demyelinating range (Kuwabara, Nakajima, Tsuboi, & Hirayama, 1993; Pastore et al., 2002). With chronic exposure, the more typical dying-back distal axonal sensorimotor neuropathy is usually observed (Wang, Chen, & Wang, 2014). Concomitant degeneration of the distal corticospinal tracts and dorsal column can occur with chronic exposure and result in the presence of spasticity or signs of CNS involvement (central-peripheral-distal axonopathy). Impairment of color vision can also be observed with chronic exposure. The histopathologic hallmark is the presence of multifocal, giant axonal swellings in distal axons, secondary to abnormalities in axonal transport. Diagnosis is made based on the presence of exposure and evidence of neuropathy, with clinical findings of neuropathy and findings in NCS. Electrodiagnostic studies can show evidence of peripheral demyelination with motor conduction slowing and occasionally partial conduction block with coexistent axonal degeneration (Kuwabara et al., 1993; Pastore et al., 2002). Urinary levels of 2,5-hexanedione (the common neurotoxic metabolite) can confirm current exposure (CDC, 2001; Pastore, Marhuenda, Marti, & Cardona, 1994).

Treatment consists mainly of cessation of exposure. As in other toxic neuropathies, there can be transient worsening and progression weeks after exposure is stopped (coasting). The prognosis for recovery after cessation of exposure in chronic industrial exposure is usually favorable, but patients with massive exposure, such as glue sniffers, may have residual spasticity and weakness.

Alcoholic Neuropathy

Chronic alcoholism has been associated to both peripheral neuropathy and myopathy. The neuropathy is often asymptomatic, with a prevalence that has ranged from 12.5% to 46.3% of alcoholics, depending on the detection methods and criteria for neuropathy (Julian, Glascow, Syeed, & Zis, 2019; Vittadini et al., 2001). The etiology of neuropathy in alcoholics is most likely multifactorial, combining both toxic effects from alcohol and nutritional deficiencies. Although in the past there has been debate as to whether alcohol or thiamine deficiency is the cause of the observed neuropathy, recent data have shown that alcohol itself, in the absence of thiamine deficiency, can result in a painful small-fiber distal polyneuropathy (Koike et al., 2003).

DIAGNOSIS AND EVALUATION

The diagnosis is based on establishing the presence of neuropathy and chronic alcohol abuse. Unhealthy drinking is defined as more than three or four drinks per day or more than 10 g of alcohol per day. The clinical features of alcohol-associated polyneuropathy are variable and many patients are asymptomatic, so a careful assessment is of utmost importance. Symptoms are primarily sensory, and clinical presentations can range from a slowly progressive, predominantly sensory small-fiber distal polyneuropathy with painful dysesthesias to, most commonly, a mixed pattern with involvement of both large and small fibers (Julian et al., 2019; Koike & Sobue, 2006; Zambelis, Karandreas, Tzavellas, Kokotis, & Liappas, 2005). Autonomic neuropathy may also be present with orthostatic hypotension and erectile dysfunction and may be related to increased mortality rate. NCSs may be normal if only small fibers are involved, although more typically they show a pattern of loss of sensory axons with abnormal sural sensory action potentials and conduction velocity as the most sensitive markers (Julian et al., 2019; Zambelis et al., 2005).

TREATMENT AND MANAGEMENT

Stopping alcohol consumption is the primary treatment for alcoholic polyneuropathy; some studies demonstrate recovery for mild to moderate alcoholic neuropathy after 4 to 5 years of abstinence. Based on the possibility of a nutritional component, a few studies have investigated the effect of vitamin supplementation for the treatment of alcoholic polyneuropathy. Short-term controlled studies have shown a beneficial effect from benfotiamine, a thiamine derivative with high bioavailability, with improvement in symptoms and sensory and motor measures (Woelk, Lehrl, Bitsch, & Kopcke, 1998). In addition, some formulations with multiple B vitamins have also shown some efficacy in controlled studies (Peters et al., 2006).

MEDICATION-INDUCED NEUROPATHIES

Numerous medications have been associated with the development of neuropathy, although definite proof is lacking in many, and there is still controversy about causation or simple association (Table 16.4). Because sensory neurons and axons are more sensitive to toxic effects, the most common pattern of medication-induced neuropathy is a distal, symmetrical, length-dependent sensory polyneuropathy. Although less common, some drugs can preferentially affect dorsal root ganglion (DRG) neurons or Schwann cells, resulting in sensory neuronopathies or demyelinating neuropathies. More recently, vasculitic neuropathies have also been reported with some immunomodulating agents, enlarging the spectrum of possible toxic mechanisms and clinical presentations of medication-induced neuropathy.

What follows is a brief discussion of some of the more commonly used drugs and relevant drug-induced neuropathies that may be encountered by a neurologist or neuromuscular specialist.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Since the basic principle of chemotherapy implies a process of controlled cytotoxicity, it is common for other nonmalignant cells, such as central or peripheral neurons, to be affected as innocent bystanders. Clinicians should be aware that susceptibility to the various agents can vary considerably, resulting in different temporal patterns and severity of toxicity in different patients. Chemotherapeutic agents that result in neuropathy typically interfere with DNA replication

Table 16.4 Pharmacologic Toxins

Drug	Indication	Clinical Manifestation	Mechanism	Diagnostic Tests	Treatment
Antineoplastic drugs					
Paclitaxel/ docetaxel	Solid tumors of lung, breast, head, and neck	Dose-dependent sensory > motor neuropathy; significant motor manifestations in severe cases	Polymerization of microtubules may interfere with axonal transport; also direct toxic effects on the axon	Sensory/motor axonal neuropathy on EMG; Wallerian-like degeneration on nerve biopsy	Reduction of dose Duloxetine 60 mg if painful
Vincristine/vinblastine	Lymphoma/leukemia, some solid tumors	Dose-dependent sensorimotor and autonomic neuropathy; painful paresthesias in hands and feet	Interference with microtubule assembly presumably disrupts axonal transport	Sensory/motor axonal neuropathy on EMG; Wallerian-like degeneration on nerve biopsy	Reduction of dose
Cisplatin	Small cell lung cancer, urogenital cancers	Sensory neuropathy/ neuronopathy (sensory ataxia, areflexia, pain); may not show typical length dependence	Binds to nuclear and mitochondrial DNA	Loss of sensory potentials on NCV studies; loss of large myelinated fibers on sural nerve biopsy	Reduction of dose Duloxetine 60 mg if painful
Oxaliplatin	Colorectal cancer	Acute paresthesias and cold-induced cramping within hours of dose; chronic length-dependent polyneuropathy	Unknown; suspected acute symptoms are due to peripheral nerve hyperexcitability resulting from sodium channel opening	Electrodiagnostic studies show peripheral nerve afterdischarges and neuromyotonia	Reduction of dose; membrane stabilizing drugs (anticonvulsants)
Epothilones ixabepilone/ sagopilone	Metastatic breast cancer/ovarian cancer	Sensory neuropathy	Microtubule polymerization	Reduced or absent sensory potentials on NCV	Dose reduction or discontinuation Duloxetine 60 mg if painful
Immune checkpoint inhibitors	Solid tumors/ hematologic malignancies	Facial nerve paralysis, mononeuropathy multiplex, inflammatory polyradiculoneuropathy, myasthenia gravis, myositis	Disruption of self-tolerance and immunosurveillance	Non-length-dependent axonal or demyelinating polyradiculoneuropathy, sensory neuronopathy, mononeuropathy multiplex	Immunosuppression corticosteroids and/ or IVIg
Bortexomib	Multiple myeloma	Painful, axonal, small-fiber distal polyneuropathy Immune-mediated demyelinating neuropathy	Aggresome formation, microtubule polymerization, mitochondrial transport	Predominantly sensory of mixed sensory and motor axonal polyneuropathy	Reduction of dose; subcutaneous administration
Amphiphilic cationic drugs					
Amiodarone	Ventricular arrhythmias	Sensory/motor neuropathy with areflexia and ataxia; not necessarily dose related	Formation of drug-lipid complexes that are lysosome resistant and toxic	Demyelinating changes on NCV; nerve biopsy shows osmophilic granules in Schwann, endothelial, and perineurial cells	Cessation of drug

Table 16.4 Pharmacologic Toxins—cont'd

Drug	Indication	Clinical Manifestation	Mechanism	Diagnostic Tests	Treatment
Chloroquine	Malaria (prophylaxis and treatment), connective tissue diseases	Neuromyopathy; may be motor predominant with significant weakness before sensory manifestations	Formation of drug-lipid complexes that are lysosome resistant and toxic	Vacuolar myopathy; osmophilic inclusions in Schwann, endothelial, and perineurial cells	Cessation of drug
Perhexiline	Angina pectoris (not used in the United States)	Sensory/motor polyneuropathy with areflexia and autonomic features	Formation of drug-lipid complexes that are lysosome resistant and toxic	Osmophilic inclusions in Schwann, endothelial, and perineurial cells	Cessation of drug

DRG, Dorsal root ganglion; *EMG*, electromyography; *IVIg*, intravenous immunoglobulin G; *NCV*, nerve conduction velocity.
Modified from Glass, J. (2006). Toxic neuropathy. In R. Johnson, J. Griffin, & J. McArthur (Eds.), *Current therapy in neurologic disease* (7th ed). Philadelphia: Mosby.

or with microtubule function or assembly. Similar to other toxic neuropathies, many patients exhibit the "coasting" phenomenon, with worsening of symptoms and signs even after completion of the chemotherapy course. Although a mild neuropathy may be the price to pay for effective cure of a malignancy, the impact on quality of life should not be underestimated, and prompt attention and intervention, if necessary, are warranted. Preexisting neuropathy such as diabetic or inherited neuropathy can increase the risk and result in a more severe grade of chemotherapy-induced neuropathy. Additionally, the possibility of a paraneoplastic neuropathy independent of the chemotherapy neurotoxicity should be an important consideration in patients undergoing treatment. The main groups of agents that result in chemotherapy-induced peripheral neuropathy include platinum-based antineoplastic agents, vinca alkaloids, epothilones (ixabepilone), taxanes, proteasome inhibitors (bortezomib), and immune checkpoint inhibitors (ICIs).

Plant alkaloids such as taxanes, vinca alkaloids, and podophyllotoxins inhibit mitosis by interfering with microtubule synthesis and function, resulting in disruption of axonal transport. Vincristine is the vinca alkaloid most commonly associated with neuropathy (Islam et al., 2019). In the early stages, small-fiber sensory impairment and dysfunction predominate with distal painful dysesthesias and sensory loss. Autonomic dysfunction also can occur early with constipation, orthostatic hypotension, and impotence. With more severe neuropathy, patients can develop motor weakness, preferentially affecting extensor muscles in the upper and lower extremities. Although the neuropathy usually improves after exposure stops, recovery may be slow and residual symptoms may last indefinitely (Islam et al., 2019; Staff, Grisold, Grisold, & Windebank, 2017). One important aspect of the use of vincristine is increased susceptibility and more severe neurotoxicity in patients with an inherited neuropathy of the Charcot-Marie-Tooth type, or hereditary susceptibility to pressure palsies. Most reported cases, undiagnosed at the time of treatment, developed a severe neuropathy after only one or two doses of vincristine (Weimer & Podwall, 2006).

Platinum-based agents such as cisplatinum, carboplatinum, and oxaliplatinum interfere with DNA replication and exert their neurotoxic effect in the DRG neurons. These agents may result in distal axonal dysfunction in the early stages or with lesser degrees of toxicity and progression to a neuronopathy with continued exposure and more severe toxicity. Unfortunately, the severity of the neurotoxicity may not be apparent until late in the course of treatment or after it is finished, precluding more effective interventions. Cisplatinum exhibits more neurotoxicity than carboplatinum, although the clinical picture is similar. Patients complain of paresthesias and dysesthesias in the toes and feet, with proximal spread on accumulating exposure. Loss of DRG neurons can result in a clinical picture of sensory neuronopathy with severely impaired proprioception and sensory ataxia. It can also produce dose-related moderate or severe hearing loss. Oxaliplatinum results in unusual cold-induced paresthesias or dysesthesias and evidence of hyperexcitability with muscle contractions resembling neuromyotonia. This may be the result of a voltage-gated channelopathy provoked by the drug (Staff et al., 2017, 2020). Platinum-based compounds are the ones most commonly associated with worsening after discontinuation of therapy, or "coasting" phenomenon, and they may also, albeit rarely, be associated with the development of GBS (Pappa et al., 2020; Staff et al., 2017).

The other group of antineoplastic agents that are commonly associated with peripheral neuropathy are the taxanes paclitaxel and docetaxel. These are used in the treatment of solid tumors and target the microtubullar system but, unlike the vinca alkaloids, not by inhibiting formation but by inhibiting disassembly and promoting polymerization. The neuropathy is dose dependent (cumulative and individual cycle) and usually begins soon after treatment is initiated. Clinical symptoms are paresthesias and dysesthesias, most often with onset in the feet but possibly in hands and accompanied by perioral and tongue numbness. Toxicity is cumulative, and weakness will develop with continued exposure. Patients can also develop an acute pain syndrome characterized by aching musculoskeletal pain that may correlate with the development of neuropathy (Staff et al., 2017; Tamburin et al., 2019). Again, with more severe toxicity, symptoms and signs may persist after discontinuing exposure and may worsen after discontinuing therapy (coasting).

Electrophysiologic studies usually show findings consistent with a symmetrical, length-dependent, axonal sensorimotor polyneuropathy (Argyriou et al., 2019). A new class of medications, the epothilones, that also interfere with microtubules are eribulin, ixabepilone, and sagopilone, all of which cause a sensory or sensorimotor peripheral neuropathy similar to the taxanes (Argyriou, Kyritsis, Makatsoris, & Kalofonos, 2014; Staff et al., 2017; Tamburin et al., 2019). The neuropathy is also dose dependent and tends to improve after discontinuation of the treatment.

Bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma, has shown preferential toxicity of small fibers, producing a painful, axonal small-fiber distal polyneuropathy in up to 30% to 60% of patients treated (Velasco, Alberti, Bruna, Psimaras, & Argyriou, 2019). Hypotensive episodes and paralytic ileus have also been reported. In patients with more severe toxicity, a demyelinating neuropathy has also been observed (Ravaglia et al., 2008; Saifee et al., 2010). In the majority of patients, symptoms resolve after stopping the medication or by modifying the dose, schedule, or mode of administration. Subcutaneous administration has a lower risk for neurotoxicity and can be an option in patients with preexisting neuropathy. Laboratory assessment is aimed at excluding alternative or coexistent conditions associated with neuropathy and establishing the severity of the neuropathy. It usually includes standard laboratory tests for acquired neuropathies and EMG/NCS.

The ICIs are a new class of medications used in certain types of solid tumors and hematologic malignancies that work through modulation of the immune system. The class is composed of several different monoclonal antibodies, pembrolizumab, ipilimubab, nivolumab, cemiplimab, atezolizumab, durvalumab, and avelumab, that act at different checkpoints of the immune response and by their nature cause an autoimmune response against the malignancies. They can also result in unintended immune-related adverse events, many of which affect the peripheral nervous system. Numerous case reports and some case series have reported facial nerve palsies, inflammatory polyradiculoneuropathy, mononeuritis multiplex, myasthenia gravis, and myositis (Dubey et al., 2019, 2020).

TREATMENT AND MANAGEMENT

The approaches commonly used in the treatment and management of chemotherapy-induced neuropathy can be summarized as (1) prevention and neuroprotection, (2) reduction or elimination of exposure if possible, (3) pain management, and (4) supportive treatment with physical and occupational therapy.

In the absence of proven or established preventive or restorative therapies, supportive and symptomatic treatments are the mainstays of management at the present time. Several neuroprotective agents have been investigated in an effort to prevent or minimize neurotoxicity without affecting the antineoplastic effect (Ibrahim & Ehrlich, 2020). Although preliminary results for some of these neuroprotective agents have been promising, none are recommended until more rigorous controlled studies are performed. Among the various agents, glutathione, vitamin E, and glutamine have all been explored, with mixed results. Acetyl-L-carnitine (ALC) is no longer recommended as it may worsen taxane-related neuropathy (Hershman et al., 2018). There are data suggesting that exercise can reduce the frequency of chemotherapy-associated neuropathy. With oxaliplatin, interspersing non-oxaliplatin regimens as maintenance therapy may reduce the incidence or severity of neuropathy. With bortezomib, the use of weekly, as opposed to twice weekly, regimens and subcutaneous, as opposed to IV, administration have been associated with less neurotoxicity.

Once symptoms are present and because neurotoxicity occurs in a dose-dependent manner and is cumulative, one of the most challenging issues is to decide whether to discontinue or reduce the dose of treatment at the expense of impaired efficacy or unsuccessful cure. Some investigators have suggested that at the moment a fixed deficit is detected, exposure should be stopped. This should be carefully assessed in discussion with the oncologist and determined on an individual basis.

Pain management in chemotherapy-induced neuropathy has proved more challenging than in other painful neuropathies. Several anticonvulsants and antidepressants used in painful neuropathies, including amitriptyline, have not shown to be effective. In patients with painful dysesthesias, duloxetine, with a slow increase in dose from 30 mg daily for 2 weeks and increased to 60 mg daily, has shown to be effective and is recommended by the American Society of Clinical Oncology (Hershman et al., 2014). One percent topical menthol has also been shown to ameliorate painful neuropathy symptoms.

Tumor Necrosis Factor-α Antagonists

Some of the immunotherapies that have been recently developed and are currently in use for the treatment of autoimmune diseases have been associated with conflicting reports of improvement or development of peripheral neuropathy. TNF-α antagonists are increasingly in use for the treatment of rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease but have also been associated with development or worsening of other autoimmune diseases. There are reports of a wide variety of peripheral neuropathies associated with the use of TNF-α antagonists (infliximab, etanercept, adalimumab), including GBS, Miller-Fisher syndrome, CIDP, multifocal motor neuropathy with conduction block, vasculitic neuropathy, sensorimotor axonal polyneuropathy, and pure sensory neuropathy, during or after finishing treatment (Stubgen, 2008; Tsouni et al., 2015). The proposed mechanisms are through both T-cell-mediated or antibody-mediated mechanisms or inhibition of axonal functions. Proper management of the neuropathy is not clear. Most patients have responded to standard immunotherapies or only by withdrawal of the medication, although this may take months. A long-term follow-up study has shown that some patients have remained stable with dose reduction only, implying that stopping the medication may not always be necessary for neuropathy control (Lozeron, Denier, Lacroix, & Adams, 2009).

Antiretroviral Agents

Among the antiretroviral agents used in the treatment of HIV infection, the ones most commonly associated with neuropathy during the pre-HAART era were the nucleoside analogs zalcitabine (ddC), didanosine (ddI), and stavudine (d4T) (Youle, 2005). More recently, some studies have suggested that the use of protease inhibitors, such as indinavir,

saquinavir, and ritonavir, may be risk factors potentially associated with the development of neuropathy (Pettersen et al., 2006), although this is still controversial (Ellis et al., 2008). Neurotoxicity is thought to be mainly through mitochondrial toxicity, given the antiretroviral agents' ability to inhibit mitochondrial polymerase gamma among other mitochondrial disruptive effects. As previously mentioned, it is not possible to distinguish ATN from HIV-associated neuropathy on clinical grounds only. The most important clue is the development of neuropathy within a short time, usually weeks to 6 months after the start of medication or an increase in dose. Some investigators have suggested that lactic acid levels may serve as a differentiating marker, but this has not been validated. As with other toxic neuropathies, treatment of ATN is based on discontinuation of the offending agent, which has become more feasible given the expanded options for treatment. Several groups have studied the use of ALC in doses that have ranged from 500 mg to 3 g/day, based on the hypothesis of mitochondrial toxicity. From the published results, it appears that ALC may improve the painful neuropathic symptoms, although it is not clear that, in the time frame studied, it resulted in regeneration or prevention of axonal loss (Youle, 2007).

Lamotrigine was shown in one controlled study to be effective for ATN at target doses of 200 mg twice a day (400 mg/day) to 600 mg/day in those receiving enzyme-inducing drugs (Simpson et al., 2003). Lamotrigine was not effective as an adjunct treatment in patients who did not respond to gabapentin, tricyclics, or opioids (Silver, Blum, Grainger, Hammer, & Quessy, 2007). The principal limitation is that it has to be started at a low dose (25 mg) and increased slowly over a period of 4 weeks to reduce the risk of skin rash.

TOXIC AND MEDICATION-INDUCED MYOPATHIES

Statin-Associated Myopathy

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have become the standard of care in treating hypercholesterolemia and are one of the most widely prescribed medications. Because hypercholesterolemia is a chronic condition, long-term use of these medications is often required. Myalgias and myotoxicity are among the most important treatment-limiting adverse effects, although other side effects such as increased frequency of type 2 diabetes, hemorrhagic stroke, and hepatoxicity have also been observed (Ward, Watts, & Eckel, 2019).

There is considerable debate about the classification of the various degrees or types of myotoxicity associated with statin use. An international expert group has attempted to establish a myotoxicity phenotype classification, expanding existing nomenclature from The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute. This classification has defined seven myopathic phenotypes related to the statins: CK elevation, myalgia tolerable, myalgia intolerable, myopathy, severe myopathy, rhabdomyolysis, and autoimmune-mediated necrotizing myositis (Alfirevic et al., 2014; Grundy & Stone, 2019; Stone et al., 2014). However, it is reasonable to state that there are four principal clinical syndromes: myalgia with or without mild hyperCKemia, self-limited toxic statin myopathy, rhabdomyolysis, and immune-mediated necrotizing myositis. Myalgias are defined as muscle aches with or without elevation of CK levels. Myalgias most often involve the thighs and the calves, but they could also be generalized. The CK elevation is usually <4 the ULN. Statin myopathy is characterized by diffuse muscle pain, tenderness, and proximal weakness. The CK levels increase >4 to <50 times the ULN and resolves on discontinuation of the statin. Contrary to the autoimmune necrotizing type, these patients do not have antibodies against HMG-CoA reductase (anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies). Rhabdomyolysis is defined as muscle symptoms with substantial CK elevation (defined as CK elevation >10 times the ULN) and associated with renal impairment (creatinine elevation). Autoimmune-mediated necrotizing myositis is characterized by progressive muscle weakness, anti-HMGCR antibodies, and progression of the symptoms and signs even after discontinuation of the statins. Muscle biopsy shows a necrotizing myopathy, with deposition of the membrane attack complex in nonnecrotic fibers and MHC class I antigen expression (Doughty & Amato, 2019).

Although not clearly established, it is estimated that about 5% of all treated patients may exhibit asymptomatic elevations in CK levels (Dalakas, 2009). In this group of patients, CK levels usually do not exceed 10 times the ULN and patients do not complain of myalgias or exhibit weakness. These patients are usually followed up clinically and with periodic laboratory evaluations. Patients with myalgias with or without CK elevation and without weakness can be changed to a statin with a lower potential for myotoxicity and followed clinically. Patients with CK elevations and weakness have become less common with increased awareness of the myotoxicity potential. In some patients, the onset of weakness sometimes cannot be temporally related to the exposure to statins, raising the question of a preexisting muscle disease being unmasked by the statin. Rhabdomyolysis is a rare complication, with markedly increased CKs, myalgias, weakness, and myoglobinuria. This is a medical emergency and requires in-hospital management to prevent renal damage. This is most likely related to drug-drug interactions and is seen most often when combined with other medications such as amiodarone, gemfibrozil, and cyclosporine or colchicine. Coadministration of nicotinic acid, azole fungals, and macrolide antibiotics also increases the risk for developing myotoxicity. Clinicians should be thoroughly aware of drug interactions that increase the risk of myopathy, and these should be recognized before starting patients on statins. This is most likely mediated through interactions with cytochrome P450 3A4 with resultant elevated levels of the statins, and most commonly associated with the lipid-soluble statins, atorvastatin, lovastatin, and simvastatin (Baker & Samjoo, 2008).

Clinicians should be aware that the myopathy can develop several weeks to years after starting treatment. One important possibility in patients with statin myotoxicity is that of a preexisting elevation of the CK or undiagnosed muscle disease that has been unmasked by statin exposure. Baseline CK determinations prior to initiation of therapy may be helpful in identifying these patients, and clinicians should be aware of a possible heightened risk. Statins should be used cautiously and CK carefully monitored in patients with a history of myopathy and rhabdomyolysis.

In the evaluation of statin-associated myotoxicity, conditions that may mimic myopathy, such as claudication, peripheral neuropathy, amyotrophy, and lumbosacral radiculopathy, should be carefully excluded. There are several known risk factors associated with the development of statin-associated myopathy, such as older age, a polymorphism in the SLC01B1 gene, female sex, alcoholism, low body mass index, and coexisting diseases associated with myopathy (diabetes mellitus, hypothyroidism, hepatic dysfunction, and renal insufficiency) (Bannwarth, 2007; Sathasivam, 2012). Therefore, baseline liver, renal, and thyroid function tests should be done before starting patients on statins.

Discontinuing the statin or switching to a less myotoxic statin continues to be the mainstay of treatment. In patients with multiple medications, lowering the dose or switching to pravastatin, fluvastatin, or pitavastatin, which are not significantly metabolized by cytochrome P450 3A4, can be an option. Physicians should not ignore patients' complaints. Patients should be examined and CK levels assessed if there is a suspicion. Patients can continue with the medication under close observation if symptoms are mild and tolerable, but the decision to continue with therapy should be in agreement with the patient after discussion of the potential risks and benefits. Statins should be discontinued if symptoms are moderate or severe or if CK levels increase to levels greater than 5 to 10 times the ULN. Patients should also be advised about the potential for heightened muscle disruption with vigorous exercise or prolonged dehydration (Baker & Samjoo, 2008).

Less commonly, patients may develop an immune-mediated necrotizing myopathy, characterized by muscle weakness that persists after discontinuation of the statin, necrotic fibers in the muscle biopsy, and positive titers of antibodies against HMG-CoA reductase (anti-HMGCR antibodies), which correlate with the CK levels and the weakness. The myopathy persists and often requires immunosuppressive therapy. Although there are no controlled studies of therapy in this condition, experienced investigators have recommended initial therapy with prednisone at a dose of 1 mg/kg/day and concomitant use of another agent such as methotrexate, mycophenolate mofetil, or azathioprine. IV gamma globulin, 2 g/kg over 5 days, can be used if there is no response after 8 to 12 weeks or as an initial agent (Mammen, 2016). Some patients may relapse after tapering of immunosuppressive therapy and may require long-term therapy. They have also recommended starting immunosuppressive therapy only if the disease does not improve or continues to worsen after discontinuation of the statin, since some patients may have spontaneous improvement.

EMG performed in asymptomatic patients with elevated CK is usually normal. However, in patients with significant weakness and in particular with immune-mediated necrotizing myopathy, EMG may show spontaneous activity such as fibrillations, positive waves, and myotonic discharges and early recruitment (Carroll, Newkirk, & Sumner, 2016). The muscle biopsy, although rarely performed, usually shows nonspecific changes or, if severely affected, may show muscle fiber necrosis with phagocytosis and small regenerating fibers and an occasional "ragged red" fiber (Dalakas, 2009). Currently, there is no proven therapy to prevent or treat statin-induced myopathy.

Steroid Myopathy

Steroid myopathy can result from both endogenous and exogenous corticosteroids and results in proximal muscle weakness and atrophy. Fluorinated glucocorticoids (triamcinolone > betamethasone > dexamethasone) have a greater propensity for producing weakness than the nonfluorinated ones (Doughty & Amato, 2019; Faludi, Gotlieb, & Meyers, 1966). There is a wide variability in dose and duration of glucocorticoid treatment among patients who develop weakness, although it is usually not seen at relatively low doses (i.e., 20 mg or less of prednisone daily) (Dalakas, 2009).

Clinically, weakness is usually more severe in the legs than the arms, and cranial-innervated muscles are spared. Patients usually exhibit other features of corticosteroid use such as cushingoid facies, fragile skin, or osteoporosis. The muscle weakness usually begins insidiously after chronic use of high-dose steroids, although some patients may develop an acute onset of severe generalized weakness, especially after receiving high doses of IV fluorinated steroids (Dalakas, 2009). Serum CK and aldolase levels are usually normal. Muscle biopsy shows preferential atrophy of type 2 muscle fibers. Necrosis or inflammation is not observed. The mechanism for corticosteroid myopathy is not clearly established, although decreased protein synthesis, altered carbohydrate metabolism, mitochondrial dysfunction, or reduced muscle membrane excitability have all been implicated (Doughty & Amato, 2019).

The recommended treatment is to reduce the steroid dose to the lowest effective level and change to an alternate-day regimen. An additional strategy is to change to a nonfluorinated steroid (Ubogu, Ruff, & Kaminski, 2004). Recovery is usually slow, and it may take months for full recovery to be observed. Ensuring adequate nutrition is important because protein deprivation may accelerate the steroid-induced myopathic process. One common dilemma encountered by clinicians is to distinguish whether patients have become weaker due to exacerbation of their condition or due to the steroids. Sparing of neck flexors would suggest steroid myopathy, because these muscles are usually weak in the inflammatory myopathies. If the patient becomes weak when steroids are being tapered, the weakness is most likely due to relapse, but if the patient becomes weak while on high-dose steroids, then the cause is most likely steroid-induced myopathy. Serum CK levels, if elevated, would point toward an exacerbation, although the opposite (normal levels) may not be true. The needle EMG may also be helpful in distinguishing between exacerbation and steroid-induced weakness by documenting increased spontaneous activity (fibrillation and positive waves), which is a feature of inflammatory myopathy but not steroid myopathy (Buchthal, 1970).

Alcoholic Myopathy

Although chronic alcohol consumption is mostly associated with neuropathy, it can cause many other significant problems such as liver cirrhosis, cardiomyopathy, and myopathy. Alcohol-induced muscle disease can result from either acute or chronic consumption, but it is mostly seen in patients with a long history of alcohol abuse. The severity of the muscle symptoms has been found to be proportional to the quantity of alcohol that is consumed. Several types of muscle disease are associated with alcohol consumption: (1) acute alcoholic myopathy, (2) acute hypokalemic myopathy, (3) chronic alcoholic myopathy, (4) asymptomatic alcoholic myopathy, and (5) alcoholic cardiomyopathy (Simon, Jolley,

& Molina, 2017). Acute alcoholic myopathy, also known as acute necrotizing myopathy, occurs in approximately 1% of chronic alcoholics, usually associated with an episode of binge drinking. These patients develop weakness, myalgias, cramps, and edema. Their CK levels can increase considerably and they can develop myoglobinuria and rhabdomyolysis, which predisposes them to acute renal failure. Their muscle biopsies show necrosis of individual muscle fibers, all in the same stage of degeneration, and inflammatory infiltrates. However, the symptoms last only several weeks and are reversible after withdrawal. Alcohol can also induce hypokalemia, causing acute generalized weakness associated with low levels of potassium and elevated CK. Unlike acute alcoholic myopathy, patients do not present with myalgias, cramps, or edema. If a muscle biopsy is done during the acute presentation, vacuolar changes can be seen. Signs and symptoms are reversed with potassium correction. On electrophysiologic evaluation, both patients with acute alcoholic myopathy and those with acute hypokalemic myopathy can present with a primary myopathic process having normal or mildly abnormal NCS and increased insertional activity, with short-duration, low-amplitude motor unit action potentials on EMG.

One third to two thirds of chronic alcoholics have chronic alcoholic myopathy, making this the most frequent muscle abnormality in alcoholics of the various types discussed (Simon et al., 2017). Patients present with progressive proximal weakness and muscle atrophy that develops over the course of weeks to months. These patients have a normal or slightly elevated CK, and their muscle biopsies show predominant atrophy of type 2b fibers but no fiber necrosis (Sieb & Gillessen, 2003). Muscle strength improves on alcohol withdrawal, but complete recovery is usually not achieved. Asymptomatic alcoholic myopathy refers to the finding of elevated CK levels in alcoholic patients who do not complain of weakness and have no abnormalities on the neurologic examination. Lastly, alcoholic cardiomyopathy refers to the development of dilated cardiomyopathy due to chronic alcohol consumption. Alcohol cardiomyopathy resembles idiopathic dilated cardiomyopathy and is considered when other causes of idiopathic dilated cardiomyopathy have been ruled out.

Treatment of the various forms of alcohol-induced myopathy is primarily supportive, with hydration and correction of electrolyte abnormalities in the acute forms and efforts directed toward helping with the alcohol dependence to eliminate the toxic exposure.

Nucleoside Analog–Induced Myopathy

Among the various nucleoside analogs that have been developed as treatment for viral and retroviral infections, muscle toxicity has been most commonly observed with zidovudine (AZT, 3-azido-3'-deoxythymidine), stavudine (d4T), and fialuridine (FIAU) (Dalakas, 2009). Those myopathies associated with antiretroviral therapy are of particular importance due to their reversible nature if identified early and their importance as signs of mitochondrial toxicity. Zidovudine-associated myopathy is the most common characterized by proximal muscle weakness 6 to 12 months after initiating treatment, myalgias in thighs and calves, fatigue, and variably increased serum CK (Dalakas, 2009; Carr & Cooper, 2000). The muscle biopsy reveals that features of mitochondrial dysfunction are prominent, with numerous "ragged red" fibers, subsarcolemmal accumulation of red granular material, sparse, if any, endomysial inflammation, lipid accumulation, many cytochrome-*c* oxidase negative fibers, and paracrystalline mitochondrial inclusions on electron microscopy. The precise mechanism of zidovudine myotoxicity is still debated but there is evidence for mitochondrial DNA depletion through inhibition of polymerase gamma; additionally, zidovudine-induced oxidative stress, direct inhibition of the mitochondrial bioenergetic machinery, mitochondrial L-carnitine deficiency, and impaired mitochondrial protein synthesis have also been proposed (Scruggs & Dirks Naylor, 2008). Zidovudine myopathy likely depends on cumulative drug dose and is therefore more common after high-dose, long-duration treatment. The frequency of zidovudine myopathy has decreased since lower doses have become the standard of therapy. Nowadays, patients complain more frequently of fatigue and myalgia without clear weakness and atrophy. Blood measurements of CK and lactic acid may be helpful in symptomatic patients to differentiate from the immune-mediated HIV myositis. There is no specific treatment for antiretroviral-induced myopathy. Treatment is based on removal of the offending agent, so switching to another nucleoside analog or antiretroviral agent, in the presence of symptoms and signs, is usually recommended.

Antimicrotubular Myopathy (Colchicine Myopathy)

Myopathies due to disruption of microtubule formation have been described with both colchicine and vincristine, although they are more common with the former agent. Both are also associated with a coexistent peripheral neuropathy in most cases. Colchicine is usually used for the treatment of gouty arthritis, although more recently it has also been used in the treatment of familial Mediterranean fever, Behçet disease, and primary biliary cirrhosis. Its mechanism of action is through the interaction with tubulin and inhibition of polymerization of microtubules affecting mitosis and other microtubule-dependent functions in the cell. Disruption of this microtubular-dependent cytoskeletal network by colchicine is believed to result in the defective movement of lysosomes and the intracellular accumulation of autophagic vacuoles (Sieb & Gillessen, 2003). Myotoxicity is more commonly seen in older patients, ages 50 to 70 years, with mild renal insufficiency and with prolonged use. Concomitant use of cyclosporine increases the risk of colchicine myotoxicity, and, more recently, cases of rhabdomyolysis have been described with concomitant use of statins (Ayubi & Safiri, 2017; Fernández-Cuadros et al., 2019; Kwon et al., 2017). Rarely, colchicine alone has been associated with rhabdomyolysis (Fernández-Cuadros et al., 2019). Patients most commonly present with proximal weakness of subacute onset associated with distal areflexia, myalgias, and elevated serum CK levels. There can also be mild elevation of serum CK in asymptomatic patients and more marked elevations in symptomatic patients. Patients commonly show signs and symptoms of a coexistent mild peripheral neuropathy. NCSs typically show findings of a mild sensorimotor axonal polyneuropathy and prominent spontaneous activity (fibrillation and positive waves) with "myopathic" motor unit potentials in proximal muscles. Myotonic discharges may be prominent and may help to differentiate from other

possibilities. The EMG changes are rapidly reversible upon discontinuation of the colchicine (Kuncl, Cornblath, Avila, & Duncan, 1989). The muscle biopsy shows a vacuolar myopathy with accumulation of lysosomes and autophagic vacuoles without necrosis.

The mainstay of treatment is stopping colchicine at the first sign of myotoxicity. Weakness and EMG changes typically resolve promptly after it is discontinued. In order to prevent colchicine myopathy in patients with reduced creatinine clearances of 50 mL/minute or less, it is recommended that the dose be no greater than 0.6 mg twice a day (Wilbur & Makowsky, 2004). Colchicine should not be administered to patients with creatinine clearances below 10 mL/min or who require dialysis, because it is not removed by dialysis. A reduced dose of the medication is also recommended for patients with reduced muscle mass.

Chloroquine Neuromyopathy

Chloroquine is an antimalarial medication that, at higher doses, has been widely used for inflammatory conditions such as sarcoidosis, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis. Its most notable side effect is retinal toxicity, but skin problems, anorexia, nausea, vomiting, diarrhea, dizziness, tinnitus, and headache are also seen. Less common side effects include myasthenia-like syndrome, cardiomyopathy, and neuromyotoxicity.

The myopathy and neuropathy usually occur after long-term use (months or years) and at high doses above the daily 500 mg range. Clinically, patients present with slowly progressive, painless proximal weakness and atrophy, mostly notably in the lower extremities. The weakness may involve the trunk and the facial muscles if the medication is not discontinued (Sieb & Gillessen, 2003). Patients can also exhibit depressed deep tendon reflexes and distal sensory loss on examination. Serum CK is usually normal or only mildly elevated. In some instances, it may resemble acid maltase deficiency with respiratory failure and cardiomyopathy. Factors that may predispose patients to develop chloroquine myopathy include renal dysfunction and concomitant use of ciprofloxacin and nonsteroidal anti-inflammatory drugs. NCSs may be normal or show findings consistent with a mild sensorimotor axonal polyneuropathy. The needle EMG shows increased insertional as well as spontaneous activity (fibrillations and positive waves), mostly in proximal limb muscles. Occasional myotonic discharges can be observed. Motor unit action potentials are mostly polyphasic, with decreased amplitude and duration (Doughty & Amato, 2019). Muscle biopsy shows involvement of type 1 fibers primarily with acid-phosphatase positive vacuoles in as many as 50% of the skeletal and cardiac muscle fibers (Walsh & Amato, 2005). With electron microscopy, these vacuoles are seen to contain myeloid debris and curvilinear structures identical to those seen in patients with neuronal ceroid lipofuscinosis. Hydroxychloroquine also produces a neuromyopathy (Khosa, Khanlou, Khosa, & Mishra, 2018; Kwon et al., 2010), but toxicity is usually less severe. In case of both medications, the symptoms are relieved after discontinuation, although recovery may not be complete.

In addition to myopathy and neuropathy, some patients exposed to chloroquine have developed a myasthenia-like syndrome, with ptosis, extraocular muscle weakness, fatigue, and response to edrophonium (Robberecht, Bednarik, Bourgeois, van Hees, & Carton, 1989). This may present shortly after starting therapy or after weeks or months of treatment. It usually resolves promptly after discontinuation of the medication, although symptoms may recur if the medication is reintroduced.

Immune Checkpoint Inhibitors

These new classes of anticancer agents rely on upregulating the immune system, modulating various points in the cellular immune response, showing efficacy in the treatment of advanced cases with metastatic disease, where other therapies have proven ineffective. These monoclonal antibodies include ipilimumab, cemiplimab, nivolumab, pembrolizumab, avelomubab, durvalumab, and atezolizumab, with mechanisms that target programmed cell death 1 receptor (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) (Johnson et al., 2019). Because of their mechanism of action, their toxic effects are related to producing autoimmunity, resulting in a number of clinically relevant neurologic and neuromuscular complications. Among them, there have been reports of encephalitis, aseptic meningitis, myasthenia gravis, and GBS, with estimates of occurring in 1%–5% of treated patients (Johnson et al., 2019). Severe neurologic complications are increasingly identified (Dubey et al., 2020). Myopathy is increasingly recognized as a complication of these treatments and can occur with any of the involved mechanisms. Patients typically develop symptoms after one of two cycles, with a median onset of symptoms at 25 days after start of therapy. On clinical exam, patients usually exhibit proximal weakness but can also exhibit weakness of axial muscles with head drop and ophtalmoplegia and dysphagia. There can be overlap between myositis and myasthenias gravis, which is another known complication. Cardiac muscle involvement (myocarditis) can occur in combination with the above or in isolation. Creating kinase is usually increased and can be higher than 10,000 U/L. EMG shows increased spontaneous activity with fibrillation and positive waves and myopathic motor unit potentials. Muscle biopsy has shown endomysial inflammation with CD68+ and CD8+ cell infiltrates and increased expression of MHC-1.

Treatment guidelines for myositis are based on the severity of weakness and the increase in CK; for moderate or more severe weakness, they recommend the use of prednisone at 0.5 to 1 mg/kg, and if more severe, IV prednisolone 1–2 mg/kg and consideration of plasmapheresis or IVIG. If symptoms and CK levels do not improve, the use of additional immunosuppressant therapy such as methotrexate, azathioprine, or mycophenolate mophetyl and possibly rituximab is recommended (Brahmer et al., 2018).

OTHER MEDICATIONS

Many other medications have been reported to cause neuropathy (Table 16.4) and myopathy. Of these, amiodarone, a commonly used antiarrhythmic agent, has been associated with CNS disorders characterized by tremors, ataxia, and optic neuropathy and with a peripheral neuropathy and myopathy (Fernando Roth, Itabashi, Louie, Anderson, & Narahara, 1990). Amiodarone neuropathy could be predominantly demyelinating, axonal, or both. Clinical and biopsy findings in myopathy are nonspecific. Rare cases might develop

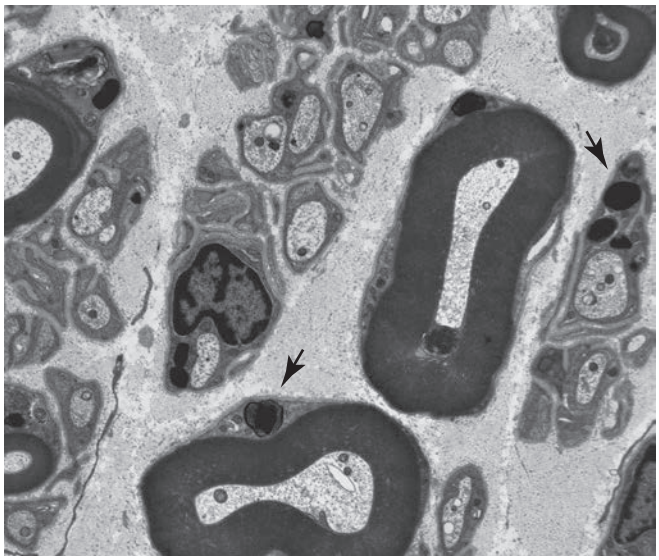


Fig. 16.4 Amiodarone neuropathy. Electron microscopy on sural nerve biopsy showing osmiophilic inclusions in cytoplasm of Schwann cells (arrows) (“10,000). (Reprinted with permission from Bertorini, T. E. (2008). *Neuromuscular case studies*. Woburn, MA: Butterworth-Heinemann.)

rhabdomyolysis, particularly with concomitant use of statins (Marot et al., 2011; Schmidt, Hoehns, Purcell, Friedman, & Elhawi, 2007).

Nerve biopsy on amiodarone neuropathy demonstrates loss of myelinated axons with regeneration and osmiophilic inclusions (Fig. 16.4).

The treatment is usually conservative and consists primarily of withdrawal of the medication.

BIOLOGIC TOXINS

Many biologic toxins are the cause of central or peripheral nervous system complications. Some are discussed in other chapters: tetanus (see Chapter 17), botulism, and snake bites.

Tick Paralysis

Tick paralysis is an uncommon paralytic syndrome caused by a salivary neurotoxin produced by one of several species of ticks of the *Dermacentor* and *Ixodes* genus. Most cases are reported from Australia and from North America, in particular from western United States and Canada, although it has been reported in other areas as well. Most cases occur in the spring and early summer, when people and the ticks are more active. It is important to recognize because it can be near fatal or fatal and is rapidly reversible. In the United States and Canada, the tick species that are associated with most cases are *Dermacentor andersonii* (the Rocky Mountain or Wood Tick) and *Dermacentor variabilis* (the American Dog tick). Other tick species have also been associated with human tick paralysis. In Australia, the most common tick species associated with tick paralysis is *Ixodes holocyclus* (the Australian scrub tick). The tick has to feed for several days (4 to 5 days) before paralysis occurs. The condition affects children and adults and in particular girls, which is thought to be due to their long hair, providing a place to hide for feeding ticks. Additionally, it is thought that children are more susceptible to the toxin, due to their small size.

DIAGNOSIS AND EVALUATION

The classic presentation is that of an initial gait disturbance progressing to an acute ascending paralysis over hours or days and that could be preceded by prodromal symptoms such as paresthesias, restlessness, irritability, fatigue, and myalgias (Edlow & McGillicuddy, 2008). If the condition is not identified and the tick is not removed, the paralysis ascends to involve bulbar and respiratory muscles, resulting in respiratory failure and death, unless respiratory support is provided. The diagnosis requires high suspicion for the condition in any adult or child who develops a rapid paralysis, with a normal sensory exam, during the spring or summer months. A very thorough complete whole-body physical inspection must be performed to detect the attached tick. It is possible for more than one tick to be attached.

There is evidence that the toxins from *Dermacentor* and *Ixodes* ticks are different. Clinically, paralysis from *Ixodes* ticks, the common vector in Australia that produce *holocyclotoxin*, is associated with elevated arterial blood pressure and dilated pupils and, unlike tick paralysis in the United States, patients continue to deteriorate up to 24 hours after the tick has been removed (Edlow & McGillicuddy, 2008). Electrodiagnostic studies based on single or only a few cases have shown variable abnormalities. Among the various studies, the most common abnormality has been reduced-amplitude CMAPs, with some reports describing prolonged distal motor latencies and slowing of motor conduction velocities (Cherington & Synder, 1968; Grattan-Smith et al., 1997; Swift & Ignacio, 1975).

TREATMENT AND MANAGEMENT

The definitive therapy is removal of the tick, but standard intensive care level supportive and respiratory care is necessary while the patient is paralyzed.

Ciguatera

Marine toxins can affect the central and peripheral nervous systems (Table 16.5) (Lewis, 1996). Of these, ciguatera is the most common marine toxin causing illness (Friedman et al., 2017). It results from the ingestion of toxins (ciguatoxin) in contaminated fish infected with the dinoflagellate in the genus *Gambierdiscus*. The ciguatoxins are lipid soluble and resistant to heat and are concentrated in the head, liver, and viscera of the fish. The distribution of ciguatera is expected to increase with the increasing fish trade, international tourism, and climate changes, which favor the growth of the dinoflaggelates. The condition is endemic in the South Pacific and the Caribbean. Ciguatoxins bind to sodium channels, resulting in prolonged opening and triggering spontaneous and repetitive action potentials and swelling at the nodes of Ranvier (Benoit, Juzans, Legrand, & Molgo, 1996; Mattei, Molgo, & Benoit, 2014).

The clinical manifestations of ciguatera vary depending on the origin of the fish, if from the Caribbean, Pacific, or Indian Ocean, and the concentrations of ciguatoxin consumed. The initial symptoms are gastrointestinal with abdominal pain, diarrhea, and vomiting, starting within 6 to 12 hours after consumption of fish. This is followed by neurologic symptoms, which start within the first 2 days

Table 16.5 Standard Treatments for Marine and Biologic Toxins

Indication	Drug/Treatment	Dose	Route	Serious Drug Side Effects
Ciguatera	Mannitol[a]	1 g/kg of a 20% solution	IV	Dehydration, hypotension, electrolyte imbalance
Tetrodotoxin ingestion	Pulmonary resuscitation	—	—	—
Scombroid poisoning	Cimetidine	300 mg	IV	Agitation, confusion, hallucinations, Steven-Johnson syndrome
	Diphenhydramine	10–50 mg	PO/IV/IM	Confusion, agitation, seizures
Pfiesteria	Cholestyramine	9 g qid for 2 weeks	PO	Constipation, pancreatitis
Jellyfish sting	Topical vinegar/hot water immersion 45°C–50°C, 113°F–120°F	—	—	—
	Antivenin (Chironex)	See package insert	IV/IM	Serum sickness, anaphylaxis
Venomous fish	Antivenin where available	See package insert	IV/IM	Serum sickness, anaphylaxis
	Heat therapy	—	—	—
Cone snail bite	Pulmonary resuscitation	—	—	—
Snake bites	Pulmonary resuscitation, hemodialysis with myotoxicity	—	—	—
Eastern coral snake bite	Coral snake antivenin	See package insert	IV/IM	Serum sickness, anaphylaxis
Viper bite	Crotalidae antivenin	See package insert	IV/IM	Serum sickness, anaphylaxis
Sea snake bite	Sea snake antivenin	See package insert	IV/IM	Serum sickness, anaphylaxis
Datura species poisoning	Physostigmine	0.5–2 mg; may repeat q 10–30 min prn	IM or slow IV (not > 1 mg/min IV)	Hypersalivation, dyspnea, seizures
Amanita phalloides mushroom poisoning	Liver transplant	—	—	—
Gyromitra mushroom poisoning	Pyridoxine	25 mg/kg over 15–30 min; may be repeated prn to a total dose of 15–20 g/day	IV	Peripheral neuropathy, neuronopathy, seizures, headache
Muscarine poisoning	Atropine	1–2 mg initially; repeat prn q 20–30 min	IV/IM	Cardiac arrhythmias, respiratory depression
Psilocybin poisoning	Haloperidol (Haldol)	2–10 mg	IM/IV	Neuroleptic malignant syndrome, cardiac arrhythmias
	Diazepam	2–5 mg	IV/PO	Sedation
Black widow spider bite	Latrotoxin antivenin; calcium gluconate	See package insert Adults: 500–800 mg IV of 10% solution (5–8 mL) Infants and children: 60–100 mg/kg (0.6–2 mL/kg)	IV	Hypotension, cardiac arrest, confusion, cardiac arrhythmias, atrioventricular block
Tick paralysis	Remove tick			

IM, intramuscular; *IV*, intravenous; *PO*, orally.
[a]Normal saline solution is also useful.
From Stommel, E., & Watters, M. (2006). Marine toxins and assorted biological toxins. In R. Johnson, J. Griffin, & J. McArthur (Eds.), *Current therapy in neurologic disease* (7th ed.). Philadelphia: Mosby.

and include paresthesias in the hands, feet, and perioral region; metallic taste; myalgia; generalized pruritus; headache; and, the most typical, paradoxical hot-cold reversal of temperature sensation or cold allodynia (Friedman et al., 2017). These may last for days, weeks, or months. Common cardiac symptoms include bradycardia, tachycardia, and orthostatic hypotension. Gastrointestinal symptoms are more prominent in Caribbean ciguatera and may not occur in the Indo-Pacific region. In the latter, ciguatera has been associated with neuropsychiatric and mental status disturbances, with hallucinations and even coma in some cases (Quod & Turquet, 1996).

The diagnosis is based on a history of recent consumption of fish, followed by the aforementioned symptoms. Electrophysiologic testing could be normal or could show slowing of sensory conduction velocity (Cameron, Flowers, & Capra, 1991).

The treatment has been primarily supportive and symptomatic. The principal treatment is IV 25% mannitol at 1.0 g/kg, administered over a 30–45-minute period (Palafox, 1992; Palafox et al., 1988). For maximum benefit, it should be provided within the initial 72 hours after toxin ingestion (Friedman et al., 2017). The treatment of the dysesthesias and the neuropathic pain associated with ciguatera poisoning presents an important challenge. There are no controlled studies and only anecdotal experience with medications for neuropathic pain. Some have reported positive responses to pregabalin, 150 mg twice daily (Brett & Murnion, 2015), or gabapentin, 400 mg three times daily (Perez, Vasquez, & Perret, 2001).

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17 Treatment and Management of Segmental Neuromuscular Disorders

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This chapter is devoted to focal disorders of the peripheral nervous system, including radiculopathies, plexopathies, and mononeuropathies. These conditions span a broad range of disorders, from radiculopathy due to Lyme disease and obturator neuropathy at the extremes of rarity to very common disorders such as cervical radiculopathy and carpal tunnel syndrome. This group of disorders makes up a large portion of neuromuscular medicine practice and only on a rare day will the neuromuscular clinician fail to see a patient with one of these conditions; on most days, this specialist is likely to see several. Intimate familiarity with the pathoanatomy, pathophysiology, clinical features, diagnosis, evaluation, and treatment of these conditions is necessary. This chapter is intended to provide a solid basis for acquiring the required expertise.

RADICULOPATHY

The intervertebral disk is the largest avascular structure in the body, depending for sustenance on the diffusion of nutrients across the endplate. The disks begin to desiccate and lose elasticity in the fifth and sixth decades; individuals in this age group are prone to intervertebral disk rupture. In the seventh to ninth decades, the tendency is to hardening and calcification, resulting in degenerative spondylosis and spinal stenosis.

CLINICAL PATHOANATOMY

Knowledge of the anatomic details of the spine and the spinal nerves is integral to managing patients with suspected radiculopathy. The vertebrae are separated by intervertebral disks, which are composed of an outer fibrous ring, the annulus fibrosus, and an inner gelatinous core, the nucleus pulposus (NP). The lateral recess is the corner formed by the pedicle, vertebral body, and superior articular facet. Hypertrophy of the facet can cause lateral recess stenosis.

The spinal nerve passes outward from the spinal canal through the intervertebral foramen, a passageway formed by the vertebral body anteriorly, pedicles above and below, and the facet mass and its articulation, the zygapophyseal joint, posteriorly. The zygapophyseal joints are innervated by the posterior primary ramus of the exiting spinal nerve and can be a source of pain. The uncovertebral joints (of Luschka), which are not true joints, are the points where the posterolateral surface of a cervical vertebra comes into apposition with a neighboring vertebra. Degenerative osteophytes projecting into the intervertebral foramen from the uncovertebral "joints" may narrow the foramen and cause radiculopathy (Fig. 17.1).

The posterior longitudinal ligament (PLL) extends along the posterior aspect of the vertebral bodies and reinforces the disks posteriorly. The PLL is weak and flimsy and narrows as it descends. Disk herniations tend to occur posterolaterally, especially in the lumbosacral region, in part because of the lateral incompleteness of the PLL (Fig. 17.2). In the cervical region, the PLL may ossify and contribute to spondylotic narrowing. The ligamentum flavum extends along the posterior aspect of the spinal canal. It buckles and folds during neck extension and may also contribute to canal narrowing.

The static anatomy of the spine provides only a partial understanding of the changes that occur on motion. Direct measurements have shown that the pressure within the lumbar disk varies markedly with different postures and activities. It is lowest when lying supine, increases 400% on standing, and increases a further 50% when leaning forward. The pressure is 40% higher when sitting than standing. The higher pressure when sitting is clinically relevant, as patients with lumbosacral disk ruptures characteristically have more pain sitting than standing. Eating meals from the mantelpiece is virtually pathognomonic. The intradiscal pressure during a sit-up is astronomical.

The size of the intervertebral foramina decreases with extension and with ipsilateral bending. In extension, the facet joints draw closer together and the posterior quadrants of the spinal canal narrow. The upper cervical spine is primarily responsible for rotational movements and the lower cervical spine for flexion and extension movements. The longitudinal and flavum ligaments alternately stretch and buckle during flexion and extension. Tethering by the dentate ligaments accentuates the mechanical stresses laterally. Cervical roots stretch with flexion and may angulate at the entrance to the foramen. The intraspinal subarachnoid pressure varies with respiration and increases markedly with Valsalva or restriction of venous outflow. Like veins everywhere, the epidural and radicular veins change in size with posture and respiration. All these dynamic changes, which are especially relevant in the presence of disease, form the basis for clinical tests and historical questions useful for distinguishing the various causes for neck pain.

The annulus provides circumferential reinforcement for the disk; the spherical NP allows the vertebral bodies above

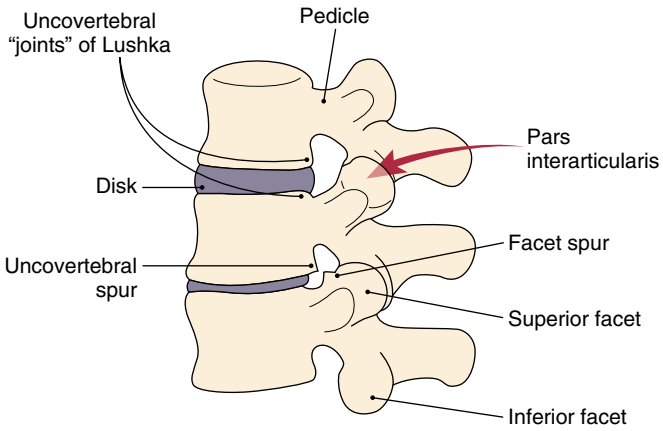


Fig. 17.1 Lateral view of the cervical spine, showing the vertebral bodies separated by intervertebral disks, the pedicles merging into the facet joint with its superior and inferior facets, and intervening pars interarticularis. The facets are oblique in the cervical region, more vertical in the lumbosacral spine. The uncovertebral joints are not true joints, but just the opposing surfaces of the vertebral bodies. The uncovertebral processes may form osteophytes, or "spurs," which then project into the foramen.

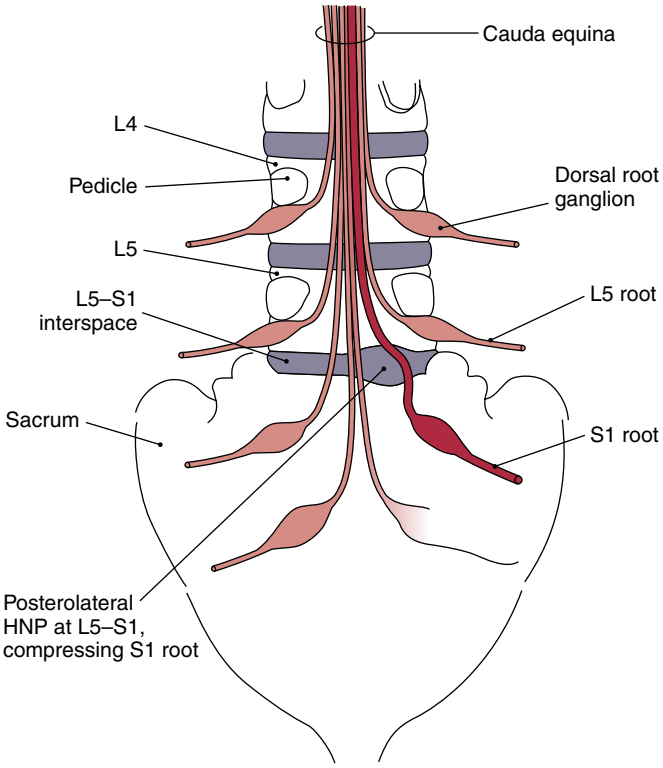


Fig. 17.2 Posterior view of the cauda equina with exiting nerve roots. The nerve roots move laterally en route to their exit foramina. A posterolateral herniated nucleus pulposis (HNP) has compressed the S1 root as it passes by the L5–S1 interspace. The dorsal root ganglion lies well lateral and below, out of harm's way, so that the peripherally recorded sensory nerve action potential would not be affected. A central HNP at any interspace could affect multiple roots.

and below to glide and slip across it, like a ball bearing. The NP is eccentrically placed, closer to the posterior aspect of the disk. The relative thinness of the annulus posteriorly is another factor contributing to the tendency of disk herniations to occur in that direction.

The great majority of the weight-bearing function of a normal disk is borne by the NP, which contains proteoglycans, macromolecules that heartily imbibe fluid. Early in life, the NP is 90% water, but it undergoes progressive desiccation over time. With desiccation of the NP and loss of viscoelasticity and compressibility, the annulus must assume more of the weight burden. This increased load, in the face of its own degenerative weakening, then makes the annulus prone to tears. Intradiscal proteoglycans are innocuous, but, spilled into the epidural space in the course of disk rupture, they can incite an inflammatory response. Other inflammatory mediators and signaling substances may be released by disk rupture, including nitric oxide, prostaglandin E_2, tumor necrosis factor, and interleukins-1 beta, -6, and -8.

The posterior aspects of the disks and the PLL are innervated by the sinuvertebral nerves, which arise from the anterior ramus just distal to the DRG, then take a recurrent course and reenter the spinal canal carrying both somatosensory and sympathetic fibers. These nerves have been implicated in discogenic pain (Edgar, 2007). An ingrowth of blood vessels and nerve fibers into the fibers of the annulus fibrosus of degenerated disks has been observed and may play a role in the development of back pain (Brisby, 2006). Both peripheral sensitization and central sensitization are likely involved in pain perpetuation.

SPINAL ROOTS

The spinal roots exit more or less horizontally in the cervical spine, although there is a slight downward slant. The downward slant increases through the thoracic region. When the cord terminates at the level of L1–2, the remaining roots drop vertically downward in the cauda equina to their exit foramina (see Fig. 17.2). In the cervical region, there is about a one segment discrepancy between the cord level and the spinous process, in the thoracic region about two segments, and in the lumbosacral region three to four segments. Therefore, the L5 nerve root exiting at the L5–S1 interspace has arisen as a discrete structure at L1–2 and had to traverse the interspaces at L2–3, L3–4, and L4–5 before exiting at L5–S1, sliding laterally all the while. So, the L5 root could be injured by a central disk at L2–3 or L3–4, a posterolateral disk at L4–5, or a far lateral disk or lateral recess stenosis at L5–S1. A posterolateral disk at L4–5 is the most likely culprit, but not the sole suspect. The clinician must correlate the clinical or electromyographic localization of a given root with the radiographic information to deduce the vertebral level involved and the proper course of action.

Cervical roots take a shorter, more direct course and occupy most of the intravertebral foramen. The lumbosacral roots take a long, oblique course, and the lumbosacral foramina are more capacious. Symptomatic radiculopathy is more likely to arise from a smaller disk herniation or osteophytic spur in the cervical region because of these anatomical factors.

PATHOLOGY OF DEGENERATIVE SPINE DISEASE

With aging and recurrent micro- and macrotrauma, degenerative spine disease develops. This involves both the disk (degenerative disk disease, or DDD) and the bony structures and joints (degenerative joint disease, or DJD). These

processes are separate but related. Together, DDD and DJD are referred to as *spondylosis*.

Small tears in the annulus may cause nonspecific, nonradiating low back pain (LBP). More extensive tears lead to disk bulging or protrusion, in which the disk herniates but remains beneath the PLL. In a disk protrusion, the base is broader than the dome and the herniation generally does not extend above or below the disk space. An extrusion breaches the PLL and allows a full-blown herniation of the NP (HNP) into the epidural space that may extend above or below the disk space. A free fragment refers to disk material that has lost its connection with the main mass of the disk.

Most HNPs in the lumbosacral spine occur in a posterolateral direction; occasionally, they are directly lateral or central (see Fig. 17.2). Which nerve roots are damaged depends largely on the direction of the herniation. In the face of disk herniation, the root may be damaged not only by direct compression but also by an inflammatory process induced by discal proteoglycans, ischemia due to pressure, and adhesions and fibrosis.

The anterior elements, vertebral body and pedicles, normally bear 80% to 90% of the weight. As degenerative changes advance with desiccation and loss of disk height, the posterior elements (facets, pars, and laminae) may come to carry up to 50% of the weight-bearing function. This increases the work of the posterior elements and accelerates their degenerative changes. They react to the increased weight-bearing role by becoming hypertrophic and elaborating osteophytes.

Osteoarthritis and synovitis of the facet joints are other sources of problems. In response to the increased loading attendant on loss of disk height and shift of weight bearing posteriorly, the facet joints develop degenerative changes: laxity of the capsule, instability, subluxation, and bony hypertrophy with osteophyte formation. The friction induced by minor instability and microtrauma leads to the formation of osteophytes. In the cervical spine, there is the added element of hypertrophy of the uncinate processes and the development of uncovertebral spurs. Degenerative osteophytes arising simultaneously from the uncus and from the vertebral body end plate region may become confluent and create a spondylotic bar or ridge that stretches across the entire extent of the spinal canal. Like any arthritic joint, the facet may enlarge, impinging on the intervertebral foramen or the spinal canal, especially in the lateral recess. Loss of disk height causes the PLL and the ligamentum flavum to buckle and bulge into the canal. The degenerative changes in the disks and bony elements eventually may culminate in the syndrome of cervical spondylosis, with radiculopathy, myelopathy, or a combination of the two.

All these degenerative changes leave less room for the neural elements. In the sagittal plane, the average cervical spinal cord is about 8 mm and the average cervical spinal canal about 17–18 mm. A sagittal canal diameter less than 10 mm may put the spinal cord at risk. The epidural space is normally occupied primarily by epidural fat and veins. When disk herniations and osteophytes intrude into the space, the resultant clinical manifestations depend in large part on how much room there is to accommodate them. Patients with congenitally narrow canals and those who have undergone past spinal fusion procedures are at increased risk for developing spinal stenosis (Figs. 17.3 and 17.4). Compression of vascular structures may introduce an additional complication of cord or root ischemia.

Because of the varied pathologic processes involved, different types of radiculopathy occur in disk disease and spondylosis. The process is frequently multifactorial, involving some combination of disk herniation and spondylosis. The most straightforward clinical syndrome is unilateral "soft disk" rupture. A similar clinical picture can result from a foraminal osteophyte, a "hard disk" problem. Some patients have soft disk superimposed on hard disk involvement. It is clinically, radiologically, and sometimes surgically difficult to distinguish between soft disk and hard disk involvement. Osteophytes, spurs, and foraminal stenosis are more common than simple soft disk disease in the etiology of cervical radiculopathy (CR). In the series of Radhakrishnan, Litchy, O'Fallon, and Kurland (1994), soft disk disease (i.e., not present in association with significant spondylosis) was responsible in only 22%; the remainder had hard disk involvement or a combination. A central HNP may compress the spinal cord.

About 75% of flexion and extension occurs at L5–S1 and 20% at L4–L5, but the L5–S1 level has only limited rotation. Approximately 90% of compressive radiculopathies occur at L4–L5 and L5–S1, about evenly divided between the two levels. Despite its higher degree of flexion and extension, the relative lack of rotation at L5–S1 helps increase its stability.

PATHOPHYSIOLOGY

The pathophysiology of radiculopathy is essentially the same regardless of etiology. Root compression due to HNP or spur tends to be concentrated on the distal portion of the root, proximal to the dorsal root ganglion (DRG). As with any nerve compression syndrome, the large myelinated fibers bear the brunt of the damage, and the degree of injury depends on the intensity and duration of the compressive force. Demyelination is the primary change with mild compression; more severe insults produce axon loss. Even with large lesions, the damage is usually only partial. With recovery, remyelination and axon regrowth occur.

ELECTRODIAGNOSIS

Electrodiagnosis will remain a mainstay in the evaluation of suspected radiculopathy for the foreseeable future. The general electrodiagnostic picture in radiculopathy includes normal motor and sensory conduction studies, with the needle electrode examination (NEE) disclosing abnormalities in a myotomal distribution, including the paraspinal muscles. Motor conduction abnormalities should reflect only axon loss, and even this is usually minimal. Sensory studies should be normal except for the occasional occurrence of an abnormal superficial peroneal (SP) sensory response due to an ectopic intraspinal DRG (Levin, 1998).

The diagnosis of radiculopathy is based primarily on the NEE and primarily on the presence of fibrillation potentials. Normal muscles may contain complex or polyphasic potentials, and it is hazardous to diagnose radiculopathy on motor unit action potential (MUAP) changes in isolation unless there are clear-cut abnormalities in a myotomal distribution. For confident diagnosis, the abnormalities should involve at least two muscles sharing the same myotomal

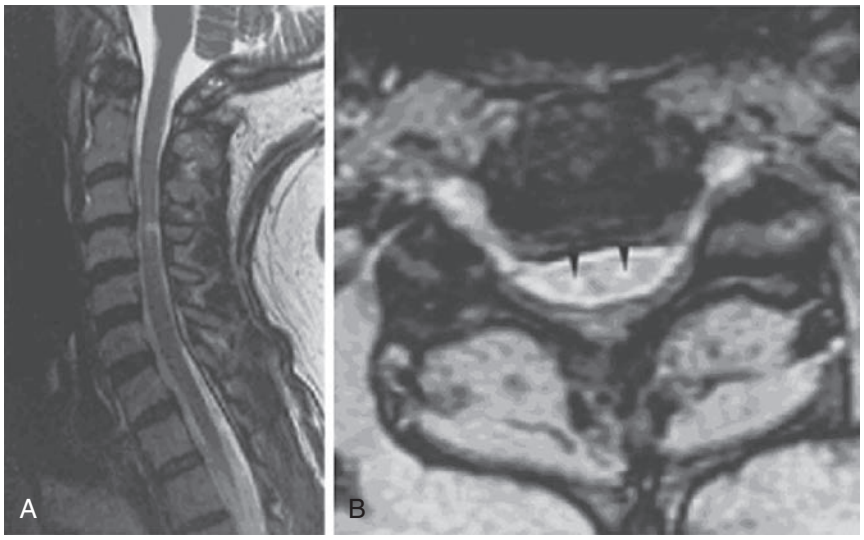


Fig. 17.3 Cervical spondylotic myelopathy with myelomalacia. Sagittal (A) and axial (B) T2-weighted magnetic resonance images showing only moderate compression of the spinal cord at C3–4 level, and focal increased signal in the cord substance indicating that damage has occurred. On axial images this often has the appearance of "snake eyes" (*black arrowheads*) within the spinal cord (From Adam, A., Dixon, A. K. (Eds.) (2008). *Grainger & Allison's diagnostic radiology* (5th ed.). London: Churchill Livingstone.)

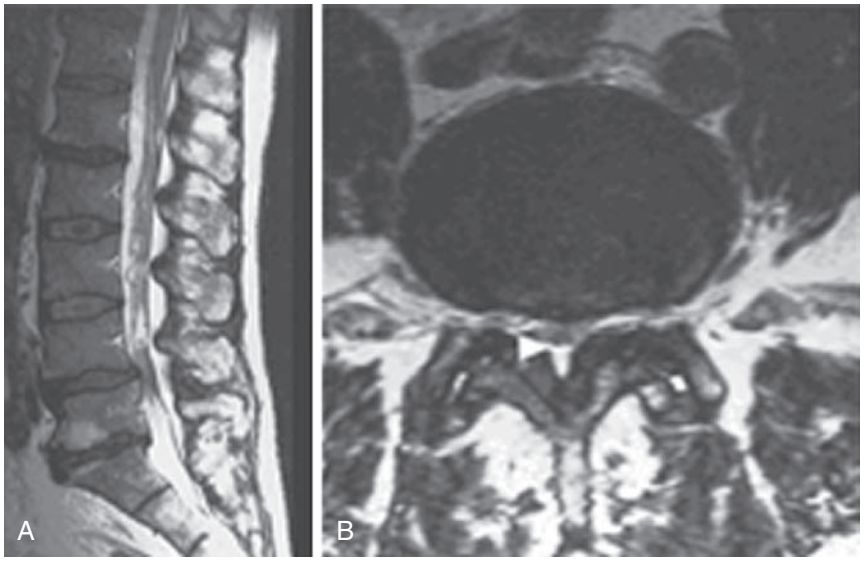


Fig. 17.4 Degenerative spinal canal stenosis. Sagittal (A) and axial (B) T2-weighted magnetic resonance images of the lumbar spine showing a severe spinal canal stenosis at L4–5 with evidence of compression of the cauda equina, namely, obliteration of cerebrospinal fluid signal from the thecal sac at the site of compression (*white arrowhead*) and some redundant coiling of intrathecal spinal roots above. (From Adam, A., Dixon, A. K. (Eds.) (2008). *Grainger & Allison's diagnostic radiology* (5th ed.). London: Churchill Livingstone.)

but different peripheral nerve innervations. The examination must be extensive enough to exclude a diffuse process (Wilbourn & Aminoff, 1998).

The timing of the study in relation to the onset of symptoms is pivotal. It generally requires 7 to 10 days for fibrillation potentials to appear in the paraspinal muscles and 2 to 3 weeks in limb muscles. Reinnervation with disappearance of fibrillation potentials occurs in the same sequence after a variable delay. A study done too early may be normal, a study done too late may also be normal or show only chronic neurogenic MUAP changes but no fibrillations. A study could show fibrillations in the paraspinals only, because limb muscles have not had time for them to develop, or in the limb muscles only because the paraspinals have reinnervated. Thus, depending on the duration of the process, fibrillations could be found in any combination of limb and paraspinal muscles. The paraspinal findings are critical in the evaluation of radiculopathy patients, and it is important to specifically examine the muscles of the multifidus compartment (Haig, Moffroid, Henry, Haugh, & Pope, 1991).

EMG has its greatest yield when focused on weak muscles and on the region of likely pathology, so familiarity with the typical clinical picture of cervical radiculopathy and LSR is useful in planning the examination. The clinical evaluation preceding the EMG should screen for nonradicular pathology and determine which root(s) is most likely involved. Dillingham (2013) proposes a streamlined examination of five limb muscles plus paraspinals as having a high diagnostic yield while minimizing patient discomfort and examiner time. The suggested muscles for cervical and lumbosacral root screens and the underlying rationale are discussed extensively in *Essentials of Electrodiagnostic Medicine* (Campbell, 2014).

There are clear limitations of electromyography (EMG) in the diagnosis of radiculopathy, related to the multiple root innervation of most muscles, the variable relationship between the root level and the vertebral level of injury, the potential for reinnervation by collateral sprouts, the severity of the radicular lesion, and whether it involves axon loss or only demyelination. A normal study does not exclude radiculopathy.

CERVICAL RADICULOPATHY

A population-based study of CR provided a wealth of interesting information (Radhakrishnan et al., 1994). The incidence is highest at ages 50 to 54, with a mean age of 47 and a male predominance. Other series have also found a similar mean age and male predominance (Campbell, 2014). In the population-based study, there was a decline in incidence after age 60 (the patients are developing spondylosis and spinal stenosis). There was a history of physical injury or exertion in only 15%; the most common precipitants were shoveling snow or playing golf. The onset was acute in half, subacute in a quarter, and insidious in a quarter, with the majority of patients symptomatic for about 2 weeks prior to diagnosis. Surgery was done in 26%. The disease tends to recur: 31% of patients had a previous history of CR and 32% had a recurrence during follow-up. At last follow-up, 90% of the patients had minimal to no symptoms. Others have noted this favorable long-term prognosis.

Acute radiculopathy due to HNP, soft disk, is seen more often in younger patients. Chronic radiculopathy is seen more often in older patients and typically has components of facet arthropathy and uncovertebral spur as well as disk pathology.

CLINICAL SIGNS AND SYMPTOMS

Two classic articles detail the history and examination findings in CR (Murphey, Simmons, & Brunson, 1996; Yoss, Corbin, MacCarty, & Love, 1957). Yoss et al. (1957) evaluated 100 patients with surgically confirmed single-level cervical radiculopathies (Table 17.1). Murphey et al. (1996) reviewed 648 cases of surgically treated single-level cervical radiculopathies. Findings in terms of pain radiation and neurologic deficits were similar to those of Yoss et al. The Murphey series did emphasize the occurrence of pain in the pectoral region in 20% of their cases; they opined that neck, periscapular, and pectoral region pain was referred from the disk itself and that arm pain was the result of nerve root compression.

In the Radhakrishnan population-based series, cervicobrachial pain was present at the onset in 98% and was radicular in 65% (Radhakrishnan et al., 1994). Paresthesias were reported by 90%, almost identical to the Yoss series. Pain on neck movement was present in 98%; paraspinal muscle spasm, in 88%; decreased reflexes, in 84% (triceps 50%, biceps or brachioradialis 34%); weakness, in 65%; and sensory loss, in 33% of participants. Employing their criteria, 45% of the patients were judged to have definite CR, 30% probable, and 25% possible. In a Cleveland Clinic series, 70% had motor and sensory symptoms, 12% had motor symptoms only, and 18% had sensory symptoms only (Levin, Maggiano, & Wilbourn, 1996).

Localizing information in suspected CR is obtainable from the history, especially from patterns of pain radiation and paresthesias. Radiating pain on coughing, sneezing, or straining during a bowel movement is significant but seldom elicited. Increased pain on shoulder motion suggests nonradicular disease. Relief of pain by resting the hand atop the head is reportedly characteristic of CR (hand on head, Bakody, or shoulder abduction relief sign), but this phenomenon can occur with a Pancoast tumor.

Physical examination in patients with suspected CR should include an assessment of the range of motion (ROM) of the neck and arm, a search for root compression signs, detailed examination of strength and reflexes, a screening sensory examination, and probing for areas of muscle spasm or trigger points (Abbed & Coumans, 2007). The cervical spine ROM is highly informative. Patients should be asked to put their chin to chest and to either shoulder, each ear to shoulder, and to hold the head in full extension; these maneuvers all affect the size of the intervertebral foramen. Pain produced by movements that close the foramen suggest CR. Pain on the symptomatic side on putting the ipsilateral ear to the shoulder suggests radiculopathy, but increased pain on leaning or turning away from the symptomatic side

Table 17.1 Clinical Findings in 100 Cervical Radiculopathy Patients

Clinical Finding	Highly Localizing to	Suggestively Localizing to
Pain only in neck and shoulder		C5
Presence of scapular/interscapular pain		C7 or C8
No pain below elbow		C5
Pain involving the posterior upper arm		C7
Pain involving the medial upper arm		C7 or C8
Paresthesias limited to the thumb	C6	
Paresthesias limited to index and middle	C7	
Paresthesias limited to ring and small	C8	
Whole hand paresthesias		C7
Depressed triceps reflex	C7 or C8	
Depressed biceps and brachioradialis reflexes	C5 or C6	
Weakness of spinatus	C5	
Weakness of deltoid	C5 or C6	
Weakness of triceps	C7	
Weakness of hand intrinsics	C8	
Sensory loss over thumb only		C6 OR C7
Sensory loss involving middle finger	C7	
Sensory loss involving small finger	C8	

Modified from Yoss, R. E., Corbin, K. B., MacCarty, C. S., Love, J. G. (1957). Significance of symptoms and signs in localization of involved root in cervical disc protrusion. *Neurology, 7,* 673-683.

suggests a myofascial origin. Radiating pain with the head in extension and tilted slightly to the symptomatic side is highly suggestive of CR (Spurling maneuver, foraminal compression test); brief breath holding in this position will sometimes elicit the pain. The addition of axial compression does not seem to add much. Light digital compression of the jugular veins until the face is flushed and the patient is uncomfortable will sometimes elicit radicular symptoms: unilateral shoulder, arm, pectoral, or scapular pain or radiating paresthesias into the arm or hand (Viets or Naffziger sign). This is a highly specific but insensitive finding. An occasional patient has relief of pain with manual upward neck traction. Patients with a globally restricted cervical spine ROM often have extensive degenerative disease. Patients with large disk ruptures or cervical spinal stenosis may have a positive Lhermitte sign on neck flexion.

See *Clinical Signs in Neurology: A Compendium* for an extensive discussion and video of physical examination signs in CR (Campbell, 2016).

Pain or limitation of motion of any upper extremity joint should signal the possibility of nonradicular disease. The patient should be asked to put the shoulder through a full active ROM, touching the hand to the opposite shoulder and the opposite ear, then reaching behind as high between the scapulae as possible. Any pain or limitation of motion on the symptomatic side suggests bursitis, capsulitis, tendonitis, or impingement syndrome rather than CR as the cause of the patient's pain.

A focused but detailed strength examination should at least assess the power in the deltoids, spinatus, biceps, triceps, pronators, wrist extensors, abductor pollicis brevis, and interossei. The sensory examination should concentrate on the hand, and particularly assess touch, since the large, myelinated fibers conveying light touch are more vulnerable to pressure injury than the smaller fibers carrying pain and temperature. Because of the extensive overlap of dermatomes, sensory loss in CR is seldom conspicuous. The reflex examination should include not only the standard upper extremity reflexes but the knee and ankle jerks and plantar reflexes as well. Increased lower extremity reflexes and extensor plantar responses suggest myelopathy complicating the radiculopathy.

Based on the foregoing, Box 17.1 outlines the clinical data that favor the diagnosis of CR.

Box 17.1 Features Favoring Cervical Radiculopathy as Opposed to Other Causes of Neck and Arm Pain

- Age 35–60 years
- Acute/subacute onset
- Past history of cervical or lumbosacral radiculopathy
- Cervicobrachial pain radiating to shoulder, periscapular region, pectoral region, or arm
- Paresthesias in arm or hand
- Pain on neck movement—especially extension or ipsilateral bending
- Positive root compression signs
- Radiating pain with cough, sneeze, or bowel movement
- Myotomal weakness
- Decreased reflex(es)
- Dermatomal sensory loss
- Pain relief with hand on top of head
- Pain relief with manual upward traction

EVALUATION AND DIAGNOSIS

Several different clinical syndromes may ensue from degenerative spine disease, including simple, single-level radiculopathy; multilevel radiculopathy; cervical myelopathy; cervical radiculomyelopathy; and occasionally a central cord or Brown-Séquard syndrome. Rarely, radiculopathy results from other processes, such as tumor (e.g., neurofibroma, meningioma, metastasis), infection (e.g., Lyme disease, zoster, cytomegalovirus, syphilis, epidural abscess), infiltration (e.g., meningeal neoplasia, sarcoidosis), or ischemia (Naftulin, Fast, & Thomas, 1993). Diabetes commonly causes a lumbosacral radiculoplexopathy syndrome but can also frequently produce a painful thoracic radiculopathy often confused with herpes zoster and rarely a cervicobrachial radiculopathy (Katz et al., 2001). With acute trauma, roots are sometimes injured along with the cervical spine or the BP and in fact may be completely avulsed from the spinal cord in a severe BP injury. Acute and chronic inflammatory radiculoneuropathies commonly involve the roots. Other rare causes include arachnoiditis, root sleeve cyst, epidural lipomatosis, and spinal arteriovenous malformation.

A number of clinical conditions may be confused with CR, primarily brachial plexopathies, entrapment neuropathies, and non-neuropathic mimickers. The more common musculoskeletal conditions causing confusion include shoulder pathology (bursitis, tendinitis, impingement syndrome), lateral epicondylitis, and DeQuervain tenosynovitis. Cervical myofascial pain, facet joint disease, and cervical vertebral body disease can cause neck pain with referred pain to the arm. Patients with cervical strain due to whiplash rarely have radiculopathy. Lyme disease can cause meningitis and radiculitis, producing neck and arm pain. A rare patient with subarachnoid hemorrhage may present with neck pain without headache. Cervical epidural abscess or hematoma may present with neck pain and various neurologic signs. Pain can be referred to the neck, arm, or shoulder from the heart, lungs, esophagus, or upper abdomen.

Clues to the potential presence of an unusual cause of radiculopathy include a history of systemic symptoms such as fever, chills or weight loss, or a history of cancer, immunosuppression or intravenous drug use.

The Quality Assurance committee of the American Association of Electrodiagnostic Medicine has recently reviewed the utility of EMG in the evaluation of patients with CR and formulated a practice parameter addressing this problem (So, Weber, Ball, & Campbell, 1999). The sensitivity of EMG for detecting abnormalities was in the range of 60% to 70%. The sensitivity is significantly higher in patients with motor involvement than in those with only pain or sensory abnormalities, and the yield increases with increasing severity of disease. Because EMG findings are rarely abnormal in normal subjects, the test is highly specific. There is generally a 65% to 85% correlation of EMG abnormalities with imaging and surgical findings. There is unanimity that C7 root lesions are the most common (±60%), C6 as the next most common (±20%), with C5 and C8 lesions making up about

equal proportions of the remainder (Levin et al., 1996; Murphey et al., 1996; Radhakrishnan et al., 1994; Wilbourn & Aminoff, 1998; Yoss et al., 1957).

The examiner should tailor EMG to probe the muscles most likely to be involved. In the absence of clear clinical direction, one must resort to a generic root screen. Choosing which muscles to study, and how many, has heretofore been a matter of personal opinion and preference. Recent investigations have provided some guidance. Lauder and Dillingham (1996) concluded that a screen of six limb muscles plus the paraspinals had a yield of 93% to 98%, and that examining more muscles made no significant additional contribution. Levin et al. (1996) studied 50 patients with surgically proven single-level cervical radiculopathies. They found stereotyped patterns with C5, C7, and C8 lesions, but a variable pattern with C6 lesions, which could resemble C5 or C7. Patients with a clinical and electrodiagnostic picture of C8 radiculopathy are particularly challenging, as more rostral pathology can mimic C8 radiculopathy and many do not actually have lesions involving the C8 root. In one study of 31 patients, only 16% had C8 root compression (Hehir, Figueroa, Zynda-Weiss, Stanton, & Logigian, 2012).

Plain cervical spine radiographs may show degenerative changes but are of little use in the diagnosis of a specific radiculopathy. Many asymptomatic patients have degenerative changes. Plain films, especially with flexion and extension views, may be useful in patients with more advanced disease to rule out any instability. Computed tomography (CT) is much more useful for visualizing bony detail but does not visualize neural structures unless contrast agent has been instilled (CT myelography). Plain myelography is rarely used. Magnetic resonance imaging (MRI) is the mainstay of diagnosis, although disk herniations are commonly observed on MRI in patients who have no symptoms, particularly in older patients. Several MRI studies have documented that asymptomatic DDD is common. In a study of 1211 healthy volunteers, disk bulging on cervical spine MRI was frequently observed in asymptomatic subjects, including patients in their 20s (Nakashima et al., 2015). Even spinal cord compression and intraparenchymal signal changes were seen in older subjects. Careful clinical and electrodiagnostic correlation therefore remains essential (Abbed & Coumans, 2007).

TREATMENT AND MANAGEMENT

Treatment relies on three approaches: mechanical, medicinal, and surgical (Box 17.2). Nerve roots lying in the foramen normally enjoy freedom of movement through a small range. The size of the intervertebral foramen and the lateral recess changes dynamically with neck movement. The mainstay of conservative treatment is to reduce neck movement and increase the size of the foramen.

A soft cervical collar is usually helpful. For compressive CR, the collar should be worn "backward," with the high side posterior to maintain the neck in slight flexion and open the foramina. Hard collars cannot be turned around in this fashion and are not as useful for a radiculopathy syndrome as for myelopathy. The soft collar should be worn at night if tolerated; otherwise, the patient should use a cervical pillow. Prolonged use of a cervical collar may weaken neck muscles, so this method of treatment should be limited to a few weeks at most.

Box 17.2 Treatment of Cervical Radiculopathy

Soft cervical collar (backward)
Hard cervical collar in some situations
Cervical pillow for nighttime use
Cervical traction
Modality physical therapy (heat, ice, ultrasound)
Cervical epidural steroids
Selective foraminal steroid injection
Nonsteroidal anti-inflammatory drugs
Other analgesics for pain control as necessary
Surgical referral for severe, unrelenting pain despite conservative therapy
Strength Medical Research Council grade 4/5 or worse in any muscle
Worsening motor deficit
Evidence of myelopathy

Cervical traction for 15 to 30 minutes three times a day is often very helpful; it distracts the spine, opens the foramina, and gives the involved root respite. An over-the-door home traction unit is adequate; referral to a physical therapist is unnecessary. The patient should start with a low weight (5–8 lb) and advance as tolerated to 12 to 15 lb. Too rapid a weight increase may cause neck or jaw soreness and limit compliance. It is theoretically best for the patient to face the door with the neck slightly flexed; the combination of flexion and distraction is more effective in opening the foramen. However, it is difficult to do anything but stare at the door during such treatment; if facing away from the door appears equally efficacious for the individual patient, it is permissible and may improve compliance. Neuroimaging should be done before traction is employed.

Modality physical therapy, or local heat or ice, may provide some relief of the axial pain component, but the effects seldom persist much beyond the individual treatment session. Cervical ROM exercises are of no proven benefit. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the radicular inflammatory component and relieve pain. Other analgesics are often necessary in addition, including occasional narcotics. When the neurologic deficit is moderate (Medical Research Council [MRC] grade 4+/5 in the most involved muscles), a course of oral steroids is reasonable (e.g., prednisone 60–100 mg/day for 7–10 days, tapering over the next 7–10 days) (Ghasemi et al., 2013; Goldberg et al., 2015). Gabapentinoids are sometimes used in both cervical radiculopathy and LSR, but there is very little evidence to support their effectiveness. Intensive conservative therapy is usually continued for 3 to 6 weeks, and if the patient is no better after that interval, surgical referral should be considered. Muscle relaxants add little and cause side effects of sedation and depression.

Epidural steroid injections have been used for the treatment of radiculopathy, first lumbosacral and later cervical, since the 1950s. Despite this long history, there is a paucity of quality clinical evidence supporting their efficacy. Cervical injections are done via either an interlaminar or transforaminal route. One prospective, randomized trail using transforaminal injections found no difference in

outcome between treatment with steroids/local anesthetic or saline/local anesthetic at 3 weeks (Anderberg, Annertz, Persson, Brandt, & Säveland, 2007). A 2015 systematic review of the literature between 1966 and 2014 found only a single high-quality study regarding epidural steroids in cervical disk herniations. A total of 120 subjects received interlaminar injections of either local anesthetic (group I) or local anesthetic and steroid (group II). Significant improvement was seen in 77% in Group I and 80% in Group II (Manchikanti, Cash, Pampati, Wargo, & Malla, 2013).

In a 2007 review of the risks of cervical transforaminal epidural steroids, the authors pointed out the lack of randomized controlled studies supporting their efficacy; that is still the case. They surveyed physician members of the American Pain Society and collected reports of 78 complications, including 16 vertebrobasilar brain infarcts, 12 cervical spinal cord infarcts, and 2 combined brain/spinal cord infarcts, including 13 fatalities. Evidence suggests an embolic mechanism due to inadvertent intra-arterial injection of particulate corticosteroid as the primary mechanism. This risk could potentially be minimized by using the nonparticulate glucocorticoid dexamethasone. Other potential mechanisms include vertebral artery perforation causing dissection/thrombosis and needle-induced vasospasm. The authors conclude that there is a significant risk of serious neurologic injury after cervical transforaminal steroid injections (Scanlon, Moeller-Bertram, Romanowsky, & Wallace, 2007).

Consider surgical referral in patients with an MRC strength of grade 4/5 or worse in any muscle or evidence of myelopathy or excruciating pain unresponsive to conservative treatment. In a population-based study, 26% required surgery. As with epidural steroids, there is scant support in the literature for the efficacy of surgery for CR. Prospective, randomized trials have either not shown a difference in outcome between anterior cervical discectomy and fusion (ACDF) and physical therapy or showed a slight difference favoring surgery early, with no difference at 12–24 months (Engquist et al., 2013; Peolsson et al., 2013; Persson, Moritz, Brandt, & Carlsson, 1997). A prospective, randomized study with 5- to 8-year follow-up showed that ACDF combined with physiotherapy reduced neck disability and neck pain more effectively than physiotherapy alone (Engquist et al., 2017).

Some surgeons now prefer anterior cervical disk replacement/arthroplasty (ACDA; artificial cervical disk replacement) over ACDF. Theoretically, ACDA more closely simulates physiologic motion, preserves segmental mobility, and reduces adjacent segment degeneration (Goedmakers et al., 2020).

One problem investigators face in determining the effectiveness of any treatment for CR, from cervical traction to surgery, is that the natural history of the condition is toward spontaneous resolution. The typical CR patient is significantly improved by 2 to 3 months. There is a generally favorable long-term prognosis; 90% have minimal to no symptoms on prolonged follow-up. A systematic review and evidence-based clinical guideline on CR from the North American Spine society, in regard to the natural history, offered the following consensus statement: "It is likely that for most patients with cervical radiculopathy from degenerative disorders signs and symptoms will be self-limited and will resolve spontaneously over a variable length of time without specific treatment" (Bono et al., 2011).

LUMBOSACRAL RADICULOPATHY

Although many patients suffer with sciatica at some time, clinically significant LSR occurs in only 4% to 6% of the population. Abnormalities on imaging studies are common in asymptomatic subjects and only loosely associated with symptoms and neurologic examination (Carrino et al., 2009; Jensen et al., 1994; Wipf & Deyo, 1995). Recent studies using standing MRI may shed light on the matter (Alyas, Connell, & Saifuddin, 2008). There are numerous potential origins for LBP. Most benign self-limited episodes of LBP arise from musculoligamentous structures, and discomfort is localized to the low back region. However, numerous pain-sensitive structures can underlie a clinical episode of LBP: the intervertebral disk, especially the outer fibers of the annulus; the facet joints; other bony structures; and spinal nerve roots. In addition, pain can be referred to the lower back from visceral structures in the abdomen and pelvis. The back may also be involved in systemic diseases, such as spondyloarthropathies.

CLINICAL SIGNS AND SYMPTOMS

Involvement of some of these pain-sensitive structures can produce referred pain that radiates to the extremity (buttock, hip, thigh) and can simulate the radiating pain of nerve root origin (Table 17.2). A study of 1293 cases of LBP concluded that referred pain to the lower limb most often originated from sacroiliac and facet joints. Referred pain to the extremity occurred nearly twice as often as true radicular pain and frequently mimicked the clinical presentation of radiculopathies (Bernard & Kirkaldy-Willis, 1987). Investigations have demonstrated that considerable pain can be referred to the buttock and thigh, with disease limited to the disk, the facet joint, or the sacroiliac joint (Milette, Fontaine, Lepanto, & Breton, 1995; Schwarzer, Aprill, & Bogduk, 1995; Schwarzer et al., 1994a). A study of 92 patients with chronic LBP concluded that 39% had annular tears or other forms of internal disk disruption as the cause of their pain. No available clinical test differentiated between patients with internal disk disruptions and those with compressive radiculopathy (Schwarzer, Aprill, Derby, et al., 1995). A similar situation seems to exist with facet joint pain (Nath, Nath, & Pettersson, 2008; Schwarzer et al., 1994b). The first suggestion that a patient may have nerve root compression usually comes because of radiating pain into one or both lower extremities. Conservative therapy still usually suffices, even in patients with HNPs, and only 5% to 10% of patients ultimately need surgery (Deyo, Loeser, & Bigos, 1990). Operative intervention is generally appropriate only when there is a combination of definite disk herniation shown by imaging studies, a corresponding syndrome of radicular pain, a corresponding neurologic deficit, and a failure to respond to conservative therapy.

Deyo, Rainville, and Kent (1992) reviewed the information that could be obtained from the history and physical examination in patients with LBP. They suggest trying to answer three basic questions: Is there a serious, underlying systemic disease present? Is there neurologic compromise that might require further evaluation? Are there psychological

Table 17.2 Clinical Signs and Symptoms in Low Back Pain and Lumbosacral Radiculopathy

Disorder	Site of Involvement	Local Pain	Referred Radiating Pain	Radicular Radiating Pain	Pain Increased by	Pain Decreased by	+ Straight Leg Raising	Weakest Muscles	Decreased Reflex
L5 radiculopathy; HNP	L5 root–posterolateral HNP at L4–5	Back	Buttock, posterior thigh	Buttock, posterior thigh, lower leg, dorsum of foot, big toe	Sitting > standing, cough, sneeze, spinal flexion	Standing, lying	Yes	TA EHL, TP, EDL/EDB, PL, TFL, GMD	MHS
L5 radiculopathy; lateral recess syndrome	L5 root-lateral recess stenosis	Back	Buttock, posterior thigh	Buttock, posterior thigh, lower leg, dorsum of foot, big toe	Standing, extension	Spinal flexion	No		
S1 radiculopathy; HNP	S1 root–posterolateral HNP at L5–S1	Back	Buttock, posterior thigh	Buttock, posterior thigh, lower leg, dorsum of foot, big toe	Sitting > standing, cough, sneeze, spinal flexion	Standing, lying	Yes	Gastrocnemius, FDL, short toe flexors, decreased toe raises	Ankle, LHS
S1 radiculopathy; lateral recess syndrome	S1 root-lateral recess stenosis	Back	Buttock, posterior thigh	Buttock, posterior thigh, lower leg, dorsum of foot, big toe	Standing, extension	Spinal flexion	No		
Diskogenic pain	Intervertebral disk–torn annulus; internal disruption	Back	Buttock, posterior thigh	None	Sitting, spinal flexion	Lying	No	No weak muscles, possible splinting due to pain	None
Musculoligamentous pain	Musculoligamentous structures of low back	Back	Buttock, posterior thigh	None	Walking, bending, stooping, minor movements	Sitting or lying	Negative or equivocal, not radiating	No weak muscles	None
Nonorganic		Back + any other; often back + neck		None	No consistent pattern	No consistent pattern	Variable and nonorganic	None	None

EDB, Extensor digitorum brevis; *EDL*, extensor digitorum longus; *EHL*, extensor hallucis longus; *FDL*, flexor digitorum longus; *GMD*, gluteus medius; *HNP*, herniated nucleus pulposus; *LHS*, lateral hamstrings; *MHS*, medial hamstrings; *PL*, peroneus longus; *TA*, tibialis anterior; *TFL*, tensor faciae latae; *TP*, tibialis posterior.

factors leading to pain amplification? Factors that suggest the possibility of underlying systemic disease include a history of cancer, unexplained weight loss, pain lasting longer than 1 month, pain unrelieved by bed rest, fever, focal spine tenderness, morning stiffness, improvement in pain with exercise, and failure of conservative treatment.

The utility, or lack thereof, of various physical examination findings has been studied. The straight leg raising (SLR) test remains the mainstay in detecting radicular compression. The test is performed by slowly raising the symptomatic leg with the knee extended. Tension is transmitted to the nerve roots between about 30 and 70 degrees and pain increases. Pain at less than 30 degrees raises the question of nonorganicity, and some discomfort and tightness beyond 70 degrees are routine and insignificant. There are various degrees or levels of positivity. Ipsilateral leg tightness is the lowest level, pain in the back is more significant, and radiating pain in the leg is highly significant. When raising the good leg produces pain in the symptomatic leg (crossed SLR sign), the likelihood of a root lesion is very high.

The positivity of the SLR should be the same with the patient supine or seated. If a patient with a positive supine SLR does not complain or lean backward when the extended leg is brought up while in the seated position (e.g., under the guise of doing the plantar response), it is suggestive of nonorganicity. The SLR can be enhanced by passively dorsiflexing the patient's foot just at the elevation angle at which the increased root tension begins to produce pain. A quick snap to the sciatic nerve in the popliteal fossa just as stretch begins to cause pain (bowstring sign, or popliteal compression test) accomplishes the same end. Patients with hip disease have pain on raising the leg whether the knee is bent or straight; those with root stretch signs have pain only when the knee is extended. Pain from hip disease is maximal when the hip is flexed, abducted, and externally rotated by putting the patient's foot on the contralateral knee and pressing down slightly on the symptomatic knee (FABERE test). There are other procedures for checking the sacroiliac joints.

See *Clinical Signs in Neurology: A Compendium* for an extensive discussion and video of physical examination signs in LSR (Campbell, 2016).

The neurologic examination should include assessment of power in the major lower extremity muscle groups, but especially the dorsiflexors of the foot and toes, and the evertors and invertors of the foot. Plantar flexion of the foot is so powerful that manual testing rarely suffices. Having the patient do 10 toe raises with either foot is a better test. Sensation should be tested in the signature zones of the major roots. The status of knee and ankle reflexes is informative about the integrity of the L3–4 and S1 roots. There is no good reflex for the L5 root, but the hamstring reflexes are occasionally useful. The medial and lateral hamstrings are both innervated by both L5 and S1, but the medial hamstring tends to be more L5 and the lateral more S1. An occasional L5 radiculopathy produces a clear selective diminution of the medial hamstring reflex. Rarely, an L5 radiculopathy will cause a deceased peroneal reflex (see http://neurosigns.org/wiki/Peroneal_reflex). In a patient with absent ankle jerks and a question of neuropathy, loss of the lateral hamstring reflex with preservation of the medial helps confirm radicular disease. Preservation of the lateral hamstring jerk with an absent ankle jerk suggests a length-dependent process (i.e., peripheral neuropathy).

Studies have found that only 8 of 27 physical tests investigated successfully discriminated between patients with chronic LBP and normal control subjects. The eight useful tests were pelvic flexion, total spinal flexion, total extension, lateral flexion, SLR, spinal tenderness, bilateral active SLR, and sit-up (Deyo et al., 1992). Tests for nonorganicity (Waddell signs) are very useful. Pain during simulated spinal rotation, pinning the patient's hands to the sides while passively rotating the hips back and forth (no spine rotation occurs as shoulders and hips remain in a constant relationship), suggests nonorganicity. This is also suggestive with a discrepancy between the positivity of the SLR between the supine and seated position, pain in the back on pressing down on top of the head, widespread and excessive "tenderness," general overreaction during testing, and nondermatomal/nonmyotomal neurologic signs. The presence of three of these signs suggests, if not nonorganicity, at least embellishment (Deyo et al., 1992).

The major radicular syndromes include HNP, lateral recess stenosis, and spinal stenosis with cauda equina compression. Virtually all patients with radiculopathy have sciatica. The odds of a patient without sciatica having radiculopathy have been estimated at 1:1000 (Deyo et al., 1992). The details of the sciatica are noteworthy, including the exact pattern of radiation, influence of body position and movement, and presence or absence of neurologic symptoms.

With HNP or lateral recess stenosis, leg pain usually predominates over back pain. With HNP, the pain is typically worse when sitting, better when standing, better still when lying down, and generally worse in flexed than extended postures—all reflecting the known changes in intradiscal pressure that occur in these positions. With lateral recess stenosis, the pain is worse with standing or walking and relieved by sitting with the torso flexed or by lying down. Patients with HNP tend to have a positive SLR, but those with recess stenosis do not. The essence of the recess stenosis picture, then, is pain on standing, lack of pain on sitting, and a negative SLR. The essence of the HNP picture is pain worse on sitting, lessened with standing, and a positive SLR. Patients with HNP are usually in the 30 to 55 years age range; those with lateral recess stenosis are a bit older. As with CR, pain may exacerbate with cough, sneeze, or Valsalva maneuver.

EVALUATION AND DIAGNOSIS

As patients mature into the seventh decade and beyond, the liability to disk rupture decreases, but degenerative spine disease attacks in a different form. Osteophytic spurs and bars; bulging disks; thickened laminae and pedicles; arthritic, hypertrophied facets; and thickened spinal ligaments all combine to narrow the spinal canal and produce the syndrome of spinal stenosis. An extension posture contributes to spinal stenosis by causing narrowing of the foramina and dorsal quadrants and buckling of the ligamentum flavum. Narrowing of the canal compresses neural and possibly vascular structures. Flexing the spine, as by leaning forward, stooping over, or sitting down, opens the canal and decreases the symptoms.

Patients with spinal stenosis and neurogenic claudication experience pain, weakness, numbness, and paresthesias/dysesthesias when standing or walking. Symptoms decrease

with sitting or bending forward. An occasional patient will have a bizarre symptom, such as spontaneous erections or fecal incontinence brought on by walking. Differentiation from vascular claudication is made by the wide distribution of symptoms, the neurologic accompaniments, and the necessity to sit down for relief. Vascular claudication tends to produce focal, intense, crampy pain in one or both calves, and the pain subsides if the patient just stops and stands. Patients with vascular claudication have even more symptoms walking uphill, because of the increased leg work. Neurogenic claudication may decrease when walking uphill because of the increased spinal flexion in forward leaning. Patients with vascular claudication have as much trouble riding a bicycle as walking because of the leg work involved, whereas forward flexion on the bicycle opens up the spinal canal, allowing patients with neurogenic claudication to ride a bike with greater ease than they can walk.

An investigation of 68 patients with lumbar spinal stenosis found that pseudoclaudication, or neurogenic claudication, was the most common symptom, producing pain, numbness, or weakness on walking, frequently bilaterally and usually relieved by flexing the spine. Mild neurologic abnormalities occurred in a minority of patients. EMG showed one or more involved roots in 90% of patients (Hall et al., 1985).

The vast majority of LSRs are due to degenerative spine disease. Other disease processes can occur and may require exclusion. As with CR, patients may develop back pain and radiculopathy with epidural abscess or hematoma, diffuse meningeal neoplasia, diabetes, and other conditions (Naftulin et al., 1993).

Plain lumbosacral spine films are rarely helpful except in the setting of acute trauma or suspected infection or malignancy. Plain CT may be useful in patients who are unable to undergo MRI; when combined with intrathecal contrast, CT is highly accurate for detecting nerve root compression (CT myelography). Plain myelography is sometimes useful, particularly in patients unable to undergo MRI because of metallic fixation and in those too obese to fit in an MRI scanner. MRI is the imaging procedure of choice in LSR, again with the caveat that many asymptomatic patients have disk disease on MRI that is not clinically relevant (Jensen et al., 1994).

TREATMENT AND MANAGEMENT

Investigators face the same problems in determining the effectiveness of treatment for LSR as for CR, since symptoms of LSR due to disk herniation are typically self-limited. In patients with underlying spondylosis due to degenerative arthritis, radicular symptomatology may wax and wane, making the long-term prognosis less favorable than with disk herniation.

Studies have clearly shown that bed rest is not efficacious in patients with nonspecific or mechanical LBP (Kinkade, 2007). There is less information about the role of bed rest in acute LSR, and brief, judicious bed rest may still be useful for short-term symptom control in patients who are in acute, severe pain. At the very least, if the patient remains up and active, he or she should avoid activities such as bending or lifting, which are known to increase intradiscal pressure. Patients often find particular positions that are comfortable and particular activities to avoid.

Any benefit from agents such as benzodiazepines and cyclobenzaprine are probably due more to the drowsiness induced, helping to keep the patient inactive, than to any muscle relaxant effects. NSAIDs may be useful both for pain control and to help reduce acute radicular inflammation, although trials have not substantiated their usefulness compared to placebo (Rasmussen-Barr et al., 2017). Opioids may be needed for pain relief in the acute situation. A short course of oral steroids is sometimes useful. Supportive evidence is marginal (Goldberg et al., 2015; Holve & Barkan, 2008). Drugs used to treat neuropathic pain, such as tricyclic antidepressants, gabapentin, and similar agents, may be useful for the management of chronic radiculopathy, but there is little evidence that they are helpful in the acute situation.

Many studies have been done regarding epidural steroids for LSR and spinal stenosis, leading in turn to a number of meta-analyses (Armon, Argoff, Samuels, & Backonja, 2007; Chou et al., 2015; Manchikanti, Knezevic, Boswell, Kaye, & Hirsch, 2016; Pinto et al., 2012). The conclusion in general is that any effect of epidural steroids is short lived and the treatment effect is small. The systematic review and meta-analysis by Chou et al. (2015) concluded that there was effectiveness for radiculopathy but the benefits were small and not sustained, and that there was no effectiveness for spinal stenosis. The 2016 systematic review and meta-analysis by Manchikanti et al. (2016) concluded that lidocaine alone and lidocaine in conjunction with steroids were equally effective. In six studies with 649 patients, there was no difference in improvement comparing lidocaine alone to lidocaine with steroids at 3 or 12 months. Epidural steroids administered with sodium chloride solution were ineffective. This raises the possibility that any benefit from steroids may arise through some mechanism other than an anti-inflammatory one and that perhaps epidural injections should use local anesthetics alone, as was routinely the practice between 1901 and the early 1950s.

Physical therapy such as back exercises should probably be avoided with an acute painful radiculopathy. After the acute stage has subsided, physical therapy may certainly be useful. However, if back exercises reproduce radicular pain, they should be stopped immediately. Numerous other nonoperative treatments are occasionally used, although demonstration of effectiveness in randomized trials is generally lacking. These treatments include transcutaneous electrical nerve stimulation, acupuncture, massage, and spinal manipulation.

The vast majority of patients with acute LSR improve with time and conservative management, even when the disk herniation remains visible on MRI. Surgical referral should be prompt if the patient develops any evidence of cauda equina syndrome. Whether patients with more routine LSR benefit from surgery remains controversial. There is no evidence that early surgery, in the absence of a severe or progressive neurologic deficit, improves the outcome for radiculopathy due to lumbar disk herniation with or without spinal stenosis. Many patients with a minor motor deficit, such as a mild foot drop, recover with nonsurgical treatment.

If surgery is required, a number of techniques are currently employed, including traditional open laminectomy and discectomy, microdiscectomy with hemilaminectomy, and minimally invasive techniques such as percutaneous discectomy, laser discectomy, percutaneous endoscopic discectomy, microendoscopic discectomy, and radiofrequency nucleoplasty (Kanno, Aizawa, Hahimoto, & Itoi, 2019).

Studies comparing surgery to nonsurgical management for radiculopathy generally show that operated patients improve more quickly but that outcomes are similar within 2 years (Peul et al., 2007; Weinstein et al., 2006). Nonspecific LBP with DDD associated with subacute or chronic LBP without radicular symptoms is another topic altogether.

PLEXOPATHIES

Numerous pathologic processes may affect either the BP or the LSP (Box 17.3). Whereas the vast majority of radiculopathies are due to compression, the plexopathies may be caused by a number of different pathologic processes. The complex anatomy makes evaluation challenging (Fig. 17.5). The most common and clinically important of the BP disorders include neuralgic amyotrophy (NA) (acute brachial plexopathy or brachial plexitis); trauma, such as with missile and stab wounds or motor vehicle (especially motorcycle) accidents; neoplasms; postradiation plexopathy; obstetric palsies; postsurgical plexopathy; the "stinger" or "burner" phenomenon that frequently affects football players, which is likely a mild form of plexus injury; and TOS. Other causes include external compression (e.g., backpack or rucksack palsy), compression from an internal process (e.g., encroachment on the lower BP from a Pancoast tumor), or involvement in systemic processes such as systemic lupus erythematosus (SLE) or sarcoid, or iatrogenic plexopathy during cardiac surgery. The BP may rarely be involved in a number of other conditions, including lupus, lymphoma, Ehlers-Danlos syndrome, and infectious or parainfectious disorders. Some of these processes are by nature progressive.

With pressure injuries, the same general rules apply as for other nerves. Mild lesions produce primarily demyelination and can cause severe clinical deficits but have an excellent prognosis. With plexopathies, there may be the additional complication of disease progression. Many of the conditions that affect the plexuses are not static. Pancoast tumors continue to grow, radiation damage tends to progress, and systemic diseases such as SLE continue their activity. All these mechanisms of injury make the pathophysiology of plexopathies complex and the clinical evaluation challenging.

EVALUATION AND DIAGNOSIS

The electrodiagnostic principles for both BP and LSP conditions are similar. From a clinical and electrodiagnostic standpoint, the most common exercise is distinguishing plexopathy from radiculopathy. The NEE is the mainstay of diagnosis and localization, although sensory (more so than motor) conduction studies, late responses, and somatosensory evoked potentials (SEPs) can sometimes provide helpful information. The key feature is abnormalities in the distribution of some plexus component, a trunk or a cord, sparing the paraspinals. The status of the sensory potentials is critical for distinguishing plexopathy from radiculopathy. In radiculopathy, the sensory potentials are normal; in plexopathy, they are frequently absent or low in amplitude in the distribution of the affected plexus component (e.g., abnormal lateral antebrachial cutaneous in upper trunk or lateral cord plexopathies and abnormal medial antebrachial cutaneous (MABC) in lower trunk or medial cord plexopathies).

Box 17.3 Causes of Brachial Plexopathy

Infectious/Parainfectious/Injections

Immunizations
Serum sickness
Botulinum toxin
Interleukin 2
Interferon
Heroin
Lyme disease
Erlichiosis
Herpes zoster
HIV infection
Epstein-Barr virus infection
Cytomegalovirus infection
Parvovirus infection
Yersiniosis

Hereditary

Hereditary neuralgic amyotrophy
Hereditary neuropathy with liability to pressure palsies (HNPP)
Ehlers-Danlos syndrome

Physical Injury

Radiation therapy
Cardiac surgery
Birth injury
Other postoperative plexopathies
Shoulder dislocation
Penetrating wounds
Axillary angiography
Clavicular nonunion
Prolonged burner

Other Causative Disorders/Conditions

Neuralgic amyotrophy
Thoracic outlet syndrome
Systemic lupus erythematosus
Pregnancy
Systemic vasculitis
Stretch
External pressure (e.g., backpack palsy, seat belts, Posey palsy)
Post–liver transplantation
Lymphoma
Metastatic disease
Pancoast tumor
Primary nerve tumors
Tattoos
Interscalene block
Myositis ossificans
Heparin therapy
Nodular fasciitis

Imaging of the Plexus and Peripheral Nerves

MRI has become the standard method for imaging the BP and the LSP. Magnetic resonance (MR) neuroradiography is very useful in the diagnosis and management of peripheral nerve lesions but is still not widely available (Griffith & Lalam, 2019; Holzgrefe, Wagner, Singer, & Daly, 2019; Pham, Bäumer, & Bendszus, 2014). Ultrasound is also useful in evaluating the BP, and MRI and ultrasound can complement each other in the evaluation of plexopathies (Baute et al., 2018; Griffith & Lalam, 2019).

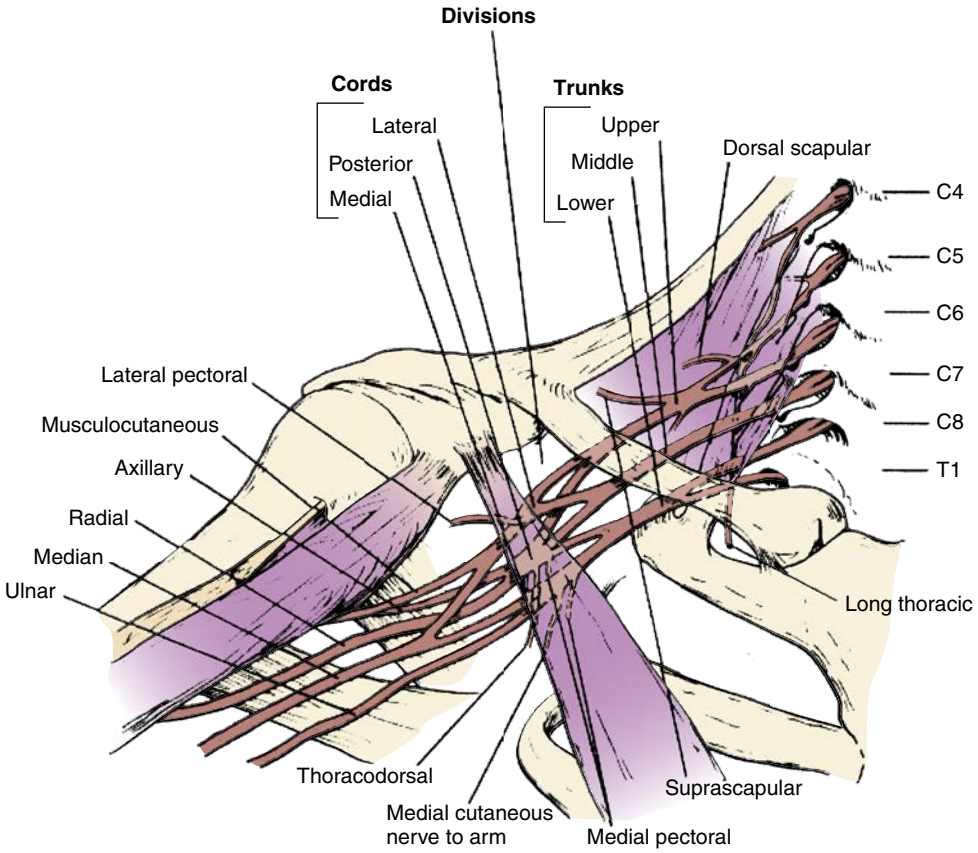


Fig. 17.5 The brachial plexus. (From Canale, S. T., Beaty, J. H. (Eds.) (2007). *Campbell's operative orthopaedics* (11th ed.). St. Louis: Mosby.)

MRI accomplishes two things in peripheral nerve and plexus lesions. It may show denervation changes in muscle that help define the distribution of the abnormality and localize the lesion to a particular nerve or branch. It can image muscles difficult or impossible to access by needle EMG, such as the subscapularis. Alternatively, it may demonstrate a nerve lesion directly.

The technique of peripheral nerve ultrasonography has exploded in recent years. Entire books have been written on the subject (Strakowski, 2014). Peripheral nerves have a characteristic ultrasonographic echotexture and other characteristics that allow differentiation among nerves, tendons, and blood vessels. By ultrasonography, peripheral nerves typically show hypoechoic areas separated by hyperechoic foci. The hypoechoic areas are the nerve fascicles and the hyperechoic areas are epineurium. On longitudinal views, the peripheral nerve shows a characteristic "tram-track" pattern due to reflection of the sound waves off the layers of epineurium that encase the nerve. This fascicular pattern is particularly clear in the median nerve, whereas the ulnar nerve tends to be more hypoechoic. Ultrasonography is particularly useful in the evaluation of peripheral nerve tumors.

Although electrophysiology will remain the primary tool for aiding in the clinical evaluation of patients with focal neuropathies for the foreseeable future, it appears that ultrasonography may be able to supplement or complement electrophysiologic testing for the detection of focal peripheral nerve abnormalities (Choi et al., 2015). Many eletromyographs now come with built-in ultrasound capability. In peripheral nerve trauma, because of the limitations of electrodiagnosis and the vagaries of anatomy, determination of the precise site of injury may remain uncertain. Critical information, such as whether or not a traumatized nerve is in continuity, the position of the proximal and distal stumps, and the presence or absence of a neuroma in continuity, until recently could be determined only by direct surgical inspection. Now both MRI and ultrasound may aid in clinical decision making. In a blinded proof-of-concept study, ultrasonography was able to identify transected nerves in the upper extremity with 89% sensitivity and 95% specificity in fresh cadavers (Cartwright, Chloros, Walker, Wiesler, & Campbell, 2007). In patients with traumatic peripheral nerve injuries, ultrasonography may be a useful tool in determining the precise localization of the injury site, the type of injury, the position of the stumps, and the presence of a neuroma (Cartwright et al., 2007).

DISORDERS OF THE BRACHIAL PLEXUS

Processes that affect the BP primarily include NA (brachial plexitis, Parsonage-Turner syndrome), trauma, cancer, radiation, postoperative plexopathy, and true neurogenic TOS (TNTOS).

Neuralgic Amyotrophy

This condition has gone by a number of names, most frequently *brachial plexitis*, *Parsonage-Turner syndrome*, and *acute brachial plexus neuropathy*. *Neuralgic amyotrophy* is the currently preferred nosology (Campbell, 2014). NA is a fairly stereotyped clinical syndrome characterized by the acute onset of pain in the shoulder and upper arm, followed by weakness

of variable severity, primarily affecting upper arm and shoulder muscles (Subramony, 1988). It runs a protracted course of slow, sometimes incomplete recovery, and sometimes as one arm is recovering the other is stricken. Recurrence is not rare. As in Guillain-Barré syndrome, many patients have some antecedent event, such as viral infection, immunizations, childbirth, or surgery, and the disease is thought to be immunologically mediated, although the precise mechanism remains uncertain. It has a predilection to affect young and middle-aged adults, although it can occur at any age.

The pain in NA is a defining feature. It tends to begin abruptly and is very intense, often more severe at night, often over the lateral deltoid. After a variable interval, usually 3 to 10 days, weakness, often patchy, begins in the shoulder and upper arm, frequently as the pain is subsiding. However, the severe pain often limits patients' ability to state precisely when the weakness began. The weakness is then followed by atrophy, often very severe. Sensory loss is minimal or absent. The disease is frequently bilateral, and in approximately 20% of patients, as the affected extremity is beginning to improve, the other arm begins to develop the condition (van Alfen, 2007).

From the earliest descriptions of NA, a pattern of involvement consistent with a mononeuropathy or multiple mononeuropathies has been observed (Spillane, 1943). Various clinical and radiological studies have demonstrated that the most common patterns of nerve involvement are the suprascapular, axillary, long thoracic, or anterior interosseous nerves (Gaskin & Helms, 2006; Parsonage & Turner, 1948; Scalf, Wenger, Frick, Mandrekar, & Adkins, 2007; Spillane, 1943; van Alfen & van Engelen, 2006). But other nerves, such as the long thoracic, phrenic, musculocutaneous, and posterior interosseous, can also be involved (England & Sumner, 1987). Pain in the shoulder region has been the unifying symptom to suggest pathology within the BP. Since the two most commonly affected nerves are the suprascapular and axillary, it is often stated that NA affects the upper components of the plexus more frequently than the lower ones. But the pattern of clinical or electrical deficits rarely adheres to a complete upper trunk or lateral cord distribution (Ferrante & Wilbourn, 2017). It is incumbent upon the clinician to recognize the neuronal pattern of muscle involvement in NA and distinguish it from the myotomal or segmental pattern of a CR. This is particularly important when normal sensory studies are obtained during electrodiagnostic testing.

There remains debate regarding the site of the primary pathology: the individual nerve proper versus fascicles within BP dedicated to the specific nerve. Most recent data favor extraplexus involvement (Ferrante and Ferrante (2017a, 2017b); Sneag et al., 2018). One ultrasound study demonstrated enlargement in the cross-sectional areas (CSAs) of the median or radial nerves at the level of the upper arm, suggesting pathology outside of the BP (van Rosmalen, Lieba-Samal, Pillen, & van Alfen, 2019). Furthermore, during peripheral nerve surgeries for NA, an hourglass-like constriction of the affected nerve has been observed, again outside of the plexus (Pan et al., 2011).

High-definition ultrasound and MRI assist in the management of NA. Either can exclude other etiologies of plexus or nerve abnormalities, such as peripheral nerve tumors. Additionally, there are abnormalities that may be unique to NA and indicative of poor prognosis. With observation of complete nerve constriction or rotational phenomena on ultrasound, reinnervation may be absent or negligible, portending a poor outcome (Arányi et al., 2017). A "bull's-eye sign" (signal hyperintensity of the nerve periphery with central hypointensity) on MRI may be representative for hourglass constrictions (HGCs) noted intraoperatively (Sneag et al., 2017). Demonstration of these findings may help distinguish suitable patients for peripheral nerve surgery.

There are little data regarding the appropriate treatment of NA. Acutely, corticosteroids can diminish the pain, but there is no solid evidence that treatment affects long-term outcome (van Alfen, van Engelen, & Hughes, 2009). Referral to peripheral nerve surgery should be considered in severe cases when there has been no clinical or electrodiagnostic evidence of spontaneous recovery within 3 months.

Some cases of NA are familial. Patients with hereditary neuropathy with liability to pressure palsies (HNPP), which is a dominant condition due to mutation or deletion in the *PMP22* gene on chromosome 17, may develop recurrent brachial plexopathy, sometimes following minor trauma, which lacks the pain of NA and has a much better prognosis for recovery, with electrodiagnostic studies showing a picture more in keeping with demyelination and less in the way of axon loss. There are three other forms of familial NA unrelated to HNPP: HNA1, HNA2, and HNA3. All are dominant; only HNA1 is on chromosome 17. In a study of 246 NA patients, the 47 HNA patients had an earlier onset (28.4 versus 41.3 years), more attacks (mean, 3.5 versus 1.5) and more frequent involvement of nerves outside the BP (55.8% versus 17.3%), a more severe maximum paresis, and a poorer eventual outcome (van Alfen & van Engelen, 2006). Some HNA patients have unusual dysmorphic features. In one series, cleft palate was present in four individuals, hypotelorism was common, there were unusual skinfolds, and creases were observed on the necks of several individuals and on the scalp of one man (cutis verticis gyrata, a striking appearance). In three families, deep skin creases were present on the limbs of infants and toddlers who were subsequently affected with HNA (Jeannet, Watts, Bird, & Chance, 2001).

There appear to be other immunologically mediated brachial plexopathies. A painless form of brachial plexopathy has been reported as the only manifestation of chronic inflammatory demyelinating polyneuropathy (CIDP) (Amato, Jackson, Kim, & Worley, 1997). When brachial plexopathy is not accompanied by severe pain or followed by atrophy, the possibility of a primarily demyelinating and potentially treatable condition such as a restricted form of CIDP, multifocal motor neuropathy, or a similar condition should be considered in the differential diagnosis (Dionne & Brunet, 2006; Veltkamp, Krause, Schranz, & Meinck, 2003).

Radiation and Neoplastic Plexopathies

Like radiation damage to other parts of the neuraxis, radiation plexopathy (RP) appears after a delay of months to years. This is also the time frame in which the radiation therapy (RT) may have kept a tumor at bay, either a primary nerve tumor such as a malignant neurofibrosarcoma or a local infiltrating neoplasm such as lymphoma or carcinoma of the breast or lung. The problem is distinguishing recurrent tumor

Table 17.3 Differential Diagnostic Points in Neoplastic versus Radiation-Induced Brachial Plexopathy

Neoplastic Plexopathy	Radiation Plexopathy
Horner syndrome common	Horner syndrome rare
Presents with pain	Presents with paresthesias
Pain is predominant symptom	Paresthesias and sensory loss are the predominant symptoms
More lower plexus (equivocal)	More upper plexus (equivocal)
Imaging study shows discrete mass	Imaging study is normal or shows only loss of tissue planes
Diffuse motor and sensory conduction abnormalities	Abnormal sensory nerve action potentials/normal motor neuron conduction velocities Conduction block across plexus Myokymia Fasciculation potentials Paraspinal fibrillations

from RP, a difficult and important differential (Table 17.3). Pain can occur with either condition but is more likely to be an early and dominant symptom in neoplastic plexopathy (Jaeckle, 2004). Sensory dysfunction with numbness and paresthesias is more likely to be the predominant symptom with RP, but some patients have significant pain. Weakness and reflex changes occur in either condition. One study suggested that painless upper trunk lesions with lymphedema suggested radiation injury, and painful lower trunk lesions with Horner syndrome implied tumor infiltration (Kori, Foley, & Posner, 1981). Other studies also suggested that RP had an upper plexus, and neoplastic, a lower plexus distribution, but this was not substantiated in subsequent investigations as a reliable differentiator because of the amount of overlap between the two groups (Campbell, 2014). Most patients in both groups have involvement of the lower trunk or the entire plexus (Harper, Thomas, Cascino, & Litchy, 1989). Patients with RP are much more likely to have prominent fasciculations. The presence of myokymia on EMG is highly suggestive of RP and is clearly the most useful electrodiagnostic discriminating feature.

Harper et al. found that the presence or absence of pain as the presenting symptom, the temporal profile of the illness, a discrete mass on imaging studies, and myokymic discharges on EMG most reliably predicted the underlying cause of the plexopathy. Distribution of weakness was not useful in discriminating between the two groups (Harper et al., 1989). A study of RP in 79 breast cancer patients from an oncologic rather than a neurologic viewpoint revealed that 35% developed RP. In 50%, the process was panplexus, but of those with more focality, 18% had involvement of the upper trunk only, and only 4%, the lower trunk. RP was more common after RT plus cytotoxic therapy than after RT alone. Most patients had no significant latency between RT and the onset of symptoms, raising the possibility of chemotherapy enhancement of radiation effects (Olsen, Pfeiffer, Mondrup, & Rose, 1990). A painful, short-latency brachial plexopathy may also occur during or after RT for Hodgkin disease.

Postoperative Brachial Plexopathy

Postoperative brachial plexopathies were noted to increase dramatically following the advent of modern open heart and coronary bypass surgical procedures. Postoperative plexopathies can occur as a presumably immunologically mediated event after procedures on parts of the body remote from the plexus. The most common situation by far is for plexopathy to follow coronary artery bypass graft (CABG) procedures. A number of injury mechanisms have been postulated, including hyperabduction of the arm, displacement of the clavicle, first rib fracture with plexus laceration, overzealous sternal spreading causing plexus stretch or compression of the plexus between the clavicle and first rib, and laceration of the plexus during attempted internal jugular vein cannulation. Injuries continued to occur when the arms were routinely adducted at the patient's sides.

In a series of 421 CABG patients studied at the Cleveland Clinic, there was a 13% incidence of peripheral nervous system complications, and the majority (5%) were plexopathies (Lederman et al., 1982). The study analyzed 451 different variables. In 74% of the plexopathy patients, there was a correlation between the site of jugular cannulation and the side of the injury, suggesting inadvertent laceration or compression by hematoma. In four of the remaining six patients, an internal mammary graft was used. These grafts require greater sternal retraction and seem more likely to stretch the plexus. So, either jugular cannulation or internal mammary grafting seemed to explain 21 of the 23 cases in this series. Blaming jugular cannulation has not gone unchallenged in the surgical literature.

In a large prospective study, 27 of 1000 patients developed postoperative BP injuries. Patients who underwent grafting of the internal mammary artery had a 10-fold increased incidence of plexus injury (10.6%) as compared with those who did not (<1%) (Vahl, Carl, Muller-Vahl, & Struck, 1991). It appears that optimal positioning and the use of minimal retraction will lessen but not eliminate these injuries.

Most cases of post-CABG plexopathy appear to be traction injuries to the C8 anterior primary ramus rather that to the lower trunk or medial cord (Wilbourn, 2007). Horner syndrome may accompany the variable pain, numbness, and weakness. Induced hypothermia may play a role by increasing the susceptibility to nerve injury. The majority of deficits resolve within several weeks, suggesting that the predominant pathophysiology is demyelination.

Nerve compression injuries may also occur in this setting. In a Cleveland Clinic series, there were five ulnar neuropathies in 421 patients (Lederman et al., 1982). In a prospective study of 20 patients undergoing CABG, conduction slowing of the ulnar nerve across the elbow was present in one third of the patients *preoperatively,* and conduction abnormalities developed in an additional 27% of the ulnar nerves postoperatively, all of which were *asymptomatic* and most of which resolved electrically on follow-up (Watson, Merchant, & Brown, 1992). So, in addition to plexopathies, there appears to be a high incidence of mild, asymptomatic, and undetected ulnar neuropathies following CABG.

Perioperative nerve injuries account for approximately 16% of all anesthesia-related claims in the United States (Barner, Landau, & Campbell, 2003). Possible etiologies include stretch, compression, ischemia, and metabolic derangement, but additional factors make some patients more prone to nerve injury than others, such as patient gender and preexisting disease. In some cases, a discrepancy between the timing of the surgery and injury diagnosis can result from delayed recognition or an insult in the postoperative setting.

Traumatic Plexopathies

Traumatic plexopathies are primarily due to blunt or penetrating trauma or to stretch. Motorcyclists are particularly prone to upper plexus stretch when falling so that the shoulder and head are forced in opposite directions. Most traumatic plexopathies affect the supraclavicular portion or are diffuse. A frequent confounding injury is root avulsion, in which the stretch is severe enough to wrench one or more spinal roots from the cord. The plexus may also suffer external compression, as in backpack palsy or seat belt trauma, or be damaged in the course of shoulder dislocation or fracture of the clavicle. External compression palsies can be severe in susceptible individuals. One of the authors once saw a young paratrooper in whom the initial manifestation of HNPP was an acute, severe backpack palsy. He stood, wearing an 80-lb rucksack, in preparation to jump, but the jump was delayed for 30 to 45 minutes because of wind conditions in the drop zone. In that span of time, he developed an acute, panplexus deficit and the left arm became flail. He jumped anyway! Recovery was prolonged and incomplete. Acute BP compression injury after drinking, akin to Saturday night radial nerve palsy, has been reported (Marchini, Zambito Marsala, Cavagna, & Ferracci, 2007).

Stretch injuries of the plexus occur during childbirth. These most often involve the upper plexus (Erb palsy) or the entire plexus, rarely the lower plexus alone (Klumpke palsy). High birth weight and complicated deliveries are predisposing factors. Some neonates have had fibrillation potentials detected in the first few days of life, suggesting an intrauterine mechanism of injury, such as compression by an amniotic band. Prognosis is generally good and the majority of patients make quick recoveries without specific treatment, suggesting that the pathophysiology is often primarily demyelination. However, any kind of injury can occur, including severe axon loss and even root avulsion, and the injury often results in a devastating disability. For many years, the injury was considered untreatable if it did not resolve on its own. In the 1970s and 1980s, J. Mallet in France revolutionized the management of these patients, showing that neonatal plexus injuries could be successfully repaired surgically and separating patients who should have surgery from those who should be managed conservatively by their ability to perform certain motor functions at certain ages (Mallet, 1972). For example, the ability to get the hand to the mouth by 3 months generally indicated that the patient would recover adequately without surgery (van der Sluijs, van Doorn-Loogman, Ritt, & Wuisman, 2006). Managing these children in the post-Mallet era with the availability of microneurosurgery, intraoperative nerve action potentials, nerve conduits, nerve grafts, and all the tools available in the twenty-first century is a very different proposition than in the past (Piatt, 2004, 2005).

Nerve transfer surgery has been a further revolutionary step in the management of brachial plexopathies (Davidge, Clarke, & Borschel, 2016). Oberlin first described the partial ulnar nerve transfer to restore biceps function, and this is the most widely performed nerve transfer procedure for brachial plexopathy (see later), but the basic concept has found increasing application (Shigematsu et al., 2006). The documentary film *Spark of Nerve* dramatically illustrates what nerve transfer surgery can accomplish.

The "stinger" or "burner" phenomenon is common in American football. Following a block or tackle, a player may develop sudden, intense, dysesthetic pain in the shoulder and arm. The injury is now thought to more likely involve the upper trunk of the plexus rather than the cervical roots. Traction when the head and neck are forcibly separated is one possibility, as in a mild form of the often-devastating upper plexus injury that occurs in motorcyclists. A study at West Point showed that it is more likely that the symptoms result from the shoulder pad being forcefully pushed into the Erb point (Markey, Di Benedetto, & Curl, 1993). A recent review concluded that burners/stingers are traumatic brachial plexopathies, most commonly involving the upper trunk (Ahearn, Starr, & Seiler, 2019). Some players have persistent symptoms, the "prolonged burner" syndrome (Speer & Bassett, 1990).

Thoracic Outlet Syndrome

TOS has a long and controversial history. First described by Kennier Wilson near the turn of the century, it was firmly established in the minds of physicians as a cause of acroparesthesias for more than 40 years before the medical community discovered the far more common entities of carpal tunnel syndrome (CTS) and CR. Surgeons are still struggling to clearly define TOS as a clinical entity nearly 100 years after its original description (Wilbourn, 1991). The surgical literature is inconsistent and often contradictory. In one center where TOS is felt to be common, 409 patients underwent TOS surgery in a 19-year span (Jamieson & Chinnick, 1996). In contrast, one peripheral nerve surgeon believes surgery for TOS should be a rare event (Mackinnon, Patterson, & Novak, 1996). Jamieson et al. find a TOS patient to operate on about every 2 weeks, but most electromyographers, who see patients with acroparesthesias and arm pain with high frequency, encounter one convincing case of TOS every 1 to 2 years (Jamieson & Chinnick, 1996). Perceptions about the prevalence of TOS between surgeons and neurologists are at variance on the order of 100:1 (Katirji & Hardy, 1995; Wilbourn, 1991).

TOS can be differentiated into five subtypes: arterial TOS, venous TOS, traumatic vascular TOS, TNTOS, and

disputed TOS. We will focus on the latter two entities. For a comprehensive review of all, the reader is referred to a two-part article by Ferrante and Ferrante (2017a, 2017b)

There is substantial agreement about the entity of true neurogenic TNTOS: it is rare, more common in young women, and most often due to compression of the lower trunk of the BP by a cervical rib or band. It typically presents with medial hand and forearm pain, medial hand and forearm sensory dysfunction, and weakness and atrophy in the thenar, hypothenar, and other intrinsic hand muscles.

The electrodiagnostic abnormalities in TNTOS include an absent or small MABC sensory amplitude, followed in decreasing frequency by absent or small median motor, ulnar sensory, and ulnar motor amplitudes (Tsao, Ferrante, Wilbourn, & Shields, 2014). The MABC abnormalities closely parallel the median motor response, leading some investigators to conclude that the damage in TNTOS is in a T1 myotomal distribution. Needle EMG shows denervation and chronic neurogenic motor unit potential changes in the distribution of the lower trunk of the plexus. Ideally, diagnosis would hinge on demonstration of focal slowing of nerve conduction in the segment of the plexus at the level of the thoracic outlet. Unfortunately, this technique is not feasible or reproducible (see later).

Contrary to TNTOS, disputed TOS is essentially a pain syndrome with minimal objective data to support its existence. The surgical literature refers to this form of TOS as "neurogenic" and is rife with various invasive treatment modalities despite the absence of the aforementioned objective abnormalities seen in TNTOS (Akkuş, Yağmurlu, Özarslan, & Kalani, 2018; Balderman et al., 2019; Perchoc, Andro, Letissier, Schiele, & Le Nen, 2019; Yin, Gong, & Zhang, 2019). Despite our own skepticism, we deem it important to fully understand the nature of the signs and symptoms that proponents of the syndrome exploit to invoke surgical interventions.

Patients typically have aching pain radiating from the scapular region; the pain can radiate across the axilla, the posterior arm, and medial forearm. There may be paresthesias or dysesthesias in the same region. Shoulder flexion or abduction worsens the pain or paresthesias. Patients complain of weakness but the distribution of the weakness need not adhere to a typical root, plexus, or nerve pattern, and there is no atrophy. Electrodiagnostic studies are normal or deemed irrelevant in diagnosis. The profusion of symptoms attributed to disputed TOS—not only arm pain and numbness but also migraine headaches and a host of other complaints—challenges credulity. No confirmatory tests can reliably substantiate the diagnosis of disputed TOS, which eludes all but clinical surgical evaluation, and can be proved only by surgical exploration, a self-fulfilling prophecy.

The clinical diagnosis of disputed TOS relies on a variety of provocative maneuvers. With the Adson, Halstead, and Wright overhead maneuvers, the limb and neck are moved into different positions while assessing the radial pulse (Wright, 1945). Disappearance of the pulse is considered a positive test. With the elevated arm stress test (EAST), reproduction of the patient's sensory complaints is considered a positive result (Roos, 1979). Other TOS tests include the costoclavicular maneuver, the upper limb tension test, and the Cyriax release test.

There have been few studies of the validity of any of these signs (Campbell, 2016). The available information indicates that the sensitivity, specificity, and LRs of the various physical examination maneuvers are singularly unimpressive. These provocative maneuvers result in a high false-positive rate in normal subjects and an even higher false-positive rate in CTS patients.

Even surgeons now admit that the Adson, Wright, and related maneuvers are useless. Sanders, Hammond, and Rao (2007) stated, "The Adson test has been shown to be of no clinical value. . . . The test is normal in most patients with true neurogenic TOS and at the same time can be positive in many control volunteers." Roos (1976), a leading TOS proponent, when describing the EAST, stated, "pulse obliteration with the arms and head in various positions is a normal finding in the majority of asymptomatic people and therefore has no relation to the etiology or presence of symptoms" and studies have shown "no correlation with impairment of circulation or positional radial pulse changes in almost all patients with true TOS." A systemic review evaluated the accuracy of these clinical tests and concluded that the methodological quality of the included studies was low (Dessureault-Dober, Bronchti, & Bussières, 2018).

A Consortium for Outcomes Research and Education of TOS developed preliminary criteria for "neurogenic TOS," i.e., disputed TOS (Thompson, 2013) (see Table 17.4). Unlike most research criteria that are devised to strictly define a disease or syndrome, these criteria are incontrovertibly nonspecific. Patients must have symptoms for a minimum of 3 months, and symptoms need to extend beyond a single cervical nerve root or peripheral nerve distribution. A criterion includes "symptoms not satisfactorily explained by another condition," but the specialist who makes that determination and the mandatory diagnostic testing to do so are not defined.

The Society for Vascular Surgery also published reporting standards for TOS (Illig et al., 2016). The definition consists of four criteria: signs and symptoms of pathology occurring at the thoracic outlet, signs and symptoms of nerve compression, absence of other pathology potentially explaining the symptoms, and a positive response to a properly performed scalene muscle test injection.

The sustained efforts to define a "neurogenic" syndrome by nonneurologists is a rather peculiar phenomenon.

The droopy shoulder syndrome shares many similarities with disputed TOS (Swift & Nichols, 1984). Some believe it accounts for most cases of TOS. Almost all droopy shoulder syndrome patients are slender young women with long, graceful necks with horizontal or downsloping, rather than the normal slightly upsloping, clavicles. The T2 or lower vertebrae may be visible on lateral cervical spine films because of the low-lying shoulders. Electrodiagnostic studies are typically normal. Symptoms have been attributed to chronic BP stretch due to the low-hanging shoulders. Pain in the shoulder, arm, hand, and sometimes neck and head accompanied by paresthesias are the usual symptoms. Supraclavicular percussion and downward traction on the arms exacerbates, and passive elevation decreases, the symptoms. Treatment is with shoulder strengthening exercises. The prudence of separating droopy shoulder syndrome from other instances of disputed TOS is debatable.

Table 17.4 Preliminary Criteria for TOS: Diagnosis Requires One Criterion in Four of the Five Categories

1. Principal symptoms	1A. Pain in the neck, upper back, shoulder, arm, and/or head 1B. Numbness, paresthesias and/or weakness in the arm, hand, or digits
2. Symptom characteristics	2A. Pain/paresthesias/weakness exacerbated with elevated arm positions 2B. Pain/paresthesias/weakness exacerbated with prolonged or repetitive arm/hand use 2C. Pain/paresthesias radiate down the arm from the supra or infraclavicular space
3. Clinical history	3A. Symptoms began after injury of the head, neck, or upper extremity (including repetitive strain or overuse) 3B. Previous clavicle or first rib fracture; or known cervical rib 3C. Previous cervical spine or peripheral nerve surgery without improvement 3D. Previous treatment for TOS
4. Physical examination	4A. Local tenderness on palpation over scalene triangle or subcoracoid space 4B. Arm/hand or digit paresthesias with palpation over either of the above 4C. Weak handgrip, intrinsic muscles, or digit 5 or thenar/hypothenar atrophy
5. Provocative maneuvers	5A. Positive upper limb tension test 5B. Positive 1- or 3-minute elevated arm stress test (EAST)

TOS, Thoracic outlet syndrome.

EVALUATION AND DIAGNOSIS OF BRACHIAL PLEXOPATHY

Electrodiagnostic assessment in plexopathies seeks to ascertain the distribution of the damage, the completeness of the lesion, the predominant pathophysiology, and whether or not there is an associated root avulsion. The findings vary with the severity and location of the lesion. Mild to moderate lesions would likely show normal motor conductions, low-amplitude sensory nerve action potentials (SNAPs), delayed or absent late responses, and recruitment abnormalities on NEE in a distribution of a trunk or cord of the plexus, sparing the paraspinals. More severe lesions would typically show absent SNAPs and late responses, low compound muscle action potential (CMAP) amplitude in affected muscles, possibly with motor nerve conduction velocity (NCV) slowing in proportion to axon loss, with more severe MUAP abnormalities and fibrillations on NEE.

If there is root avulsion, the DRG and the peripheral processes remain intact and the peripherally recorded sensory potentials remain normal in the face of clinical anesthesia in the same distribution and marked motor abnormalities. However, it is difficult to avulse a root without some associated plexus stretch. Myelography may show a traumatic meningocele in root avulsion, but both false-positive and false-negative studies occur. The correlation between the myelographic and the neurophysiologic data was only 50% in one study (Trojaborg, 1994).

The electrodiagnostic picture in TNTOS is characteristic. Patients have a low-amplitude or absent ulnar SNAP, a low-amplitude median CMAP recorded from the thenar muscles, generally normal conduction velocities except for slowing in proportion to axon loss, delayed or absent median and ulnar F wave responses, and chronic neurogenic motor unit potential changes in the distribution of the lower trunk, sparing the paraspinals. The MABC SNAP is abnormal more frequently than the ulnar SNAP (Campbell, 2014). The reason for the paradoxical involvement of ulnar sensory and median motor fibers is unclear but may be related to the internal fascicular anatomy and selective fascicular vulnerability of the lower trunk.

Conduction slowing across the plexus with stimulation at Erb's point was touted for many years, after the publication of Urschel and Razzuk, as the best method of electrically demonstrating the pathology in TOS (Urschel, 1972). The technique failed utterly in the hands of most EMG operators. Wilbourn and Lederman (1984) later exposed this research as fraudulent, and the Urschel paper was retracted, accompanied by editorial comment regarding ethics in research and followed by a flurry of correspondence. To this day, there is still no convincing evidence that such across-plexus conduction studies have any value. Other techniques, especially SEPs, have been advocated but also proved disappointing, likely due largely to the rarity of compression of neural structures in suspected TOS.

NA produces a stereotyped clinical syndrome, a spotty axon loss pattern on NEE, and abnormal SNAPs (Subramony, 1988). Myokymia and the absence of pain suggest RP in the patient with a history of cancer and radiotherapy. Traumatic plexopathies can follow stretch, external pressure, and penetrating wounds; lower trunk lesions occur in 5% to 10% of patients undergoing CABG procedures. Electrodiagnosis can help in determining the pathophysiology, distribution, and completeness of the lesion and in ruling out root avulsion. TNTOS has a characteristic clinical and electrodiagnostic picture. The disputed neurogenic form of TOS is muddy clinically and electrodiagnostically.

In the past, MRI served primarily to exclude other pathology, such as rotator cuff disease, that might mimic NA clinically and to demonstrate muscle denervation changes. With the advent of 3.0 T MRI and MR neurography, MRI has become more useful in the evaluation of NA. It may demonstrate HGCs involving plexus branches and peripheral nerves and even portions of the plexus proper (Nakagawa & Hirata, 2018; Sneag et al., 2018). The "bull's-eye sign" on MRI, peripheral signal hyperintensity, and central hypointensity orthogonal to the long axis of the nerve can accurately localize HGCs in the suprascapular, axillary, radial, and median nerve anterior interosseous and pronator

teres fascicles and help confirm NA (Sneag et al., 2017). Ultrasonographic abnormalities in involved nerves, especially the anterior interosseous, causing swelling of the nerve or fascicle, may also be useful (Arányi et al., 2017). Ultrasound may show enlargement of the major nerves of the upper limb, especially the median nerve and radial nerve at the level of the upper arm, in some patients with NA (van Rosmalen et al., 2019).

TREATMENT AND MANAGEMENT OF BRACHIAL PLEXOPATHY

There is no specific treatment for most nontraumatic brachial plexopathies. In NA, steroids may help alleviate the severe pain but do not improve the weakness or change the eventual outcome. Physical therapy and occupational therapy are useful to maintain joint mobility, maintain strength in uninvolved muscles, and improve function. Surgical exploration is sometimes done when the distinction between neoplastic and radiation-induced plexopathy cannot be made noninvasively. Radiotherapy is usually given when tumor has invaded the plexus.

Treatment for traumatic brachial plexopathy is primarily surgical. See earlier discussion of traumatic plexopathy due to birth injury. In adults, exploration is usually carried out at about 3 months if there have been no signs of recovery. Careful preoperative evaluation to exclude root avulsion is mandatory before exploration. Intraoperative nerve action potentials are often used to help distinguish reparable from irreparable damage. Repair usually involves end-to-end neurorrhaphy or grafting. Even under the best of circumstances, the outcome is often poor. There is movement gaining momentum to forgo direct repair of the plexus in favor of nerve transfers (Slutsky & Hentz, 2006). Nerve transfers employ other intact motor nerves that have a minor function to reinnervate critical muscles. The distal end of a freshly cut normal nerve is joined to the distal stump of an injured nerve. A variation is to join selected fascicles from a normal nerve to an injured nerve. For instance, fascicles of the ulnar nerve may be implanted into the musculocutaneous nerve or biceps muscle in order to gain elbow flexion (Oberlin procedure).

DISORDERS OF THE LUMBOSACRAL PLEXUS

Diseases that affect the LSP primarily include neoplastic, traumatic, radiation-induced, and inflammatory/microvasculitic processes. The clinical and pathophysiological manifestations of a lumbosacral radiculoplexitis as seen in the diabetic, postsurgical, and idiopathic varieties are similar and can be subsumed under the heading of inflammatory/microvasculitic processes. A simplified version of the relevant anatomy is shown in Fig. 17.6.

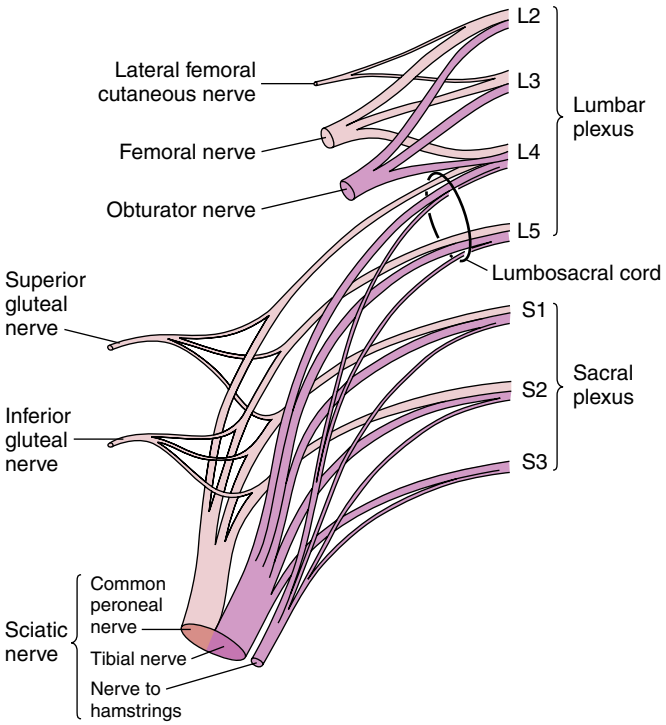


Fig. 17.6 The lumbosacral plexus. (From Canale, S. T., Beaty, J. H. (Eds.) (2007). *Campbell's operative orthopaedics* (11th ed.). St. Louis: Mosby.)

Inflammatory/Microvasculitic

Diabetic lumbosacral radiculoplexus neuropathy (DLSRP), also called diabetic amyotrophy (DA), Bruns-Garland syndrome, and diabetic proximal neuropathy, is the most common syndrome with inflammatory and microvasculitic pathology of the LSP. The clinical manifestations are relatively stereotyped with the subacute onset of unilateral or significantly asymmetric pain in the hip or thigh that becomes quite severe. Weakness develops in the knee extensors, hip flexors and adductors, and gluteal muscles. With progressive weakness, patients develop marked gait disturbances and falls primarily due to poor knee stabilization. Sensory symptoms other than the severe pain are less prominent, although many patients may complain of numbness or paresthesias. The process eventually stabilizes and a slow and occasionally incomplete recovery follows over months to a couple of years (Chokroverty & Sander, 1996). It is not unusual to develop the same entity on the contralateral side during the remission phase of the initially affected limb. The typical patient who develops DLSRP is older (median age 70 years) with mild, or occasionally not previously diagnosed, type II diabetes mellitus (Ng et al., 2019). Weight loss is a common manifestation that can precede or coincide with the neurological symptoms.

The clinical deficit most often involves the lumbar plexus diffusely. The sacral plexus is minimally involved or spared, although patients sometimes develop a mild foot drop. Examination shows bilateral but asymmetric weakness and atrophy of pelvic girdle muscles, and knee extensors greater than knee flexors. The knee jerk is usually absent, often with preservation of the ankle reflexes. Sensory loss is minimal or absent. These findings may be superimposed upon a distal symmetric sensory-motor polyneuropathy.

The differential diagnosis primarily includes high lumbar HNP, involving L2, L3, or L4. Diagnosis is often delayed due to lack of disease recognition and the inappropriate presumption that commonly observed lumbar degenerative disease on lumbosacral MRI is causative. Unwarranted decompressive laminectomies do occur and have been personally observed. Diabetic muscle infarction or myonecrosis is a rare entity that has clinical manifestations that overlap with DLSRP. Over 70% of cases present with acute thigh pain and

swelling (Horton, Taylor, Ragland, & Subauste, 2015). Patients are weak and have difficulty walking. Unlike DLSRP, this syndrome typically occurs in poorly controlled diabetics, type I or II. MRI of the thigh demonstrates hyperintense signal on T2-weighted images with associated perifascial, perimuscular, or subcutaneous edema; the findings are confined to one muscle, vastus medialis or vastus lateralis being the most common.

Idiopathic or non-DLSRP has nearly identical clinical, electrophysiological, and pathological manifestation of DLSRP other than there is no evidence of diabetes (Dyck, Engelstad, Norell, & Dyck, 2000). Sensory nerve biopsies in both diabetic and idiopathic varieties are indistinguishable, demonstrating strong evidence of ischemic injury from microvasculitis.

Pathological evidence of microvasculitis can also be seen in perioperative LSPs (Staff et al., 2010). In such cases, inflammatory mechanisms are responsible for the neurological deficits as opposed to direct mechanical factors (compression, stretch, contusion, or transection). There is a delay between surgery and onset of neurological symptoms, the neurological symptoms can progress over time, and surgical sites are more often outside the region of the LSP. Nerve biopsies demonstrate epineural perivascular lymphocytic inflammation consistent with a microvasculitis. The mainstay in the diagnosis of DLSRP, and the other inflammatory etiologies, relies upon the correlation of the clinical and electrophysiological assessment.

MRI and cerebrospinal fluid (CSF) analysis are primarily used to rule out other causes of an LSP. MRI of the plexus is useful to exclude tumors, hematomas, and abscesses that affect the plexus, and MRI of the lumbar spine can exclude high lumbar radiculopathies. A study of MR neurography demonstrated multifocal nerve lesions in the setting of DLSRP (Hlis, Poh, Bryarly, Xi, & Chhabra, 2019). Abnormalities were noted in the lumbosacral nerve roots and their peripheral branches, with significantly greater CSAs than control subjects. CSF in DLSRP demonstrates protein elevation with normal cell count. Detection of CSF pleocytosis would raise suspicion for other etiologies such as neurosarcoid LSP or lymphoma.

Suspicion and early recognition of inflammatory/microvasculitic pathophysiology of LSP injury are important as therapeutic interventions could potentially prevent further neurological decline and allow for earlier remyelination and axon regeneration (Ogawa, Taguchi, Tanaka, Ikeguchi, & Nakano, 2001; Baba, 2001). Currently, there is no definitive scientific evidence from double-blind placebo-controlled trials that would necessitate usage of immunomodulatory agents in these scenarios. However, given what is known about the underlying pathology and potential for poor outcome in untreated cases, there is a logical argument for short-term treatment with corticosteroids, immunoglobulins, or other immune-mediated therapy. The most recent systemic review concluded that there is no evidence from randomized trials to support immunotherapy in DLSRP (Chan, Lo, & Chan, 2017). Many experts would argue that if diagnosed promptly and accurately, the potential benefits of short-term immunological intervention outweigh the risks (Thaisetthawatkul & Dyck, 2010). One treatment algorithm consists of 1 g of intravenous methylprednisolone weekly for 12 weeks.

Painless Proximal Diabetic Neuropathy

This syndrome has different clinical manifestations from classic DLSRP: Patients present with slowly progressive, bilaterally symmetric, proximal lower extremity weakness without pain, constituting many features of a diabetic CIDP (Hernalsteen, Cosnard, Peeters, & Duprez, 2005). However, cutaneous nerve biopsies demonstrate abnormalities more akin to DLSRP with epineurial perivascular inflammation, with none of the pathological findings of a chronic demyelinating process (Garces-Sanchez et al., 2011). Notably, the subjects in this study had distal upper and lower extremity involvement, clearly suggesting disease beyond the LSP. Some of the subjects had clinical progression for weeks following therapy, suggesting a chronic progressive course rather than the monophasic course of typical DLSRP. The authors opted to categorize this as a variant of DLSRP based on identical pathological features. However, given the distinguishing clinical manifestations, terminology such as diabetic microvasculitic axonal neuropathy may be more suitable to avoid nosologic confusion.

Radiation and Neoplastic Plexopathies

Neoplasms may metastasize to the LSP, or directly invade it. The most common tumors are colorectal, breast, and cervical carcinomas, sarcomas, and lymphomas. As with the BP, RT given as treatment for the tumor may itself damage the plexus, and it is common to be faced with distinguishing neoplastic lumbosacral plexopathy (NLSP) from radiation lumbosacral plexopathy (RLSP).

Patients with NLSP typically present with insidious pelvic or lumbosacral pain with variable radiation into the leg, followed by paresthesias, sensory loss, and weakness, with weakness in a unilateral, multiroot distribution, sensory loss, and reflex asymmetry. Leg edema and a palpable mass are occasionally present. The process may affect the upper, lower, or entire plexus (Jaeckle, Young, & Foley, 1985). RP usually presents after a long latency period, a mean of 6.5 years, with progressive asymmetric leg weakness. Pain is present at onset in only 10% and occurs at some time in the course in only 50%. Weakness is bilateral in most. Prognosis is poor in either condition.

Helpful EMG findings in RLSP include paraspinal fibrillations (50%), fasciculations (35%), and myokymia. In a study of 20 patients with RLSP, myokymia was present in 60% vs. none of 21 patients with NLSP. Paraspinal fibrillations probably result from RT damage to roots, and this condition has also been called a radiculoplexopathy (Thomas, Cascino, & Earle, 1985).

Other Etiologies

Multifocal motor neuropathy can present as chronic progressive proximal leg weakness (Maurer, Stoll, & Toyka, 2004). Retroperitoneal hematoma in the setting of a bleeding diathesis, such as hemophilia, disseminated intravascular coagulation, or, most commonly, the use of anticoagulants, is a known cause of LSP injury. Other causes of LSP include aortic aneurysm, amyloidosis, sarcoidosis, trauma, and obstetrical injury (Antoine et al., 1991; Feasby, Burton, & Hahn, 1992; Plecha, Seabrook, Freischlag, & Towne, 1995; Zuniga, Ropper, & Frank, 1991).

EVALUATION AND DIAGNOSIS

The electrodiagnostic picture in DA is one of axon loss in a lumbar plexus distribution (Campbell, 2014). Paraspinal fibrillations are frequently present and do not necessarily

indicate structural radiculopathy because the condition is by its nature a radiculoplexopathy. It would not be unusual to elicit findings of an underlying distal symmetric sensory-motor polyneuropathy. Helpful EMG findings in RLSP include paraspinal fibrillations (50%), fasciculations (35%), and myokymia. In a study of 20 patients with RLSP, myokymia was present in 60% compared to none of 21 patients with NLSP. Paraspinal fibrillations probably result from RT damage to roots, and this condition has also been called a radiculoplexopathy (Thomas et al., 1985).

Imaging studies, especially CT and MRI, are helpful in the diagnosis of structural plexopathies, such as retroperitoneal hematoma or neoplasm. At other times, imaging can be outright misleading, as in showing evidence of lumbosacral spine disease, common even in asymptomatic older patients, in a patient who clinically has DLSRP and whose subsequent course of slow, spontaneous resolution or response to immunoglobulins clearly demonstrates that the acute condition was not due to a structural radiculopathy.

TREATMENT AND MANAGEMENT

Discrete hematomas should be evacuated and invasive tumors should be irradiated. Except for these two instances, there is no specific treatment for lumbosacral plexopathy; intravenous immunoglobulin is often given empirically when lumbosacral plexopathy occurs for no apparent reason.

FOCAL NEUROPATHIES

Focal neuropathies may result from compression, entrapment, ischemia, stretch, direct trauma such as lacerations and missile wounds, involvement in fractures or dislocations, and other processes. The terms *compression* and *entrapment* are often used more or less interchangeably, sacrificing some accuracy. *Compression neuropathy* refers to nerve damage due to pressure applied to a nerve, whatever the source. The term *entrapment neuropathy* is appropriate when the pressure is exerted by some anatomic or pathoanatomic structure, such as the transverse carpal ligament (TCL) in CTS. All entrapment neuropathies are compression neuropathies, but not all compression neuropathies are due to entrapment. Entrapment neuropathies are all chronic conditions; compression neuropathies due to externally applied pressure can develop acutely over several hours (postoperative ulnar neuropathy, tourniquet paralysis, Saturday night radial nerve palsy), subacutely over days to weeks (peroneal neuropathy at the fibular head [FH] due to prolonged bed rest or a short leg cast), or chronically over months to years (ulnar neuropathy in the retroepicondylar [RTC] groove). In some instances, a nerve is injured by relatively low force applied repetitively over a long period of time (RTC ulnar neuropathy, ulnar neuropathy at the wrist due to bicycling, peroneal neuropathy at the FH due to habitual leg crossing). Almost any nerve in the body can be compressed or entrapped, and by definition involvement is limited to the distribution of a single peripheral nerve.

PATHOLOGY AND PATHOPHYSIOLOGY OF COMPRESSION/ENTRAPMENT NEUROPATHIES

At the most minimal levels of nerve compression, reversible symptoms without accompanying structural changes, the familiar "falling asleep" sensation, are the primary manifestation. Referred to as *acute*, or *rapidly reversible*, *physiologic block*, these symptoms are due to nerve ischemia. Transient symptoms in some entrapment syndromes, such as the nocturnal paresthesias in CTS, may have an ischemic component. Although ischemic infarction of nerve clearly occurs, as in vasculitis, in most instances of compression or entrapment, the predominant clinical manifestations are primarily related to pathologic changes in the myelin sheath or axon directly due to pressure; ischemia seems to play a relatively minor role in most instances. In certain acute and chronic compression syndromes in which axon loss is disproportionate to the apparent level of applied pressure or to the accompanying demyelination, ischemia may be a significant factor (Murphey et al., 1996).

Pathologic changes involving the myelin sheath are the earliest indication of pressure applied to a nerve. Low levels of force produce selective paranodal demyelination, and greater levels of force cause myelin loss along a longer section of the nerve, involving both paranodal and internodal sections, referred to as *segmental demyelination.* Depending on the length of the segment involved, conduction velocity may simply slow or conduction may fail entirely, producing conduction block. Not all nerve fibers are equally susceptible to pressure injury. In experimental compression, large fibers are more susceptible than small, and peripheral fibers are more vulnerable than central ones. In addition, different fascicles within a nerve at a given point exhibit different susceptibilities to pressure injury, mostly reflecting the relationship between the fascicle's position within the nerve and the force vectors being applied. Several problematic phenomena are probably explicable on this basis of selective fascicular vulnerability, including sparing of the forearm flexors with ulnar lesions at the elbow, different degrees of involvement of different hand muscles in ulnar neuropathy, and lumbrical sparing in CTS. Selective fascicular vulnerability creates another level of difficulty in the evaluation of focal neuropathies, and the traditional concept of focal neuropathies as transverse lesions with equal involvement of all fibers below the level of the lesion needs revision. For example, a lesion of the median nerve in the upper arm may involve only the fascicles of the anterior interosseous nerve, a fasciculopathy (Pham, Bäumer, Meinck, et al., 2014). Peripheral nerves have significant potential for repair and recovery (Campbell, 2008). After nerve compression is relieved, or proceeding pari passu with chronic repetitive trauma, nerve repair occurs. Axolemmal and partially digested myelin proteins are mitogenic for Schwann cells and induce proliferation and elaboration of myelin. Remyelination after purely demyelinating processes occurs over a period of several weeks to several months. Generally, myelin repair is complete within 12 weeks. With axonal damage, recovery is much more protracted. Reinnervation after axon loss occurs by sprouting, which has two patterns. In the periphery, intact axons adjacent to injured ones rapidly send collateral sprouts to denervated muscle fibers. At the site of injury, the intact stump of the injured axon forms growth cones, which attempt to span any gap present and regenerate the axon. If the growth cones can span the gap and regenerating axons can find their way into a Schwann cell tube, reinnervation is enhanced. Axons then grow at a rate of about 1 to 3 mm/day from the injury site to the

target. When intraneural fibrosis prevents axons from spanning the gap, the proliferating fibers form a chaotic mass of disorganized, contorted axons known as a *traumatic neuroma*. A neuroma in continuity is one formed on a nerve that remains grossly intact but is severely disrupted internally.

As attempts at repair and regeneration occur at the injury site, important changes are occurring in the target organs. Muscle fibers deprived of innervation and not promptly rescued by collateral sprouts undergo neurogenic atrophy. After some period of time, atrophic fibers are replaced by fat and fibrosis. As a general rule, muscle fibers that have not been reinnervated within 12 to 18 months begin to undergo irreversible changes.

Traumatic nerve injuries can be classified by several systems. Seddon's system, the most commonly used classification scheme, divides nerve injuries into three types: neurapraxia, axonotmesis, and neurotmesis (Seddon, 1943). In neurapraxia, the injury involves only the myelin. Although the initial deficit may be severe, recovery is rapid and generally complete within 12 weeks. In axonotmesis, there is discontinuity of axons. The nerve trunk remains intact and in continuity, and regenerating axons can find their way into surviving endoneurial tubes. Axonotmesis is almost invariably associated with at least some degree of neurapraxia. In neurotmesis, the nerve is discontinuous. Supporting elements as well as axons are disrupted, and the nerve is separated into a proximal and distal stump with an intervening gap of variable width. Regenerating axons must first span any gap present and find the distal stump before reinnervation can proceed.

Sunderland (1951) added two useful subclasses of axonotmesis. In a third-degree injury, there is endoneurial fibrosis that inhibits regeneration and results in variably incomplete recovery. In a fourth-degree injury, nerve continuity is maintained only by scar formation and there is no effective reinnervation. The Sunderland first-, second-, and fifth-degree lesions correspond to Seddon's neurapraxia, axonotmesis, and neurotmesis.

In neurapraxia, there is no axonal loss. Recovery occurs over days to weeks and there is no Tinel sign at the site of the lesion. With a second-degree injury, axonal regeneration produces a Tinel sign at the injury site, which then advances distally at the average rate of 1 inch per month. With a third-degree injury, the Tinel sign also advances, but ultimate recovery is incomplete and aberrant reinnervation may occur. Unfortunately, an advancing Tinel sign is associated with significant functional recovery in only 50% of cases. With a fourth-degree injury, the Tinel sign never advances beyond the injury site and no recovery occurs. Fifth-degree (neurotmetic) injuries are associated with lacerating or rupture injuries and the proximal and distal stumps are not in continuity. Neither fourth- nor fifth-degree lesions improve without surgery.

FOCAL NEUROPATHY SYNDROMES

CTS, ulnar neuropathy at the elbow, peroneal neuropathy at the knee, and retrohumeral radial neuropathy make up the majority of focal neuropathies, but virtually any nerve in the body can be compressed or entrapped (Table 17.5). Many other interesting and important focal neuropathies occur, some of which are summarized in Table 17.6. Several excellent monographs and other publications discuss these less common syndromes (Campbell, 1997, 2014).

CARPAL TUNNEL SYNDROME

CLINICAL PATHOANATOMY

The median nerve crosses from the distal forearm to the hand through the carpal tunnel. The walls and floor of the tunnel are formed by the carpal bones and the roof by the TCL. The TCL evolves from the antebrachial fascia at about the level of the wrist crease and extends 4 to 6 cm into the palm. The passageway is narrowest 2.0 to 2.5 cm distal to its origin, which corresponds to the usual site of median nerve compression (Kimura, 1979; Rosenbaum & Ochoa, 2002). Lying with the median nerve in the canal are the eight tendons of the flexor digitorum profundus and superficialis and the tendon of the flexor pollicis longus, surrounded by a complex synovial sheath.

The palmar cutaneous branch of the median nerve leaves the main trunk 5 to 8 cm proximal to the wrist crease. It travels through its own separate passageway in the TCL and provides sensation to the thenar eminence; it does not traverse the carpal tunnel. Loss of sensation over the thenar eminence is not part of CTS and suggests a lesion proximal to the wrist. After exiting the tunnel, the median nerve gives off its recurrent thenar motor branch, which curves backward and radially to innervate the thenar muscles.

Entrapment of the median nerve beneath the TCL is often brought on or exacerbated by excessive hand/wrist/finger movements; the combination of repetitive finger flexion with wrist motion seems to be the most hazardous ergonomic stress. Both vocational and recreational activities (e.g., gardening, metal scavenging, fly fishing, refinishing furniture, knitting/needlepoint, karate) can incite or aggravate the condition. CTS can rarely result from mass lesions narrowing the passageway (e.g., ganglion, osteophyte, lipoma, aneurysm, anomalous muscle). Numerous systemic conditions predispose to CTS, including rheumatoid arthritis, diabetes mellitus, chronic renal insufficiency, hypothyroidism, amyloidosis, myeloma, and pregnancy.

CLINICAL SIGNS AND SYMPTOMS

CTS produces a characteristic clinical picture of hand pain, numbness, and paresthesias (all usually more severe at night), along with varying degrees of weakness (Ross & Kimura, 1995). Symptoms do not always follow a strict median nerve distribution. Proximal upper extremity pain, usually in the forearm but sometimes as far as the shoulder, is less typical but not uncommon. Many patients initially complain of "whole hand" symptoms, and others have symptoms restricted to the medial two digits of the hand (Colorado & Osei, 2019). The reason for the nocturnal exacerbation of symptoms remains obscure, but the diagnosis should remain suspect in the absence of this feature. Patients frequently complain of dropping objects without detectable weakness on examination, which may be a manifestation of decreased proprioceptive sensation.

Findings on examination vary with the severity of the condition. Patients with mild CTS may have normal findings on physical examination, or trivial sensory loss over the fingertips. The earliest sensory loss seems to occur over the volar

Table 17.5 Common Compression or Entrapment Neuropathies

Condition	Clinical Features	Treatment
Carpal tunnel syndrome	Pain in hand/wrist/forearm; numbness in hand especially at night or provoked by certain activities, weakness, occasional atrophy of thenar muscles, clumsiness	Wrist splints, nonsteroidal anti-inflammatory drugs, low-dose oral prednisone, steroid injection into carpal tunnel, avoid inciting activities, surgery (open or endoscopic) with failure to respond to conservative therapy or for significant or progressing motor deficit
Ulnar neuropathy at the elbow	Typically presents with numbness and tingling of ring and small fingers dependent on elbow position, pain not a prominent feature, with progression weakness of ulnar hand intrinsic muscles develops, often with atrophy of interossei and evolution of a claw deformity; some cases follow clear elbow trauma, most are idiopathic	Elbow pads (wrestler's or hockey player's) to avoid pressure on ulnar groove and to avoid prolonged elbow flexion; soft, cloth pads (e.g., Heelbo) not usually sufficient; avoid activities that produce pressure on the ulnar groove or require prolonged or repetitive elbow flexion; high incidence of spontaneous resolution; consider surgery for significant or progressive motor deficit
Retrohumeral radial neuropathy	Typically due to prolonged pressure on radial nerve in or near spiral groove presenting with wrist and finger drop; eventual complete recovery is typical	No specific treatment; need splints to maintain finger extension and physical therapy to maintain joint motion
Common peroneal neuropathy at the fibular head	Compression of the nerve where it lies superficially as it crosses the fibular head; prolonged squatting or focal pressure are usual precipitants; foot drop is the usual presentation, primary differential diagnosis consideration is L5 radiculopathy	No specific treatment; physical therapy to maintain joint mobility, ankle-foot orthosis for ambulation safety; knee pads rarely useful; failure of deficit to improve, or worsening of deficit, raises possibility of mass lesion in the region of the fibular tunnel and may require surgical exploration
Meralgia paresthetica (compression or entrapment of the lateral femoral cutaneous nerve)	Pain, numbness, and tingling of the lateral thigh, usually brought on by weight gain or wearing tight garments, belts, or other paraphernalia that compress the nerve in the region of the anterior superior iliac spine and lateralmost aspect of the inguinal ligament	Weight loss, avoidance of constricting garments and other things that cause pressure near the anterior superior iliac spine

Table 17.6 Clinical Features of Some Uncommon Focal Neuropathies

Syndrome	Clinical Features
Posterior interosseous neuropathy	Finger drop without wrist drop; pure motor; entrapment in the region of the supinator muscle
Median neuropathy due to supracondylar spur	Median entrapment by the ligament of Struthers running from distal humeral spur to medial epicondyle
Pronator teres syndrome	Main trunk median entrapment at the level of the pronator teres; motor and sensory dysfunction
Anterior interosseous neuropathy	Entrapment just distal to the pronator teres after anterior interosseous nerve leaves the main trunk, fasciculopathy in the upper arm; motor dysfunction only
Ulnar neuropathy at the wrist	Various combinations of motor and sensory dysfunction depending on precise location of lesion, external pressure frequently a factor (e.g., bicyclist's palsy)
Tarsal tunnel syndrome	Entrapment behind medial malleolus; pain and sensory dysfunction in sole of foot
Femoral neuropathy	May be injured at the inguinal ligament, in the pelvis or within the psoas muscle; hip/thigh weakness with decreased knee jerk and sensory loss in saphenous distribution (medial lower leg)
Suprascapular neuropathy	May be injured or entrapped at suprascapular or spinoglenoid notch, often associated with vigorous exercise, may be involved in neuralgic amyotrophy
Obturator neuropathy	May be injured in pelvic fracture or mass or compressed by obturator hernia or injured during hip replacement; difficulty stabilizing the hip joint
Sciatic neuropathy	May be injured in the hip/gluteal region by trauma, pelvic mass, or hip surgery; may be injured in the thigh by blunt or penetrating trauma; involvement of the short head of the biceps femoris by electromyography is the diagnostic clue to most sciatic neuropathies

tip of the middle finger. Patients with more advanced disease have more easily demonstrable sensory loss and frequently have weakness of the thenar muscles. Patients with severe involvement demonstrate thenar atrophy and dense sensory loss. Such patients with long-standing, untreated end-stage CTS often have surprisingly few symptoms. Provocative tests, such as the Tinel sign, Phalen sign, carpal compression maneuver, and the flick sign have proved disappointing, with high proportions of false-positive and false-negative results (Hansen, Micklesen, & Robinson, 2004; Kuschner, Ebramzadeh, Johnson, Brien, & Sherman, 1992; Sawaya & Sakr, 2009; Stewart, 1993).

EVALUATION AND DIAGNOSIS

The most common differential diagnostic exercise is between CTS and CR, most often at C6. Neck and shoulder pain, weakness in C6 innervated muscles, reflex changes, sensory loss restricted to the thumb, the absence of nocturnal paresthesias, and reproduction of the paresthesias with root compression maneuvers all favor CR. Other conditions occasionally meriting consideration include proximal median neuropathy, neurogenic TOS, and upper brachial plexopathy. Various musculoskeletal conditions, especially de Quervain tendonitis, can cause hand and wrist pain suggestive of CTS.

Nerve conduction studies (NCSs) are currently the gold standard for CTS diagnosis (Jablecki et al., 2002; Robinson, 2007). The earliest change is prolongation of the median SNAP latency. There are numerous methodologies to demonstrate this finding (Jablecki et al., 2002). The least sensitive techniques employ relatively longer distance measurements, typically 13–14 cm between stimulating and recording electrodes, while utilizing reference values derived from an asymptomatic population. The more sensitive techniques use shorter distances or internal control variables or both. For example, comparisons between the median and ulnar SNAP latency while recording over the 4th digit (ringdiff) or between the median and radial SNAP latency while recording over the 1st digit (thumbdiff) use internal control variables. The 8-cm orthodromic, palm to wrist, technique compares median and ulnar nerve conduction with shorter segments of unaffected nerve included in the latency determination (palmdiff) (Jablecki et al., 2002). Each of these three diagnostic tests has sensitivities approximating 70%–75% for CTS. With more severe involvement, there is loss of nerve action potential amplitude, prolongation of the motor distal latency, and development of denervation in thenar muscles.

As there are numerous techniques for defining prolongation of the median SNAP latency, it can be tempting to perform one test after another until an abnormality is found. But this approach will significantly increase the false-positive rate (Rivner, 1994). The combined sensory index (CSI), developed by Robinson, has the highest sensitivity, 83%, for CTS (Robinson, Micklesen, & Wang, 1998). The CSI is a summation of three latency differences: ringdiff + thumbdiff + palmdiff. By summing up these differences, as opposed to evaluating each individually, the specificity remains >95%. Robinson also developed a protocol that defines the necessity for performing all three of these tests after data acquisition from the first (Robinson, Micklesen, & Wang, 2000). In general, if the initial test is clearly normal or abnormal, there is no need to continue further. But in cases where the first test is borderline, it is useful to complete the others. Using Robinson's strategic approach, we routinely perform the orthodromic palmar median vs. ulnar conduction study in cases of suspected CTS. When the median latency is 0.2 to 0.4 milliseconds slower than the ulnar, we will complete the other sensory studies to obtain a CSI. The range is slightly different from what Robinson recommended, but the approach is conceptually the same.

Neuromuscular ultrasound is rapidly evolving in the evaluation of CTS and other focal entrapment neuropathies. The most common and reproducible finding is nerve enlargement just proximal to the site of entrapment. An increase in the CSA of the median nerve at the distal wrist crease has a sensitivity and specificity greater than 85% for the diagnosis of CTS (Cartwright & Walker, 2013). One possible explanation for the focal enlargement is blocking of fast axoplasmic transport (damming), but inflammatory and vascular factors may also play a role with increased permeability of intraneural vessels and associated epineural edema (Ochs, 1971; Rydevik & Lundborg, 1977). Other findings include greater nerve hypoechogenicity, flattening or pinching at the compression site, increased vascularity on Doppler ultrasound, and changes in nerve mobility (Cartwright & Walker, 2013).

Unlike electrodiagnostic testing, ultrasonography is painless and provides anatomical information, but its place in the diagnostic armamentarium is yet to be determined. In a prospective study of 207 patients with a clinical diagnosis of CTS, Visser, Smidt, and Lee (2008) found the accuracy of sonography (CSA) to be similar to that for electrodiagnostic studies (using ringdiff). In one study designed to determine whether HRS can be an alternative method to NCS in the diagnosis of CTS, it was found that sensitivity was similar between HRS and NCS, but specificity was significantly lower for HRS; the investigators concluded that sonography is not accurate enough to replace NCS for the diagnosis of CTS (Kwon, Jung, & Baek, 2008). In one study, high-resolution ultrasound confirmed clinically diagnosed CTS in about half of the patients with normal NCSs (Al-Hashel et al., 2015).

MRI of the median nerve in CTS has demonstrated abnormal T2 signal in the nerve, proximal nerve enlargement, flattening distally and anterior bowing of the TCL (Ng et al., 2020). MRI is not routinely performed as part of the CTS evaluation.

TREATMENT AND MANAGEMENT

Initial attempts at treatment should involve trying to identify predisposing vocational or avocational activities that may be inducing or aggravating the symptoms (Box 17.4). The ergonomonics of CTS have been studied extensively. The greatest ergonomonic stress is activities that involve repetitive flexion and extension of the wrist accompanied by flexion and extension of the fingers. This activity is prone to induce flexor tendon tenosynovitis, which is well recognized to be associated with CTS. Occupational activities likely to induce CTS include those requiring heavy use of the hands, such as carpentry, bricklaying, and other manual labor. The most frequently blamed activity is use of a typewriter or computer keyboard, but there are minimal data to support this claim. A 2007 systematic review found no to support an association between CTS and keyboard and computer work

Box 17.4 Treatment of Carpal Tunnel Syndrome

Avoidance of aggravating/inciting activities
Wrist splints (worn constantly until better, then at night only)
Nonsteroidal anti-inflammatory drugs
Low-dose oral steroids
Steroid injection
Carpal tunnel release
  Open
  Endoscopic
No evidence to support use of pyridoxine

(Palmer, Harris, & Coggon, 2007). The patient should stop suspicious activities for a trial period consistent with the limits of their employment. Avocational activities that may cause CTS include such things as heavy gardening, woodworking, metal scavenging, knitting and crocheting, and many others.

Splints are clearly helpful. The splint should be lightweight and neutral or slightly dorsiflexion in position. If the patient only is having occasional nocturnal symptoms, then wearing the splint only at night is acceptable. If the patient is having symptoms more than three or four nights per week, multiple times per night, or having symptoms during the day, then an effective strategy is to have the patient wear the splint day and night for the first few weeks and to drop back to nighttime use only when the symptoms have improved.

Several types of medications are used in CTS; none are especially useful. NSAIDs are used to combat the tenosynovitis but have not been shown to be very helpful. Some physicians use pyridoxine despite the fact there is not one scintilla of evidence to support its use and it can cause neuropathy if used chronically at a dose as low as 200 mg/day (and is sold over the counter in capsules with doses as high as 500 mg). Low-dose prednisone at a dose of 20 mg for 1 week and 10 mg for 1 week has been shown to be of benefit (Herskovitz, Berger, & Lipton, 1995).

If immobilization, NSAIDs, and low-dose prednisone are not useful, many physicians proceed to a steroid injection, using 20 mg or equivalent or methylprednisolone and 1 mL of 1% lidocaine. In a prospective study, local steroid injection resulted in long-term improvement in nerve conduction parameters, symptom severity, and functional scores in patients with mild CTS (Agarwal et al., 2005). Details on how to perform an injection are given elsewhere. Anyone administering an injection should be very familiar with the technique. Rarely, an injection is given when CTS is considered likely but the clinical picture is ambiguous and the electrodiagnostic picture is not definitive.

Conservative therapy is most likely to be effective when the CTS is relatively acute, developing over days or weeks due to tenosynovitis developing in response to an identifiable activity. More long-standing CTS is much less likely to respond to conservative therapy and more likely to need surgical decompression.

Surgical carpal tunnel release has excellent long term outcome results (De Kleermaeker, Meulstee, Bartels, & Verhagen, 2019). There are two surgical approaches: open and endoscopic, with advantages and disadvantages to each. There are two surgical approaches: open and endoscopic, with advantages and disadvantages to each. Several studies have demonstrated similar outcome measures between the two techniques (Martínez-Catasús et al., 2019; Michelotti, Vakharia, Romanowsky, & Hauck, 2020). A meta-analysis of 13 randomized controlled trials concluded that limited incision release allowed for earlier return to activities, less operative time, and decreased risk of adverse events compared to endoscopic release (Li et al., 2019).

ULNAR NEUROPATHY AT THE ELBOW

Ulnar neuropathy at the elbow (UNE) is the second most common compression neuropathy after CTS.

CLINICAL PATHOANATOMY

After descending without branches through the upper arm, the nerve traverses the RTC groove between the medial epicondyle (ME) and olecranon process (OP). The nerve then passes beneath the humeroulnar aponeurotic arcade (HUA), a dense aponeurosis joining the humeral and ulnar heads of origin of the flexor carpi ulnaris (FCU), which typically lies 1.0 to 2.5 cm distal to a line connecting the ME and the OP (Campbell, Pridgeon, Riaz, Astruc, & Sahni, 1991). After passing under the HUA, the nerve runs through the belly of the FCU, then exits through the deep flexor pronator aponeurosis lining the deep surface of the muscle 4.0 to 6.0 cm beyond the ME.

Anatomic factors account for much of the susceptibility of the ulnar nerve to injury at the elbow. The lack of protective covering over the nerve in its course through the ulnar groove accounts for its susceptibility to external pressure. This is particularly pronounced in patients with a low body mass index, who have an increased risk of developing UNE (Landau, Barner, & Campbell, 2005). Repetitive flexion and extension may predispose to UNE because of the dynamic changes in the nerve's passageway with motion. With elbow joint derangement due to trauma or arthritic changes, the nerve's vulnerability increases even further. Valgus deformities increase the stretch on the nerve with elbow flexion, and osteophytic overgrowth further narrows an often already narrow passageway. The nerve may be entrapped at the HUA or at the point of exit from the FCU (Campbell, 2014).

A number of problems arise in the differential diagnosis of suspected UNE. There are at least three potential sites of ulnar compression in the region of the elbow. Most lesions are located in the ulnar groove (60%–80%), with fewer at the HUA (Omejec & Podnar, 2016). Lesions at the exit site from the FCU, a.k.a. deep flexorpronator aponeurosis, are rare and underrecognized (Campbell, Pridgeon, & Sahni, 1988). The clinical manifestations of disease at the wrist, elbow, and more proximal sites can be similar. The nerve's branching pattern limits both clinical and electrodiagnostic localization. Selective vulnerability may produce varying degrees of involvement of different fascicles (Campbell et al., 1989). Forearm muscles are often spared in lesions at the elbow.

A terminology morass has grown out of imprecision in the use of terms such as *tardy ulnar palsy* and *cubital tunnel*

syndrome. Tardy ulnar palsy was first used to describe UNE developing after remote elbow trauma, generally after an old fracture or dislocation. It soon degenerated into a nonspecific, generic term for any ulnar neuropathy at the elbow, on the weak presumption that remote trauma must have occurred but the patient simply could not recall it. Feindel and Stratford coined the term *cubital tunnel syndrome* (*cubit* is Latin for elbow or forearm) to refer to patients with compression of the nerve by the HUA (Feindel & Stratford, 1958). They were attempting to define a subgroup of "tardy ulnar palsy" patients who suffered from a focal entrapment by the FCU aponeurosis and who could be spared a transposition procedure and managed with simple release of the aponeurotic arcade. As with tardy ulnar palsy, the term *cubital tunnel syndrome* soon degenerated into a useless, nonspecific, generic label for any UNE as the term increasingly grew in popularity, with few bothering to read the original paper. Many clinicians, even neurologists, neurosurgeons, and orthopedists, now use *cubital tunnel syndrome* the way their predecessors not many years ago used *tardy ulnar palsy*: to refer to any UNE. All these terms except *UNE* now invite confusion and miscommunication and should be stricken from the lexicon.

CLINICAL SIGNS AND SYMPTOMS

The physical examination of a patient with suspected UNE should include detailed assessment of strength, sensation, and reflexes and examination of the elbow for ROM and deformity. Atrophy of the hypothenar eminence and first dorsal interosseous can be readily observed by comparing to the asymptomatic limb. The fingers may be relatively splayed due to weakness of the intrinsic adductor muscles. Wartenberg sign consists of involuntary abduction of the small finger due to weakness of the 4th palmar interosseous muscle and unopposed action of the extensor digiti minimi. Froment sign is merely a tactic to elicit weakness of the adductor pollicis muscle. The clawing in an ulnar neuropathy is a manifestation of 4th and 5th digit lumbrical weakness with sparring of the long forearm flexors to these digits. As a result, there is inadvertent extension of the 4th and 5th metacarpophalangeal (MCP) joints and flexion of the proximal (PIP) and distal (DIP) phlalangeal joints. This should be readily distinguishable from finger drops that can occur in posterior interosseous nerve palsy and CR that result in flexion at the MCP, DIP, and PIP (Campbell, Buschbacher, Pridgeon, & Freeman, 1995). Weakness of nonulnar C8 muscles is the usual clue to disease involving the lower BP or C8 root. This finding should in turn prompt further examination of the cervical spine and a check for Horner syndrome. Weakness in the ulnar innervated long finger flexors and FCU may help separate UNE from a more distal lesion, although normal strength in these muscles is still entirely consistent with an elbow-level lesion. Ulnar neuropathy is not the only condition that can cause hand clawing.

A careful sensory examination can be rewarding. The cutaneous field of the ulnar nerve does not extend more than a few centimeters proximal to the wrist crease. Involvement of the distribution of the MABC nerve over the medial forearm excludes UNE, because this nerve runs anterior to the ME and not through the ulnar groove. Impaired sensation over the dorsum of the hand establishes the location of the lesion as proximal to the takeoff of the dorsal cutaneous branch, but sparing of the dorsal cutaneous territory does not exclude UNE because of possible selective sparing of its fascicles. Involvement of the palmar cutaneous branch distribution likewise suggests a proximal lesion. Splitting of the ring finger fairly reliably excludes plexopathy and radiculopathy.

Impaired elbow ROM or a valgus deformity strongly suggests UNE. Reproduction of symptoms with elbow flexion and ulnar groove pressure can be informative. Examining for subluxation is seldom helpful. Ulnar nerve subluxation is a common phenomenon in normal individuals. The most recent publications have concluded that there is no difference in the incidence of subluxation between patients with UNE and healthy controls (Van Den Berg, Pompe, Beekman, & Visser, 2013). It is important to recognize subluxation during electrodiagnostic testing to ensure that distance measurements accurately reflect the nerve location. Eliciting a Tinel sign can be useful, but many normal patients exhibit Tinel signs over all their nerves; only the presence of a disproportionately active Tinel sign over the clinically suspect ulnar nerve has any localizing value. In one study, the sensitivity and specificity for a Tinel test for UNE were 62% and 53%, respectively (Beekman, Schreuder, Rozeman, Koehler, & Uitdehaag, 2009).

EVALUATION AND DIAGNOSIS

Lesions of the BP and lower cervical roots cause signs and symptoms occasionally difficult to distinguish from UNE. Patients with anterior horn cell disease and other myelopathies may develop small hand muscle wasting resembling that seen in UNE. The sensory symptoms of UNE can mimic those of CR, plexopathy, and ulnar lesions at the wrist or upper arm.

The mainstay of the evaluation of suspected UNE is electrodiagnosis. However, the ulnar is a difficult nerve to study and there are persistent problems with sensitivity and specificity, especially in inexperienced hands. The sensitivity for UNE diagnosis is less than for CTS because there is no consistent and reproducible technique to measure sensory conduction across the elbow (Kothari, Heistand, & Rutkove, 1998). The earliest electrodiagnostic finding is slowing of motor nerve conduction across the elbow, which may not be detectable when the clinical manifestations are strictly sensory. Also, the curvilinear distance measurement required to calculate the nerve conduction velocity is prone to experimental error (Landau, Diaz, Barner, & Campbell, 2002). Technical components that can result in false-positive studies include low across elbow temperature, distance measurement attained with elbow extended, or minimally flexed or short distance between below (BE) and above elbow (AE) stimulation points (Landau & Campbell, 2013). False-negative studies can result from distance measurements completed without accounting for nerve subluxation or very long distance between BE and AE stimulation points. The Practice Parameter of the American Association of Neuromuscular and Electrodiagnostic Medicine is an exhaustive discussion of the matter of ulnar electrodiagnosis (Campbell, 1999). The summary recommendations are listed in Box 17.5. A 2003 review article provides a nice summary (Kern, 2003).

Subsequent studies have shown that the optimal distance for screening for UNE, considering both sensitivity and

Box 17.5 Evaluation of Ulnar Neuropathy at the Elbow

Synopsis of the Recommendations of the Practice Parameter of the American Association of Neuromuscular and Electrodiagnostic Medicine

1. When using moderate elbow flexion (70–90 degrees from horizontal), a 10-cm across-elbow (AE) distance, and surface stimulation and recording, the following abnormalities suggest a focal lesion involving the ulnar nerve at the elbow. The most important criterion is the presence of multiple internally consistent abnormalities. Multiple abnormalities are more convincing than isolated abnormalities, which raise the possibility of artifact or technical mishap.
   a. Absolute motor nerve conduction velocity from AE to below-elbow (BE) of less than 50 m/sec.
   b. An AE to BE segment greater than 10 m/second slower than the BE to wrist (W) segment.
   c. A decrease in compound muscle action potential (M wave) negative peak amplitude from BE to AE greater than 20%.
   d. A significant change in M wave configuration at the AE site compared to the BE site.
2. If routine motor studies are inconclusive, the following procedures may be of benefit:
   a. Nerve conduction studies recorded from the first dorsal interosseous (FDI) muscle.
   b. An inching or short segment study.
3. Needle examination should include the FDI, the most frequently abnormal muscle, and ulnar innervated forearm flexors. Neither changes limited to the FDI, nor sparing of the forearm muscles, exclude an elbow lesion. If ulnar innervated muscles are abnormal, the examination should be extended to include nonulnar C8/medial cord/lower trunk muscles to exclude brachial plexopathy and the cervical paraspinals to exclude radiculopathy.

specificity, is significantly less than the standard 10 cm between AE and BE stimulation points. Considering the likely locations of focal lesions, we recommend using a distance of 6–8 cm (Landau, Barner, & Campbell, 2003). To distinguish lesions at the RTC from the HUA, the utility of "inching" or short segment incremental studies at 1 or 2 cm has been demonstrated repeatedly since the original descriptions (Campbell, Pridgeon, & Sahni, 1992; Kanakamedala, Simons, Porter, & Zucker, 1988; Omejec & Podnar, 2015; Visser, Beekman, & Franssen, 2005). These techniques can demonstrate focal conduction block, temporal dispersion, or focal slowing of conduction within a 1–2 cm span. Keeping the elbow warm during ulnar conduction studies is vital and will markedly decrease the incidence of false-positive studies (Landau, Barner, Murray, & Campbell, 2005). The most vital step is correlating the electrodiagnostic findings with the clinical manifestations.

MRI of the ulnar nerve at the elbow has proved more useful than in CTS. Abnormalities on MRI include increased T2 signal and increased caliber. The sensitivity and specificity range between 83% and 97% and between 85% and 100%, respectively, compared to 60%–75% sensitivity for routine NCS (Bäumer et al., 2011; Britz et al., 1996; Vucic, Cordato, Yiannikas, Schwartz, & Shnier, 2006). Studies reaching this conclusion did not rely on advanced conduction techniques such as short segment incremental studies. Radiomic analysis of ulnar nerve MRI can assess inner structural changes due to the loss of fascicular pattern, intraneural edema, or fibrosis even when the nerve CSA does not change (Rossi et al., 2020). When assessing the claims of MRI sensitivity, it is vital to stress the long-ago established entity of asymptomatic enlargement of the ulnar nerve in the groove and the concept of subclinical ulnar neuropathy (Neary & Eames, 1975; Neary, Ochoa, & Gilliatt, 1975).

Ultrasound of the ulnar nerve is a useful technique when executed by well-trained individuals and is expected to become increasingly available in the future. The sensitivity of enlarged CSA as measured by high-resolution ultrasound (HRUS) has a sensitivity of approximately 80% for UNE (Beekman et al., 2004; Ellegaard, Fuglsang-Frederiksen, Hess, Johnsen, & Qerama, 2015), whereas slowing of motor NCV has a sensitivity of about 70%. Using both techniques can enhance sensitivity. With decreased motor NCV as the gold standard, the sensitivity and specificity of CSA for UNE were 93.1% and 50.0%, respectively; i.e., HRUS may be associated with increased false-positive rates (Ellegaard et al., 2015). HRUS can be very useful in cases of ulnar neuropathy in which the electrodiagnostic tests are abnormal but cannot confirm precise localization (Alrajeh & Preston, 2018). This would be particularly relevant in severe ulnar neuropathies associated with marked axonal loss that can hinder the ability to demonstrate focal demyelination. At this time, HRUS and electrodiagnosis are complementary methods for diagnostic accuracy in UNE. Caution is required before relying too heavily on either MRI or US abnormalities as the sole findings in the diagnosis of UNE.

TREATMENT

Ideally, treatment of UNE would be based on the precise lesion localization: distinct modalities (conservative or surgical) for lesions at the RTC groove versus those at the HUA. To date, only one study has documented results in such a manner (Omejec & Podnar, 2018). The authors treated RTC lesions conservatively and HUA lesions with surgical release of the HUA and found similar outcome results for each. There is not as yet any surgical literature in which a specific surgical technique is tailored to the preoperative determination of lesion localization.

Patients with UNE may improve with conservative treatment (Box 17.6). De Jesus and Steiner (1976) followed a group of patients managed nonsurgically for periods up to 4 years. At follow-up, 46% were normal after nonoperative management and 15% were significantly improved. The likelihood of spontaneous recovery was greatest in those patients with the mildest electrophysiologic abnormalities. Dellon, Hament, and Gittelshon (1993) prospectively evaluated 128 patients with UNE managed nonoperatively. Just 11% of those with symptoms only eventually had surgery as compared with 33% of those with mild to moderate abnormalities on examination and 62% of those with more severe abnormalities. The presence of persistent paresthesias, abnormal two-point discrimination, and any degree of muscle wasting moved patients into the category of likely eventual surgery. Electrodiagnostic abnormalities were not found to have predictive value. A history of elbow injury significantly worsened the outcome.

Box 17.6 Conservative Treatment of Ulnar Neuropathy at the Elbow

Minimization of elbow flexion
Arms never crossed
Forearm supinated and resting on thigh while sitting
Telephone in asymptomatic hand only
Bookstand for reading
Avoidance of external pressure
Elbow pads
Night splints
Elbow resting on pillow during desk work

Patients who require ulnar nerve surgery may undergo any of several procedures, depending largely on the preference and habits of the surgeon. Complications are unlikely with simple decompression of the HUA. Anterior transposition is usually safe, but can go terribly awry. Most ulnar nerve disasters occur in patients who have undergone transposition. Although debate continues, evidence increasingly seems to favor in situ decompression as just as efficacious and with a lower incidence of complications compared to transposition (Altay, Yamak, Koyuncu, Kayali, & Sözkesen, 2018; Buchanan, Chieng, Hubbard, Law, & Chim, 2018; Dunn et al., 2019). Increasingly, ulnar nerve decompression is done endoscopically.

Conclusions from the Cochrane systemic review of UNE treatment included the following: Only two trials using conservative treatment as a comparison were available, and were insufficient to determine when surgical therapy was necessary. Written information alone of conservative techniques was as effective as using splint or exercises. There was no evidence that corticosteroid injections were effective. Moderate-quality evidence indicates that simple decompression and decompression with transposition (subcutaneous or submuscular) were equally effective, but the latter was associated with more deep and superficial wound infections. Endoscopic surgeries were more likely to have hematomas (Caliandro, La Torre, Padua, Giannini, & Padua, 2016).

ULNAR NEUROPATHY NOT AT THE ELBOW

The ulnar nerve may be entrapped by the medial intramuscular septum, the so-called arcade of Struthers, most typically in a patient who has had ulnar transposition with an inadequate proximal release. The nerve may be entrapped at its point of exit from the FCU muscle in the upper forearm, more rarely in the distal forearm (Campbell, 1989; Campbell et al., 1988). Ulnar neuropathy at the wrist occurs in the Guyon canal. There are several subtypes, and the deficit depends upon the exact site of compression, varying from involvement of the entire nerve in proximal Guyon canal compression to involvement of only the deep ulnar branch producing a pure motor deficit with more distal compression.

RADIAL NEUROPATHY

Acute compression of the radial nerve in the retrohumeral spiral groove, frequently referred to as *Saturday night* or *bridegroom's palsy*, results from sustained compression over a period of several hours during sleep or a drug- or alcohol-induced stupor. Weakness involves all muscles distal to the triceps, which receives its innervation from a branch arising proximal to the spiral groove. The most prominent complaint and finding is wrist drop. Sensory loss is usually present in the superficial radial nerve distribution. Confusion commonly arises on two points: (1) because of mechanical factors, the interossei cannot exert normal power in the face of finger drop and may seem weak and (2) weakness of thumb abduction occurs due to dysfunction of the radial innervated abductor pollicis longus (APL). Mislocalization is possible due to the apparent weakness of the interossei, suggesting superimposed ulnar nerve involvement and attributing weakness of thumb abduction to median nerve involvement (i.e., presuming weakness is due to involvement of the abductor pollicis brevis rather than the APL). To adequately assess the interossei in the face of a wrist drop, the wrist should be maintained in a neutral position by the examiner. The primary differential diagnostic considerations include C7 radiculopathy, posterior interosseous nerve palsy, and lesions involving the middle trunk or posterior cord of the BP. Acute ischemic stroke can also resemble a radial nerve palsy. The radial nerve seems particularly prone to involvement in systemic vasculitis.

COMMON PERONEAL NEUROPATHY AT THE FIBULAR HEAD

In its arc across the FH, the peroneal nerve is superficial and vulnerable to external compression, and peroneal neuropathy at the knee most often develops in the setting of external pressure. The nerve may also be susceptible to stretch injury or entrapment at its point of passage through the fibrous arch at the origin of the peroneus longus muscle (the "fibular tunnel").

Habitual leg crossing is the classic cause of peroneal neuropathy at the knee, but external pressure damage may come from a variety of potential sources. Other causes include prolonged squatting and sudden, forceful plantar flexion or inversion of the ankle. Rarely, a mass lesion, such as a ganglion or peripheral nerve tumor, may compress the nerve, or it may suffer entrapment at the fibular tunnel.

The most important element in the workup is the medical detective work necessary to detect the mechanism of compression or stretch. In most patients, a meticulous history will uncover a likely explanation. Searching for a dimple, discoloration, or callus over the FH may help confirm an external pressure mechanism. Failure to find a satisfactory explanatory mechanism of injury, failure of the neuropathy to resolve, or progression of the deficit under observation raises the possibility of mass lesion or fibular tunnel entrapment.

The most common differential diagnostic exercise is between common peroneal neuropathy at the FH (CPNFH) and L5 radiculopathy in the patient with foot drop. The presence of back and leg pain, weakness of foot inversion, positive root stretch signs, and depression of the medial hamstring reflex favor radiculopathy. The absence of pain, weakness limited to ankle eversion and foot/toe dorsiflexion, and preservation of the medial hamstring reflex favor CPNFH.

In rare patients, sciatic neuropathy, deep peroneal neuropathy, or lumbosacral plexopathy may simulate CPNFH.

Patients with sciatic neuropathy have involvement of the short head of the biceps femoris on EMG; otherwise, it is clinically difficult to distinguish proximal sciatic neuropathy from peroneal neuropathy. Patients with SP neuropathy, a rarity, only have involvement of the foot evertors. In deep peroneal neuropathy, the peroneus longus and brevis are spared, foot eversion is clinically intact, and the deficit depends on the exact level of the lesion. In deep peroneal neuropathy due to anterior tarsal syndrome, there is no foot drop and involvement is limited to deep peroneal innervated intrinsic foot muscles. A number of generalized conditions may require consideration, especially if foot drop is bilateral, including generalized neuropathies, motor neuron disease, and several types of primary muscle disease (e.g., distal myopathy, inclusion body myositis, myotonic dystrophy, and scapuloperoneal syndromes).

The standard electrodiagnostic technique is to record from the extensor digitorum brevis or tibialis anterior muscle while stimulating the peroneal nerve above and below the FH searching for focal slowing, temporal dispersion, or conduction block. When stimulating in the popliteal fossa, there is a significant chance of inadvertent spread of the stimulus current to the tibial nerve, which produces spurious and confusing M-wave amplitude variations. Because of the dictates of the "10 cm rule" (see earlier discussion under ulnar neuropathy), many EMG operators stimulate below the FH and then measure at least 10 cm into the popliteal fossa. Again, there is a tradeoff of experimental error against lesion detection, and the proximal stimulation in this instance can become frankly problematic because of stimulus spread. To detect spread, in addition to noting changes in M-wave amplitude and waveform, it is useful to observe the motion of the foot. Peroneal stimulation will produce an extension/eversion movement. Tibial stimulation will produce plantar flexion. If both nerves are being stimulated, the foot will simply "quiver" and move neither up nor down.

CPNFH can produce almost any combination of demyelination and axon loss, which may involve any of the target muscles to different degrees. The M-wave amplitude with stimulation below the FH, compared with laboratory reference values or the contralateral leg, provides an index of the degree of axon loss. The difference in M-wave amplitude with below FH versus above FH stimulation reflects the degree of demyelinating neurapraxia. Slowing across the FH indicates the NCV in demyelinated but not blocked fibers. Which of these features is paramount is a matter of debate.

The SP SNAP is very useful in evaluating CPNFH. Although some mild, demyelinating lesions may spare the SP SNAP, with lesions causing any significant axon loss, this potential will be reduced in amplitude or absent. In contrast, the most common process mimicking CPNFH, L5 radiculopathy, should leave a robustly normal SP SNAP.

Needle EMG should focus not only on peroneal innervated muscles but also on nonperoneal L5 muscles, such as the tibialis posterior and flexor digitorum longus, and should always include the short head of the biceps femoris. Because the short head of the biceps is the only peroneal innervated muscle lying proximal to the FH, any abnormality there suggests a lesion above the midthigh. Because a lesion severe enough to cause neurapraxia or significant conduction slowing is usually severe enough to damage at least a few axons, some, occasionally many, fibrillation potentials can be seen in peroneal innervated muscles even with a primarily demyelinating CPNFH. The M-wave amplitude and SP SNAP amplitude are better indicators of the extent of axon loss.

Traditional MRI had limited usefulness in the evaluation of CPNFH. The newer 3.0 T MR and particularly MR neurography, unfortunately not widely available, may prove much more powerful (Chhabra et al., 2012; Garwood, Duarte, & Bencardino, 2018). As with other mononeuropathies, ultrasound has been increasingly applied to the problem of CPNFH (Bucklan, Morren, & Shook, 2019). A 2017 study of 40 adult patients with clinically suspected CPNFH and 40 healthy controls found that the diagnostic accuracy of ultrasound was slightly higher than that of MRI (Bignotti, Assini, Signori, Martinoli, & Tagliafico, 2017).

There is no specific treatment for CPNFH except to remove any persistent or recurrent compression, avoid prolonged squatting, and eliminate other such etiologic factors. If there has been no substantial axon loss, the nerve should remyelinate with good recovery. If there has been axon loss, recovery is likely to be incomplete and sometimes the patient is left with a foot drop. If the neuropathy progresses under observation after predisposing factors have been eliminated, consideration should be given to surgical exploration to exclude nerve sheath tumor and to decompress the fibular tunnel.

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18 Treatment and Management of Disorders of Neuromuscular Hyperexcitability and Periodic Paralysis

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DISORDERS OF NEUROMUSCULAR HYPEREXCITABILITY

Muscle pain, stiffness, and cramps are symptoms frequently seen in neuromuscular practice. The differential diagnosis of these symptoms is wide and includes systemic disorders, neurologic disorders involving the pyramidal or extrapyramidal systems, and neuromuscular diseases (Box 18.1). The neuromuscular diseases that manifest with muscle stiffness, cramps, and muscle pain as the predominant symptoms are referred to as the "syndromes of neuromuscular hyperexcitability." They include central conditions such as stiff-person syndrome, syndromes of peripheral nerve hyperexcitability such as Isaacs syndrome and cramp fasciculation syndrome, skeletal muscle channelopathies that manifest clinically as the nondystrophic myotonias, and the periodic paralyses (PPs), among others (Ahmed, Bertorini, Narayanaswami, & Senthilkumar, 2003). As a group, these disorders are rare. However, a working knowledge of them is important for several reasons: genetic implications in some, autoimmune and potentially paraneoplastic causes in others, and the need for monitoring for serious systemic complications in others. This review discusses the clinical features, diagnosis, and treatment of the syndromes of neuromuscular hyperexcitability (Fig. 18.1).

CENTRAL DISORDERS

STIFF-PERSON SYNDROME

In 1956, Moersch and Woltman described a syndrome characterized by "progressive fluctuating muscular rigidity and muscle spasms" without other neurologic signs (Moersch & Woltman, 1956). This condition, originally "stiff-man syndrome," subsequently became known as "stiff-person syndrome" (SPS) as the disorder was recognized in females (Blum & Jankovic, 1991). SPS was defined by the insidious onset of muscle rigidity, usually beginning symmetrically in the lumbar and thoracic paraspinal muscles and the proximal lower extremity muscles. Since this initial description, additional forms of the disorder have been reported, and this group of disorders now includes classical SPS, partial SPS (stiff limb syndrome), and progressive encephalomyelitis with rigidity and myoclonus (PERM) (Barker, Revesz, Thom, Marsden, & Brown, 1998). These conditions share the core features of stiffness, spasms, and heightened stimulus sensitivity and have been grouped together as stiff-person spectrum disorders (SPSDs) (Balint & Meinck, 2018). SPS-plus refers to many additional symptoms and signs that may be present at the onset of illness or develop during the course of the illness. These features include cerebellar ataxia (Ali, Rowley, et al., 2011; Rakocevic, Raju, Semino-Mora, & Dalakas, 2006), epilepsy (Ali, Rowley, et al., 2011; Dalakas, 2009), abnormal eye movements (Economides & Horton, 2005; Zivotofsky, Siman-Tov, Gadoth, & Gordon, 2006), and personality changes (Dalakas, 2009). The discovery of autoantibodies to glutamic acid decarboxylase (GAD) by Solimena et al. in 1988 confirmed the autoimmune nature of SPS. GAD is the rate-limiting enzyme for the synthesis of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (Solimena & De Camilli, 1991; Solimena et al., 1988). Since this breakthrough, the SPSDs have been tied to several other antibodies associated with inhibitory synaptic transmission, discussed below.

CLINICAL PRESENTATION

SPS is rare, with an estimated prevalence of one to two cases per million (Dalakas, 2009). Classical SPS typically presents with the slow onset of muscle rigidity progressing over the course of months to years. Symptoms usually begin symmetrically in the lumbar and thoracic paraspinal muscles and the proximal lower extremity muscles. The disorder has a female predominance (2–3:1), with onset between 30 and 50 years of age (Dalakas, 2009; Martinez-Hernandez et al., 2016). Clinically, episodic muscle spasms are superimposed on muscular rigidity. These spasms, along with difficulty in bending the trunk because of the rigidity, may cause unexplained falls. These falls are often described as "log-like" without the usual reflexive features to soften the impact (Baizabal-Carvallo & Jankovic, 2015; Blum & Jankovic, 1991). Voluntary movements become slow and stiff. Gait anxiety is common and ambulation is often cautious to avoid falling. Breathing difficulty may occur due to stiffness in the thoracic muscles and resultant restriction of chest movements. Muscle spasms may be precipitated by movement, auditory or tactile stimuli (startle), or by negative emotion. The spasms are often painful and typically begin with an abrupt jerk followed by a more sustained, tonic contraction that slowly subsides over seconds to minutes. "Status spasticus" or sustained generalized spasms that may last as long as 2 weeks have been described (Dalakas, Fujii, Li, & McElroy, 2000). Stiffness and spasms fluctuate during

Box 18.1 Disorders Associated with Muscle Pain, Stiffness, and Cramps

1. Corticospinal tract dysfunction
2. Extrapyramidal disorders: akinetic-rigid syndromes (Parkinson disease and parkinsonian syndromes, progressive supranuclear palsy) other degenerative disorders, dystonia
3. Anterior horn cell disorders
   - Stiff-person syndrome and variants
   - Myelopathies: traumatic, ischemic, spinal arteriovenous malformation, spondylotic, neoplastic
   - Toxins: tetanus, black widow spider venom, strychnine
4. Peripheral nerve disorders
   - Tetany: hypocalcemia, hypomagnesemia, alkalosis
   - Isaacs syndrome, Morvan syndrome, cramp fasciculation syndrome
   - Cramps: postexertion, dehydration/salt depletion, pregnancy, denervation (motor neuron disease, neuropathies), idiopathic
5. Disorders of muscle
   - Myotonic disorders: myotonia congenita, paramyotonia congenita, myotonic dystrophy (DM1), proximal myotonic myopathy (DM2), Schwartz-Jampel syndrome
   - Metabolic myopathies: deficiencies of myophosphorylase (McArdle disease), phosphofructokinase (Tarui disease), phosphorylase b kinase, phosphoglycerate mutase, phosphoglycerate kinase, lactate dehydrogenase
   - Rippling muscle disease
   - Brody's disease
   - Inherited disorders causing weakness and muscle contractures: rigid spine syndrome, Emery-Dreifuss muscular dystrophy, Bethlem myopathy
   - Acquired diseases of muscle: inflammatory myopathies, endocrine myopathies (hypothyroidism, Addison disease)
6. Contractures
   - Bony (ankylosis)
   - Soft tissue (Volkmann ischemic contracture)

the day and improve or disappear in sleep. Spasms may be severe enough to cause femoral fractures, joint subluxation or ankylosis, and herniation of abdominal contents (Asher, 1958; Cohen, 1966; Gordon, Januszko, & Kaufman, 1967; O'Connor, 1958). Most descriptions of SPS report sparing of the facial muscles, while some note facial muscle involvement with a "tight-faced" or "pursed-lipped" expression that may limit speech, mask-like facies, risus sardonicus, and dysphagia (Gordon et al., 1967; Levy, Dalakas, & Floeter, 1999). Abnormalities of eye movements including impaired saccades and gaze evoked nystagmus have been reported (Economides & Horton, 2005; Oskarsson et al., 2008; Zivotofsky et al., 2006). Rarely, painful spasms provoked by swallowing, resulting in weight loss, may occur (Cuturic, Harden, Kannaday, Campbell, & Harding, 2011). Autonomic dysfunction, with hyperthermia, diaphoresis, pupillary dilation, tachycardia, tachypnea, and hypertension may be seen. Repeated muscle spasms accompanied by autonomic dysfunction necessitating intensive care management have been reported (Meinck & Thompson, 2002). Rhabdomyolysis may result as a complication of the muscle spasms and rigidity (Petzold et al., 2004). Sudden death has been noted in about 10% of patients (Goetz & Klawans, 1983; Martinelli, Montagna, Pazzaglia, & Coccagna, 1978).

Focal SPS presents with focal stiffness of a lower extremity, often with progressive involvement of trunk muscles (Brown & Marsden, 1999). Myoclonic SPS or "jerking stiff-person syndrome" exhibits the core features of muscle rigidity and spasms with additional characteristics of spontaneous, high-frequency, synchronous myoclonus affecting the axial muscles and lower extremities (Leigh, Rothwell, Traub, & Marsden, 1980).

PERM manifests as a more rapidly progressive form of SPS with brainstem dysfunction, dysautonomia, and prominent myoclonus (Whiteley, Swash, & Urich, 1976). These patients may require mechanical ventilation and mortality has been described to be as high as 40% (Duddy & Baker, 2009). An underlying malignancy may be found in about 20% (Mas et al., 2011).

SPS is frequently associated with several autoimmune conditions (Rakocevic, Alexopoulos, & Dalakas, 2019). Over 30% of patients with SPS have insulin-dependent diabetes mellitus (Dalakas et al., 2000). Studies have also shown an association with autoimmune thyroiditis, pernicious anemia, celiac disease, myasthenia gravis, and, rarely, systemic lupus erythematosus (Dalakas et al., 2000; Goeb, Dubreuil, Cabre, Jean-Baptiste, & Arfi, 2004; Lorish, Thorsteinsson, & Howard, 1989; Meinck & Thompson, 2002; Munhoz, Fameli, & Teive, 2010; Raju et al., 2005). SPS may be a paraneoplastic phenomenon in about 5% of patients (De Camilli et al., 1993; Espay & Chen, 2006; Folli et al., 1993). Malignancies associated with paraneoplastic SPS include breast cancer, small cell lung cancer, thymoma, adenocarcinoma of the colon, and Hodgkin lymphoma (Dropcho, 1996; Folli et al., 1993; Liu, Lo, Tseng, Tsai, & Yang, 2010; Sarva, Deik, Ullah, & Severt, 2016; Schmidt et al., 2010; Werbrouck, Meire & De Bleecker, 2005). SPS has been described following autologous bone marrow transplant and interferon treatment for multiple myeloma (Clow, Couban, & Grant, 2008).

On physical examination, patients with SPS exhibit increased tone in the paraspinal muscles. The continuous muscle contractions give rise to a board-like, rigid appearance of the abdomen while co-contraction of the abdominal and paraspinal muscles gives rise to the typical exaggerated lumbar lordosis that is an almost universal finding in individuals with SPS (Fig. 18.2). Muscle hypertrophy may be present, and exaggerated tendon reflexes and loss of abdominal cutaneous reflexes may be seen (Gordon et al., 1967; Meinck & Thompson, 2002). Although tone may be increased diffusely in the extremities, cog-wheel rigidity and spasticity are absent. The Babinski sign has been described in a few patients (Dalakas et al., 2000). Extrapyramidal, lower motor neuron, sensory, and sphincter abnormalities are absent (Espay & Chen, 2006).

DIAGNOSIS AND EVALUATION

SPS is a clinical diagnosis supported by autoantibody testing and electrodiagnostic features (Baizabal-Carvallo & Jankovic, 2015; Dalakas, 2009) (Box 18.2). Imaging of the brain and spinal cord is essential to exclude structural mimics of SPS such as focal lesions of the spinal cord (intrinsic cord tumors, syringomyelia, spinal cord ischemia), which have been reported to cause an SPS-like picture (Lourie, 1968; Rushworth, Lishman, Hughes, & Oppenheimer, 1961; Tarlov, 1967), although SPS itself is not associated with any pathognomonic imaging features. Electrodiagnostic testing is useful in establishing a diagnosis of SPS and

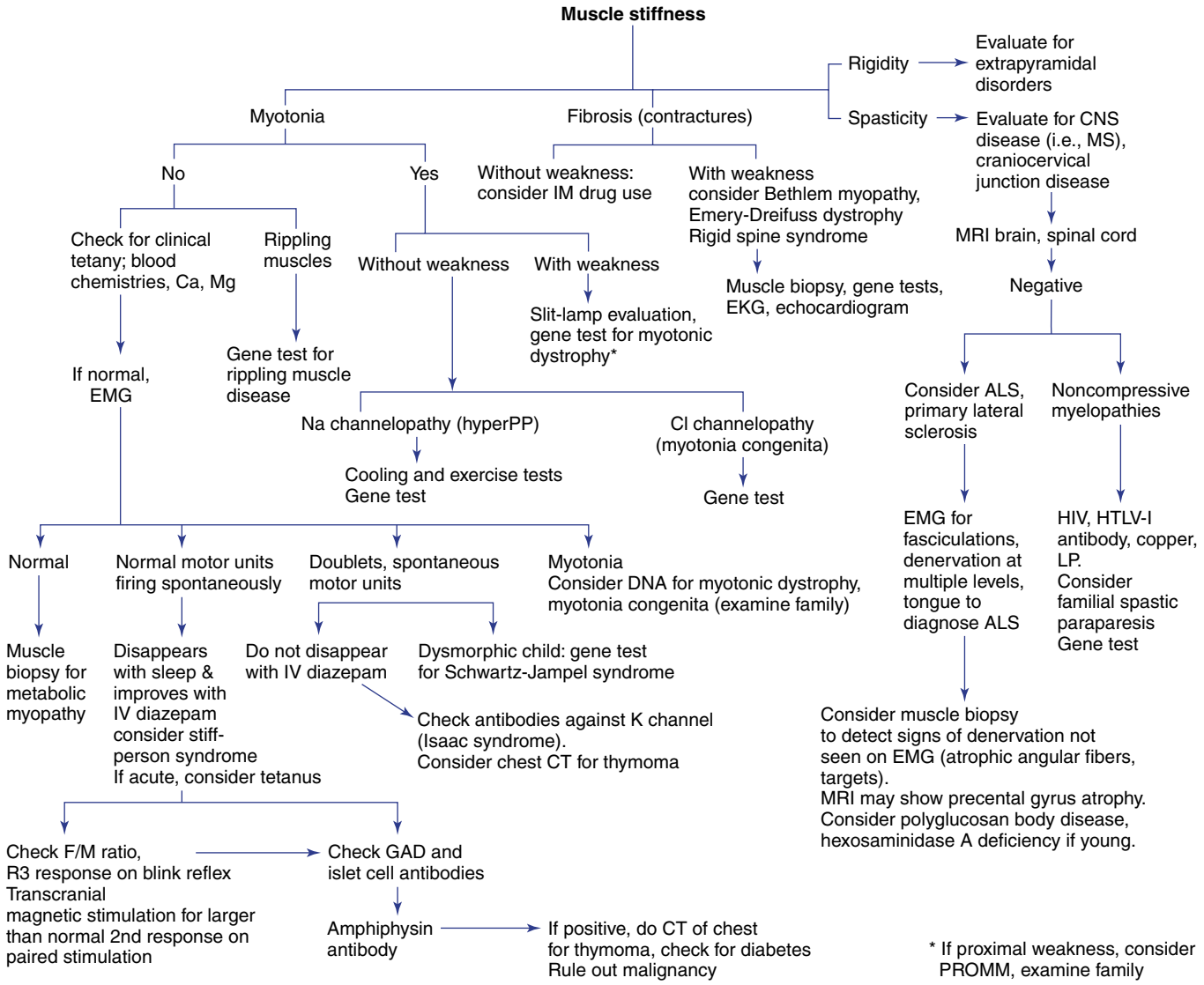


Fig. 18.1 Evaluation of a patient presenting with muscle stiffness. *ALS*, Amyotrophic lateral sclerosis; *Ca*, calcium; *Cl*, chloride; *CNS*, central nervous system; *CT*, computed tomography; *EKG*, electrocardiogram; *EMG*, electromyogram; *F/M ratio*, F-response to M-response amplitude ratio; *GAD*, glutamic acid decarboxylase; *HIV*, human immunodeficiency virus; *HTLV-1*, human T-lymphotrophic virus-1; *IM*, intramuscular; *IV*, intravenous; *K*; potassium; *LP*, lumbar puncture; *Mg*, magnesium; *MRI*, magnetic resonance imaging; *MS*, multiple sclerosis; *PP*, periodic paralysis; *PROMM*, myotonic dystrophy type 2 (DM2). (Edited and reproduced with permission from Bertorini, T. E. (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Philadelphia: Butterworth-Heinemann, Fig. A1.7.)

differentiating it from other disorders that present with muscle stiffness. Routine motor and sensory nerve conduction studies (NCSs) are normal. On needle electromyography (EMG) of involved muscles, continuous activation of motor unit action potentials (MUAPs) that persists despite attempts at relaxation is observed. The MUAPs appear normal, with a normal firing pattern. The continuous motor activity is abolished by sleep, general anesthesia, peripheral nerve block, and benzodiazepines (Auger, 1994). There is co-contraction of agonist and antagonist muscles during voluntary movement, instead of the normal pattern of agonist activation and antagonist relaxation (Espay & Chen, 2006). The silent period is normal, in contrast to chronic tetanus, in which the silent period in involved muscles is absent (Mamoli, Heiss, Maida, & Podreka, 1977; Struppler, Struppler, & Adams, 1963). The R1 response of the blink reflex occurs both ipsilaterally and contralaterally, and a third response, R3, occurs bilaterally with stimulus intensity above the detection threshold (Meinck, Ricker, & Conrad, 1984).

Autoantibodies in SPS (Fig. 18.3, Table 18.1)

Antibodies to GAD were the first to be identified in SPS (Solimena & De Camilli, 1991). Subsequently, other antibodies directed against proteins that are integral to inhibitory neuronal pathways have been described in SPS and SPSD. These proteins include the α1-subunit of the glycine receptor (GlyRα1) (Carvajal-González et al., 2014; Hutchinson et al., 2008; Martinez-Hernandez et al., 2016; McKeon et al., 2013), amphiphysin (De Camilli et al., 1993; Dropcho, 1996; Martinez-Hernandez et al., 2016), gephyrin (Butler et al., 2000), dipeptidyl peptidase-like protein-6 (DPPX) (Balint et al., 2014; Boronat et al., 2013), and γ-aminobutyric acid-A receptor (GABA-aR) (Petit-Pedrol et al., 2014; Raju et al., 2006) (Fig. 18.3, Table 18.1).



Fig. 18.2 Prominent lumbar lordosis in a patient with stiff-person syndrome. (From Bertorini, T. E. (2002). *Clinical evaluation and diagnostic tests for neuromuscular disorders*. Philadelphia: Butterworth-Heinemann, Fig. 2.3B.)

Box 18.2 Diagnosis of Stiff-Person Syndrome

Major criteria

1. Stiffness in the axial and limb muscles, prominently in the abdominal and thoracolumbar paraspinal muscles leading to a fixed deformity (hyperlordosis)
2. Superimposed painful spasms precipitated by unexpected noises, emotional stress, or tactile stimuli
3. Electromyography: confirmation of continuous motor unit activity in agonist and antagonist muscles
4. Absence of other neurological disorders or cognitive impairment that could explain the stiffness

Minor criteria

5. Positive anti-GAD65 or other known associated antibody serum and/or cerebrospinal fluid, assessed by immunocytochemistry, Western blot or radioimmunoassay
6. Clinical response to benzodiazepines

Modified Dalakas criteria for diagnosis of stiff-person syndrome adapted from Baizabal-Carvallo and Jankovic (2014).

Anti-GAD antibodies are the most common antibody associated with SPS, present in approximately 60%–80% of patients (Martinez-Hernandez et al., 2016; Murinson et al., 2004; Solimena, Folli, Aparisi, Pozza, & De Camilli, 1990). These antibodies are directed against two isoforms of GAD, 65 kDa and 67 kDa (Solimena & De Camilli, 1991; Solimena et al., 1988, 1990). About 80% of SPS patients have serum anti-GAD65 antibodies, while antibodies against the GAD67 isoform occur in less than 50% of patients and at much lower titers (Alexopoulos & Dalakas, 2010; Dinkel, Meinck, Jury, Karges, & Richter, 1998). While anti-GAD antibodies may also be seen in other disorders such as insulin-dependent diabetes mellitus (IDDM), very high titers are detected in the sera of patients with SPS (Dalakas, Li, Fujii, & Jacobowitz, 2001; Saiz et al., 2008; Solimena, Butler, & De Camilli, 1994; Solimena & De Camilli, 1991; Solimena et al., 1990). In IDDM, the antibodies recognize different epitopes of GAD than in SPS. These differences in epitope specificity may explain the low incidence of SPS in patients with IDDM (≈1 in 10,000 persons) (Ellis & Atkinson, 1996; Kim et al., 1994; Lohmann, Londei, Hawa, & Leslie, 2003). Serum GAD antibodies may be present in 1% of the normal population and approximately 5% of patients with other neurological disorders (Meinck et al., 2001). GAD antibodies are usually absent in the cerebrospinal fluid (CSF) of patients with other disorders, while intrathecal synthesis of GAD antibodies is not uncommon in SPS, suggesting that CSF antibodies to GAD are specific for SPS (Dalakas, Lee et al., 2001; Rakocevic, Raju, & Dalakas, 2004). Thus, concurrent testing of serum and CSF has the highest diagnostic accuracy for SPS. Antibodies to GAD are not useful in predicting disease severity, and antibody titers do not correlate with disease duration (Mamoli et al., 1977). CSF oligoclonal bands and elevated IgG index have been described in SPS (Rakocevic et al., 2019). GAD antibodies are rarely associated with underlying malignancy in the clinical setting of classical SPS but more frequently so with atypical syndromes (Ariño et al., 2015).

Initially described in PERM (Hutchinson et al., 2008), immunoglobulin G antibodies to GlyRα1 are present in 10%–15% of patients with classical SPS and may also be seen in focal SPS (Alexopoulos, Akrivou, & Dalakas, 2013; Hinson et al., 2018; McKeon et al., 2013). Approximately 30% of patients with SPSD are positive for both GlyR and GAD antibodies (Hinson et al., 2018). GlyRα1 antibodies may be detected in both serum and CSF (Hinson et al., 2018). Seizures are part of the clinical spectrum in many patients with these antibodies (Carvajal-González et al., 2014; McKeon et al., 2013). GlyRα1 antibodies may be associated with underlying malignances including breast cancer, lung cancer, thymoma, and Hodgkin lymphoma in up to 20% of patients (Carvajal-González et al., 2014; Hinson et al., 2018).

Rare patients with SPSD have serum antibodies against amphiphysin, a synaptic vesicle protein (De Camilli et al., 1993; Folli et al., 1993; Murinson & Guarnaccia, 2008). Compared to anti-GAD–positive SPS, patients with amphiphysin antibodies tend to be older and female. In one study, prominent stiffness of the arms and neck was noted compared to the lower extremity predominant symptoms in SPS associated with anti-GAD antibodies. Diabetes was infrequent in these patients (Murinson & Guarnaccia, 2008). The presence of anti-amphiphysin antibody defines paraneoplastic SPSD, particularly associated with breast and small cell lung cancer (De Camilli et al., 1993; Folli et al., 1993; Murinson & Guarnaccia, 2008; Pittock et al., 2005). This association supports prior clinical observations that a paraneoplastic cause should be suspected in SPS involving the upper extremities. Paraneoplastic SPS has also been described associated with anti-Ri (antineuronal nuclear autoantibody type 2, ANNA-2) antibodies (McCabe et al., 2004; Thümen & Moser, 2010). Antibodies to gephyrin

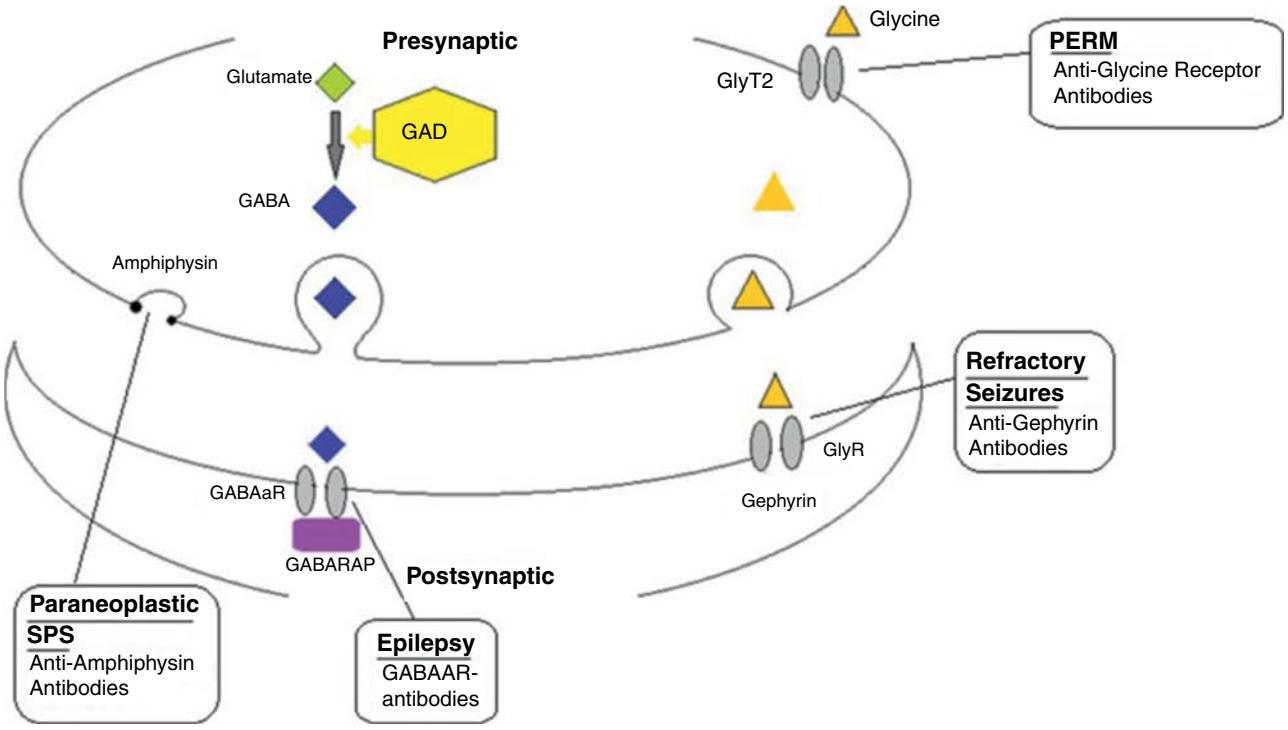


Fig. 18.3 Autoantibody targets in stiff-person syndrome: schematic of an inhibitory synapse. *GABAaR*, Gamma-aminobutyric acid type A receptor; *GABARAP*, gamma-aminobutyric acid type A receptor associated protein; *GAD*, glutamic acid decarboxylase; *GlyR*, glycine receptor; *GlyT2*, glycine transporter. (From El-Abassi, R., Soliman, M. Y., Villemarette-Pittman, N., & England, J.D. (2019). SPS: Understanding the complexity. *JNS*, *404*, 137-149, Figure 1. With permission from Elsevier.)

have been reported in a single patient with SPS and mediastinal cancer (Butler et al., 2000).

GABA-aR antibodies may be seen concurrently with GAD antibodies, or as the sole antibody in SPS. The clinical syndrome is variable. In a case series of 12 patients, six had encephalitis with seizures, four had SPS (one with seizures and limbic involvement), and two had opsoclonus-myoclonus. Six patients had other neuronal antibodies: GAD65 in five and N-methyl-D-aspartate (NMDA)-receptor antibodies in one. Associated autoimmune disorders included Hashimoto thyroiditis and type 1 diabetes mellitus (Petit-Pedrol et al., 2014). Cerebellar dysfunction was noted in 17/25 patients with high GABA-aR antibodies in another series (Raju et al., 2006).

Recently, antibodies against DPPX have been described in stiff person spectrum disorders (SPSD). These patients have a clinical picture characterized by acquired hyperekplexia, cerebellar ataxia, and trunk stiffness (Balint et al., 2014). Prominent gastrointestinal dysautonomia was a feature in one series; in the same series, 2/20 patients had B-cell neoplasms: gastrointestinal lymphoma and chronic lymphocytic leukemia (Tobin et al., 2014). Psychosis with delusions and hallucinations may be prominent (Boronat et al., 2013; Stokin et al., 2015). Approximately 20%–30% of patients meeting diagnostic criteria for SPS lack an identifiable autoantibody.

TREATMENT AND MANAGEMENT

There are two approaches to the treatment of SPS: (1) symptomatic treatment of the rigidity and muscle spasms, usually with agents that potentiate GABA-ergic inhibitory neurotransmission, and (2) immunomodulation (Table 18.2). Agents that have been used for symptomatic therapy include diazepam and other benzodiazepines, baclofen, sodium valproate, levetiracetam, vigabatrin, tiagabine, gabapentin, clonidine, tizanidine, cannabis, and dantrolene (Cohen, 1966; Kuhn, Light, & Kuhn, 1995; Meinck et al., 1984; Miller & Korsvik, 1981; Murinson & Rizzo, 2001; Portman, Donovan, & Bobonis, 2020; Ruegg, Steck, & Fuhr, 2004; Schreiber et al., 2012; Sechi et al., 2008; Spehlmann, Norcross, Rasmus, & Schlageter, 1981; Vasconcelos & Dalakas, 2003; Vermeij, van Doorn, & Busch, 1996). However, there are few controlled trials of these medications; most data are from case reports or small case series. Vigabatrin is available in the United States only through a special restricted distribution program for approved indications because of the risk of permanent visual loss. Diazepam is usually the first choice unless contraindicated or not tolerated. High doses of diazepam, up to 100 mg/day, may be required (Mitsumoto et al., 1991). Other benzodiazepines such as clonazepam have also been used (Westblom, 1977). Oral baclofen is usually next in the treatment algorithm and may be used in addition to or instead of benzodiazepines. Intrathecal baclofen may be more effective than oral baclofen, although complications such as spasm-induced rupture and dislocation of the catheter should be borne in mind (Abbatemarco et al., 2018; Maramattom, 2010; Penn & Mangieri, 1993; Piovano, Piattelli, Spina, Iervese, & Bosco, 2002; Seitz, Blank, Kiwit, & Benecke, 1995; Silbert et al., 1995). A small double-blind, placebo-controlled trial of intrathecal baclofen in three patients revealed improvement in electrophysiologic parameters in all but clinical improvement was noted in only one (Silbert et al., 1995). In another more recent retrospective series of seven patients with refractory SPS who underwent intrathecal baclofen, five had improvement in spasticity and pain at 6–12 months. In addition to spinal headache and

Table 18.1 Antibodies Associated with Stiff Person Syndrome

	Glutamic Acid Decarboxylase (GAD)	α-1 Subunit of the Glycine Receptor (GlyRα1)	Amphiphysin	GABA-A Receptor–Associated Protein (GABA-aR)	Dipeptidyl Peptidase-Like Protein-6 (DPPX)	Gephyrin
Target	Presynaptic GAD65-synaptic vesicles GAD67-Cytosol	Neuronal cell surface, mediate chloride influx, and hyperpolarization	Presynaptic synaptic vesicle protein	GABA-aR α1 and β3 subunits	Membrane glycoprotein, an auxiliary subunit of Kv4.2 channels (potassium voltage-gated channel subfamily D member 2)	Postsynaptic cytoplasmic protein associated with receptors for GABA and glycine
Frequency	70%	10%	5%			1 case report
Clinical features	Axial muscles in the abdomen and thoracolumbar paraspinals, lower extremity involvement. Variants (stiff limb). May have overlap with cerebellar ataxia and epilepsy.	Prominent myoclonus, cranial nerve, brainstem, autonomic symptoms (PERM phenotype)	Neck and upper extremity involvement	Encephalitis with seizures, opsoclonus-myoclonus, cerebellar dysfunction, limbic encephalitis associated with SPS	Acquired hyperekplexia, cerebellar ataxia, gastrointestinal dysautonomia, psychosis with delusions, hallucinations	Tongue muscle stiffness, dysarthria, and dysphagia
Associated malignancy	Infrequent (~5%)	10%–20% with malignancy (thymoma, lung, breast, lymphoma)	Breast, lung			Undifferentiated carcinoma of the mediastinum
Other	Frequently associated with other autoimmune disorders (type I diabetes mellitus, thyroid, celiac, pernicious anemia)		Antibody can be associated with sensory neuronopathy, myelopathy	Hashimoto's thyroiditis, type I diabetes mellitus		

GABA, Gamma aminobutyric acid; *PERM*, progressive encephalomyelitis with rigidity and myoclonus; *SPS*, stiff-person syndrome.

pump motor malfunction, the most serious complication was *Pseudomonas aeruginosa* infection at the pump site in one patient (Abbatemarco et al., 2018). Low doses of continuous intravenous propofol (10 μg/kg/min) were used successfully to control severe spasms as a bridge to intrathecal baclofen in one patient (Hattan, Angle, & Chalk, 2008). Botulinum toxin A injections into the paraspinal and limb muscles have improved spasms and rigidity in three case reports (Conners, Betcher, Shahinian, & Janda, 2019; Davis & Jabbari, 1993; Liguori, Cordivari, Lugaresi, & Montagna, 1997). Tricyclic antidepressants and levodopa may worsen stiffness (Meinck & Conrad, 1986). Rapid withdrawal of therapy can cause life-threatening worsening of symptoms (Murinson & Vincent, 2001).

In patients with inadequate response to symptomatic treatment, immunotherapies are the next step. Large controlled clinical trials of any of these treatments are lacking and the evidence is limited to case reports or small case series. Small case series or uncontrolled trials suggest benefit for intravenous immunoglobulin (IVIg) (Gerschlager & Brown, 2002; Karlson et al., 1994). A randomized, placebo-controlled, cross-over trial in 16 GAD antibody–positive SPS patients demonstrated significant improvement in stiffness scores and ability to ambulate and complete household tasks in patients who received IVIg vs. those who received placebo. The duration of benefit ranged from 6 weeks to a year (Dalakas, Fujii et al., 2001). A recent report of two patients who had good response to IVIg maintained this response up to a year of follow-up when switched to subcutaneous immunoglobulin (Fileccia et al., 2020). Plasmapheresis has both ameliorated clinical symptoms and reduced antibody titers in several case reports of SPS and in isolated case reports of PERM (Brashear & Phillips, 1991; Fogan, 1996; Hao et al., 1999; Hayashi, Nakamagoe, Ohkoshi, Hoshino, & Shoji,

Table 18.2 Treatment of Stiff-Person Syndrome

Medication	Daily dose	Comment
Symptomatic Treatment		
Diazepam	Up to 100 mg in three doses	Avoid abrupt withdrawal; pregnancy Category C
Clonazepam	2.5–18 mg in three doses	Pregnancy Category D
Sodium valproate	600 mg–2 g in three doses	Fatal hepatoxicity, pancreatitis, teratogenesis, low platelet counts, tremor. Monitor liver function tests, platelet count, and amylase at baseline and frequently at least during the first 6 months.
Levetiracetam	2 g in two doses	Risk of suicidality, hepatotoxicity, pancytopenia, pregnancy Category C
Tiagabine	6 mg in two to four doses	Sedation, dizziness, gastrointestinal side effects, pregnancy Category C
Gabapentin	300–3600 mg in three doses	Risk of suicidality, Steven-Johnson syndrome, sedation, ataxia, pregnancy Category C
Vigabatrin[a]	2–3 g in two doses	Diplopia, abnormal color perception, visual field defects, optic atrophy, and changes in retinal pigmentation
Baclofen	10–100 mg in two to three doses orally 50–150 μg/d intrathecal	Weakness, somnolence, Pregnancy Category C Spinal headache, pump motor malfunction, implant site infection
Tizanidine	12–18 mg in three doses	Weakness, dizziness, sedation, pregnancy Category C
Clonidine	0.0025 mg/kg in two doses	Sedation, pregnancy Category C
Botulinum toxin type A	Injections into paraspinal muscles	
Cannabis (CBD/THC 1:1 tincture)	Oral	One case report, safety of cannabis use not established
Dantrolene	Oral 50 mg four times daily	One case report
Immunotherapy		
Prednisone	0.5–1 mg/kg/day	Monitor blood pressure, blood glucose, electrolytes, cataracts, glaucoma, osteoporosis, reactivation of pulmonary tuberculosis
Intravenous immunoglobulin	1 g/kg/day for 2 days	Aseptic meningitis, renal failure. Monitor blood pressure, creatinine during infusions, pregnancy Category C
Plasmapheresis	Four exchanges of 3 L over 8 days	
Rituximab	375 mg/m^2, max 1 g, two infusions at 2-week intervals	Fatal infusion reactions, progressive multifocal leukoencephalopathy (PML), hematologic toxicity, pregnancy Category C
Tacrolimus	3 mg/day	Nephrotoxicity, posterior reversible leukoencephalopathy
Mycophenolate mofetil	1–3 g/day	Long-term risk of lymphoma, PML, hematologic toxicity, Pregnancy Category D
Azathioprine	2–3 mg/kg/day	Acute hypersensitivity reaction, hematologic toxicity, hepatotoxicity, Pregnancy Category D
Cyclophosphamide	1–5 mg/kg/day	Alopecia, hemorrhagic cystitis, bone marrow suppression, pregnancy Category D

CBD, Cannabidiol; *THC*, tetrahydrocannabinol.
[a]Available only through a special restricted distribution program because of the risk of permanent visual loss.

1999; Vicari et al., 1989). Shariatmadar and Noto (2001) suggested that antibody-negative patients may not respond as well to plasma exchange (PLEX) in a case report of two patients, but Nakamagoe, Ohkoshi, Hayashi, Hisahara, and Shoji (1995) reported a good response to PLEX in an antibody-negative patient. A small retrospective case series of nine patients with SPS treated with PLEX noted significant improvement in five patients (Pagano, Murinson, Tobian, & King, 2014). The authors performed a literature review and identified 26 patients with SPS treated with PLEX, with improvement in 11 (Pagano et al., 2014). Prednisone has been reported to improve symptoms in some reports, but not others (Blum & Jankovic, 1991; Harding et al., 1989; McEvoy, 1991; Meinck et al., 1994; Piccolo, Cosi, Zandrini, & Moglia, 1988). Single case reports describe a good response and lasting remission of symptoms in SPS with

rituximab (Baker, Das, Isaacs, Fawcett, & Bates, 2005; Katoh, Matsuda, Ishii, Morita, & Ikeda, 2010; Dupond, Essalmi, Gil, Meaux-Ruault, & Hafsaoui, 2010; Qureshi & Hennessy, 2012; Kyskan, Chapman, Mattman, & Sin, 2013). However, a recent randomized controlled trial (RCT) of 24 patients with GAD antibody–positive SPS failed to show an improvement in the primary outcome, the stiffness index, in rituximab-treated patients over those given placebo at 6 months. The authors noted placebo effect, insensitive outcome measures, and clinical heterogeneity as possible contributors to these negative findings, since four patients reported meaningful clinical improvements that were captured on video recordings (Dalakas, Rakocevic, Dambrosia, Alexopoulos, & McElroy, 2017). Case reports of treatment with tacrolimus (Nakane et al., 2013), azathioprine, mycophenolate mofetil, and cyclophosphamide are available (McKeon, 2012). SPS associated with amphiphysin antibodies may be responsive to corticosteroids and treatment of underlying malignancy (Murinson, & Guarnaccia, 2008). Treatment of an underlying malignancy followed by immunotherapy is the usual approach in paraneoplastic SPS (Folli et al., 1993). The prognosis is variable and depends on the initial presentation. Persistent symptoms and disability are not uncommon, necessitating ongoing treatments with multiple symptomatic and immune therapies concurrently or sequentially.

TETANUS

Tetanus is an infectious disease characterized by central nervous system hyperexcitability, resulting in muscle rigidity and spasms. The causative organism, *Clostridium tetani*, is a gram-positive anaerobic bacterium normally present in spore form in the gastrointestinal tract of mammals and in soil. When these spores gain access to damaged human tissue, they transform into the vegetative form and produce the toxins tetanospasmin and tetanolysin. The primary toxin is tetanospasmin, a neurotoxin that is transported to the spinal cord and brain stem by retrograde axonal transport, where it irreversibly inhibits the release of glycine and GABA at inhibitory synapses (Curtis & De Groat, 1968). This results in disinhibition, initially affecting the alpha motor neurons and, subsequently, the preganglionic autonomic neurons, causing the clinical signs of the disease. The role of tetanolysin in the pathogenesis of the disease is not completely understood, but it is thought to cause local tissue damage and make conditions for bacterial multiplication favorable (Bleck, 1986, 1991).

CLINICAL PRESENTATION

Tetanus is preceded by an obvious injury in most patients. In the majority of cases, tetanus arises from minor skin cuts or abrasions that are trivial and not serious enough to seek medical attention (Thwaites et al., 2004). Other risk factors include penetrating injuries, burns, gangrene, ulcers, unsterile intramuscular or subcutaneous injections, septic abortions, and surgical procedures especially with necrotic infections involving bowel flora. In 20%–50% of cases, no obvious portal of entry is seen (Patel & Mehta, 1999; Cook, Protheroe, & Handel, 2001; Edmondson & Flowers, 1979). Intravenous drug use is now recognized as a risk factor (Beeching & Crowcroft, 2005; Nakajima, Aso, Matsui, Fushimi, & Yasunaga, 2018). The average incubation period (time from the presumed infection to the first symptom) is about 3 to 21 days but varies from 1 day to several months depending on the site of the wound, reflecting the distance that the toxin must travel to the nervous system (Farrar et al., 2000; Patel & Mehta, 1999; Weinstein, 1973). The onset time from the first symptom to the first spasm is about 1 to 7 days. Shorter incubation periods and onset times are associated with more severe disease (Cook et al., 2001; Farrar et al., 2000).

The disease is characterized by tonic muscle rigidity, intermittent muscle spasms, and dysautonomia. In most patients, the disease is generalized. Early symptoms include irritability, restlessness, tachycardia, and diaphoresis. Trismus or "lockjaw" due to rigidity of the masseters is often the presenting symptom. Spasm of the facial muscles gives rise to the characteristic facies, "risus sardonicus," or sardonic smile. The rigidity and spasms spread caudally to involve all muscles. Retraction of the head and opisthotonus result from rigidity of the neck and truncal muscles. Superimposed on the rigidity are intermittent spasms, either spontaneous or triggered by external stimuli such as noise, light, or touch. Spasms may be strong enough to cause fractures. Sudden generalized spasms result in opisthotonus, adduction at the shoulders, flexion at the elbows and wrists, and extension of the lower extremities, associated with a rise in body temperature. Consciousness is preserved throughout the illness, and the rigidity and spasms are intensely painful (Weinstein, 1973). Respiratory failure may occur due to several factors: chest wall rigidity and spasm, airway obstruction due to pharyngeal and laryngeal spasms, and aspiration pneumonia. The most important direct cause of death is respiratory failure (Farrar et al., 2000). Autonomic dysfunction may manifest as diaphoresis and cardiovascular instability (Cook et al., 2001; Kokal, Dastur, Mahashur, & Kolhatkar, 1984; Rhee, Nunley, Demetriades, Velmahos, & Doucet, 2005). After the first 2 weeks of the illness, once the spasms and respiratory function stabilize, dysautonomia is a major cause of mortality (Trujillo, Castillo, Espana, Manzo, & Zerpa, 1987).

Local tetanus is the term used to describe a limited form of the disease characterized by rigidity and spasms restricted to one limb or body region. Local tetanus has a milder course but often progresses to become generalized (Dutta, Padmanabhan, Hamide, & Ramesh, 1994). Localized tetanus resulting from head injuries and involving the cranial nerves is referred to as *cephalic tetanus*. It is defined as trismus associated with paralysis of one or more cranial nerves. Cephalic tetanus tends to progress to generalized tetanus in about two thirds of the cases (Jagoda, Riggio, & Burguieres, 1988). *Tetanus neonatorum*, or neonatal tetanus, presents in the first 2 weeks of birth with feeding difficulty and convulsions and is due to poor umbilical stump care in newborns of unimmunized mothers (Roper, Vandelaer, & Gasse, 2007). Lastly, rare cases of "chronic tetanus" that have a prolonged, nonfulminant course over months have been reported (Risk et al., 1981; Wakasaya et al., 2009).

DIAGNOSIS AND EVALUATION

Tetanus is a clinical diagnosis. Other disorders that may present with muscle rigidity and spasms include tetany, SPS, dystonic reactions, strychnine poisoning, and rabies. Wound cultures often do not detect *C. tetani* or may detect

the organism in patients without tetanus (Levy et al., 2014). Tetanus is rare, but not unknown, in the presence of protective concentrations of antibody (serum antibody titers >0.1 IU/mL by enzyme-linked immunosorbent assay) (Crone & Reder, 1992; Yen & Thwaites, 2019). Bioassays can detect tetanus toxin in the serum and may be useful when there is clinical suspicion of the disease in patients with low antibody titers. However, a negative bioassay does not exclude tetanus (Yen & Thwaites, 2019). Electrophysiologic studies in patients with chronic tetanus reveal an increase in the F-response amplitude to M-response amplitude ratio (F/M ratio). The silent period is usually absent but may be normal (Garcia-Mullin & Daroff, 1973; Rich, Sabin, & Cros, 1992; Risk et al., 1981; Struppler et al., 1963). Motor units are usually normal; the spasms are characterized by involuntary bursts of motor unit activity (Auger, 1994).

TREATMENT AND MANAGEMENT

Three principles guide the management of tetanus: (1) control of active *C. tetani* infection to stop further production of toxin, (2) neutralization of circulating toxin, and (3) supportive care. Wound debridement is essential to eliminate the anaerobic environment that encourages the growth of *C. tetani*. Penicillin G was the traditional antibiotic of choice, in a dose of 100,000 to 200,000 IU/kg/day in divided doses intravenously for 7 to 10 days. However, the GABA-antagonistic properties and epileptogenic effects of intravenous penicillin have raised concerns about the use of penicillin in tetanus (Walker & Johnson, 1945). Therefore, metronidazole is often used preferentially as the first-line antibiotic, 400 mg rectally or 500 mg intravenously every 6 hours for 7 to 10 days. An open, nonrandomized study reported 24% mortality (18/76 patients) in patients receiving procaine penicillin, compared with 7% (7/97 patients) in those receiving metronidazole (Ahmadsyah & Salim, 1985). In a large study by Yen, Dao, and Day (1997), although mortality rate was no different in patients treated with metronidazole or penicillin, patients treated with metronidazole required fewer muscle relaxants and sedatives. An unblinded randomized trial demonstrated similar requirement for tracheostomy and mechanical ventilation, requirement for neuromuscular blockade, and frequency of dysautonomia, nosocomial infections, and mortality in patients treated with intramuscular benzathine penicillin, intravenous benzyl penicillin, or metronidazole (Ganesh Kumar, Kothari, Krishnan, & Karnad, 2004). Alternative antibiotics include erythromycin, tetracycline, chloramphenicol, and clindamycin (Bleck, 1986; Chambers & Sande, 1996).

Tetanus toxin that is bound to the central nervous system cannot be neutralized. However, neutralization of circulating toxin with human tetanus immune globulin (HTIG) improves survival and is considered standard of care. HTIG is usually given in a dose of 3000 to 6000 units intramuscularly (Alfery & Rauscher, 1979). In the UK, intravenous HTIG is used (Yen & Thwaites, 2019). In a large case series from India, no antitoxin and low dose of antitoxin were associated with higher mortality (Patel & Mehta, 1999). A Brazilian randomized controlled study compared intrathecal tetanus immunoglobulin plus intramuscular immunoglobulin to intramuscular immunoglobulin alone in 128 patients with tetanus. Patients treated with both intrathecal and intramuscular immunoglobulin had a shorter duration of spasms and hospitalization and a reduced need for assisted ventilation. It is not clear, however, whether tetanus immune globulin or human lyophilized immunoglobulin was used (Miranda-Filho Dde et al., 2004). However, the conclusions of two meta-analyses are inconsistent regarding the benefit on intrathecal immunoglobulin (Abrutyn & Berlin, 1991; Kabura, Ilibagiza, Menten, & Van den Ende, 2006). Two open studies published subsequent to the meta-analyses reported lower mortality with intrathecal immunoglobulin (Wateba et al., 2008).

Supportive care of tetanus includes the treatment of muscle rigidity and spasms and treatment of dysautonomia. Several agents have been used, but controlled trials are few. Benzodiazepines serve the dual purpose of controlling spasms and rigidity and reducing autonomic instability. Diazepam is most commonly utilized, and large doses may be required, 3 to 8 mg/kg/day. A Cochrane review that included two trials concluded that diazepam may be more effective at reducing mortality than chlorpromazine or phenobarbital (Okoromah & Lesi, 2004). The large doses required, combined with the long half-life (72 hours) and the presence of active metabolites, commonly result in respiratory depression necessitating ventilatory support (Farrar et al., 2000). Midazolam, 5 to 15 mg/hour, and propofol, 20 to 80 mg/hour, intravenously have also been used with some success in case reports and small case series (Borgeat, Popovic, & Schwander, 1991; Gyasi, Fahr, Kurian, & Mathew, 1993; Orko, Rosenberg, & Himberg, 1988). Other agents used for sedation include phenobarbital, morphine, and chlorpromazine (Jenkins & Luhn, 1962; Prys-Roberts, Corbett, Kerr, Smith, & Spalding, 1969; Rie & Wilson, 1978). Intravenous ketamine (2 mg/kg) alternating with diazepam has been used in one case report of cephalic tetanus with severe laryngospasm (Obanor, Osazuwa, & Amadasun, 2008). Oral baclofen does not penetrate the blood-brain barrier. While intrathecal baclofen has been reported to be useful for muscle spasms in case reports and case series, three case series found higher rates of mortality than that reported for other agents and a high incidence of adverse effects including respiratory depression and meningitis (Dapul, Patel, Pannu, & Meythaler, 2014; Dressnandt, Konstanzer, Weinzierl, Pfab, & Klingelhofer, 1997; Engrand, Guerot, Rouamba, & Vilain, 1999; Müller, Börner, Zierski, & Hempelmann, 1987; Santos et al., 2004; Saissy et al., 1992). Studies of magnesium sulfate have provided conflicting results for the control of spasms and management of dysautonomia (Attygalle & Rodrigo, 2002; James & Manson, 1985; Ali, Kamal, & Khan, 2011; Ogun & Ogunniyi, 2008; Thwaites et al., 2006). A meta-analysis of three RCTs did not show benefit of magnesium sulfate compared to diazepam on mortality. Other outcomes including hospital stay and need for mechanical ventilation were conflicting (Ali, Kamal, et al., 2011; Ogun & Ogunniyi, 2008; Rodrigo, Samarakoon, Fernando, & Rajapakse, 2012; Thwaites et al., 2006).

Neuromuscular blockade is used when sedation is inadequate to control the spasms. Pancuronium has been used, but may worsen autonomic dysfunction due to catecholamine reuptake inhibition (Buchanan, Cane, Wolfson, & De Andrade, 1979). Vecuronium has the advantage of minimal cardiovascular side effects but is short acting and requires continuous infusion (Fassoulaki & Eforakopoulou, 1988). Dantrolene was reported to be useful in controlling spasms without need for neuromuscular blockade in one case (Tidyman, Prichard, Deamer, & Mac, 1985).

Although sedation is the first line in the management of dysautonomia, several other classes of agents have been used to control hypertension and tachycardia. Morphine may be useful in the management of dysautonomia because it does not worsen cardiovascular instability (Rie & Wilson, 1978; Rocke, Wesley, Pather, Calver, & Hariparsad, 1986). Beta blockade with propranolol does not appear to be beneficial; on the contrary, it may cause hypotension, pulmonary edema, and even sudden death (Buchanan, Smit, Cane, & De Andrade, 1978; Edmondson & Flowers, 1979). Labetalol is also not recommended for similar reasons (Wesley, Hariparsad, Pather, & Rocke, 1983). Esmolol infusion was used with success in a single case report (King & Cave, 1991). Small series and case reports of the use of clonidine, atropine, and epidural or spinal bupivacaine are available (Dolar, 1992; Gregorakos, Kerezoudi, Dimopoulos, & Thomaides, 1997; Shibuya et al., 1989; Southorn & Blaise, 1986).

Ancillary care includes early tracheostomy and ventilatory support, management of tracheal secretions, nutritional support including gastrostomy tube placement, prophylaxis of deep venous thrombosis, management of nosocomial infections, and prevention of decubiti and gastrointestinal stress ulcerations. Corticosteroids were found to reduce mortality in an open labeled study of 63 patients with severe tetanus (Paydas, Akoglu, Akkiz, Ozer, & Burgut, 1988). Administration of tetanus toxoid in three doses at least 2 weeks apart after recovery is recommended because the disease does not confer immunity.

DISORDERS OF PERIPHERAL NERVE HYPEREXCITABILITY

Peripheral nerve hyperexcitability (PNH) is the term used to describe a spectrum of disorders characterized electrophysiologically by the presence of abnormal discharges generated by the distal motor axon. These discharges possess the EMG waveform appearance of a MUAP, with variations in the frequency and cadence of firing ranging from fasciculations to grouped fasciculations (doublets and triplets), rhythmic myokymia (bursts of MUAPs firing repeatedly, with a semiregular interburst frequency), and the very-high-frequency neuromyotonic discharges. By the same analogy, patients with these disorders manifest symptoms on a scale of escalating severity, from benign fasciculations to diffuse and continuous muscle contractions, dysautonomia and encephalopathy. There is however, significant overlap between these syndromes.

Although PNH syndromes have been recognized as clinical entities since the 1890s (Morvan, 1890), understanding of the syndromes and their pathology has evolved substantially in recent years. However, the terminology used in the literature for these disorders continues to vary considerably, including *syndrome of continuous muscle fiber activity*, *Isaacs syndrome*, *idiopathic generalized myokymia*, *acquired neuromyotonia*, *armadillo syndrome*, and *quantal squander* (Jamieson & Katirji, 1994). To add to the confusion, the term *neuromyotonia* is also used for the EMG finding of continuous irregular bursts of single motor units firing as doublets, triplets, or multiplets firing at very high intraburst frequencies of up to 150 to 300 Hz. The electrophysiologic terminologies *myokymia*, *neuromyotonia*, *continuous muscle fiber activity*, *continuous motor neuron discharges*, and *neurotonia* are used interchangeably and inconsistently (Gutmann, 2004). The clinical syndrome of neuromyotonia may be associated with the EMG finding of neuromyotonia or myokymia, as described later, and should be distinguished from the EMG finding of neuromyotonia.

Box 18.3 Clinical Classification of Disorders of Peripheral Nerve Hyperexcitability

1. Autoimmune
   - Associated with CASPR2, LGI-1, and contactin-2 antibodies: Isaacs syndrome and Morvan syndrome
   - Paraneoplastic: thymoma, small cell lung cancer, lymphoma, plasmacytoma with IgM paraproteinemia
   - Associated with peripheral neuropathy: idiopathic, CIDP, Guillain-Barré syndrome
   - Associated with other autoimmune disorders: myasthenia gravis, diabetes mellitus, hypo/hyperthyroidism, Addison disease, SLE, systemic sclerosis, rheumatoid arthritis, celiac disease, pernicious anemia, amyloidosis
2. Non–immune-mediated
   - Drugs and toxins: gold, d-penicillamine, oxaliplatin, mercury, timber rattlesnake venom
   - Associated with motor neuron disease
3. Hereditary
   - Associated with episodic ataxia with myokymia (EA-1)
   - Associated with neonatal epilepsy
   - Associated with hereditary neuropathy (HMSN 1a, HNPP)
   - Schwartz-Jampel syndrome

Adapted from Maddison, P. (2006). Neuromyotonia. *Clinical Neurophysiology*, 117, 2118-2127, with permission from Dr. Maddison and the Editor, *Clinical Neurophysiology*.

CASPR2, Contactin-associated protein-like 2; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *HMSN*, hereditary motor sensory neuropathy; *HNPP*, hereditary neuropathy with predisposition to pressure palsies; *LGI-1*, leucine rich glioma inactivated 1; *SLE*, systemic lupus erythematosus.

Disorders of PNH can be genetic or acquired. Box 18.3 details the clinical classification of PNH. Multiple hereditary disorders in which PNH is a prominent feature have been described. Usually associated with mutations in genes encoding voltage-gated potassium channels (VGKCs), these disorders lead to clinical myokymia with other features such as neonatal epilepsy, episodic ataxia, and skeletal deformities (Browne et al., 1994; Dedek et al., 2001; Eunson et al., 2000; Kinali et al., 2004; Wuttke et al., 2007). A familial form of epilepsy has been linked to the leucine-rich, glioma inactivated-1 (LGI1), a protein associated with the VGKC complex (Morante-Redolat et al., 2002). Recently, hereditary axonal neuropathy with prominent PNH has been attributed to mutations in the histidine triad nucleotide binding protein 1 (*HINT1*) gene (Jerath, Shy, Grider, & Gutmann, 2015; Peeters, Chamova, Tournev, & Jordanova, 2017).

In this chapter, we focus on acquired PNH. The three main acquired PNH disorders are Isaacs syndrome, Morvan syndrome, and cramp-fasciculation syndrome (CFS). Limbic encephalitis is a related central syndrome that can overlap with the peripheral syndromes (Table 18.3) (Takahashi et al., 2008). Acquired autoimmune forms of PNH were previously attributed to antibodies against VGKCs (Barber, Anderson, & Vincent, 2000; Hart, Maddison, Newsom-Davis,

Table 18.3 The Syndromes of Peripheral Nerve Hyperexcitability: Clinical Features

Disorder	Gender/Age	Symptoms and Signs	Electrophysiology	Autoantibodies
Cramp fasciculation syndrome	2:1 (M:F) Average age 45 years	Muscle aching, stiffness, cramps (painful muscle contractions precipitated by movement, relieved by stretching) Fasciculations on examination Paresthesia	NCS: afterdischarges with repetitive nerve stimulation EMG: cramp discharges and fasciculations; neuromyotonia, myokymia, fibrillations absent	20%–30% VGKC-complex antibodies (CASPR2) 6% ganglionic AChR antibodies, striational antibodies
Isaacs syndrome	2:1 (M:F) Average age 45 years	Muscle stiffness, fasciculations, myokymia (continuous vermiform movements) that disappear with neuromuscular blockade, persist in sleep and after general anesthesia, and have a variable response to peripheral nerve block Hyperhidrosis, muscle hypertrophy Abnormal postures of hands and feet	Routine NCS: afterdischarges following CMAP or F/H waves EMG: myokymia or neuromyotonia; may be accentuated by hyperventilation or ischemia; fibrillations and fasciculations may be seen	40% with VGKC-complex antigens CASPR2, LGI1, contactin 2.8% with AChR
Morvan syndrome	9:1 (M:F) Average age 60 years	Muscle stiffness, fasciculations, myokymia, hyperhidrosis, autonomic instability, encephalopathy, hallucinations, severe insomnia	EMG/NCS: as in Isaacs syndrome EEG: diffuse slow wave abnormalities	CASPR2 (70%), LGI1 (75%), contactin-2
Limbic encephalitis	M > F Average age 60–70 years	Amnesia, psychiatric features, and seizures	EMG/NCS: normal EEG: focal seizures, medial temporal lobe with semiology of manual and orofacial automatisms	LGI1 > CASPR2

AChR, Acetylcholine receptor; *CASPR2*, contactin-associated protein 2; *CMAP*, compound muscle action potential; *EEG*, electroencephalogram; *EMG*, electromyography; *LGI1*, leucine-rich glioma inactivated protein 1; *NCS*, nerve conduction study; *VGKC*, voltage-gated potassium channel.

Vincent, & Mills, 2002; Liguori et al., 2001; Shillito et al., 1995) but are now known to target specific components of the VGKC complex: LGI1, contactin-associated protein-2 (CASPR2), and less frequently, contactin-2 (Vincent et al., 2018). PNH has been reported due to exposure to drugs such as gold (Mitsumoto, Wilbourn, & Subramony, 1982), penicillamine (Reeback, Benton, Swash, & Schwartz, 1979), oxaliplatin (Saadati & Saif, 2009; Wilson et al., 2002), and toxins such as mercury (Gil, Lefevre, Neau, Guillard, & Hulin, 1984; Zhou et al., 2014), or as a secondary phenomenon in peripheral neuropathies (Hahn, Parkes, Bolton, & Stewart, 1991; Newsom-Davis & Mills, 1993; Odabasi, Joy, Claussen, Herrera, & Oh, 1996; Vasilescu, Alexianu, & Dan, 1984). PNH may be paraneoplastic, in association with small cell carcinoma of the lung, thymoma, and, rarely, thyroid carcinoma and lymphoma (Caress, Abend, Preston, & Logigian, 1997; Newsom-Davis & Mills, 1993; Partanen, Soininen, Saksa, & Riekkinen, 1980; Vernino, Auger, Emslie-Smith, Harper, & Lennon, 1999; Vernino & Lennon, 2002). Nine percent of patients with acquired neuromyotonia had autoimmune myasthenia gravis (MG) in one study (Vernino & Lennon, 2002). Case reports describe PNH associated with human immunodeficiency virus infection and idiopathic hypoparathyroidism, systemic sclerosis, and following bone marrow transplantation (Garea et al., 1998; Benito-Leon, Miguelez, Vincent, Masjuan, & de Blas, 1999; Liguori et al., 2000; Zambelis, Licomanos, Leonardos, & Potagas, 2009).

DIAGNOSIS AND EVALUATION

ISAACS SYNDROME

Isaacs syndrome, or acquired autoimmune neuromyotonia, is characterized by continuous muscle fiber hyperactivity that manifests with muscle stiffness, fasciculations, and clinical myokymia and is characterized clinically by continuous vermiform movements across muscles that have been likened to a bag of worms under the skin (Table 18.3). The disorder is usually insidious in onset, with a male predominance (M:F 2:1) and average age of onset in the mid-40s (Hart et al., 2002), although it has been reported in infants and children (Auger, Daube, Gomez, & Lambert, 1984; Thomas, Heckmatt, Rodillo, Ransley, & Dubowitz, 1994). The movements are usually seen in distal and proximal limb muscles but may also involve the axial muscles, face, and tongue (Maddison, 2006; Newsom-Davis & Mills, 1993). Dyphonia and dyspnea due to involvement of laryngeal muscles have been reported (Jackson, Satya-Murti, Davis, & Drachman, 1979). Persistent contraction of muscles results in abnormal postures with flexion or extension of the hands and feet, resembling carpopedal spasm. Other features include muscle

cramps that may worsen following voluntary muscle contraction. Hyperhidrosis and muscle hypertrophy are frequently present and are attributed to the continuous muscle fiber activity. Pseudomyotonia is a clinical diagnostic feature of Isaacs syndrome but is seen only in about a third of the patients. It refers to delayed muscle relaxation after voluntary contraction without percussion myotonia and is so termed to differentiate it from myotonia, which originates in the muscle membrane. It commonly affects hand grip. Weakness is reported in approximately a third of patients, usually involving the most overactive muscles. Pain and paresthesia are not uncommon. Tendon reflexes may be normal or absent (Ahmed & Simmons, 2015; Hart et al., 2002; Maddison, 2006; Thompson, 1994; Vincent et al., 2018). The continuous muscle activity persists during sleep and general anesthesia. The response to peripheral nerve block is variable but it is abolished by neuromuscular blockade with curare, establishing the distal peripheral nerve as the impulse generator (Thompson, 1994). A report of hypersensitivity to a nondepolarizing muscle relaxant (rocuronium), causing prolonged postoperative paralysis highlights the need for caution during surgical procedures (Ginsburg, Forde, Martyn, & Eikermann, 2009).

MORVAN SYNDROME

A more severe, less frequent form of PNH associated with dysautonomia and central nervous system (CNS) dysfunction is referred to as Morvan syndrome or Morvan fibrillary chorea (Table 18.3) (Morvan, 1890). The vast majority of patients are male, with disease onset in adulthood. Dysautonomia manifests with hyperhidrosis, tachycardia, cardiac arrhythmia, and bladder dysfunction. CNS symptoms include hallucinations, agitation, delirium, confusion, and amnesia. Sleep disturbances, especially insomnia, are characteristic. Neuropathic pain is common (Irani et al., 2012). "Status dissociatus" (agrypnia excitata, oneiric stupor), characterized by nighttime unresponsiveness with eyes closed, continuous dream-like mentation (vivid, lucid dreams), continuous motor activity (muscles, respiration, and eye movements), dream-enacting behaviors, and feeling of having slept despite the absence of conventional sleep markers, has been described. Although this behavior resembles rapid eye movement (REM) behavior disorder (RBD), the polysomnogram does not show REM sleep, and the behavior is continuous for hours (Abgrall, Demeret, Rohaut, Leu-Semenescu, & Arnulf, 2015). Polysomnogram evidence of the absence of sleep has been reported (Josephs et al., 2004). Brain magnetic resonance imaging (MRI) is usually unremarkable (Irani et al., 2012; Josephs et al., 2004). An association with thymoma with or without acetylcholine receptor antibody (AChR-ab) positive MG is reported (Irani et al., 2012; Lee, Maselli, Ellis, & Agius, 1998). As with Isaacs syndrome, Morvan syndrome is also associated with CASPR2, LGI1, and contactin-2 autoantibodies, especially the former (Galié et al., 2016; Irani et al., 2012; Nikolaus, Jackowski-Dohrmann, Prüss, Schuelke, & Knierim, 2018).

CRAMP-FASCICULATION SYNDROME

In 1991, Tahmoush and colleagues reported nine patients with a syndrome of PNH characterized by exercise intolerance, muscle pain and stiffness, cramps, and diffuse fasciculations, predominantly in the lower extremities. They defined cramps as painful muscle contractions precipitated by movement and relieved by stretching (Tahmoush, Alonso, Tahmoush, & Heiman-Patterson, 1991). It is now recognized that Isaacs syndrome and CFS appear to differ only quantitatively along a continuum; the symptoms are more severe and widespread in patients with Isaacs syndrome compared to those with CFS (Table 18.3) (Hart et al., 2002; Vernino & Lennon, 2002). Although CFS is usually benign, rare instances of CFS progressing to amyotrophic lateral sclerosis have been reported (de Carvalho & Swash, 2004). Antibodies to the VGKC complex have been described only in a small proportion of CFS; these patients may have associated central and autonomic hyperexcitability (Liewluck, Klein, & Jones, 2014; Vernino & Lennon, 2002).

The diagnosis of Isaacs syndrome, Morvan syndrome, and CFS is based on the clinical and electrophysiologic features. NCSs are useful to detect underlying peripheral neuropathies causing secondary PNH. The terms that have been used to describe the EMG spontaneous activity seen in Isaacs syndrome include *neuromyotonic discharges* and *myokymic* discharges. Electromyographically, neuromyotonia refers to continuous irregular bursts of single motor units firing as doublets, triplets, or multiplets. The intraburst frequency is 150 to 300 Hz. Bursts may be short or last a few seconds, with abrupt onset and termination. The amplitude often wanes. The bursts may be spontaneous, precipitated by needle movement, or nerve percussion. Myokymic discharges on EMG are similar except that the intraburst frequency of the discharges is much lower at 5 to 150 Hz, and these bursts repeat at regular or irregular intervals, semirhythmically, followed by a few seconds of silence. The interval between bursts depends on the length of the bursts, with longer bursts firing less frequently. Electrophysiologically, both neuromyotonic discharges and myokymia are felt to represent a continuum of the same abnormality (Gutmann, 2004; Vernino & Lennon, 2002). Electrical neuromyotonia is characterized by persistent muscle contraction, while the clinical correlate of myokymia is muscle twitching without sustained muscle contractions (Gutmann, Libell, & Gutmann, 2001). Myokymia is less specific for PNH and can be seen in other settings. Fibrillations and fasciculations may also be noted (Hart et al., 2002). The spontaneous activity persists in sleep, is unchanged or diminished by peripheral nerve block, and disappears after neuromuscular blockade with curare. The discharges may be accentuated by hyperventilation or ischemia. In addition, after-discharges are often seen following the compound motor action potential or after the F or H wave on routine NCS (Auger, 1994; Auger et al., 1984; Gutmann, 2004).

In CFS, after-discharges occur only after repetitive nerve stimulation, not after a single stimulus. EMG findings are less prominent, mainly fasciculations and cramp discharges. Myokymia, neuromyotonia, and fibrillations are usually absent (Auger et al., 1984). Benatar et al. studied repetitive nerve stimulation of motor nerves with supramaximal stimuli at 1, 5, 10, and 30 Hz in patients with CFS. They defined after-discharges as individual electrical potentials following the train of stimuli. When individual potentials could not be identified because the frequency of after-discharges was too high, the term *cramp potential* was used. At 10 Hz stimulation, the test had a sensitivity of 79% and a specificity of 88% (Benatar, Chapman, & Rutkove, 2004). In a subsequent

study, tibial nerve repetitive stimulation correctly classified the presence or absence of CFS in 75% of patients (Harrison & Benatar, 2007).

Laboratory evaluation of patients with PNH should include tests for VGKC-complex antibodies. Since PNH can be associated with systemic autoimmunity including thyroiditis, psoriasis, and Coombs-positive hemolytic anemia, serologic testing for antinuclear antibodies, rheumatoid factor, antiparietal cell, thyroid, Sjogren syndrome, striational, voltage-gated calcium channel, gliadin, GAD, and muscle acetylcholine receptor antibodies has been recommended (Ahmed & Simmons, 2015; Rubio-Agusti et al., 2011; Taylor, 2005). Serum creatine kinase (CK) may be elevated (Hart et al., 2002; Rubio-Agusti et al., 2011). Oligoclonal bands may be detected in the CSF (Newsom-Davis & Mills, 1993). It is important to evaluate for underlying malignancy. The malignancy may precede the diagnosis of PNH by up to 4 years or follow the diagnosis (Hart et al., 2002). Malignancy associations include thymoma, thyroid carcinoma, prostate cancer, non–small cell lung cancer, and Hodgkin lymphoma (Ahmed & Simmons, 2015; Caress et al., 1997; Newsom-Davis & Mills, 1993; Partanen et al., 1980; Rubio-Agusti et al., 2011; Taylor, 2005; Vernino & Lennon, 2002), and comprehensive malignancy screening is indicated. Whole-body positron emission tomography scan should be considered in patients with negative cancer screening, and serial cancer screening may be indicated.

TREATMENT AND MANAGEMENT

The symptomatic effect of several drugs has been described in case reports or small series of the three PNH syndromes (Elangovan, Morawo, & Ahmed, 2018). Controlled studies are lacking. Many studies include patients with secondary PNH. Since the treatments of the three disorders overlap, they are discussed together. Most case reports describe patients who have received more than one symptomatic agent in addition to immunomodulatory treatments, making it difficult to evaluate the effect of these agents individually. Agents that have been used with varying benefits are sodium channel blockers, of which the most commonly used are phenytoin and carbamazepine; others include oxcarbazepine, mexiletine, lamotrigine, and lacosamide (Ahmed & Simmons, 2015; Barber et al., 2000; Caress & Walker, 2002; Elangovan et al., 2018; Ganos, Munchau, Baumer, Gerloff, & Magnus, 2011; Hurst & Hobson-Webb, 2016; Imam, Edwards, & Hanemann, 2009; Liewluck et al., 2014; Martinelli et al., 1996; Poyraz et al., 2017). Treatment with phenytoin sodium resulted in reduction in muscle fiber activity as well as muscle hypertrophy in one patient (Zisfein, Sivak, Aron, & Bender, 1983). A small retrospective study of 23 patients with cramps and electrophysiologic evidence of PNH found a 70% and 77% response rate to the two most frequently prescribed agents, gabapentin and carbamazepine, respectively (Hurst & Hobson-Webb, 2016). Case reports of the use of GABA-ergic agents including sodium valproate, baclofen, gabapentin, pregabalin, diazepam, clonazepam, and the carbonic anhydrase inhibitor acetazolamide are available (Abou-Zeid, Boursoulian, Metzer, & Gundogdu, 2012; Ansell, Kirby, & Benstead, 1997; Barber et al., 2000; Caress & Walker, 2002; Celebisoy, Colakoglu, Akbaba, & Yuceyar, 1998; Dhand, 2006; Gonzalez, Barros, Russi, Nunez, & Scavone, 2008; Hurst & Hobson-Webb, 2016; Liewluck et al., 2014; Maddison, 2006; Newsom-Davis & Mills, 1993; Nishioka, Kanai, & Hattori, 2017; O'Brien & Gates, 1994; Odabasi et al., 1996; Poyraz et al., 2017; Tahmoush et al., 1991; Toosy et al., 2007; Vasilescu, Alexianu, & Dan, 1987; Wallis, Van Poznak, & Plum, 1970; Wasserstein, Shadlen, & Dorfman, 1992). Dantrolene has been used in one case for cramps and pain (Nishioka et al., 2016). The doses of these agents used are not specific for PNH; assessment for CNS and other side effects and laboratory monitoring for adverse effects (hepatotoxicity, bone marrow toxicity, metabolic derangements such as hyponatremia etc.) are important aspects of management. Treatment of insomnia in Morvan syndrome with melatonin, doxepin, and oxycodone has been reported (Josephs et al., 2004). Sodium oxybate was used, with improvement in insomnia in one patient with MG and Morvan syndrome with status dissociatus, but caused side effects (Abgrall et al., 2015).

Several immunosuppressive and immunomodulating agents have been used in case reports or small case series of PNH disorders. Successful treatment of one patient with Isaacs syndrome and thymoma with IVIg has been reported (Ho & Wilson, 1993). One patient failed to respond after six PLEXs and could not tolerate steroids and azathioprine, but had good benefit from IVIg (Alessi, De Reuck, De Bleecker, & Vancayzeele, 2000). Newsom-Davis and Mills (1993) used PLEX or a combination of prednisone (60–80 mg on alternate days) and azathioprine (1.5–2.5 mg/kg daily) in three of five patients, with improvement in two. Ishii et al. (1994) treated one patient with Isaacs syndrome with PLEX with remission of symptoms for about 5 months. With subsequent IVIg treatment, dysphagia worsened and dyspnea appeared. The symptoms improved after another PLEX. van den Berg, van Engelen, Boerman, and de Baets (1999) made a similar observation in one patient with Isaacs syndrome associated with thymoma, in whom IVIg at 0.4 g/kg for 5 days was ineffective. A subsequent course of PLEX resulted in rapid, dramatic improvement. PLEX has been used in other cases, either alone or in combination with oral immunosuppressants (Ansell et al., 1997; Martinelli et al., 1996). It has been suggested that the worsening of symptoms following IVIg administration may be due to IVIg-mediated increase in intracellular calcium and subsequent muscle cramps. Additionally, PLEX may be more effective than IVIg in reducing autoantibody titers (van den Berg et al., 1999; Van Engelen, Benders, Gabreels, & Veerkamp, 1995). Intravenous methylprednisolone and other immunosuppressive agents such as cyclosporine and cyclophosphamide have been used in a few cases. A review by Merchut (2010) summarizes these treatments. Paraneoplastic PNH requires management of the tumor.

CFS is usually managed with symptomatic agents such as carbamazepine and gabapentin. In their initial report, Tahmoush et al. (1991) noted a "fair to good" response to carbamazepine titrated up to effect, with a maximum dose of 1600 mg/day. Treatment with prednisone 25 to 30 mg/day improved cramps in one patient with MG, CFS, and thymoma (Table 18.2) (Vernino et al., 1999). One patient with diabetes and Hashimoto disease responded well to PLEX (Liewluck et al., 2014).

Box 18.4 Classification of Rippling Muscle Disease

Hereditary

Autosomal dominant, chromosomal locus 1q41–42 (gene defect unknown)
Autosomal dominant, chromosomal locus 3p25 (caveolin-3 gene)
Autosomal recessive, chromosomal locus 3p25 (caveolin-3 gene)

Acquired

Sporadic, due to de novo mutations in the caveolin-3 gene
Autoimmune: associated with myasthenia gravis, thymoma, lymphoma, and other autoimmune disorders

PRIMARY DISORDERS OF MUSCLE

RIPPLING MUSCLE DISEASE

Rippling muscle disease (RMD) is a myopathy with hyperexcitability of the muscle. Initially described by Torbergsen (1975) in five affected members in a family over three generations, Ricker, Moxley, and Rohkamm (1989) subsequently reported two German families with the disorder and introduced the term *rippling muscle disease*. It is now known that most cases of the disorder are associated with mutations in the caveolin-3 (*CAV3*) gene (also implicated in limb-girdle muscular dystrophy 1C). Autosomal dominant, autosomal recessive, and apparently sporadic cases with *CAV3* mutations have been reported (Betz et al., 2001; Cagliani et al., 2003; Fischer et al., 2003; Kubisch, Ketelsen, Goebel, & Omran, 2005; Traverso et al., 2008; Van den Bergh et al., 2004; Woodman, Sotgia, Galbiati, Minetti, & Lisanti, 2004; Yabe et al., 2003). A second autosomal dominant locus on chromosome 1q is described, but the mutation is not known (Stephan et al., 1994). RMD associated with MG and AChR-ab is the most frequently reported form of acquired, likely immune mediated RMD (Box 18.4) (Ansevin & Agamanolis, 1996; Bettini et al., 2016; Greenberg, 2004; Jacobi et al., 2010; Müller-Felber et al., 1999; Vernino et al., 1999; Vernino & Lennon, 2002). A few cases of acquired RMD without MG have been reported; one patient developed autoimmune hemolytic anemia a year after the onset of RMD, and another developed malignant lymphoma 3 years after the onset of RMD (Ashok Muley & Day, 2003; Takagi, Kojima, Watanabe, Ida, & Kawagoe, 2002). Immune-mediated RMD has been described in a patient with hypothyroidism (Ducci et al., 2017). In one patient, sporadic RMD was provoked by simvastatin therapy. This patient developed MG about a year after the onset of RMD (Baker & Tarnopolsky, 2006). In one report, MG, thymoma, AChR-ab, or *CAV3* mutations were not detected in three patients. One patient recovered spontaneously with normalization of caveolin expression, and another responded to PLEX and immunosuppression, suggesting that this was immune-mediated RMD and that additional, as-yet unidentified antibodies may be associated with this disorder (Lo et al., 2011). Thymoma has been reported in several cases of RMD and MG (Ansevin & Agamanolis, 1996; Greenberg, 2004; Schulte-Mattler et al., 2005; Vernino et al., 1999).

DIAGNOSIS AND EVALUATION

The disease usually presents in the first two decades. In a review of 46 individuals from two families, the age of onset ranged from 5 to 54 years (mean, 22 years). Patients presented with muscle stiffness that was most pronounced in the proximal lower extremities and sometimes painful (Vorgerd et al., 1999). Slowness of movements after a period of rest and muscle cramping are other features. Muscle pain, cramps, or stiffness may be induced by exercise in some patients, while, in others, muscle cramps occur when standing and walking after a period of rest and disappear with continuing exertion (Perez, Bertorini, & Narayanaswami, 2006; Vorgerd et al., 1999).

On examination, there are three main signs: the rippling phenomenon, muscle mounding, and percussion-induced rapid muscle contractions (PIRC). The rippling phenomenon is elicited by forceful muscle contraction followed by abrupt relaxation, such as forceful extension of the knee followed by abrupt flexion, or forceful flexion of the elbow followed by abrupt extension. This induces slow rolling movements across the muscle. The mechanical stretch is a stimulus to muscle rippling. The speed of muscle rippling has been shown to be 0.6 m/second, 10 times slower than muscle fiber conduction velocity (Ricker et al., 1989; Torbergsen, 2002). Muscle mounding is characterized by a visible localized swelling of muscles that is elicited by tapping the muscle at various intensities. It may be generalized or confined to a few muscles and may be painful. When generalized, it tends to be most prominent in the deltoid, biceps brachii, brachioradialis, extensor digitorum, thenar muscles, and quadriceps. Slight muscle percussion may result in instant, pronounced contraction that may be sustained for several seconds, termed PIRC. PIRC may be elicited in the extremity muscles and the sternomastoids. They are usually painless and do not habituate. Other features of RMD include focal (usually calf) or generalized muscle hypertrophy. Mild proximal muscle weakness may be seen (Ricker et al., 1989; Vorgerd et al., 1999). There may be a tendency to toe-walk, especially on awakening in the morning or after a prolonged period of rest. The toe-walking improves after several minutes of walking and has been attributed to disproportionate stiffness of the calf muscles (Madrid, Kubisch, & Hays, 2005; Ricker et al., 1989; So, Zu, Barraza, Figueroa, & Pulst, 2001; Vorgerd et al., 1999). Recurrent myoglobinuria has been reported (Aboumousa et al., 2008; Vorgerd et al., 1999).

Vorgerd et al. have proposed diagnostic criteria for RMD: (1) PIRC in at least two muscles of the upper and two muscles of the lower extremity in the presence of normal tendon reflexes and (2) at least one of the following: muscle mounding, muscle rippling, or elevated serum CK. In their series, PIRC was the most reliable clinical sign of RMD. PIRC and muscle mounding are uniformly present in RMD, whereas muscle rippling is seen in only about two thirds of patients, despite the fact that the disease bears the name of the phenomenon (Vorgerd et al., 1999). It has been suggested that the absence of PIRC may distinguish acquired RMD associated with MG from genetic RMD (Greenberg, 2004). The clinical course is relatively mild and either nonprogressive or slowly progressive (Ricker et al., 1989; Torbergsen, 2002; Vorgerd et al., 1999).

The diagnostic evaluation of patients with suspected RMD includes estimation of serum CK levels, which are often

significantly elevated (3–30-fold) (Aboumousa et al., 2008). Routine laboratory tests are usually normal. Thyroid functions should be tested because the muscle mounding seen in RMD is similar to "myoedema" described in hypothyroidism. Muscle and ganglionic AChR-ab, VGKC-complex antibodies, and striated muscle antibodies may be detected in patients with the autoimmune form of RMD (Vernino et al., 1999; Vernino & Lennon, 2002). Radiologic evaluation for thymoma is appropriate, especially in non-familial cases.

Needle EMG is usually normal in RMD. The clinical diagnostic signs of RMD including muscle rippling, mounding, and PIRC are electrically silent (Ansevin & Agamanolis, 1996; Torbergsen, 1975, 2002; Vorgerd et al., 1999). Increased insertional activity and spontaneous high-frequency motor unit discharges associated with muscle rippling have been reported in patients with both genetic and autoimmune RMD (Maki et al., 2011; Vernino et al., 1999; Vernino & Lennon, 2002). Routine muscle biopsy may be normal. Inflammatory infiltration has been reported in acquired RMD (Greenberg, 2004; Müller-Felber et al., 1999; Schulte-Mattler et al., 2005; Vernino et al., 1999). One report describes myopathic features with T-cell infiltration, a mosaic pattern of reduced caveolin-3 and dysferlin with loss of caveolae and T-tubular dilatation on electron microscopy. This patient had serum antibodies to striated muscle and titin (Schulte-Mattler et al., 2005). Other cases of immune-mediated RMD with patchy reduction in caveolin-3 immunostaining have also been reported (Bettini et al., 2016; Schoser et al., 2009). A secondary reduction in dysferlin may be seen in both genetic and acquired forms of the disease. A mosaic pattern of caveolin-3 immunostaining (with some fibers showing reduced staining and others demonstrating normal staining) may be suggestive of immune-mediated rather than hereditary RMD (Aboumousa et al., 2008; Schulte-Mattler et al., 2005). A vacuolar myopathy has been reported (Sadeh, Berg, & Sandbank, 1990). In patients with suspected genetic RMD, genetic testing for *CAV3* is appropriate as the initial test instead of muscle biopsy.

TREATMENT AND MANAGEMENT

Literature on the treatment of RMD is sparse. The disorder tends to be benign, and the rippling phenomenon and PIRC do not seem to affect quality of life (Aboumousa et al., 2008). Medications that have been reported to be useful include dantrolene and nifedipine. Phenytoin and tocainide have been ineffective (Mion, Tsanaclis, Lusvarghi, Brotto, & Levy, 1984; Ricker et al., 1989). Isolated case reports suggest that carbamazepine, tizanidine, and mexiletine may not be useful. Immune-mediated RMD may respond to immunosuppressive therapy with azathioprine or prednisone or to treatment of an underlying thymoma, although coexistent MG may be the primary indication for immunosuppressive treatment (Ansevin & Agamanolis, 1996; Ashok Muley & Day, 2003; Greenberg, 2004; Müller-Felber et al., 1999; Vernino et al., 1999). Surgical Achilles tendon lengthening for toe-walking has been reported in two cases (Madrid et al., 2005) but is unlikely to be used frequently. Pyridostigmine may worsen muscle rippling (Müller-Felber et al., 1999). This is important in the management of patients with RMD coexisting with MG. It may be prudent to discuss the risk for exertional myoglobinuria with patients. The halothane contracture test or in vitro contracture tests may be positive in RMD but there is discordance between these tests and clinical susceptibility to malignant hyperthermia syndrome (MHS) (Sundblom, Melberg, Rücker, Smits, & Islander, 2013; Torbergsen, 2002). Vigilance for MHS is probably reasonable.

MUSCLE CHANNELOPATHIES

Ion channels subserve several essential functions in maintaining the normal excitability of nerve/muscle membranes. Channelopathies are disorders that result from abnormal ion channel function. Two groups of channelopathies result in skeletal muscle weakness and hyperexcitability: the nondystrophic myotonias and the PPs. These disorders were the first conditions wherein a genetic defect in voltage-gated ion channel function was identified. Other skeletal muscle channelopathies such as malignant hyperthermia, central core disease, and congenital myasthenic syndromes (Kullmann & Hanna, 2002) present with weakness or fatal anesthetic complications and are not discussed in this chapter. Malignant hyperthermia is discussed in Chapter 10. The molecular genetics of the nondystrophic myotonias and PPs are summarized in Table 18.4 (Jurkat-Rott & Lehmann-Horn, 2001).

DIAGNOSIS AND EVALUATION

Nondystrophic Myotonias

Myotonia refers to the impaired relaxation of muscle following voluntary contraction. The nondystrophic myotonias are distinguished from myotonic dystrophy (DM) (see Chapter 20) by the lack of progressive weakness and associated systemic features. Two major disorders compose the family of the nondystrophic myotonias: myotonia congenita (MC) and paramyotonia congenita (PMC). A recently published guideline discusses the clinical presentation and management of these disorders (Stunnenberg et al., 2020).

Myotonia Congenita. Patients with MC present with muscle tightness, cramps, or pain. They may notice difficulty in relaxing muscles after contraction, such as difficulty in releasing handgrip after a handshake. Muscles may "lock up" when sudden activity is attempted, resulting in falls. The stiffness is most pronounced during rapid voluntary activity after a period of rest and improves with repeated contractions of the muscle group involved (the "warm-up" phenomenon). The disorder may be autosomal dominant (Thomsen disease) or recessive (Becker disease), both caused by mutations in the chloride channel gene *CLCN1*. It may be useful to note here that the eponym "Becker disease" used for autosomal recessive MC is distinct from late-onset dystrophinopathy or Becker muscular dystrophy.

Thomsen disease presents in infancy or early childhood, usually in the first 2 years of life, and tends to be milder than the recessive form. The face and upper extremities are usually more involved than the legs. Infants may be noted to have difficulty in eye opening after a crying spell. Falls occur due to leg stiffness. Facial myotonia can cause chewing and swallowing difficulty. Prominent, generalized muscle hypertrophy, including the face, is noted in approximately a third of male patients and 10% of female patients and has been referred to as a "Hercules-like" appearance; muscle weakness is usually not a feature. Pregnancy may provoke or

Table 18.4 The Skeletal Muscle Channelopathies

Disorder	Inheritance	Affected Channel	Chromosomal Locus	Gene
Myotonia congenita (Thomsen disease)	Autosomal dominant	Chloride	7q35	*CLCN1*
Myotonia congenita (Becker disease)	Autosomal recessive	Chloride	7q35	*CLCN1*
Hyperkalemic periodic paralysis	Autosomal dominant	Sodium	17q23	*SCN4A*
Paramyotonia congenita	Autosomal dominant	Sodium	17q23	*SCN4A*
Potassium-aggravated myotonias[a]	Autosomal dominant	Sodium	17q23	*SCN4A*
Hypokalemic periodic paralysis 1	Autosomal dominant	L-type calcium	1q32	*CACNA1S*
Hypokalemic periodic paralysis 2	Autosomal dominant	Sodium	17q23	*SCN4A*
Hypo/hyperkalemic periodic paralysis	Autosomal dominant	Auxiliary potassium channel subunit (MiRP2)	11q13–14	*KCNE3*
Anderson-Tawil syndrome	Autosomal dominant	Potassium	17q	*KCNJ2*

[a]The potassium-aggravated myotonias include myotonia fluctuans, myotonia permanens, and acetazolamide responsive myotonia.

worsen symptoms (Davies & Hanna, 1993, 2001; Matthews et al., 2010; Ryan, Matthews, & Hanna, 2007; Saperstein, 2008). Emotional stimuli or cold exposure may transiently worsen stiffness, but, unlike PMC, weakness with cold exposure is not noted (Gutmann & Phillips, 1991).

Becker disease is the only autosomal recessive skeletal muscle channelopathy. It usually presents later than Thomsen disease, in the first or second decade, but the myotonia is more severe, muscle hypertrophy is more frequent and pronounced (especially in the lower extremities), and depressed tendon reflexes may be noted. The disease progresses slowly until 30 to 40 years of age and then stabilizes. The legs are more severely involved than the face or arms, and severe myotonia of the lower extremities may result in disability. Severe myotonic episodes may be associated with transient muscle weakness, especially in the hands. Brief episodes of transient generalized muscle weakness lasting seconds may occur upon initiating an action, such as attempting to get up from a recumbent position after rest. Mild, fixed distal weakness and atrophy may develop (Davies & Hanna, 2001, 2003; Fialho et al., 2007; Matthews et al., 2010; Ryan et al., 2007; Saperstein, 2008). Fifty-six percent of patients with Becker disease (compared with 12% in Thomsen disease) develop lower extremity symptoms first. It has therefore been referred to as ascending MC (Heatwole & Moxley, 2007).

Myotonia can be evoked by voluntary contraction of a muscle followed by attempts at relaxation, as in making and releasing a fist ("grip myotonia"). Tightly closing the eyes for a few seconds results in difficulty opening them (eyelid myotonia). Myotonia can also be elicited by percussion of muscles such as the thenar eminence with a percussion hammer, causing a muscle contraction "dimple" that persists for several seconds. With the forearm extended and the wrist flexed, striking the extensor muscles of the forearm with a percussion hammer induces sustained extensor posturing of the wrist similar to PIRC in RMD. Masticatory myotonia and neck myotonia are also described (Heatwole & Moxley, 2007). Clinical myotonia displays the "warm-up phenomenon" in that it improves with repeated voluntary contraction.

Myotonia levior and fluctuating MC are both autosomal dominant *CLCN1* disorders, probably variants of Thomsen disease. In myotonia levior, stiffness is provoked by prolonged rest, and there is no muscle hypertrophy. In fluctuating myotonia, stiffness is provoked by movement after rest, cold exposure, pregnancy, fasting, and emotional stress. The myotonia may subside for weeks to days spontaneously. Legs are more affected and muscle hypertrophy is absent (Hudson, Ebers, & Bulman, 1995; Wagner et al., 1998).

Paramyotonia Congenita. In contrast to MC, PMC is characterized by myotonia that worsens with exercise. It is caused by autosomal dominant mutations in the sodium channel gene *SCN4A*. PMC manifests at birth or in early infancy and tends to predominantly affect the face, tongue, and arms. The characteristic feature of PMC is worsening of myotonia with cold exposure. Cold exposure may not only aggravate myotonia but also cause focal or generalized weakness that may persist for several hours even after warming. Patients complain of tongue slowness after eating ice cream or a "frozen smile" with cold exposure. The "warm-up" phenomenon does not occur; in contrast, myotonia worsens with repeated voluntary contraction. Some patients may also have episodic weakness, an overlap syndrome with hyperkalemic PP (Hyper PP). Symptoms tend to be nonprogressive. Muscle hypertrophy is less frequent than in MC and has been described in up to 30% of patients. Infants may have prolonged eye closure and grimacing after crying or having their face washed (Davies & Hanna, 2001, 2003; Heatwole & Moxley, 2007; Matthews et al., 2008, 2010; Miller et al., 2004; Ryan et al., 2007; Saperstein, 2008; Streib, 1991). The differential diagnosis of MC and PMC includes DM, especially DM2, where myotonia may be the predominant complaint with mild weakness and systemic features may be subtle (Fialho et al., 2007).

Potassium-Aggravated Myotonias

The potassium-aggravated myotonias (PAMs) comprise a group of potassium-sensitive disorders that manifest with myotonia similar to MC, but without episodic weakness, in contrast to the PPs. Unlike MC, these disorders are caused by *SCNA4* sodium channel mutations similar to PMC. PAMs may be distinguished from autosomal dominant MC by a worsening of the myotonia with potassium ingestion (Heine, Pika, & Lehmann-Horn, 1993). The PAMs include *myotonia fluctuans, myotonia permanens,* and *acetazolamide responsive myotonia.*

In *myotonia fluctuans,* patients have myotonia that occurs with a delay of 10–30 minutes after exercise, fluctuates widely, and varies in severity. Additional features include the presence of the "warm-up phenomenon" and eyelid paramyotonia. Patients may be asymptomatic for days and then spontaneously experience marked stiffness of facial and limb muscles (Lennox, Purves, & Marsden, 1992; Ricker, Lehmann-Horn, & Moxley, 1990). Patients with *myotonia permanens* have almost constant, severe myotonia that can involve respiratory muscles (Lerche et al., 1993; Maddison, 2006; McClatchey et al., 1992; Zambelis et al., 2009). *Acetazolamide responsive myotonia* presents in childhood with painful muscle stiffness predominantly involving the face and hands. Myotonia is provoked by fasting, potassium, and exercise and is alleviated by a high carbohydrate meal. Myotonia improves with acetazolamide (Ptáček et al., 1994; Rudel & Lehmann-Horn, 1997; Trudell, Kaiser, & Griggs, 1987). All of the PAMs are cold insensitive, and episodic weakness is absent. Other pure myotonic syndromes due to *SCNA4* mutations are described, but with the additional feature of cold sensitivity (Heine et al., 1993; Koch, Baumbach, George, & Ricker, 1995; Wu et al., 2001). Matthews et al. (2010) suggest that sodium channel myotonias may be divided based on clinical features into two groups: PMC (cold-sensitive myotonia and episodic weakness) and sodium channel myotonias (cold insensitive, no episodic weakness) (Fournier et al., 2004, 2006).

Schwartz-Jampel Syndrome

Although Schwartz-Jampel syndrome (SJS) is not a channelopathy, it bears mentioning in the differential diagnosis of the nondystrophic myotonias. This is a rare disorder characterized by short stature, skeletal deformities, a characteristic facies, muscle stiffness, and myotonia. The disease manifests in the first year of life, and motor development may be delayed. Patients have congenital blepharophimosis, masklike or "stiff" face, micrognathia, low-set ears, low hairline, high arched palate, short neck, pigeon chest, contractures, spinal deformities, hip dysplasia, and osteochondroplasia on radiographs. Muscle hypertrophy, particularly involving proximal muscles, is common; the distal muscles may become progressively atrophic. Action and percussion myotonias are present, and continuous muscle activity in the form of rippling movements may be seen in limb muscles. Tendon reflexes may be diminished. Cataract formation, laryngeal stridor, and high-pitched voice have been reported. The disease is slowly progressive to adulthood and then stabilizes. A rare neonatal form has been termed SJS2. SJS2 presents at birth with feeding and respiratory difficulty, stiffness, and myotonia. Episodes of malignant hyperthermia may be seen, resulting in early death. Skeletal deformities may be detected even prenatally (Al-Gazali et al., 1996; Cao et al., 1978; Nicole, Topaloglu, & Fontaine, 2003). SJS is typically an autosomal recessive disorder with a chromosome 1p35–36 mutation on the *HSPG2* gene encoding perlecan, a heparan sulfate proteoglycan found in basement membranes. Autosomal dominant inheritance has been reported (Nicole et al., 1995, 2000; Pascuzzi, Gratianne, Azzarelli, & Kincaid, 1990).

Laboratory evaluation in the nondystrophic myotonias and SJS may reveal mild elevation of serum CK. In patients with PMC or Hyper PP overlap, serum potassium may be elevated during attacks. Other routine laboratory tests are usually normal. Routine motor and sensory NCSs are normal. The effect of cold on PMC has been harnessed during electrodiagnostic evaluation by recording the compound muscle action potential (CMAP) before and after cooling the limb to 20°C for 15 to 30 minutes. In PMC, a CMAP decrement greater than 50% is typically observed. These features are not seen in MC (Miller, 2008; Nielsen, Friis, & Johnsen, 1982; Subramony, Malhotra, & Mishra, 1983). The most prominent abnormality is the presence of myotonic discharges on needle EMG. These discharges comprise spontaneous painless bursts of repetitively firing potentials that wax and wane in both amplitude and frequency (the "dive bomber" discharges). The potentials fire at a rate of 20 to 80 Hz and are of two types: brief (less than 5 milliseconds) biphasic spike potentials that resemble fibrillation potentials or positive waves 5 to 20 milliseconds in duration that resemble positive sharp waves (American Association of Electromyography and Electrodiagnosis glossary, 1987). The discharges are present in most limb muscles and may be evoked by needle movement and percussion. They may also follow voluntary activity. Repeated contractions decrease the discharges in MC (the electrophysiologic equivalent of the warm-up phenomenon), whereas the discharges become more prominent after repeated contractions in PMC (Fuglsang-Frederiksen, 2006). When severe, continuous myotonia may obscure examination of volitional motor units. Motor unit morphology and recruitment are usually normal, although myopathic features with early recruitment of brief small amplitude motor units may be seen in recessive MC. In PMC, cooling the limb can evoke fibrillation potentials, worsen myotonia, and eventually cause electrical inexcitability (Nielsen et al., 1982). Rarely, EMG at room temperature can be normal in PMC (Russell & Hirsch, 1994). In SJS, EMG reveals continuous high-frequency discharges at rest that increase with needle movement, percussion, or voluntary activation. The discharges resemble neuromyotonia rather than myotonia and are abolished by neuromuscular blockade with curare or succinylcholine in some, but not all, cases (Cao et al., 1978; Taylor, Layzer, Davis, & Fowler, 1972). Myotonic discharges are reported in some cases (Aberfeld, Hinterbuchner, & Schneider, 1965; Huttenlocher, Landwirth, Hanson, Gallagher, & Bensch, 1969).

Other tests that may be useful in the diagnosis of nondystrophic myotonias include repetitive nerve stimulation and the exercise tests. Repetitive nerve stimulation at 5 to 10 Hz results in a decremental response, which is attributed to transient inexcitability of the muscle membrane. The decremental response is greater at higher stimulus frequencies, begins later in the train without a tendency to plateau, and can be elicited by direct muscle stimulation, in contradistinction to

APPENDIX 18.1 Exercise Tests for Periodic Paralysis

SHORT EXERCISE TEST (FOURNIER ET AL., 2004; STREIB, 1987)

1. The hand to be tested is rested for 10 minutes before testing.
2. The hand is immobilized, and CMAPs are recorded over the ADM with surface electrodes and supramaximal stimulation of the ulnar nerve at the wrist.
3. Baseline CMAP is recorded every 60 seconds for 2 minutes.
4. The ADM is maximally contracted by forceful abduction of the fifth digit against resistance for 10 seconds.
5. The CMAP is recorded again immediately after exercise and every 10 seconds until no change in amplitude is observed.
6. The test may be repeated three times with 60 seconds of rest between trials.
7. The percentage change in amplitude is calculated as follows:

Increase = 100 × (greatest amplitude after exercise - amplitude before exercise)/amplitude before exercise
Decrease = 100 × (greatest amplitude after exercise - smallest amplitude after exercise)/greatest amplitude after exercise
The normal limit for amplitude increase is less than 20% and for amplitude decrease is less than 10%.

LONG EXERCISE TEST (KUNTZER ET AL., 2000; MCMANIS ET AL., 1986)

1. The hand to be tested is rested for 10 minutes before testing.
2. The hand is immobilized, and CMAPs are recorded over the ADM with surface electrodes and supramaximal stimulation of the ulnar nerve at the wrist.
3. Baseline CMAP is recorded every 60 seconds for 2 minutes.
4. The ADM is maximally contracted by forceful abduction of the fifth digit against resistance for 5 minutes with 3- to 5-second rest periods every 30 seconds.
5. The CMAP is recorded every minute postexercise for 50 minutes or until no change in amplitude is noted for 5 minutes.
6. The percentage change in CMAP amplitude is calculated as for the short exercise test.

Normal limit for amplitude increase is less than 30% and for amplitude decrease is less than 41%.

ADM, Abductor digiti minimi; *CMAP*, compound motor action potential.

the decrement seen in MG (Aminoff, Layzer, Satya-Murti, & Faden, 1977; Brown, 1974; Gutmann & Phillips, 1991).

Specialized electrophysiologic protocols of exercise testing are useful to confirm the diagnosis and to differentiate between the skeletal muscle channelopathies. These tests evaluate sarcolemmal excitability by measuring the variation in CMAP amplitude following repeated stimulation (McManis, Lambert, & Daube, 1986; Streib, Sun, & Yarkowsky, 1982) (Appendix 18.1). Using the short exercise test (SET) and long exercise test (LET) protocols in combination, Fournier et al. (2004) identified five distinct patterns that correlate with each of the nondystrophic myotonias and PPs and may guide confirmatory genetic testing. They also describe postexercise myotonic potentials, defined as several potentials of decreasing amplitude that follow the CMAP evoked by a single supramaximal stimulus after SET. These potentials disappear 10 to 30 milliseconds after completion of exercise and are seen in the nondystrophic myotonias but not in the PPs (Fournier et al., 2004). The SET results in a transient decrease in the amplitude of the CMAP in MC. On repeated trials of SET, the CMAP amplitude does not change (pattern II of Fournier) (Fournier et al., 2004). In PMC, CMAP amplitude may either increase or decrease during the first trial of SET and decreases with repeated trials (pattern I of Fournier) (Fournier et al., 2004). The LET may show decreased CMAP amplitude in PMC but no change in MC. The LET is more useful in evaluating the PPs. Table 18.5 summarizes the electrodiagnostic features of the nondystrophic myotonias and the PPs.

Muscle biopsy may be normal or may demonstrate mild myopathic features in the nondystrophic myotonias. The absence of type 2b muscle fibers is a feature of MC. A vacuolar myopathy may be seen in PMC patients who have Hyper PP (Saperstein, 2008). In SJS, muscle biopsy may be normal, may demonstrate mild nonspecific features, or may show mild to moderate dystrophic changes (Aberfeld et al., 1965; Huttenlocher et al., 1969; Taylor et al., 1972). However, muscle biopsy is seldom necessary, and the clinical and electrophysiologic evaluation is usually followed by genetic testing to confirm the diagnosis.

TREATMENT AND MANAGEMENT OF NONDYSTROPHIC MYOTONIAS

Many patients with nondystrophic myotonia have mild symptoms that do not require treatment, except to avoid precipitating factors such as cold exposure. If the myotonia is severe enough to necessitate treatment, the usual agents used include antiepileptic medications, and antiarrhythmic agents that block muscle sodium channels such as phenytoin, tocainide, procainamide, flecainide, propafenone, and mexiletine have been tried (Alfonsi et al., 2007; Kwiecinski, Ryniewicz, & Ostrzycki, 1992; Ricker, Haass, Hertel, & Mertens, 1978; Rosenfeld, Sloan-Brown, & George, 1997; Rudel, Dengler, Ricker, Haass, & Emser, 1980). Procainamide use is limited by toxicity and is not recommended. Tocainide was withdrawn from the market due to the risk of agranulocytosis. In a 12-week RCT comparing procainamide, quinine, and prednisone in DM1 and MC, not genetically confirmed, patients received all three medications for 3 weeks each. Myotonia improved in 15/20 patients who received procainamide and 15/19 patients who received prednisone, but only six patients improved with quinine (Leyburn & Walton, 1959). The Class Ib antiarrhythmic agent mexiletine has generally been used widely as the treatment of choice. An international multicenter RCT of 59 patients with nondystrophic myotonias using a cross-over design (4 weeks treatment, 1 week washout, and 4 weeks crossover treatment) revealed modest improvement in patient-reported stiffness severity score (Statland et al., 2011) and in quality of life measures. Period effects were presented. There was concern about maintenance of blinding. Mexiletine was well tolerated (Statland, 2012). In a combined Bayesian analysis of 30 n-of-1 trials followed by a frequentist reanalysis, the symptoms severity score improved by about 3 points in the mexiletine treatment period. The minimal clinically meaningful difference in the stiffness score is unknown; the

Table 18.5 Electrodiagnostic Features of the Nondystrophic Myotonias and the Periodic Paralyses

Disorder		Myotonia Congenita	Paramyotonia Congenita	Hyperkalemic Periodic Paralysis	Hypokalemic Periodic Paralysis
CMAP after SET	First trial	Transient decrease	Increase/decrease	Increase	No change
CMAP after SET	Repeat trials	No change	Gradual decrease	Gradual increase	No change
CMAP after LET	Immediate amplitude change	No change/slight decrease	Decrease	Increase	No change
CMAP after LET	Late amplitude change	None	Decrease	Decrease	Decrease
Needle EMG	Myotonic discharges	+++	+++	+/-	-
SET sensitivity, % (95% CI)		83(53–100)	100(81–100)	83(53–100)	0(0–23)
LET sensitivity, % (95% CI)		25(1–50)	89(76–100)	93(81–100)	84(72–97)

Adapted from Fournier, E., Arzel, M., Sternberg, D., et al. (2004). Electromyography guides toward subgroups of mutations in muscle channelopathies. *Annals of Neurology, 56*, 650-661. Copyright *Annals of Neurology* 2004; with permission from John Wiley and Sons, Inc.
CI, Confidence interval; *CMAP*, compound motor action potential; *EMG*, electromyogram; *LET*, long exercise test; *SET*, short exercise test.

authors used a 0.75 point change as clinically meaningful. Gastrointestinal side effects were commonly seen (70%). An allergic skin reaction occurred in one patient. A difference in the degree of response favoring the *CLCN1* disorders was noted (Stunnenberg et al., 2018). Mexiletine may also be useful in preventing the transient weakness that can accompany severe myotonia in recessive MC and for the treatment of myotonia in myotonia fluctuans (Lennox et al., 1992; Saperstein, 2008). It is usually started at doses of 150 mg daily and increased to efficacy, with a maximum dose of 300 mg three times daily. Lightheadedness, diarrhea, and dyspepsia are the major adverse effects. An electrocardiogram (ECG) should be performed prior to initiation of mexiletine to evaluate conduction abnormalities and the QT interval (Saperstein, 2008). Mexiletine is contraindicated in the presence of second- or third-degree atrioventricular block. It should be used with caution in patients with first-degree atrioventricular block, sinus node dysfunction, or intraventricular conduction defects. Blood counts, liver function tests, and ECG should be monitored during treatment.

Acetazolamide may be useful in some cases of nondystrophic myotonia. In a series of seven patients with MC and two with PMC, all patients improved with acetazolamide (Trudell et al., 1987). There is a report of one patient with PMC who developed quadriparesis 12 hours after acetazolamide (Griggs, Moxley, Riggs, & Engel, 1978). A case series reported improvement with acetazolamide in three children with nondystrophic myotonia (Markhorst et al., 2014). The myotonia and pain of acetazolamide responsive myotonia respond to acetazolamide, as the name implies. Acetazolamide is started at 125 mg/day and increased as needed to 250 mg three times a day. It has been suggested that a therapeutic trial of acetazolamide is appropriate in patients with a clinical syndrome resembling MC who complain of pain (Saperstein, 2008; Trudell et al., 1987). Treatment of SJS is directed at the stiffness. Isolated reports of improvement with phenytoin, carbamazepine, procainamide, and diazepam are available (Huttenlocher et al., 1969; Nicole et al., 2003; Pascuzzi et al., 1990). Botulinum toxin has been used for blepharophimosis (Vargel, Canter, Topaloglu, & Erk, 2006).

The nondystrophic myotonias may be associated with prolonged recovery times after general anesthesia, and propofol and depolarizing neuromuscular blockade may worsen myotonia (Russell & Hirsch, 1994). Patients should be advised of this risk.

PERIODIC PARALYSIS

The primary PPs are disorders of skeletal muscle excitability characterized by recurrent attacks of muscle weakness and temporary paralysis. They are rare, autosomal dominant disorders caused by mutations in skeletal muscle sodium, potassium, and calcium channels (Cannon, 2015; Fontaine, 2008). The classic forms are Hyper PP and hypokalemic PP (Hypo PP), defined by the serum potassium levels during the paralytic attacks and the clinical response to potassium. PMC closely overlaps with PP, and the nomenclature may depend on the predominant symptom, myotonia, or weakness. Andersen-Tawil syndrome (ATS) is a rare disorder distinguished by the triad of PP, cardiac arrhythmias, and skeletal deformities (Tawil et al., 1994).

DIAGNOSIS AND EVALUATION

Hyperkalemic Periodic Paralysis

Hyper PP is characterized by recurrent episodes of generalized or focal muscle weakness that occur in association with elevated serum potassium levels. The disease is inherited as an autosomal dominant trait with high penetrance, with the majority of cases secondary to mutations in the sodium channel gene *SCN4A* on chromosome 17q23. It usually manifests early in the first decade, in infancy or childhood. Episodes are triggered by high potassium foods and may

occur when the patient is resting, about 20 to 30 minutes after exercise. Other triggers include cold exposure, emotional stress, fasting, pregnancy, glucocorticoids, anesthesia, and alcohol (Davies & Hanna, 2001, 2003; Fialho, Griggs, & Matthews, 2018; Ryan et al., 2007; Saperstein, 2008; Statland et al., 2018). Attacks usually occur in the morning but may occur at any time of the day. The muscle weakness varies in severity. Weakness usually starts in the lower extremities and spreads to the trunk and upper extremities. Respiratory and bulbar muscles are usually spared, although there are rare reports of involvement of these muscles during a severe attack. Attacks last from less than an hour up to 2 hours and may be shortened by mild exercise. On rare occasions, the weakness may persist for days. Reflexes are diminished or absent during attacks and are normal in between attacks. The frequency of the episodes is variable and tends to diminish with age; some patients have daily attacks. In between attacks, approximately 50% of patients experience muscle stiffness due to myotonia or paramyotonia (Davies & Hanna, 2001, 2003; Fialho et al., 2018; Jurkat-Rott, & Lehmann-Horn, 2006; Plassart et al., 1994; Ryan et al., 2007; Saperstein, 2008; Statland et al., 2018). Lid lag and eyelid myotonia may be evident on examination between attacks. Many patients over the age of 40 develop fixed proximal muscle weakness that does not appear to be related to the frequency of episodes, and a third develop a chronic progressive myopathy (Statland et al., 2018). In a patient survey of genetically confirmed Hyper PP, a quarter of the respondents reported involvement of respiratory muscles and nearly two thirds reported facial muscle involvement during an attack. Although the typical description of attacks is that they spare the sphincters, two respondents reported bowel incontinence and seven reported bladder incontinence during episodes (Charles, Zheng, Lehmann-Horn, Jurkat-Rott, & Levitt, 2013). One family with Hyper PP and malignant hyperthermia linked to the *SCN4A* locus has been reported (Moslehi, Langlois, Yam, & Friedman, 1998). Box 18.5 lists the diagnostic criteria for Hyper PP.

Box 18.5 Diagnostic Criteria for Primary Hyperkalemic Periodic Paralysis

1. Two or more attacks of muscle weakness with documented serum potassium >4.5 mEq/L
2. One attack of muscle weakness in the proband and one attack of weakness in one relative with documented serum potassium >4.5 mEq/L in at least one attack
3. Three of six clinical or laboratory features as outlined here:
   - Onset before third decade of life
   - Duration of attack (muscle weakness involving one or more limbs) <2 hours
   - Positive triggers (exercise, stress)
   - Myotonia
   - Positive family history or genetically confirmed skeletal sodium channel mutation
   - Positive McManis short exercise test
4. Exclusion of other causes of hyperkalemia (renal, adrenal, thyroid dysfunction; potassium-sparing diuretic use)

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Hypokalemic Periodic Paralysis

Hypo PP is the most frequent form of PP. It is an autosomal dominant disorder, but up to one third of cases are sporadic and the penetrance in women is only 50%, so a family history may not be present (Saperstein, 2008). About 60% of patients with Hypo PP have mutations in the gene encoding the calcium channel CACNA1S on chromosome 1q32, *HypoPP-1* (Jurkat-Rott et al., 1994; Ptácek et al., 1994). In 20% of patients, the disorder is due to mutations in the gene encoding the sodium channel SCN4A on chromosome 17q23, *HypoPP-2* (Jurkat-Rott et al., 2000; Sternberg et al., 2001). In both instances, the genetic mutations result in the development of a pathogenic "gating pore," which makes the resting membrane potential susceptible to hyperpolarized or hypopolarized states (Matthews et al., 2009; Sokolov, Scheuer, & Catterall, 2007; Struyk & Cannon, 2007). Hypo PP typically presents in late childhood or adolescence and less frequently in the second decade, slightly later than Hyper PP. The patient often awakens in the morning with weakness. The attacks are triggered by strenuous physical activity or a carbohydrate-rich meal the previous day. Attacks may also be precipitated by sodium-rich foods, alcohol ingestion, cold exposure, intercurrent viral infections, lack of sleep, menstruation, and certain medications (beta agonists, corticosteroids and insulin). Some patients report a prodrome of paresthesias, fatigue, and behavioral/cognitive changes the day before an attack. Attacks of flaccid paralysis are longer than those in Hyper PP, lasting hours to days, and tend to be more severe but are less frequent. Weakness may be generalized or focal. When generalized, the lower limbs are affected before the upper extremities. Bulbar, extraocular, respiratory, and sphincter muscles are usually spared. Similar to Hyper PP, reflexes are diminished or absent during the attack. Sensation is normal. As with Hyper PP, attack frequency varies but tends to diminish with age. In between attacks, patients are normal and do not usually have myotonia. A fixed weakness may develop after repeated attacks (Jurkat-Rott & Lehmann-Horn, 2006; Ryan et al., 2007; Saperstein, 2008; Venance et al., 2006). Box 18.6 lists the diagnostic criteria for Hypo PP.

Andersen-Tawil Syndrome

The triad of PP, ventricular arrhythmias, and skeletal dysmorphisms defines ATS, a rare autosomal dominant disorder caused by mutations in the gene for the inward rectifying potassium channel *KCNJ2* on chromosome 17q23 (Plaster et al., 2001). The dysmorphisms seen in ATS include clinodactyly or syndactyly, low-set ears, mandibular hypoplasia, and hypertelorism. Short stature may be associated. Scoliosis, high-arched palate, brachydactyly, ptosis, single palmar crease, vaginal atresia, and unilateral dysplastic kidney have all been reported in ATS. The facial dysmorphisms may be mild and easily overlooked. Episodes of paralysis and cardiac arrhythmia begin in early childhood. Although patients may have either hypokalemic or hyperkalemic paralysis, potassium loading typically provokes attacks. A proximal myopathy is often associated. The initial presentation may be due to ventricular arrhythmias, especially bidirectional ventricular tachycardia. The expression of the disorder varies widely within families, with some family members having only asymptomatic QT interval prolongation on ECG

or minimal dysmorphisms (Andersen, Krasilnikoff, & Overvad, 1971; Davies & Hanna, 2001; Ryan et al., 2007; Sansone et al., 1997; Tawil et al., 1994). A distinct pattern of neurocognitive impairment characterized by deficits in executive functioning and abstract reasoning has been described in patients with ATS (Yoon et al., 2006).

Secondary Periodic Paralysis

Secondary forms of PP including thyrotoxic PP (TPP) should be excluded in patients who meet clinical criteria for Hyper PP and Hypo PP and do not have an identifiable genetic mutation, or if the first attack of weakness occurs in adulthood. Secondary hyperkalemia may be due to an underlying endocrinopathy such as Addison disease, hyporeninemic hypoaldosteronism, treatment with potassium supplements or potassium-sparing diuretics, and chronic renal failure. In these instances, serum potassium levels typically are greater than 7 mEq/L. Clinical or electrical myotonia is not seen in PP due to secondary hyperkalemia (Evers, Engelien, Karsch, & Hund, 1998; Saperstein, 2008). Secondary causes of hypokalemia include thyrotoxicosis, renal tubular acidosis, Bartter syndrome, hyperaldosteronism, chronic diuretic use, licorice ingestion, corticosteroid use, amphotericin B toxicity, and laxative abuse (Chen, Schneider, Zhang, He, & Chen, 2012; Prasad, Agarwal, Malhotra, & Beniwal, 2014; Shree et al., 2016; Stapleton, 2018).

TPP is probably the best described form of secondary PP. The paralysis develops in the setting of hyperthyroidism in genetically predisposed individuals, especially of Southeast Asian or Hispanic heritage, although it is increasingly reported in patients from varied racial and ethnic backgrounds (Fialho et al., 2018). Although thyrotoxicosis is more frequent in women, TPP predominantly affects men (Kelley, Gharib, Kennedy, Duda, & McManis, 1989). Signs of thyroid disease may be subtle, and the paralysis may be the presenting sign of the thyroid disease (Fialho et al., 2018; Kelley et al. 1989). The attacks resemble those of Hypo PP, with prolonged, severe, generalized weakness, low potassium during attacks, and similar triggers. The attacks occur only during the thyrotoxic state and resolve when the patient is euthyroid. Rarely, respiratory insufficiency requiring support has been described (Liu, Tsai, Chau, & Lin, 2004). Mutations in the potassium channel gene *KCNJ18* encoding the inward rectifying potassium channel have been described in a quarter to a third of patients with TPP from various populations, but only in about 3% in a Chinese study of 127 individuals with TPP, suggesting genetic heterogeneity (Li et al., 2015; Ryan et al., 2010). Two novel TPP risk loci were recently described in a meta-analysis of genome-wide association studies comprising 319 individuals with TPP and 3516 healthy controls from three cohorts, 2 from Hong Kong and one from Shanghai (Hoi-Yee Li et al., 2020).

Box 18.6 Diagnostic Criteria for Primary Hypokalemic Periodic Paralysis

1. Two or more attacks of muscle weakness with documented serum potassium <3.5 mEq/L
2. One attack of muscle weakness in the proband and one attack of weakness in one relative with documented serum potassium <3.5 mEq/L in at least one attack
3. Three of six clinical or laboratory features as outlined here:
   - Onset in the first or second decade of life
   - Duration of attack (muscle weakness involving one or more limbs) >2 hours
   - Positive triggers (carbohydrate-rich meal, rest after exercise, stress)
   - Improvement with potassium intake
   - Positive family history or genetically confirmed skeletal calcium or sodium channel mutation
   - Positive McManis short exercise test
4. Exclusion of other causes of hypokalemia (renal, adrenal, thyroid dysfunction; renal tubular acidosis; diuretic and laxative abuse)

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Laboratory testing between attacks of PP is typically normal. During an attack, serum potassium is elevated in Hyper PP. However, the potassium level may be within the normal range or may correct early in the attack, and it is only when the potassium level is rechecked after the weakness improves that a relative increase in potassium during attacks becomes apparent. The name *potassium sensitive periodic paralysis* has been suggested for Hyper PP to reflect the relative, rather than absolute, increase in potassium levels that trigger attacks (Saperstein, 2008). Tall T-waves on ECG are a useful ancillary indicator of hyperkalemia. In Hypo PP, serum potassium levels are usually low (less than 3 mEq/L) during attacks. During episodes of Hypo PP, ECG reveals flattening of T waves, which subsequently disappear, followed by the appearance of U waves and prolonged PR and QT intervals.

Electrophysiologic testing is not always possible during the acute attacks, but if performed, motor NCS reveals reduced CMAP amplitudes. Needle EMG may reveal fibrillations and positive sharp waves during the attack, but when the weakness is complete, the muscle is electrically silent. In between attacks, EMG may reveal myotonia in Hyper PP. Some patients with Hypo PP may have myopathic features on EMG. Both the SET and LET may be abnormal in PP, but the LET is more useful in the evaluation of PP (see Appendix 18.1 for test protocols). In Hyper PP, the LET results in an immediate increment in the CMAP amplitude, with a late decrement (Fournier pattern IV). In Hypo PP, the CMAP amplitude does not show an immediate change but a late decrement is seen (Fournier pattern V) (Fournier et al., 2004). A recent study evaluated two different methods of calculating the CMAP decrement and the cut-off values used for abnormal decrement (base to nadir, cut-off for abnormal decrement >20%, vs. peak to nadir, cut off >40%). In a Bayesian analysis of data from 55 patients, with a pretest probability of ≤50%, a peak-to-nadir method with cut-off amplitude and area of 40% and 50%, respectively, had optimal diagnostic utility (Simmons et al., 2019) (Table 18.5).

Serum CK is usually elevated in all forms of PP during the episodes of weakness and returns to normal with resolution of weakness. Thyroid function studies and other workup for secondary causes should be performed. In ATS, a prolonged QT interval is seen on ECG in about 80% of patients (Saperstein, 2008). Muscle biopsy is usually not necessary for diagnosis. If performed, the presence of a vacuolar myopathy or tubular aggregates supports a diagnosis of PP. Commercially

available genetic testing reveals the causative mutations in approximately 70% of patients.

PROVOCATIVE TESTS

Provocative tests for PP were useful in the pre–genetic testing era but are infrequently performed now because of the potential risks of cardiac arrhythmias and the time-consuming nature of the tests (Griggs, 1995). They are briefly described later. Oral potassium loading may precipitate an attack of weakness in *Hyper PP*. After an overnight fast, potassium chloride 0.05 g/kg in a sugar-free solution is given orally over 3 minutes. Muscle strength and serum potassium are monitored per a standard protocol for 4 hours to evaluate whether hyperkalemia and a clinical attack are induced. If the test does not induce weakness, it can be repeated at another sitting with a higher dose of potassium chloride, 0.1 to 0.15 g/kg. Exercise and a high carbohydrate meal the day before the provocative test may be useful in provoking an attack (Griggs, 1995).

In *Hypo PP*, episodes of weakness can be precipitated by glucose/insulin loading after an overnight fast. Muscle strength, serum potassium, and glucose levels are monitored per a standard protocol for 5 hours to evaluate whether hypokalemia and a clinical attack are induced. ECG monitoring and close medical supervision are necessary during the tests, and they should not be performed in patients with cardiac or renal dysfunction (Griggs, 1995).

TREATMENT AND MANAGEMENT OF PERIODIC PARALYSIS

The management of PP includes treatment of acute attacks and prevention of attacks by avoidance of triggers, dietary measures, and use of pharmacologic agents (Table 18.6).

MANAGEMENT OF ACUTE ATTACKS

Acute attacks of Hyper PP may be aborted by a single dose of acetazolamide, a thiazide diuretic, or an inhaled beta-adrenergic agonist such as albuterol if used early. Mild nonresistance exercise such as walking or shaking the arms may be useful at the onset of the attacks, and a carbohydrate snack may abort mild attacks (Bendheim, Reale, & Berg, 1985; Davies & Hanna, 2003; Hanna et al., 1998; Statland et al., 2018; Wang & Clausen, 1976). Mild hyperkalemia is managed with oral carbohydrates or intravenous glucose. In more severe hyperkalemia, intravenous insulin with glucose may be needed (Griggs, 1995). Acute attacks of Hypo PP are managed with oral potassium supplementation (0.25 mEq/kg) repeated every 30 minutes until strength improves. In severe cases, intravenous potassium chloride (0.05–0.1 mEq/kg or 20–40 mEq in 5% mannitol) may be used. For both types of PP, cardiac monitoring is essential (Griggs, 1995; Statland & Barohn, 2013).

PREVENTION OF ATTACKS

Counseling patients and caregivers regarding lifestyle modifications is an important aspect of long-term management of PP. Dietary measures include avoidance of potassium-rich foods and consumption of multiple small high-carbohydrate snacks in Hyper PP and avoidance of alcohol and high-carbohydrate and high-salt meals in Hypo PP (Fontaine, 2008; Venance et al., 2006).

Pharmacologic treatment with various agents is used in both Hypo PP and Hyper PP. In Hyper PP, thiazide diuretics (hydrochlorothiazide 25–50 mg daily) are useful in preventing attacks and are often chosen as the first line of therapy (Imbrici et al., 2016; Tricarico & Camerino, 2011). The

Table 18.6 Treatment of Periodic Paralysis

Disorder	Prophylactic Therapy	Treatment of Acute Attacks[a]	Diet and Lifestyle
Hyperkalemic periodic paralysis	Hydrochlorothiazide 25–75 mg/day	Early in the attack: Mild exercise Acetazolamide or hydrochlorothiazide orally or inhaled β-agonist, e.g., albuterol	Avoid potassium-rich foods, use small, multiple high-carbohydrate snacks
	Acetazolamide up to 1500 mg/day in two or three doses Pediatric dosing: 5–10 mg/kg/day	Mild hyperkalemia: Oral or intravenous glucose	Avoid triggers such as fasting or strenuous exercise
	Dichlorphenamide 50–100 mg twice daily	Severe hyperkalemia: intravenous insulin and glucose	
Hypokalemic periodic paralysis	Acetazolamide up to 1500 mg/day in two or three doses Pediatric dosing: 5–10 mg/kg/day	Mild exercise at onset Oral potassium 1 mEq/kg repeated every 30 minutes, up to 200 mEq in 24 hours	Avoid high-carbohydrate meals
	Dichlorphenamide 50–100 mg twice daily	Severe hypokalemia: Intravenous potassium chloride 0.05–0.1 mEq/kg or 20–40 mEq in 5% mannitol	Avoid triggers such as fasting or strenuous exercise, dehydration
	Triamterene 50–150 mg/day		
	Spironolactone 25–100 mg/day		
	Oral potassium supplementation		

[a]Cardiac monitoring is recommended in both forms of periodic paralysis during acute attacks.

carbonic anhydrase inhibitors acetazolamide, and, more recently, dichlorphenamide, are commonly used in the prophylactic treatment of PP (Griggs, 1995; Tawil et al., 2000). Acetazolamide 125–1000 mg per day may be useful in Hyper PP (Sansone, Meola, Links, Panzeri, & Rose, 2008).

In Hypo PP, preventive options include potassium sparing diuretics, carbonic anhydrase inhibitors, and oral potassium supplements. Triamterene 50–150 mg/day and spironolactone 25–100 mg daily have been used (Saperstein, 2008; Statland et al., 2018; Statland & Barohn, 2013). Acetazolamide has a long history of use in Hypo PP and is probably the initial drug of choice (Griggs, Engel, & Resnick, 1970; Matthews et al., 2011; Resnick, Engel, Griggs, & Stam, 1968; Sansone et al., 2008; Vroom, Jarrell, & Maren, 1975). In a retrospective study of genetically confirmed Hypo PP, 46% reported improvement in the frequency, severity, and duration of attacks following treatment with acetazolamide. The response rate was 56% in patients with *CACNA1S* mutations compared to 16% in those with *SCN4A* mutations, although the total number of patients with *SCN4A* mutation was only 19 compared to 74 with *CACNA1S* mutations (Matthews et al., 2011). Increased frequency and severity of attacks induced by acetazolamide have been reported in a family with Hypo PP carrying a specific *SCN4A* mutation (Sternberg, 2001). The efficacy of oral potassium supplementation, which is often intuitively used in Hypo PP, remains unproven.

Dichlorphenamide is another carbonic anhydrase inhibitor that has been used in PP for some years (Dalakas & Engel, 1983; Tawil et al., 2000) and has been studied in a RCT recently, leading to its approval by the US Food and Drug Administration for use in PP. This 9-week RCT enrolled 44 Hypo PP and 21 Hyper PP patients. The median attack rate was lower in the treated group in Hypo PP (0.3 vs. 2.4, $P = 0.02$) but not in Hyper PP (0.9 vs. 4.8, $P = 0.1$) (Sansone et al., 2016). One study reported improvement in interepisode muscle weakness after treatment with dichlorphenamide in three patients who were resistant to or worsened by acetazolamide. The optimal treatment of myopathy associated with PP is unknown (Dalakas & Engel, 1983). Ultra-high-field (7T) MRI of muscle chloride and sodium homeostasis using isotopes ^{23}Na and ^{35}Cl has been suggested as a potential tool to monitor the efficacy of treatment in PP, especially to differentiate between muscle edema and fatty infiltration in chronic cases with fixed weakness (Jurkat-Rott et al., 2009; Weber et al. 2016).

Acetazolamide is usually started at 125 mg daily and increased in 125-mg increments to a maximum dose of 1500 mg daily in two or three divided doses. The dose of dichlorphenamide is 50 to 100 mg twice daily. Adverse effects associated with carbonic anhydrase inhibitors include perverted taste, perioral and extremity paresthesias, nausea, anorexia, and kidney stones (10%). Patients with allergies to sulfa drugs may be cross-allergic to carbonic anhydrase inhibitors.

TREATMENT AND MANAGEMENT OF ANDERSEN-TAWIL SYNDROME

In ATS, carbonic anhydrase inhibitors may be useful in preventing acute episodes of weakness. Since attacks may be hypo- or hyperkalemic, it is useful to define the potassium level during the attack in individual patients to manage both the cardiac conduction abnormalities and weakness effectively (Venance et al., 2006). The recognition and management of ventricular arrhythmias are important. Beta-blockers have been used for long-term management. There are not many studies of optimal management of arrhythmias in ATS, but it is suggested that conventional antiarrhythmics may not be effective. Amiodarone and imipramine have been noted to be useful in anecdotal reports. Flecainide has been shown to be useful in the treatment of ventricular arrhythmias and tachycardia-induced cardiomyopathy. Cardioverter-defibrillator implantation may be necessary (Bokenkamp, Wilde, Schalij, & Blom, 2007; Chun et al., 2004; Davies & Hanna, 2001, 2003; Fox et al., 2008; Gould et al., 1985; Pellizzon, Kalaizich, Ptacek, Tristani-Firouzi, & Gonzalez, 2008; Sansone & Tawil, 2007; Tawil et al., 1994). Annual cardiac screening with ECG and rhythm monitor is recommended (Statland et al., 2018). Patients should be counseled regarding the use of prescription drugs that may precipitate arrhythmias.

TPP, unlike familial PP, may not respond to carbonic anhydrase inhibitors. Beta-blockers may be useful in reducing the frequency and severity of attacks. Treatment of thyrotoxicosis abolishes the attacks, which may recur if the hyperthyroid state recurs (Saperstein, 2008).

BRODY DISEASE

In 1969, Brody described a disorder characterized by increasing impairment of relaxation during exercise (Brody, 1969). In 1986, Karpati et al. characterized the disorder in four patients from two families. These patients experienced exercise-induced stiffness and cramping in the limbs, first appearing in childhood. Exercise such as deep knee bends or opening and closing the hand resulted in progressive stiffening of the exercised muscles with difficulty in relaxing them. Sarcoplasmic calcium adenosine triphosphatase (SR Ca^{2+} ATPase) was reduced in type 2 muscle fibers in these patients, impairing ATP-dependent calcium transport and accumulation of myofibrillar calcium. Since type 2 fast-twitch muscle fibers appear to be selectively involved, symptoms occur during phasic exercise. During the delayed relaxation after exercise, the muscle is electrically silent, thus differentiating this condition from the myotonic disorders. The differential diagnosis includes metabolic myopathies such as McArdle disease that are associated with exercise-induced contractures that are electrically silent. However, the delayed relaxation in Brody disease is much shorter in duration, and painless (Karpati, Charuk, Carpenter, Jablecki, & Holland, 1986). Brody disease is caused by mutations in the *ATP2A1* gene on chromosome 16p that encodes the fast-twitch isoform of sarcoplasmic/endoplasmic reticulum Ca2 + ATPase type 1 (SERCA1) protein (Odermatt et al., 1996). A recent study of 40 patients recommended that Brody disease should be considered in cases of exercise-induced muscle stiffness where examination reveals delayed relaxation and the EMG lacks myotonic discharges. The authors recommend sequencing of the *ATP2A1* gene or next generation sequencing with a myopathy panel for confirmation of the diagnosis. Measurement of SERCA1 activity and SERCA1 Western blot can assist in evaluating the functional significance of novel *ATP2A1* mutations. These patients may be a risk for malignant hyperthermia-like episodes. Many agents have been used to treat the stiffness, including dantrolene,

verapamil, mexiletine, carbamazepine, ibuprofen, nifedipine, and acetazolamide. Verapamil and mexiletine improved symptoms in a few patients but their use was limited by side effects (Molenaar et al., 2020).

METABOLIC MYOPATHIES

Several metabolic myopathies present clinically with muscle cramps, exercise-induced muscle contractures, and myoglobinuria (see Box 18.1). These disorders are discussed in Chapter 23.

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19 Treatment and Management of Disorders of the Neuromuscular Junction

Shin J. Oh, MD

Disorders of the neuromuscular junction include myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), botulism, congenital myasthenic syndrome (CMS), snakebite myasthenia, organophosphate poisoning (OPP), and hypermagnesium-induced paralysis.[1]

For this chapter, I reviewed all existing major literature on the subjects of management and treatment of these diseases and analyzed critically the data for evidence-based information. The literatures include review articles and large case series from MEDLINE and Cochrane reviews. On the basis of evidence-based data, the studies are categorized into four classes: class I, randomized controlled trials available; class II, controlled trials without randomization or randomized trial with small patient number; class III, uncontrolled trials; and class IV, case series. This classification and the recommendations are based on guidance by the European Federation of Neurological Societies (EFNS) scientific task forces, which were modified slightly from the American Academy of Neurology guidelines in 1999 (Brainin et al., 2004; Franklin, Zahn, & American Academy of Neurology, 2002).

The therapeutic guidelines are formulated largely on the basis of best available evidence-based data in principles, and the ratings of recommendation are made depending on the evidence-based classification: Level A (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent convincing class II studies; Level B (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence; and Level C (possibly effective, ineffective, or harmful) requires at least two convincing class III studies. The European Task Force adopted "good practice point" recommendations when there is a uniform consensus for recommendation among the experts, although there is inadequate evidence for a formal recommendation (Skeie et al., 2006). Usually, this recommendation is based on class IV data. When there is no consensus among the experts, therapeutic guidelines and recommendations are made on the basis of my personal experience or my personal choice for the best possible regimen.

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is due to an antibody-induced postsynaptic defect of the neuromuscular junction, producing *exertional weakness* or *easy fatigability* and, commonly, *oculobulbar palsy*. Electron microscopic studies show simplification of the postsynaptic fold at the neuromuscular junction, which is induced by the acetylcholine receptor (AChR) antibody.

MG is the most common disorder of neuromuscular junction. The prevalence of MG is approximately 5 to 10:100,000 population. The disease affects all ages. In the 1970s–1980s, two peaks were identified in MG: young females and old males. In more recent studies, an upsurge of MG was noted in older patients, especially males, whereas female predominance was maintained in young patients.

With the advent and widespread use of immunotherapy and the improvement in respiratory care and intensive care unit (ICU) management during MG crisis over the past 40 years, the prognosis of MG patients has improved vastly. In a Danish population-based study, the overall 3-, 5-, 10-, and 20-year survival was 85%, 81%, 69%, and 63% respectively (Christensen et al., 1998). Most MG patients can return to a full, productive life with adequate therapy.

There is considerable evidence indicative of an autoimmune mechanism in the pathogenesis of MG. The strongest evidence is seen in experimental autoimmune myasthenia gravis. Within 2 weeks after injection of AChR antigen purified from electric eels, animals develop weakness, which is reversed by edrophonium. Their electrophysiological and pharmacological responses are identical to those in human MG. The thymus seems to be the major organ initiating AChR antibody formation in MG, which eventually damages the postsynaptic fold.

MG is characterized by a fluctuating weakness of skeletal muscles with remission and exacerbation. Classically, weakness got worse with exertion or exercise and oculobulbar symptoms are common, seen in 90% of MG patients. Commonly, such patients complain of droopy eye lid, diplopia, swallowing or speech difficulty, and proximal muscle weakness. In 85% of the patients, MG becomes generalized, usually within 3 years. Rarely, respiratory difficulty is the initial symptom. Exertional weakness (myasthenic or fatigable weakness) can be documented on examination by the repetitive exercise.

DIAGNOSIS AND EVALUATION

The diagnosis of MG is based on history and clinical findings. This is confirmed by the edrophonium test, AChR-Ab test, muscle-specific kinase (MuSK)-Ab test, lipoprotein receptor–related protein 4 (LRP4) and agrin antibody (Ab) tests, the repetitive nerve stimulation (RNS) test, and single-fiber electromyography (SFEMG).

The diagnosis of MG is easily confirmed by the intravenous (IV) edrophonium test, a short-acting acetylcholinesterase

[1] Tick paralysis is excluded from this chapter because it is due to conduction block at the node of Ranvier.

inhibitor (AChEI) (Oh & Cho, 1990). Dramatic improvement is noted within 1 minute after injection. This test is positive in 95% of MG patients. The edrophonium test is still the most helpful, simple, and rapid test for the diagnosis of MG. To perform an adequate edrophonium test, placebo injection and objective measurement of two or three clinical parameters are crucial. Placebo injection has been helpful in sorting out many pseudo-MG patients in whom both the edrophonium test and placebo test were positive. A positive edrophonium test has also been reported in other diseases. Understandably, it is positive in penicillamine-induced MG and in MG unmasked or precipitated by drugs. The edrophonium test was positive in 89% of patients with MLOS (myasthenia-gravis Lambert-Eaton mysthenic syndrome overlap syndrome), in 37% of patients with LEMS, and in 27% of those with botulism. Among the CMSs, patients with endplate AChR deficiency and choline acetyltransferase (ChAT) deficiency (familial infantile myasthenia) showed a positive test. A false-negative edrophonium test may be seen in ocular MG (OMG), especially when ophthalmoplegia is severe, or when ophthalmoplegia is too minimal for objective measurement. In this case, the prostigmine test is often positive. A positive edrophonium test is less common in MuSK MG than in other forms of MG, being positive in half of the cases. Since 1979, a simple and inexpensive "ice-pack test" (application of ice over one eye for 5 minutes) has been found to be positive for OMG (Ertaş, Araç, Kumral, & Tunçbay, 1994). This test was used in patients with MG, normal individuals, and a few cases of third nerve palsy and was positive only for MG in 90% of cases.

The serum AChR antibody has become the more specific test for MG, although it is positive in 70%–95% of cases, with an average of 85% of cases (Vincent et al., 2003). False-positive responses have rarely been reported in other diseases. However, the titer is not correlated with disease severity. MuSK antibody was positive in an average of 20% to 49% of seronegative generalized MG (GMG), with an average rate of 39% (Wolfe, Trivedi, & Oh, 2007). MuSK-Ab is negative in OMG. MuSK-Ab should be tested in all AChR-Ab-negative cases. In recent years, two new antibodies were found in MG. LRP4 antibody was identified in 1.4% (United States)–50% (Germany) of AChR-Ab-negative MG patients. Agrin antibody was found in 7.5%–15% of MG patients regardless of AChR antibody status (Yan, Xing, & Mei, 2018; Zisimopoulou et al., 2014).

Other objective diagnostic tests include the RNS test and the SFEMG (Oh, 1998; Stalberg & Trontelj, 1994).

The RNS test is the time-honored test for the neuromuscular transmission (NMT) disorders and offers the advantages of relative simplicity and rapid results. Although certain patterns on the RNS test are indicative of MG, it is less specific than the AChR-Ab assay. The distinct advantages of the RNS test over the AChR-Ab assay are that this test can provide a rapid and objective diagnosis of MG and can be used serially for the evaluation of severity of disease. The RNS test is positive in 75% of cases when the distal muscles (usually hand muscles) and proximal muscles (usually facial and trapezius muscles) are tested together. The most common types of RNS abnormalities are those typical of postsynaptic NMT blocks: (1) normal compound muscle action potential (CMAP) amplitude, (2) normal or minimal postexercise facilitation (PEF), (3) decremental response at low-rate stimulation (LRS), (4) normal or decremental response at high-rate stimulation (HRS), and (5) posttetanic facilitation (PTF) followed by posttetanic exhaustion (PTE) (Figs. 19.1 and 19.2). Among these, the decremental response at LRS is the most common and characteristic RNS finding in MG. In MuSK-MG, an RNS test of limb muscle had a relatively low yield (25%–57%), whereas an RNS test of facial muscles showed a decrement in 85% of cases. This is because of the predominant involvement of facio-bulbar muscle in MuSK-MG.

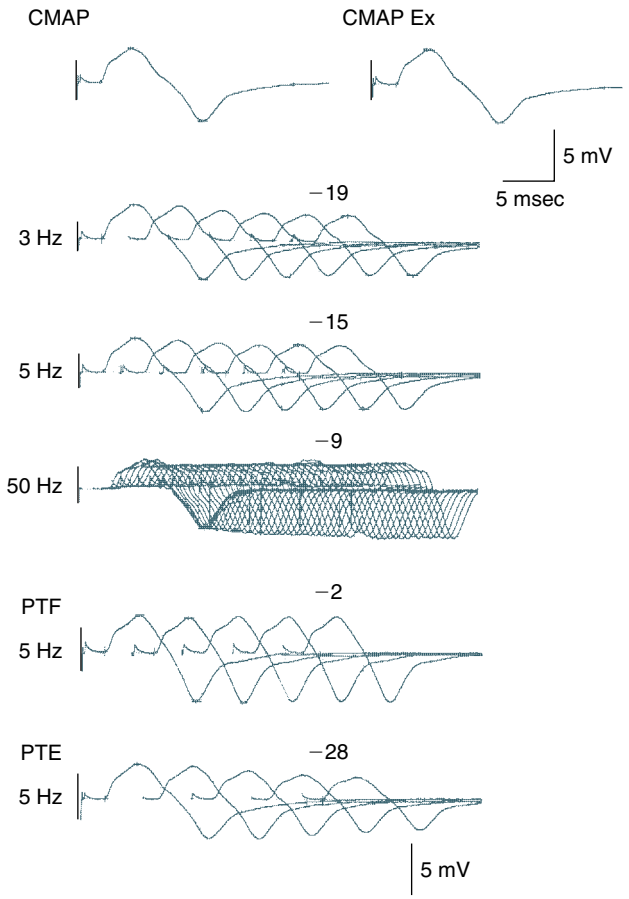


Fig. 19.1 Typical repetitive nerve stimulation pattern in the abductor digiti quinti muscle in mild myasthenia gravis. Normal compound muscle action potential (CMAP) amplitude at rest and after exercise (CMAP Ex). Decremental response (–19% at 3 Hz and –15% at 5 Hz at low-rate stimulation. Normal response at high rate response (50 Hz). Posttetanic facilitation (PTF, 5 Hz stimulation immediately after 50 Hz) and posttetanic exhaustion (PTE, 5 Hz stimulation) 4 minutes after 50 Hz stimulation are present.

The SFEMG is the single most sensitive clinical test for MG, being positive in 77%–100% of MG cases, with an average rate of 95%. The test is so sensitive that Stålberg and Trontelj concluded that the diagnosis of MG can be abandoned if abnormal jitter is not present in a weak muscle. The classic SFEMG pattern in MG is characterized by a definite increase in jitter with or without neuromuscular blocking. For obvious reasons, the SFEMG is most useful in "double or triple" seronegative MG cases in which the RNS test was negative. In mild GMG and OMG, in which the RNS test and AChR-Ab are often normal, this test can be the crucial means of confirming the diagnosis of MG. In none of

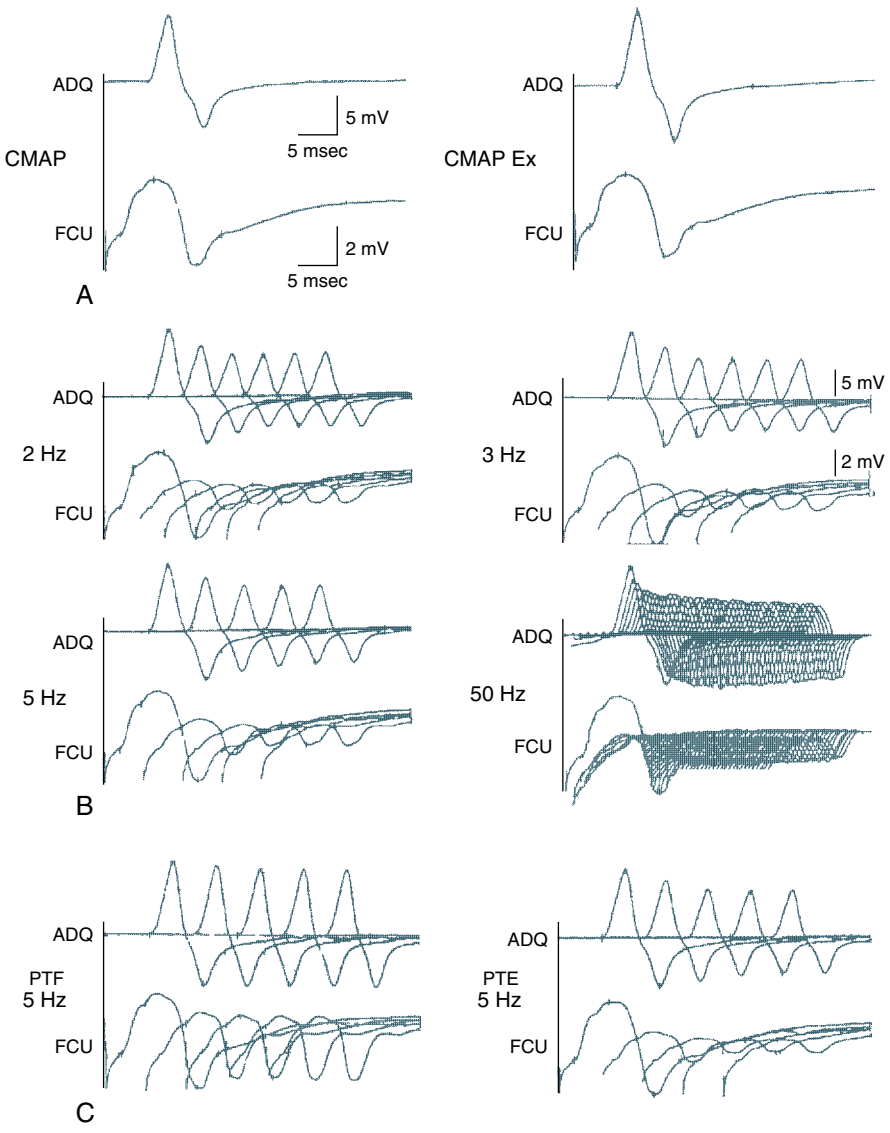


Fig. 19.2 Typical repetitive nerve stimulation (RNS) pattern in the abductor digiti quinti and flexor carpi ulnaris (FCU) muscles in severe myasthenia gravis (MG). (A) Normal compound muscle action potential (CMAP) at rest and after exercise (CMAP Ex). (B) Decremental response at low-rate stimulation (2,3,5 Hz) and at high-rate stimulation (50 Hz). (C) Posttetanic facilitation (PTF) and posttetanic exhaustion (PTE) are also present.

our MG patients were all three tests found to be negative. Thus, MG can be confidently ruled out if all three tests are negative.

TREATMENT AND MANAGEMENT

In 2016, an international consensus guidance for management of MG was published (Sanders et al., 2016). In 2006, the EFNS Task Force published consensus guidelines for the treatment of autoimmune NMT disorders (Skeie et al., 2006). In general, we will follow these consensus guidelines with some modification. There are two main modes of treatment in MG: (1) symptomatic treatment and (2) immunotherapy.

SYMPTOMATIC TREATMENT OF MYASTHENIA GRAVIS

Acetylcholinesterase Inhibitors

The mainstay of symptomatic treatment is AChEI, which is effective in almost all cases. Poorer response was reported in MuSK-MG. One series showed unresponsiveness in 71% of 14 cases (Hatanaka et al., 2005).

AChEIs inhibit the breakdown of ACh at the neuromuscular junction and increase the availability of ACh to stimulate AChR and facilitate muscle activation and contraction. AChEIs used in MG bind reversibly to AChE as opposed to organophosphate (OP) AChEIs, which bind irreversibly (Table 19.1). These drugs cross the blood-brain barrier poorly and generally remain in the extracellular space.

The adverse effects of AChEI are caused by the increased concentration of ACh at both nicotinic and muscarinic synapses. The common muscarinic effects are gut hypermotility (diarrhea and stomach cramps), increased sweating, salivation, and, when severe, bradycardia. The main nicotinic adverse effects are fasciculations and, sometimes, muscle cramps. Muscarinic effects are relieved by oral atropine (usual dose 0.4 mg bid or tid), glycopyrrolate (Robinul; usual dose, 1 mg or 2 mg bid or tid), or 5 mg diphenoxylate with atropine (Lomotil), which have no effects on the neuromuscular junction. Glycopyrrolate is better for this purpose because it does not enter the brain and so will not cause blurring of vision or toxic delirium expected with a high dose of atropine. However, it does not dry up secretions as much as atropine. Lomotil can be obtained without any prescription.

Table 19.1 Pharmacological Properties of Acetylcholine-Esterase Inhibitors

Drug	Dosage Form	Equivalent Doses	Onset, Peak, and Duration of Drugs	Initial Dose (Adults)	Side Reactions	Other Comments
Pyridostigmine bromide (Mestinon tablet)	60 mg/tablet	60 mg	Onset: 30 minutes Peak: 1–2 hours Duration: 3–5 hours	60 mg tid in daytime Up to 1 g a day	Most common side effect: GI symptoms	
Pyridostigmine bromide TS (extended-release tablet; Mestinon TS)	180 mg/tablet	180 mg	Onset: 30–60 minutes Duration: 6–10 hours	180 mg at night Up to 360 mg/day	Less than pyridostigmine tablet	Absorption is erratic
Pyridostigmine bromide syrup (liquid; Mestinon syrup)	60 mg/5 mL	5 mL	Onset: 30 minutes Peak: 1–2 hours Duration: 3–5 hours	60 mg tid in daytime Up to 1 g a day	Same as pyridostigmine tablet	Patient who has swallowing difficulty
Pyridostigmine bromide IV injection (Regonol) IV	5 mg/mL (2 and 5 mL ampule)	2 mg	Onset: 2–5 minutes Duration: 3–5 hours	1–2 mg q 2–3 hours Administer slowly	Cardiac dysrhythmia	During MG crisis
Neostigmine bromide (Prostigmine tablet)	15 mg/tablet	15 mg	Onset: 30 minutes Duration: 2–3 hours	15 mg qid in daytime Up to 150 mg/day	More GI side effects than pyridostigmine	Patients allergic to pyridostigmine
Neostigmine methyl sulfate (Prostigmine solution) SC, IM	0.5 mg/mL 1 mg/mL 2.5 mg/mL	1 mg	Onset: 20–30 minutes Duration: 2–3 hours	0.5–1 mg q 3 hours Up to 10 mg/day		
Neostigmine methylsulfate (ProstgmineÆ solution) IV	0.5 mg/mL 1 mg/mL 2.5 mg/mL	0.5 mg	Onset: 4–8 minutes Duration: 2–3 hours	0.5 mg administered slowly every hour Up to 10 mg/day		
Ambenonium chloride (Mytelase)	10 mg tablet 25 mg tablet	10 mg	Duration: 6–8 hours	10 mg bid Up to 100 mg/day	Fewer GI side effects than pyridostigmine Headache	Patients allergic to pyridostigmine
Edrophonium chloride (Tensilon)	10 mg/ml		Onset: immediately Duration: 2–5 minutes	2–10 mg IV/IM	Bradycardia Bronchospasm Increased weakness	Used for diagnostic test

GI, Gastrointestinal; *IM*, intramuscular; *IV*, intravenous; *MG*, myasthenia gravis; *qid*, four times a day; *SC*, subcutaneous; *tid*, three times a day; *TS*, time span.

It is important to tell patients in advance about the possible side reactions of AChEIs and relieve side reactions with glycopyrrolate or atropine so that they would not be alarmed about them. This is because this is the most common cause for MG patients not taking AChEIs.

The most serious side reaction of AChEIs is cholinergic weakness and crisis. This is due to too much AChEI medications, which lead to overaccumulation of Ach at the neuromuscular junction, producing sustained endplate depolarization without ample time for repolarization (depolarization block). This was a common phenomenon before immunotherapy in MG and was one of the well-known causes for MG crisis. However, this is extremely rare these days because we do not use a higher dose of AChEIs anymore, but it has been observed in MuSK-MG patients at the usual dose of AChEIs for MG (Hatanaka et al., 2005).

Although this drug has been extensively used since 1935 when Walker used Prostigmine as the first miracle drug for

MG, there were no placebo-controlled randomized studies for these drugs (Keesey, 1998; Walker, 1935). However, case series demonstrate an objective and marked clinical effect (class IV evidence). Among the various AChEIs, Mestinon (pyridostigmine) is the most commonly used drug because of the 6 hours duration of the drug effect. The starting dose is 60 mg three to four times a day, depending on symptoms. This is usually given in daytime and at night; pyridostgmine time span (TS) is the preferred agent because of its slow-releasing benefit. Pyridostigmine syrup is used for children or for those who experience difficulty swallowing pills. Parenteral use of AChEIs is rarely necessary during the postoperative period or during MG crisis by some. IV pyridostigmine should be given at about 1/30 of the oral dose. In my practice, I have not used the intramuscular or IV forms of AChEIs in recent years. Neostigmine (Prostigmine) is an alternative choice of AChEIs in patients who are allergic to pyridostigmine. It has a slightly shorter duration of action and slightly greater muscarinic effects. Ambenonium (Myetelase) has been suggested as the last resort for patients who cannot take pyridostigmine or Prostigmine for whatever reason.

The optimal dose is determined by the balance between clinical improvement and adverse effects and can vary over time with concomitant treatment. The adjustment of dose should be gradual and achieved usually by the patient. The patient's report of definite improvement following AChEI intake or the physician's assessment of the patient's condition at its peak of effectiveness is a reliable index of appropriate dose and effectiveness. The latter is almost impossible for nonhospitalized patients. Thus, the patients should be taught to adjust the dose. The maximal daily dose of pyridostigmine is 1 g a day. If the patients need more than 720 mg (12 tablets) of pyridostigmine for control of MG symptoms, we recommend immunotherapy. Patients with mild disease can often be managed adequately with AChEIs alone. In patients with immunotherapy, patients' symptoms can be controlled with AChEIs.

Another symptomatic agent is ephedrine. This can be used for relief of fatigue as an adjunctive symptomatic treatment at dose of 25 mg of ephedrine sulfate. This drug is banned by the Food and Drug Administration (FDA) in the United States for safety reasons.

Potassium Channel Blocker: 3,4-Diaminopyridine

3,4-Diaminopyridine (DAP), a recently FDA-approved potassium channel blocker, was tested in MG in two studies: two MG patients by Lundh et al., with clinical and electrophysiological improvement with IV and oral 3,4-DAP, and 3,4-DAP in eight patients with MG by Sanders et al., with an improvement of >3 quantitative MG (QMG) score in two patients on a 15–45-mg daily dose (Oh, 2019).

IMMUNOTHERAPY

Since MG is an autoimmune disease, it is natural to treat this disorder with various immunotherapies. These include immunosuppressive therapy, immunomodulating therapy, and thymectomy.

Immunosuppressive Therapy

Steroids. In a large nonrandomized study, remission or marked improvement was reported in 63%–82% of GMG and in 66%–86% of OMG patients treated with oral corticosteroids, usually prednisone (class IV evidence) (Sathasivam, 2008) (Table 19.2).

The efficacy has been established in double-blind, placebo-controlled trials with methylprednisolone but not with prednisone. A randomized trial compared double-blind IV methylprednisolone (10 patients) versus placebo (9 patients) for GMG (Table 19.3). The steroid group showed a 7.2 times greater improvement in muscle strength than the placebo group did after 2 weeks of treatment, indicating a significant short-term benefit from steroid. A randomized, double-blind trial of prednisone (six patients) versus placebo (seven patients) for GMG showed no significant difference in improvement at 6 months. This study lacks credence because of the small number of patients for each group. In a randomized controlled trial with methylprednisolone vs. IV immunoglobulin (IVIg), no significant difference was noted at day 14, indicating that methylprednisolone is as good as IVIg. Thus, steroids are useful as short-term immunosuppressants (class II). Long-term use of steroids is associated with many adverse effects, including weight gain, fluid retention, diabetes, psychosis, glaucoma, cataracts, gastrointestinal (GI) bleeding, and osteoporosis. Steroids should be used ideally as short-term (60 mg/day for 3–4 months) immunosuppressants. However, long-term use of a steroid is not unusual. The risk of osteoporosis is reduced by giving bisphosphonates (class IV).

Oral prednisone is recommended as the first drug of choice when immunosuppressive drugs are necessary in MG (class IV). This is because steroid is known to induce the earliest onset of improvement among the various immunosuppresants. Controversy exists regarding the most prudent method of initiating therapy (high-dose daily, high-dose alternate day [AD] or low-dose AD, with a gradually increasing regimen). Low doses (20–30 mg) are recommended by those who believe that some patients develop steroid worsening, including MG crisis, in 4 to 10 days on higher doses (class IV) (Table 19.4). The low dose is gradually increased to a high dose over a period of a few weeks. High doses (>60 mg/day) are recommended by others, including this author, who believe that improvement is more rapid with high-dose daily regimens and steroid worsening represents natural worsening of MG because we start steroid in patients with unstable MG. I personally believe that steroid worsening is exaggerated and extremely rare these days since we use a smaller daily dose of AChEIs. Thus, I recommend an initial high-dose regimen unless there is any compelling reason not to do so. Once the maximal benefit or pharmacological remission is achieved, owing to the potential adverse effects with prolonged use of steroids, the dose should be slowly reduced to the minimum effective maintenance dose or withdrawal and the simultaneous use of a long-term immunosuppressant are initiated.

Azathioprine. Azathioprine (AZA) is extensively used as immunosuppressive. The onset of therapeutic response may be delayed for 4–10 months, and maximal effect is obtained in 1–2 years. AZA is usually well tolerated, but idiosyncratic flu-like symptoms or GI disturbances, including pancreatitis, occur in 10%, usually within the first few days of treatment. Side effects include bone marrow suppression and hepatotoxicity, which usually respond to drug reduction or withdrawal. When the white blood cell falls below 4000 mm^3, the dose should be reduced; if it is below 3000 mm^3, AZA should be discontinued. The incidence of malignancy was

Table 19.2 Literature Review of Nonrandomized Studies of Various Immunosuppressants in Myasthenia Gravis

Study	Number of Patients	Patients with Good Overall Improvement		Other Information
		Improvement	Remission	
Steroid				
Brunner et al. (1972)	9	9		Multiple short course of methylprednisone. Severe MG
Arsura et al. (1985)	15	12		IV MP followed by oral prednisone
Pascuzzi et al. (1984)	116	61 (52.6%) marked	32 (27.6)	
Sghirlanzoni et al. (1984)	60	18 (30.0%) marked	25 (41.7%)	
Cosi et al. (1991)	142	42 (29.6%) marked	48 (33.8%)	
Evoli et al. (1992)	104	44 (42.3%) marked	41 (39.4%)	
Bu et al. (2000)	600	95%		151 generalized; 449 pure ocular
Kupersmith et al. (1996)	32	21 (66%)		Ocular MG
Sommer et al. (1997)	45	19 (86)		Ocular MG
Azathioprine (AZA)				
Matell (1976)	26	(78%)		Unresponsive to steroid or ACTH
Mertens et al. (1981)	78	91%		Alone, in combination with steroid, thymectomy or both
Matell (1987)	99	72% (38% marked)		Alone, in combination with steroid, thymectomy or both
Witte et al. (1984)	18	15 (83%)		Alone for more than 6 months
Kuks et al. (1991)	41	41 (100%)		Alone or with prednisone for more than 3 years
Mantegazza et al. (1988)	32	75%		Alone
	57	70%		With prednisone
Heckmann et al. (2001)			50%	2-year class 2 study. Early high dose with prednisone vs. 16% in low dose control
Cyclophosphamide (CPP)				
Perez et al. (1981)	47		47 (100%)	With steroid in 33; thymectomy in 5; at 3 years
Cyclosporin				
Goulon et al. (1988)	10	8 (80%) marked		12-month open-label trial. Severe MG, unresponsive to AChEI or thymectomy plus steroid or AZA
Bonifati and Angelini (1997)	9	7 (78%) marked		2-year open-label trial. Unresponsive to thymectomy, AZA, and steroid
Lavrnic et al. (2005)	52	44 (85%) marked		30-month open-label trial. Severe MG unresponsive to thymectomy, steroid, and AZA
Mycophenolate mofetil				
Cos et al. (2000)	22	15 (68%)		2–18-month open-label trial. 3/5 alone; 4/7 unresponsive to AZA; 7/10 with steroid
Ciafaloni et al. (2001)	12	8 (67%) marked		6-month open-label trial. Unresponsive to AZA, steroids, CsA for <6 months

Continued

Table 19.2 Literature Review of Nonrandomized Studies of Various Immunosuppressants in Myasthenia Gravis—cont'd

Study	Number of Patients	Patients with Good Overall Improvement		Other Information
		Improvement	Remission	
Chaudhry et al. (2001)	32	19 (59%)		Alone, 4; 28 on other immunosuppresants
Meriggioli et al. (2003)	85	73%		48 thymectomy; 66 with CsA, steroid, AZA, MTX
Tacrolimus				
Konishi et al. (2003)	19	7 (37%)		16-week open-label study: thymectomy and steroid
	12	8 (67%)		2-year treatment
Kawaguchi et al. (2004)	17	12 (71%)		Open-label trial. Mean follow-up of 19.2 months
Ponseti et al. (2005)	79		69 (87%) Pharmacologic	Open-label trial. Severe MG. Thymectomy, steroid, and CSA. Mean follow-up of 2.5 years
Etanercept				
Rowin et al. (2004)	11	6 (55%)		Open-label trial

References: Brunner, Namba, and Grob (1972); Arsura, Brunner, Namba, and Grob (1985); Pascuzzi, Coslett, and Johns (1984); Sghirlanzoni et al. (1984), Cosi et al., 1991; Evoli, Batocchi, Palmisani, Lo Monaco, and Tonali (1992); Bu et al., 2000; Kupersmith, Moster, Bhuiyan, Warren, and Weinberg (1996); Sommer et al. (1997); Matell et al., 1976; Mertens, Hertel, Reuther, and Ricker (1981); Matell (1987); Witte, Cornblath, Parry, Lisak, and Schatz (1984); Kuks, Djojoatmodjo, and Oosterhuis (1991); Mantegazza, Antozzi, Peluchetti, Sghirlanzoni, and Cornelio (1988); Heckmann, LeePan, and Eastman (2001); Perez, Buot, Mercado-Danguilan, Bagabaldo, and Renales (1981); Goulon, Elkharrat, Lokiec, and Gajdos (1988); Bonifati and Angelini (1997); Lavrnic et al. (2005); Cos et al. (2000); Ciafaloni, Massey, Tucker-Lipscomb, and Sanders (2001); Chaudhry, Cornblath, Griffin, O'Brien, and Drachman (2001); Meriggioli, Ciafaloni, et al. (2003); Konishi et al. (2003); Kawaguchi et al. (2004); Ponseti et al. (2005); Rowin, Meriggioli, Tüzün, Leurgans, and Christadoss (2004).

AChEI, Anticholinesterase inhibitor; *ACTH*, adrenocorticotrophic hormone; *CsA*, cyclosporine A; *IV*, intravenous; *MG*, myasthenia gravis; *MP*, methylprednisone; *MTX*, methotrexate.

Table 19.3 Literature Review of Randomized Studies of Various Immunotherapies for Myasthenia Gravis

Study	Agent	Method(s)	Intervention(s)	Outcome	Notes
Steroids					
Mount (1964)	ACTH (n = 43)	RCT, PC	ACTH (580 units) 8 days vs. placebo	No evidence of efficacy of ACTH	Ocular MG
Howard (1976)	Prednisone (n = 13)	RCT, DB, PC	Prednisone 100 mg (n = 6) on alternate day vs. placebo (n = 7)	No significant difference In 6 months, 3 improved on placebo and 3 on prednisone	Small number for statistical analysis
Lindberg (1998)	Methylprednisone (MP)	RCT, DB, PC	2 g MP IV for 2 days (n = 10) vs. placebo (n = 10)	Significant improvement in IV MP at 2 weeks Improved in 8 of 10 in MP and in 1 of 9 in placebo	Mean duration of improvement: 8 weeks
Bromberg (1997)	Prednisone (n = 10)	RCT	Prednisone 60 mg daily (n = 5) vs. AZA 2.5 mg/kg daily (n = 5)	No difference in improvement Improvement in 4 of 7 in prednisone and in 1 of 3 in AZA	Small number for statistical analysis
Schuchardt (2004)	MP (n = 33)	RCT	MP 1–1.5 mg/kg for 14 days vs. 3 g IVIg daily for 5 days	No difference between the two groups at day 14	MG with exacerbation
Immunosuppressants					
Gajdos (1993)	Azathioprine (AZA) (n = 41)	RCT, unblinded	AZA 3 mg/kg daily plus initial prednisone (n = 21) vs. prednisone (n = 20) 1 mg/kg daily	No difference in remission or marked improvement between the two groups at 1, 2, and 3 years	Prednisone treatment for months in AZA group
Palace (1998)	AZA (n = 34)	RCT, blind	AZA 2.5 mg daily (n = 15) vs. placebo (n = 19) All patients on prednisone 1.5 mg/kg or 100 mg on alternate days	No difference between the two groups at 12 months. Significant reduction of prednisone dose in AZA at 36 months (0 in AZA vs. 40 mg in placebo)	Prednisone-sparing effect
De Feo (2002)	Cyclophosphamide (CPP) (n = 23)	RCT, DB	CPP 0.5 g/m^2 of body surface IV monthly (n = 12) vs. placebo (n = 11) All patients on prednisone more than 50 mg initially	No significant difference between the two groups at 12 months	IV every other month after the first 6 months
Tindall (1987)	Cyclosporine A (CsA) (n = 20)	RCT, DB, PC	Cyclosporine (6 mg/kg daily) (n = 10) vs. placebo (n = 10)	Significant greater increase in QMG score in CsA at 6 and 12 months	–
Tindall (1993)	Cyclosporine (n = 39)	RCT, DB	Cyclosporine (5 mg/kg daily) plus prednisone 60–100 mg on alternate days (n = 20) vs. prednisone plus placebo (n = 19)	Significant greater increase in QMG score in CsA plus prednisone at 6 months	No steroid-sparing effect
Nagane (2005)	Tacrolimus (n = 34)	RCT, unblinded	Tacrolimus 3 mg/day plus steroids (n = 18) vs. no tacrolimus plus steroid (n = 16) Plasmapheresis is given if necessary to either group	Significantly less number of treatment with plasmapheresis plus high-dose IV MP in tacrolimus during early and follow-up phase treatment at 1 year The period of early-phase treatment is significantly shorter in tacrolimus The oral prednisone dose is significantly lower in tacrolimus	Reduction in need for other immunotherapy, to include steroid-sparing effect

Continued

Table 19.3 Literature Review of Randomized Studies of Various Immunotherapies for Myasthenia Gravis—cont'd

Study	Agent	Method(s)	Intervention(s)	Outcome	Notes
Meriggioli (2003)	Mycophonolate mofetil (MM) (n = 14)	RCT, DB	MM (n = 7) vs. placebo (n = 7). Cyclosporine, prednisone, or no immunosuppressants in either group	No difference between the two groups Improvement in 1 in each group	–
Sanders (2008)	MM (n = 80)	RCT, DB	MM (2.5 g daily) (n = 41) vs. placebo (n = 39) All on prednisone 20 mg/day	No difference in QMG score change at 3 months	–
Sanders (2008)	MM (n = 176)	RCT, DB	MM (2 g/day) (n = 88) vs. placebo (n = 88) All on prednisone 20 mg/day for 1 month	No difference in QMG score change at 9 months	–
Immunomodulating therapies					
Gajdos (1983)	Plasma exchange (PE) (n = 14)	RCT	Prednisone (n = 7) vs. prednisone plus PE (n = 7) PE: Three PEs over a 10-day period with PE once a week if necessary All on prednisone 1 mg/kg/day for 1 month	No difference in muscle strength score change at 1 month or 1 year Significantly less relapse in prednisone: 1 in prednisone vs. 8 in PE in 1 year	4 in each group in MG crisis
Gajdos (1997)	IVIg (n = 87)	RCT	3 PEs vs. IVIg 2 g/kg or IVIg 1.2 g/kg	No difference in MM score change at day 15	MG exacerbation
Gajdos (2005)	IVIg (n = 173)	RCT	IVIg 1 g/kg vs. IVIg 2 g/kg	No difference in MM score change at day 15	MG exacerbation
Rønager (2001)	IVIg (n = 12)	RCT, crossover	IVIg 0.4 g/kg for 3 days plus 5 PE vs. opposite schedule	No difference in QMG change 7 days after treatment	–
Wolfe (2002)	IVIg (n = 12)	RCT	IVIg 1 g/kg for 2 days vs. 5% albumin for 3 days	No difference in QMG change at day 42	–
Zinman (2007)	IVIg (n = 51)	RCT, DB, PC	IVIg 1 g/kg for 2 days vs. 5% dextrose for 2 days	Significance in QMG change and postintervention status in IVIg at day 14	Treatment effect maintained for 28 days after infusion

References: Mount (1964); Howard, Duane, Lambert, and Daube (1976); Lindberg, Andersen, and Lefvert (1998); Bromberg, Wald, Forshew, Feldman, and Albers (1997); Schuchardt et al. (2005); Benatar et al. (2016); Gajdos and Myasthenia Gravis Clinical Study Group (1993); Palace, Newsome-Davis, and Lecky (1998); De Feo, Schottlender, Martelli, and Molfino (2002); Tindall et al. (1987); Tindall, Phillips, Rollins, Wells, and Hall (1993); Nagane, Utsugisawa, Obara, Kondoh, and Terayama (2005); Meriggioli, Rowin, Richman, and Leurgans (2003); Sanders et al. (2008); Heckmann, Rawoot, Bateman, Renison, and Badri (2011); Pasnoor et al. (2016); Gajdos, Simon, De Rohan-Chabot, Raphael, and Goulon (1983); Gajdos, Chevret, Clair, Tranchant, and Chastang (1997); Gajdos et al. (2005); Rønager, Ravnborg, Hermansen, and Vorstrup (2001); Wolfe et al. (2002); Zinman, Ng, and Bril (2007); Barth, Nabavi Nouri, Ng, Nwe, and Bril (2011); Wolfe et al. (2016); Howard et al. (2013).

ACTH, Adrenocorticotrophic hormone; *DB*, double blind; *IV*, intravenous; *IVIg*, intravenous immunoglobulin; *MG*, myasthenia gravis; *PC*, placebo controlled; *QMG*, quantitative myasthenia gravis; *RCT*, randomized controlled trial.

not increased over 22 years of AZA treatment in Matell's (1987) study.

Several observational series of AZA treatments showed 70%–100% improvement with AZA alone or in combination with other treatments, mostly with steroids (class IV) (Sathasivam, 2008). One study comparing early high-dose immunosuppressive with AZA and prednisone resulted in 50% of patients achieving remission after 2 years, compared with a remission rate of only 16% in those on a low-dose regimen.

One large double-blind randomized study (Palace et al., 1998) has demonstrated the efficacy of AZA as a steroid-sparing agent with a better outcome in patients on a combination of AZA and steroids than in patients treated with steroids alone (class I). In a randomized, unblinded

Table 19.4 Pharmacological Properties of Various Immunotherapies

Drug	Mechanism of Action	Typical Dose	Onset and Duration of Action	Contraindication
Steroid	Inhibit the activation and antigen processing of T cells. Decrease of the number of circulating T cells Increase muscle AChR synthesis	Initial: 60 mg/day Maximum: 100 mg/day	Onset: 2–3 days Peak: 3–6 months	Severe diabetes
Azathioprine (AZA)	Purine antagonist Inhibit T-cell and B-cell proliferation	Initial: 150 mg/day Maximum: 400 mg/day	Onset: 4–10 months Peak: 2–3 years	Pregnancy, TPMT Deficiency, liver failure, cancer
Mycophenolate mofetil (MM)	Purine antagonist Inhibit T-cell and B-cell proliferation	Initial: 1.5 gm/day Maximum: 4 gm/day	Onset: 4 weeks–10 months (mean, 11 weeks) Peak: 8–26 months (mean, 7 months)	Pregnancy
Cyclosproine (CsA)	Calcineurin inhibitors Decease IL-2 production in T-cells	Initial: 300 mg/day	Onset: 1 week–8 months	Severe hypertension, renal failure
Tacrolimus	Calcineurin inhibitors Prevents IL-2 transcription in T cells	Initial: 3 mg/day	Onset: 2 weeks–4 months Peak: 4 months–2 years	Pregnancy, renal failure, severe diabetes
Cyclosphosphamide	Alkylating agent Nonspecific cell-cycle inhibitor, more effect on B cells	Initial: 150 mg/day	Onset: 2 months Peak: 3–12 months	Pregnancy, cancer, Impaired bone marrow function
Rituximab	Chimeric human-murine monoclonal CD20 antibody Reduce B cell activation and proliferation	Initial: 375 mg/m^2 q week x 4 weeks.	Onset: 1–2 months Peak: 7 months	Cardiac disease
Plasma exchange (PE)	Removal of AChR antibody	5 PE session qod 2–3 L removal each session	Onset 1 day Peak: 2 weeks Duration: 1–3 months	CI: coronary artery disease. Coagulopathy
Intravenous immunoglobulin (IVIg)	Neutralize the blocking effects of MG IgG antibodies to AChR	2 gm/kg a day over 2 or 5 days	Onset: 5 days Duration: 1 m	Renal failure IgA deficiency
Eculizumab	Inhibits the formation of C5b-9 membrane attack complex	900 mg/week for 4 weeks 1200 mg/week every 2 weeks after that	Peak: 12 weeks	Meningococcal infection: meningococcal vaccination 2 weeks before the first injection
Thymectomy	Removal of thymic cells		Onset: 3–4 minutes Peak: 9–12 minutes	

AChR, Acetylcholine receptor; *AZA*, azathioprine; *CsA*, cyclosporine A; *IgG*, immunoglobulin A; *IL-2*, interleukin 2; *IVIg*, intravenous immunoglobulin; *MG*, myasthenia gravis; *MM*, mycophenolate mofetil; *TPMT*, thiopurine methyltransferase.

trial of AZA plus initial prednisone versus prednisone alone, no difference was found in remission or marked improvement between two groups in 1–3 years of long-term treatment.

Because AZA has been associated with relatively few treatment failures and steroid-sparing effect in two randomized controlled trials (class I), we do recommend AZA as the first-choice long-term immunosuppressant drug. Some prefer to start AZA together with steroids to allow tapering of steroids to the lowest dose possible. The usual recommended daily dose is 150 mg/day.

Cyclosphosphamide. In one observational study in 42 patients who were given cyclophosphamide (CPP) with a duration of treatment from 2 to 37 months, remission was achieved in 58% of patients who underwent 1 year of treatment, 85% of patients who underwent 2 years of treatment, and 100% of patients who underwent 32 months of treatment (Sathasivam, 2008). In a randomized, double-blind trial of CPP plus prednisone versus prednisone plus placebo in GMG, CPP significantly improved muscle strength at 12 months, but not at 6 months (De Feo et al., 2002). The CPP-treated patients were on significantly lower dos-

es of prednisolone at 6 and 12 months. Thus, this study showed that CPP is clinically effective in GMG and that it has a steroid-sparing effect (class II). The usual oral dose of CPP has been 5 mg/kg/day (usual initial dose, 150 mg/day). CPP can be given as monthly pulse therapy at an IV dose of 1 gm/m^2/month. High-dose CPP (50 mg/kg/day for 4 days) followed by granulocyte colony stimulating factor was also used for "rebooting" of the immune system in refractory MG. In three MG patients refractory to plasma exchange (PE), thymectomy, and conventional immunosuppressants, remission was achieved (Drachman, Jones, & Brodsky, 2003). In view of the relative high risk of toxicity including bone marrow suppression, opportunistic infections, bladder toxicity, sterility, and neoplasm, this drug is recommended as the last choice of immunosuppressants to patients who are intolerant of or unresponsive to other immunosuppressants. The usual recommended oral daily dose is 150 mg/day.

Cyclosporine A. This is the first agent in MG that showed a definite benefit in a randomized controlled trial. Three observational studies on severe MG unresponsiveness to thymectomy, AZA, or steroid showed marked improvement in 75%–80% of patients in 1–3 years of treatment. One placebo-controlled, double-blind randomized study in 20 patients for 6 months with an open extension (class I) showed significantly improved strength and reduction in AChR antibody titers compared with the placebo group at 6 and 12 months. Another double-blind randomized controlled study with 39 patients showed significantly improved muscle strength at 6 months in the cyclosporine (CsA) plus prednisone group compared with the placebo plus prednisone group, but a steroid-sparing effect was not observed. Thus, two randomized controlled trials have shown that CsA is clinically effective in GMG. Initial daily dose is 4–6 mg/kg/day. However, because of significant side effects such as nephrotoxicity, hypertension, and malignancy, it should be considered only in patients intolerant of or unresponsive to AZA. Other common side effects include hypertrichosis, gingival hyperplasia, myalgia, and "flu-like" symptoms. Nonsteroidal anti-inflammatory drugs should be avoided with CsA because they increase nephrotoxicity. CsA should be considered in patients intolerant of or unresponsive to AZA (level B recommendation). The usual recommended daily dose is 200 mg/day.

Mycophenolate Mofetil. Two open-label trials and two observational studies in MG patients unresponsive to steroid, AZA, or CsA showed 59%–73% improvement over a treatment period of 2–18 months. Improvement occurred in monotherapy as well as with other immunosuppressants. Two randomized, double-blind trials of mycophenolate mofetil (MM) plus steroid versus steroid plus placebo for GMG failed to demonstrate any efficacy of MM in trials of 3 or 9 months' duration. Another study of a small randomized, double-blind trial of MM plus either CsA or prednisolone or no immunosuppresants versus placebo plus either CsA or prednisolone or no immunosuppressants also did not show any benefit of MM. Although MM has been reported to be not efficacious in randomized controlled trials in GMG, this drug is well tolerated, with a relatively good adverse effect profile (Sanders et al., 2008),

The adverse effects of MM were usually mild (nausea, headache, or diarrhea). Serious adverse effects such as infections and hematopoietic suppression are rare. One advantage of MM, compared with other immunosuppressants, is a lesser carcinogenic tendency: a kidney transplant patient on MM had a lesser cancer incidence in the long-term follow-up. Lymphoma was reported as a rare complication. The European Task Force recommends MM as the second-line long-term therapy in MG patients intolerant of or unresponsive to AZA (level B recommendation). This view might have to be modified in view of the negative results of two randomized controlled studies. The usual recommended daily dose is 1.5 gm.

Tacrolimus. Although tacrolimus and CsA act in a similar fashion, the potency of tacrolimus appears to be 10–100 times greater than that of CsA. Tacrolimus at 3 mg/day for MG is 20% of the dose given to organ transplant patients. One 4-month open-label study showed an improvement in 37% of cases. Three observational studies with longer than 19 months' duration showed an improvement in 67%–71% of patients and pharmacological remission in 87% of patients. A randomized, unblinded, non-placebo-controlled trial of tacrolimus plus steroids with or without PE versus no tacrolimus plus steroids with or without PE showed significantly fewer treatments with PE plus high-dose IV methyl-prednisone, a significantly shorter period of early-phase treatment, and significantly lower prednisone dose in tacrolimus-treated groups (Nagane et al., 2005). Thus, this study showed that tacrolimus reduces the need for other immunotherapy, indicating that this drug is effective in GMG. Tacrolimus seems to be relatively safe at the doses used in MG, so it should be recommended as third-line treatment for patients who are intolerant of or unresponsive to AZA. Common side effects of the drug include hypertension, renal insufficiency, hyperkalemia, headache, and hyperglycemia. If tacrolimus is used in patients with existing impaired glucose intolerance or diabetes mellitus, this impaired glucose tolerance will be almost always exacerbated (Murai, 2015). The usual recommended daily dose is 3 mg.

Methotrexate. The European Task Force recommends methotrexate as second-line drug because it is well studied in other autoimmune disorders (Skeie et al., 2006). Two studies reported conflicting results (Heckmann, Rawoot, Bateman, Renison, & Badri, 2011; Pasnoor et al., 2016). On one hand, Heckmann et al. compared the effect of methotrexate (17.5 mg weekly) versus AZA (2.5 mg/kg daily) in a single-blind study. At 2 years, there was a substantial and comparable decrease in the average daily prednisone dose and in the QMG scores in both groups, suggesting both drugs as effective steroid-sparing agents (Heckmann et al., 2011). On the other hand, in a randomized, double-blind, placebo-controlled trial of methotrexate 20 mg/week by mouth versus placebo in prednisone-dependent MG patients, Pasnoor et al. (2016) showed no difference in the prednisone area under the curve between methotrexate and placebo over a 12-month period, suggesting no steroid-sparing effect of methotrexate. We recommend this drug as the last choice if all other immunosuppressants fail or the patient cannot take others. One advantage of this medication is the one-time weekly administration. Initial starting dose is 7.5 mg

weekly and maximum weekly dose is 30 mg. The usual recommended weekly dose is 7.5 mg.

Immunomodulating Therapy

Plasma Exchange. PE or plasmapheresis removes antibodies from patient sera by membrane filtration or centrifugation. The patients typically undergo five sessions of PE at 20–50 mL/kg body weight per session over a span of 2 weeks. The plasma is separated from blood cells using membrane filtration or centrifugation, and then the blood cells are reinfused into another vein with diluted albumin, colloids, or crystalloids, while plasma is removed. The onset of improvement is within the first week and the effect lasts for 1–3 months. Side effects are associated with the insertion of the IV catheter and hypotension. Since PE has been extensively used as the treatment of choice in acute MG exacerbation, there is no randomized, double-blind control study for its short-term benefit (Cosi et al., 1991). There are, however, two nonrandomized controlled studies (Kornfeld, Ambinder, Papatestas, Bender, & Genkins, 1979; Newsom-Davis, Wilson, Vincent, & Ward, 1979). One study in 1979 compared six patients who received PE over 2 to 2.5 weeks and six patients who were assigned to a control group. None of the control group improved, while all treated patients improved strikingly (Kornfeld et al., 1979). Another study in 1979 compared the long-term effect in severe patients treated with PE plus immunosuppressive drugs and seven patients treated with immunosuppressants alone (Newsom-Davis et al., 1979). PE was associated with short-term improvement in all seven patients. At 6 to 12 months, clinical outcome and AChR antibody titer decline were similar in both groups. Many observational studies have shown short-term clinical improvement in 65%–100% of cases. A Cochrane research revealed only one eligible controlled trial (Gajdos, Chevret, & Toyka, 2008; Gajdos et al., 1983). The aim of this trial was to compare the long-term effect of prednisone (seven patients) versus prednisone plus PE (seven patients). No difference was found in muscle strength score change at 1 month or 1 year between the two groups. Significantly, there were fewer relapses in the prednisone group. Thus, this trial failed to demonstrate any long-term benefit of prednisone and PE versus prednisone alone (Gajdos et al., 1983). There are several randomized studies comparing the efficacy of PE with IVIg showing comparable therapeutic efficacy (Barth et al., 2011; Gajdos, Vhevrer, & Clair, 1997; Liew et al., 2014; Rønager et al., 2001). On the basis of these findings, the 1986 National Institutes of Health consensus (Gajdos et al., 2008) is still valid: PE can be useful in strengthening patients with MG before thymectomy and during the postoperative period, and it can also be valuable in lessening symptoms during the initiation of immunosuppressants and during an acute crisis (class IV). Therefore, sham controlled trials would be unethical. A Cochrane review (2008) concluded that there are no adequate randomized controlled trials to establish whether PE improves the long- or short-term outcome from MG, but many case series report short-term benefit from PE in MG, especially in myasthenic crisis (MC) (Gajdos et al., 2008). Repeated PE is thus not recommended as a treatment to obtain continuous and lasting immunosuppression in MG.

Intravenous Immunoglobulin (IVIG). IVIg is a fractionated blood product consisting primarily of immunoglobulin G (IgG), derived from 3000 to 10,000 human plasma donors. The mechanism of action of IVIg is complex, including almost all aspects of the immune system. The most relevant mechanisms for MG were the neutralizing effect of commercial polyclonal IgG (IVIg) on the blocking effects of myasthenic IgG antibodies to nicotinic AChR and the inhibiting effect on the production of autoantibodies by inhibiting the body's ability to produce globulin. IVIg is relatively easier to administer than PE. The usual IVIg dose is 0.4–1 gm/kg body weight given over 2–5 days. After infusion, serum IVIg levels increase fivefold, then decline by 50% in 72 hours and return to pretreatment levels after 21–28 days. Severe reactions from IVIg are rare. The most serious reactions so far reported include anaphylactic reaction, hepatitis C outbreak, aseptic meningitis, acute renal failure, hemolysis, and cerebral infarction (Oh, 1996). Anaphylactic reaction following IVIg has been reported in patients with selective IgA deficiency due to IgG or IgE antibodies to IgA; IgA deficiency occurs in about 1 of every 200 to 800 persons. Thus, IgA deficiency is the only contraindication for the use of IVIg, and the IgA level should be checked when IVIg therapy is considered. If IVIg has to be given in an IgA-deficient patient, it should be infused with IVIg with low IgA levels (e.g., Gamimmune and Gammagard). An outbreak of hepatitis C was last reported with IVIg in early 1994. Death from acute renal failure in diabetic patients has been reported. Aseptic meningitis has become the most common troublesome side reaction to clinicians, seen in about 11% of patients. Most of other reactions are mild and self-limited and are associated with too rapid infusion of IVIg.

In a review of seven nonrandomized observational studies with 10 participants or more, Jongen et al. reported an overall rate of improvement of 76% (90/119), with a median of 87% (range, 48% to 92%) (Gajdos et al., 2008; Jongen, van Doorn, & van der Meché, 1998). There were two randomized studies on IVIg versus placebo (Wolfe et al., 2002; Zinman et al., 2007). In one randomized controlled trial comparing IVIg (1 g/kg for 2 days) with placebo (5% dextrose for 2 days) in patients with MG worsening, there was a significant improvement in QMG in favor of the IVIg group on day 14 (class I) (Zinman et al., 2007). The treatment effect was maintained for 28 days after infusion in this study. Importantly, this effect was not observed in mild MG but was significant in moderate to severe MG. In another study comparing IVIg for 2 days versus 5% albumin for 3 days, there was not any significant difference in QMG change between the two groups (Wolfe et al., 2002).

In a comparison of IVIg versus PE, four randomized controlled trials showed no difference in improvement between PE and IVIg (Barth et al., 2011; Gajdos et al., 1997; Liew et al., 2014; Rønager et al., 2001), suggesting that the efficacy of IVIg is as good as that of PE. Two randomized controlled trials compared the efficacy of two IVIg doses, 1 and 2 gm/kg, and found no difference in improvement between PE and IVIg and between the 1 and 2 gm/kg IVIg regimens.

IVIg was proposed as a maintenance therapy for MG. IVIg 2 gm/kg over 5 days was followed by 0.4 gm/kg once monthly or once every 6 weeks (Eienbröker et al., 2014; Hilkevich, Drory, Chapman, & Krezyn, 2001; Wegner & Ahmed, 2002). One study was conducted in 16 patients with severe GMG (Eienbröker et al., 2014), and another, in 11 patients with severe MG with bulbar palsy (Hilkevich et al., 2001). All patients were unresponsive to steroid and immunosuppresants.

All patients improved after a mean period of 20 months. One study compared PE and IVIg as maintenance therapies for 27 juvenile MG patients and concluded that there is class III evidence that PE and IVIg both have high response rates as maintenance therapy (Liew et al., 2014).

A Cochrane review concluded that IVIg is effective in severe MG exacerbation in one randomized controlled trial, but there is insufficient evidence from randomized trials to determine whether IVIg is efficacious in chronic MG (Gajdos et al., 2008).

On the basis of these findings, we recommend IVIg to be used in lieu of PE for acutely worsening MG (class I) and preparation of weak patients for surgery including thymectomy (class IV) and to be used as an adjuvant to immunosuppressive therapy to minimize the long-term side effects of oral immunosuppressants and maintain an improved status of MG (Alabdali, Barnett, Katzberg, Breiner, & Bril, 2014). In MuSK-MG, a retrospective multicenter study on 52 patients showed a poorer outcome with IVIg compared with PE (class IV) (Pasnoor et al., 2010).

Eculizumab. Complement has been known to play an important role in the pathogenesis of MG, leading to the hypothesis that complement inhibition may lead to clinical improvement in MG (Engel & Arahata, 1987). Eculizumab, a complement inhibitor, is a C5 monoclonal antibody that inhibits the formation of C5b-9 membrane attack complex. Eculizumab is the first approved drug for MG by the FDA for treatment for adult patients with AChR-positive GMG after successful trials in 14 patients with severe refractory GMG (class I in Table 19.5) (Howard et al., 2013). Six of seven (86%) patients treated with eculizumab for 16 weeks achieved the primary endpoint of a 3-point reduction in the QMG score ($P = 0.014$ compared with placebo). In a subsequent phase 3 study in 125 patients, 62 receiving eculizumab and 63 receiving placebo for 26 weeks, the change in the QMG score showed a benefit with eculizumab compared with placebo ($P = 0.02$) at week 26, but not in MG-ADL (activity of daily living) score. Most of the treatment effects occurred by week 12 and were sustained to week 26. The most common side reactions were headache and upper respiratory infection (Howard et al., 2017). Thus, this drug is recommended for patients with moderate/severe GMG who are refractory to adequate trials with existing immunotherapy. The drug is given via IV infusion with a recommended dosage regimen of 900 mg/week for the first 4 weeks, 1200 mg for the fifth week, and 1200 mg every 2 weeks thereafter. Meningococcal vaccinations should be given 2 weeks before starting the first therapy to prevent any possible meningococcal infection.

Zilucoplan. Zilucoplan is another complement inhibitor that binds to C5b with high affinity and specificity, thus preventing the cleavage of C5 into C5a and C5b comple-

Table 19.5 Evidence-Based Class and Recommendations of Various Immunotherapies

Drug	Evidence Class[a]	Recommendations
Anticholinesterase inhibitors (AChEIs)	Class IV	Symptomatic treatment.
Steroids	Class II	First-line immunotherapy. Mainly for short-term use. For long-term use if the dose can be reduced to a dose at which side reactions are negligible.
Azathioprine (AZA)	Class I	First-line long-term immunotherapy. Can be used to spare the steroid dose or for patients unresponsive to or intolerant of steroids.
Cyclosporin (CsA)	Class I	Second-line long-term immunotherapy. For patients intolerant of or unresponsive to steroids or AZA.
Cyclophosphamide (CPP)	Class II	Last-choice long-term immunotherapy. For patients unresponsive to or intolerant of steroids, AZA, CsA, or tacrolimus.
Mycophenolate mofetil	Class IV	Adjunct long-term immunotherapy. This can be used as an additional agent to any long-term immunosuppressant.
Tacrolimus	Class I	Third-line long-term immunotherapy. For patients unresponsive to or intolerant of steroid, AZA, or CsA.
Plasma exchange (PE)	Class III	Indicated for severe MG, acute exacerbation, and MG crisis. For patients unresponsive to or intolerant of IVIg.
IVIg	Class I	Indicated for severe MG and acute exacerbation and used as adjunct to immunotherapy to maintain an improved status. For patients unresponsive to or intolerant of PE.
Thymectomy	Class I	Any early-onset generalized MG patient who needs immunotherapy is candidate.
Eculizumab	Class I	Moderate/severe generalized MG patients who are refractory to adequate trials with existing immunotherapy.

[a]Evidence class I, randomized controlled trials available; class II, controlled trials without randomization or randomized trial with small patient number; class III, uncontrolled trials; class IV, case series.
IVIg, Intravenous immunoglobulin; *MG*, myasthenia gravis.

ment component and also blocking binding of C5b to C6 complement component. Unlike eculizumab, this agent is administered subcutaneously by the patient daily. A phase 2 randomized, double-blind, placebo-controlled multicenter trial was conducted in 44 AChR-Ab-positive Myasthenia Gravis Foundation of America (MGFA) II–IV GMG patients using three treatment groups (placebo, 0.3 mg/kg SC, and 0.1 mg/kg SC) over a 12-week period (Howard et al., 2020). All participants were vaccinated against *Neisseria meningitidis*. Clinically meaningful and statistically significant improvements ($P < 0.05$) in primary and key secondary efficacy end points were achieved in primary (QMG and MG-ADL scores) and secondary (MG Composite and MG Quality of Life Score) end points in the 0.3-mg/kg SC treated group compared with the placebo group. Outcomes for the 0.1-mg/kg SC daily dose were also statistically significant but were slower in onset and less pronounced than with the 0.3-mg/kg dose. The onset of action was rapid, with separation of the 0.3-mg/kg arm from the placebo arm beginning after 1 week. Twenty-eight percent of participants did not experience an improvement as per the minimal clinically important difference of 3 points on the QMG score. The drug was well tolerated, with mild adverse events and a low incidence of local injection site reaction. Zilucoplan may have an advantage over ecluzumab in view of the easy subcutaneous injection route. As of March 1, 2020, this drug has not been approved for MG by the FDA.

Rituximab. Rituximab is a chimeric mouse/human anti-CD20 monoclonal immunoglobulin. According to a 2017 review, 169 MG (59% AChR-Ab positive; 34% MuSK-Ab positive) patients were treated with rituximab (Tandan, Hehir, Waheed, & Howard, 2017). Rituximab treatment achieved minimal manifestation (LMm) or better status, according to the modified MGFA postintervention scale, in 44% of treated patients and combined pharmacologic and chronic stable status in 27%. MM or better status was achieved in 72% of MuSK MG and 30% of AChR MG patients ($P < 0.001$). Response predictors were MuSK MG, less severe disease, and younger age at treatment. A multicenter blinded review study showed that patients treated with rituximab met the end goal of an MG Status and Treatment Intensity score of 2 higher, which was statistically significant compared with the control group: 58% (14/24) of rituximab-treated patients versus 16% (5/21) of control patients (class IV) (Hehr et al., 2017). These two studies suggest that rituximab may be more effective in MuSK MG. However, this drug needs to be evaluated more extensively against the current immunosuppressants before it can be recommended. Common infusion-related side effects of rituximab are fever, chills, nausea, vomiting, flushing, and bronchospasm. Other, more serious side effects include neutropenia and increased risk of infection.

Thymectomy. In 1939, Blalock et al. reported the remission of GMG in a 21-year-old woman after removal of a cystic thymic tumor and subsequently performed thymectomy on MG patients without thymoma, found hyperplasia in the thymus glands, and reported improvement in at least half of their patients (Blalock, Mason, Morgan, & Riven, 1939). Since this report, thymectomy has been accepted widely as a standard form of treatment for MG on the basis of class II evidence (Gronseth & Barohn, 2000). In 2016, the first randomized trial comparing thymectomy with medical management in nonthymomatous patients was published (Wolfe et al., 2016). A total of 126 recently diagnosed patients, ages 18 through 65 years, with AChR antibody-positive GMG with duration of 3 to 5 years were randomized to receive either extended transsternal thymectomy plus prednisone versus medical management with prednisone. Over a 3-year follow-up period, the time-weighted average QMG score was lower in the patients who underwent thymectomy (6.15 vs. 8.99; $P < 0.001$), and alternate-day prednisone dose requirement was lower (32 vs. 54 mg; $P < 0.001$). In the thymectomy group, fewer patients required immunosuppression with AZA or were hospitalized for exacerbation ($P < 0.001$). The effects of thymectomy began to be observed as early as 3 to 4 months but became definite at 9–12 months and were maintained for the entire 3-year study. The results of this study provides class I evidence for thymectomy in all generalized AChR-positive patients to improve MG status and decrease the required dose of immunotherapy in GMG. A recent analysis on 50 patients (24 prednisone alone and 26 prednisone and thymectomy) showed that at 5 years, thymectomy plus prednisone continues to confer benefits in patients with generalized nonthymomatous GMG compared with prednisone alone (Wolfe et al. 2019). Current evidence does not support an indication for thymectomy in patients with MuSK, LRP4, and agrin antibodies (Clifford et al., 2019; Oh, 2009).

At this time, the indication for thymectomy in AChR-negative GMG patients is controversial. Two retrospective cohort studies showed comparable responses among AChR-positive and AChR-negative groups (Guillermo et al., 2004; Romi et al., 2003; Yuan, Huan, Kung, & Kao, 2007).

Age is another controversial subject in thymectomy (Evoli, 2010; Sanders et al., 2016). Thymectomy is often avoided in children because of the theoretical possibility of impairing the developing immune system. However, reports of thymectomy in children as young as 2 to 3 years of age have shown favorable results, without adverse effects on the immune system (Finnis & Jayawant, 2011). Thymectomy has been largely discouraged in late-onset MG (>65 years of age) mainly because of frequent observations of an atrophic, involuted thymus. One series showed a less favorable outcome of thymectomy in late-onset MG: postthymectomy improvement was transitory and no longer detectable at 2 years after thymectomy (class IV) (Romi et al., 2003). The age at MG onset is a more important factor than the age at thymectomy(Romi et al., 2003). Considering the benefit of thymectomy up to 65 years of age in the randomized study, it is reasonable to extend thymectomy age to 65 years (Wolfe et al., 2016).

A randomized thymectomy trial mandated an extended transdermal thymectomy (Wolfe et al., 2016). Less invasive procedures are now available for thymectomy: transcervical, video-assisted thoracoscopic surgery (VATET), and robotic video-assisted thoracoscopic surgery. VATET offers shorter hospital duration and stay and limited morbidity.

In comparing the various surgical approaches, Sonett and Jaretzki (2008) employed Kaplan-Meier life table analysis at 5 years and concluded that the combined transcervical-transsternal, extended transsternal, extended cervical, and VATET procedures appear to produce more or less the same percentage (40%–55%) of remission at

5 years. It appears that the more thorough the removal of all tissue that may contain thymus, the better the longer-term results. Therefore, conceptually, the combined transcervical-transsternal thymectomy best fulfills these criteria.

Sonett and Jaretzki also stated that it is far preferable to leave behind small amounts of suspected thymus, or even likely thymus, than injuring the recurrent laryngeal, the left vagus, or the phrenic nerve. Injuries to these nerves can be devastating to a patient with MG (Thomas et al., 1997).

On the basis of this information, we believe that thymectomy is indicated in any early-onset (<65 years of age) GMG patients whose symptoms are not satisfactorily controlled with AChEIs alone and initial immunotherapy (class I recommendation for AChR-Ab-positive patients and level B recommendation for AChR-Ab-negative patients. We take this view on the basis of the findings that AChR antibodies were found in 66% of seronegative sera by a clustered AChR cell–based assay) (Leite et al., 2008; Farmakidid, Pasnoor, Dimachkie, & Barohn (2018), on the other hand, listed thymectomy as the first-line treatment of MG in their recommendation. Thymectomy induces long-term improvement and remission. About 33% of patients will achieve remission in the first 3 years after thymectomy, and 50% within 5 years (Gronseth & Barohn, 2000). Thymectomy produces a stable remission by eliminating thymic centers. The effects are delayed because of the long life-span of the existing pool of small immunocompetent lymphocytes.

MYASTHENIC CRISIS

Myasthenic crisis (MC) is a life-threatening complication of MG. Traditionally, it is defined as respiratory failure due to worsening MG requiring intubation and mechanical ventilation (MGFA class V). Here, we define MC as respiratory failure due to worsening MG requiring mechanical ventilation to accommodate noninvasive mechanical ventilation, which was introduced as a treatment mode for serious respiratory failure in MG (Thomas et al., 1997). About 15% to 20% of patients with MG experience an MC at some point in the duration of this disease, but MC can be the first manifestation of MG in 14%–69% of MG (Oh, Jeong, Lee, & Alsharabati, 2019). Thymoma was observed in 32% of cases of MC and may be a risk factor (Thomas et al., 1997). Patients with MuSK-MG have a higher risk of MC because of predominant bulbar weakness (Wolfe et al., 2007).

MC is caused by severe weakness of respiratory muscles, upper airway muscle (bulbar myasthenia), or both. It occurs in AChR-positive, MuSK-positive, and double seronegative MG. Infections are known to be the most common precipitating factor for MC, accounting for 38% of cases in one series. Other rare, recognized precipitating factors for crisis are surgery, pregnancy, and medications (Box 19.1). Excessive dosing of AChEIs can potentially increase weakness due to depolarization blockade at neuromuscular junction. Previously, it was customary to differentiate between cholinergic crisis and MC by edrophonium test in MC patients with a known diagnosis of MG taking high doses of AChEIs.

Box 19.1 Drugs/Factors Associated with Unmasking or Aggravating Myasthenia Gravis (MG)[a]

Definite Association

Drugs/factors that are known to induce autoimmune MG and thus are contraindicated in patients with MG
- Alpha interferon
- Bone marrow transplantation
- D-Penicillamine

Drugs/factors that are known definitely to unmask or aggravate MG and thus should be avoided in patients with MG
- Botulinum toxin, type A (Botox)
- Antibiotics—ketolide (telithromycin [Ketek])
- Depolarizing and nondepolarizing neuromuscular blocking agents
- Iatrogenic hypermagnesemia including that due to magnesium sulfate

Probable Association

Drugs/factors that are known to unmask or aggravate MG in more than two cases and thus are not recommended for use in patients with MG; if used, then close monitoring is required
- Antibiotics
  - Aminoglycosides: gentamicin, kanamycin, netilmicin, neomycin, streptomycin
  - Fluoroquinolones: ciprofloxacin, ofloxacin
  - Other antibiotics: bacitracin, colistin, polymyxin
- Cardiovascular drugs
  - Beta blockers: propranolol
  - Verapamil
  - Procainamide
  - Statins
- Quinolones: chloroquine, fluoroquinolone antibiotics, quinidine, quinine
- Iodinated contrast media
- Ophthalmologic medication: timolol maleate eye drops
- Psychotropic medication: lithium carbonate

Possible Association

Drugs/factors that are known to unmask or exacerbate MG in one or two cases and thus can be used safely in most patients with MG, with close monitoring recommended
- Antibiotics: amino acid antibiotics, ampicillin, azithromycin, clarithromycin, clindamycin, erythromycin, imipenem and cilastatin sodium, macrolides, nitrofurantoin, pyrantel pamoate, ritonavir, sulfonamides, tetracyclines, vancomycin
- Beta blockers: accubutol, oxprenolol, practolol
- Other cardiac drugs: bretylium, propafenone HCl, trimethaphan
- Anticonvulsant medications: carbamazepine, ethosuximide, gabapentin, trimethadione
- Ophthalmologic medications: betaxolol hydrochloride, echothiophate, proparacaine, tropicamide
- Psychotropic medication: phenothiazide
- Other medicines neurologists often prescribe: riluzole, glatiramer acetate, methocarbamol, trihexyphenidyl (Artane)
- Miscellaneous drugs/agents: fludarabine, cisplatin, interleukin, carnitine, nicotine patch, diatrizoate meglumine, chlorine gas

[a] For further information, consult www.myasthenia.org/docs/MGFA_Medications

Cholinergic crisis is rare in today's practice because high doses of AChEI are not used anymore (Oh et al., 2019).

Diagnosis of MC in patients with an established diagnosis of MG is relatively easy. In those MG patients with MC as the first manifestation, the diagnosis of MG is based on the clinical findings and should be confirmed by edrophonium test, RNS test, or, rarely, SFEMG. The RNS test can provide a rapid objective diagnostic confirmation of MG in 92% of cases and identify cholinergic crisis pattern (Oh et al., 2019).

CLINICAL SIGNS OF MYASTHENIC CRISIS

Prompt recognition of impending respiratory paralysis is the key to successful management of MC. Features of impending MC include severe bulbar weakness, marginal vital capacity (20 to 25 mL/kg), weak cough with difficulty clearing secretions from the airway, or paradoxical breathing, while supine. These patients should be admitted to the ICU and monitored closely. These patients should also receive no food or liquid by mouth to prevent aspiration. Careful observation and bedside measurements (pulse rate, blood pressure, oxymetry, vital capacity, tidal volume, and peak inspiratory and expiratory pressure) are more important than repeated monitoring of blood gases. The 20/30/40 rule (vital capacity <20 mL/kg [or 1 L]; peak inspiratory pressure >-30 cm H_2O; and peak expiratory pressure <40 cm H_2O) is probably the most helpful guide to decide when intubation is necessary. In MC, the clinician should anticipate the need for respiratory assistance rather than deal with emergency intubation ("when in doubt, intubate").

Noninvasive mechanical ventilation with bilevel positive pressure ventilation (BIPAP) has been used as an alternative to intubation and mechanical ventilation in MG, but experience is still relatively limited. One retrospective study showed that in 14 (58%) of 24 cases initially treated with BIPAP, endotracheal intubation was avoided and patients treated with BIPAP had shorter stays in the ICU and the hospital than those treated initially with intubation. The only predictor of BIPAP failure was a pCO_2 level exceeding 45 mm Hg on BIPAP initiation. This study suggests the possibility that some patients with MC or impending crisis might be managed with BIPAP (Seneviratne, Mandrekar, Wijdicks, & Rabinstein, 2008).

TREATMENT OF MYASTHENIA GRAVIS DURING MYASTHENIC CRISIS (BOX 19.2)

To date, treatment of MG during MC is based on clinical consensus, not on evidence-based data. There is a general agreement among experts that high-dose steroids in combination with PE or immunoglobulin are the cornerstone of MG treatment during MC.

There have been few treatment trials in MC, and both PE and IVIg are comparable in terms of efficacy on the basis of clinical evidence. Since response to PE is more predictable and a good clinical response to PE in some myasthenic patients refractory to IVIg was reported (Stricker, Kwiatkowska, Habis, & Kiprov, 1993), many experts take the view that PE is probably more effective than IVIg in MC, and thus PE has become the most commonly used immunotherapy for MC (Chaudhuri & Behan, 2009; Jani-Acsadi & Lisak, 2007). In one retrospective multicenter review of 54 episodes of MC, PE had a superior outcome for ventilatory status at 2 weeks and functional outcome at 1 month, despite higher complication rate with PE (Qureshi et al., 1999).

IVIg represents an alternative short-term immunomodulating therapy for MC in patients who are poor candidates for PE due to various medical reasons, including vascular access problems, septicemia, and cardiac failure. The wider availability and ease of administration of IVIg make it an automatic choice as the first-line therapy for MC in patients who have difficulty accessing a medical center that can perform PE.

Steroids are the drug of choice as the immunotherapeutic agent for maintaining an improved status by PE or IVIg. This is because an initial stable improvement is achieved within weeks (average, 13–39 days) of steroid treatment in contrast to within months with other immunosuppressants (Bromberg & Carter, 2004). Most experts recommend high-dose (1 gm/kg) prednisone daily as the initial regimen.

IV pyridostigmine infusions at 1 to 2 mg/hour have been advocated by Berroushot, Barumann, Kalishewski, Sterker, and Schenrider (1997) in patients during crisis. In 63 episodes with MC treatment in an acute care setting with pyridostigmine (n = 24), pyridostigmine and prednisolone (n = 18), and PE alone (n = 23), they did not find any signficant differences in short-term efficacy; there were comparable long-term outcomes and side effect profiles among the different regimens. On the basis of these results, they advocated an approach tailored to the individual patient considering the precrisis condition of the patient and the precipitating factors of MC. However, because of possible cardiac complications, sometimes fatal, cholinergic crisis, and excessive secretions, most experts recommend stopping pyridostigmine during crisis (drug holiday) and reinstituting it orally when patients

Box 19.2 Principles of Management of Myasthenic Crisis

1. Provide airway assistance and ventilation: This step is most critical; *always* intubate when in doubt.
2. Discontinue AChEIs initially.
3. Remove and treat precipitating factors.
4. Routine monitoring
   - Cardiac monitoring
   - Oximetry
   - Pulmonary function monitoring: forced vital capacity, peak inspiratory pressure, and expiratory pressure, every 2–4 hours
5. General medical care
   - Institute prophylaxis for deep vein thrombosis with low-molecular-weight heparin.
   - Identify and treat infection.
   - Identify and treat cardiac arrhythmia and congestive heart failure.
6. Initiate specific treatment for MG.
   - Plasma exchange (removal of 2 to 3 L of plasma volume on each session × 5)
   - Alternatively, IVIg (0.4 mg/kg/day × 5)
   - High-dose steroid (prednisone 1 mg/kg/day)
   - Start a low-dose AChEI when the patient gets stronger and benefit is found with trial

AChEI, Acetylcholinesterase inhibitor; *IVIg*, intravenous immunoglobulin; *MG*, myasthenia gravis.

are getting stronger and the benefit is found with a trial (Bedlack & Sanders, 2000). This is usually around the extubation time. Some believed that a drug holiday heightens patient sensitivity to AChEIs (Bedlack & Sanders, 2000). The usual recommendation is to start at a low dose (60 mg every 8 hours enterally) and gradually increase to a dose that produces a clear benefit.

Immunosuppressants are usually not recommended because the improvement from treatment with these agents is generally not seen for several months. They may be used in place of prednisone, however, when steroid therapy is contraindicated, but not for MC. There is no indication of thymectomy during MC.

RESPIRATORY MANAGEMENT AND TREATMENT DURING MYASTHENIC CRISIS

This will be discussed in detail in another chapter. When intubation is performed, nasotracheal intubation is preferred as nasotracheal tubes are more comfortable than orotracheal tubes. Tracheostomy should be considered for patients requiring more than 2 weeks of mechanical ventilation.

Weaning trials should begin after patients demonstrate a clear trend of improved respiratory muscle strength. The general guideline is the 10/20/40 rule: vital capacity >10 mL/kg, maximum negative inspiratory force <-20 cm H_2O, and peak positive expiratory force >40 cm H_2O.

The three most common complications are fever (69%), pneumonia (51%), and atelectasis. Aggressive treatment for pneumonia and atelectasis is mandatory.

Mortality in MC has declined from over 40% in the early 1960s to approximately 5% in the 1970s (Thomas et al., 1997), due in large part to the improvement in respiratory care and ICU management. Current statistics still report a 4% mortality rate despite newer treatments and better intensive medical care, indicating no documented improvement in fatality rates over the last several decades (Jani-Acsadi & Lisak, 2007). All deaths were ascribed to severe medical comorbidity (Thomas et al., 1997). The most common causes of death in MC are cardiac arrhythmia or infections.

TREATMENT IN THE SPECIFIC SUBTYPES OF MYASTHENIA GRAVIS

OCULAR MYASTHENIA GRAVIS

Pyridostigmine is usually effective for ptosis, but not for double vision, a more troublesome symptom. Steroids are effective in OMG as well as in GMG. AZA was also used as the second line immunosuppressive medication. Oral steroid produces improvement in 66%–85% of OMG patients (Antonio-Santos & Eggenberger, 2008). However, permanent remission is associated with steroids in only 10% of patients.

A major question in the treatment of OMG is whether steroids or immunosuppressant drugs may prevent the development of GMG (Benatar et al., 2016; Kerty, Elsais, Argov, Evoli, & Gilhus, 2014). In 49%–69% of patients, OMG progressed to GMG. This occurs in 2 years in 50%–88% of cases. In AChR-Ab-positive OMG, this conversion occurs in 45%–71% of cases.

Retrospective studies have suggested reduced rates of generalization with steroids in four studies and AZA in one study (Kerty et al., 2014). Only 7%–17% of OMG patients treated with prednisone developed GMG compared with 36%–83% of those not treated with immunosuppressants. In OMG patients who received AZA treatment, GMG developed in 16% of patients in 2 years and 23% in 4 years. There are no randomized controlled trials to support this finding (Antonio-Santos & Eggenberger, 2008).

Thymectomy is not generally indicated in OMG because of its benign course (Kerty et al., 2014). Two case series claimed its benefits (class IV): no generalization in 18 patients in 26 months and "cure" in 51% in 61 patients with a mean follow-up of 9 years (Luchanok & Kaminski, 2008).

MUSCLE-SPECIFIC KINASE–MYASTHENIA GRAVIS

MuSK is a surface receptor that plays an essential role in the clustering of AChR during development. MuSK-Ab-positive MG (MuSK-MG) was first reported in 2001. MuSK-Ab is negative in OMG. MuSK-Ab is reported to be positive in 0% in Norway to 49% in Turkey, with a mean frequency of approximately 35% of generalized seronegative MG (Oh, 2009). MuSK-MG is predominantly observed in females, and the onset is younger. Patients tending to have a more severe form of MG and crisis are more common in MuSK-MG. Prominent cranial and bulbar weakness is the most consistent pattern. Profound facial and tongue atrophy has been observed in some of these cases. Predominant neck, shoulder, and respiratory involvement, but without ocular weakness, is another rare manifestation. MuSK-MG patients tend to have a more severe form of MG and crisis is common.

A positive edrophonium test is less common in MuSK-MG than other forms of MG, being positive in half of the cases. The RNS test of limb muscle had a relatively low yield (25%–57%) in MuSK–MG, but the RNS test of facial muscles showed a decrement in 85% of cases (Oh, 2009). Percentage decrements in the RNS test in the facial muscle are of greater magnitude than in the other two forms. Thus, including facial muscles in the RNS protocol is important when evaluating patients with suspected MuSK-MG. In SFEMG, many series reported a relatively low yield of abnormality in the limb muscles, but when the proximal and cranial muscles are added for the study, it is abnormal in the majority of MuSK-MG patients.

The clinical response to anticholesterase agents in MuSK-MG has generally been disappointing (Oh, 2009). With standard pyridostigmine doses, unresponsiveness, actual worsening, and intolerance manifested by severe muscarinic and nicotinic side effects are common. Most patients need one or a combination of immunotherapies. Among the various immunotherapies, steroid and PE seem to result in the best response (Pasnoor, Wpfe, Nation et al., 2010). However, a general impression is that MuSK-MG is refractory to the standard treatment because finding the right combination of immunotherapy is time-consuming and difficult.

3,4-DAP was used in a few MuSK-MG patients, with some success. One adult patient showed an improvement of 3 in the QMG score with 3,4-DAP 40 mg/day (Evoli, Alboini, Damato, & Iorio, 2016). In one randomized study in seven patients, the end-points were met but the other randomized study did not meet the end-points, but a definite study is needed to prove this (Oh, 2019).

MYASTHENIA GRAVIS WITH LIPOPROTEIN RECEPTOR–RELATED PROTEIN 4 AND AGRIN ANTIBODY

LRP4 and agrin antibodies were two recent additions to AChR and MuSK antibodies for MG. LRP4 and agrin antibody–positive MG is rarer than MuSK-MG. Almost all patients with LRP4 or agrin antibodies had GMG, but few had thymoma (Yan et al., 2018; Zisimopoulou et al., 2014). In terms of treatment, no specific difference is advised from AChR-negative GMG. Overall, the response of LRP4-MG patients to treatment was similar to published responses of AChR-negative MG rather than to MuSK-MG patients.

PREGNANCY

The course of MG during pregnancy is unpredictable; approximately one third of patients remain the same, one third improves, and the remaining one third worsens (Gajdos et al., 1997). Worsening of MG symptoms is more likely in the first trimester and the puerperal periods and is possibly related with level of alfa-fetoprotein, which is known to block the binding of AChR antibody to AChR. The clinical state of MG at the beginning of pregnancy or in one pregnancy does not predict the occurrence of exacerbations or remission during gestation. MG does not provide any adverse effect on the course of pregnancy. The coexistence of MG and preeclampsia, although rare, may produce a high degree of morbidity and mortality in both the mother and the fetus. Magnesium sulfate, the drug of choice in the treatment of preeclampsia, is contraindicated in MG because hypermagnesemia inhibits the release of ACh at the neuromusuclar junction and worsens MG muscle weakness, causing a severe MC.

Management of Myasthenia Gravis During Pregnancy

Patients should be evaluated more frequently for possible worsening of MG throughout pregnancy. Screening for asymptomatic bacteriuria should be regularly performed and appropriate treatment of urinary tract infections is required because infection is a known cause of MG worsening and crisis. Pregnant women with MG should carefully monitor fetal movements and seek medical advice as soon as they find these reduced. If indicated, fetal ultrasound evaluations should be done to detect any sign of the fetal akinesia sequence.

Oral AChEIs are the drug of choice for the symptomatic treatment of MG and can be used alone in mild cases of MG. Pyridostigmine is considered to be safe during pregnancy when used at the recommended dosage of less than 1000 mg (14 tablets) a day.

Steroids are the drug of choice for immunotherapy because they present little, if any, teratogenic risk to the fetus, and only a slight increase in the incidence of cleft palate has been reported (Sanders et al., 2016). Another advantage of steroids is that they work much faster than many immunosuppresants in achieving the stable course of MG. All other immunosuppressants should be avoided before and during pregnancy whenever possible because of potential teratogenic effects.

PE or IVIg can be and has been used as an effective treatment for severe worsening of MG or crisis during pregnancy without any major complication. Thymectomy during pregnancy has no role because of its delayed effect and possible surgical risk.

Management of Myasthenia Gravis During Labor and Delivery

Most labors can safely be completed vaginally (Ferrero et al., 2008). Epidural anesthesia is preferred for vaginal and surgical delivery because many myasthenic patients are sensitive to many anesthetic agents (Ciafaloni & Massey, 2004). Local anesthetics can be used, but high doses should be avoided because they may interfere with NMT. Lidocaine is the recommended local anesthetic because it is an aminoacyl amide and is not affected by AChEIs. Women taking steroids during pregnancy should continue the treatment during labor and stress doses should be given (an extra dose of 50–100 mg of prednisone IM at the first stage of labor or Solu-medrol 200 mg IV drip during labor).

During the second stage of labor, which involves the voluntary expulsive effort, the patient may become exhausted and may require immediate AChEIs. Neostigmine (1.5–2.0 mg IM or 0.5 mg IV every 3–4 hours) is preferred to pyridostigmine. Contrary to expert recommendation, many MG women prefer C-section for delivery of the baby because of an overall increased rate of delivery complications and a higher rate of intervention during delivery (Hoff, Daltveit, & Gilhus, 2003),

Neonatal Myasthenia Gravis

Neonatal MG (NMG) is a syndrome that occurs in 10%–20% of newborns of myasthenic mothers shortly after birth. NMG is reported in all types of MG. Symptoms develop most commonly 12 to 48 hours after birth and include generalized weakness, hypotonia, difficulty feeding, feeble cry, ptosis, facial paresis, and respiratory distress. NMG usually resolves within 3 weeks but occasionally persists for as long as 4 months. This spontaneous improvement is most likely due to the gradual degradation of the maternally derived IgG in a newborn baby. NMG symptoms usually respond to anticholinesterase medications, and ventilatory support should be used as necessary until the weakness resolves.

Arthrogryposis Multiplex Congenita

Maternal MG is a rare cause of arthrogryposis multiplex congenita, which consists of nonprogressive multiple congenital joint contractures developing in utero from the lack of fetal movements caused by maternal AChR antibodies to fetal AChR.

Breastfeeding

The American Academy of Pediatrics classifies pyridostigmine and steroids as compatible with breastfeeding and methotrexate as contraindicated during breastfeeding (American Academy of Pediatrics Committee on Drugs, 1994). Although there are no firm data for the safety of other immunosuppresants, in general, breastfeeding is not recommended for other immunosuppresants.

THYMOMA

Thymoma is an epithelial neoplasm of the thymus and represents the most common primary neoplasm of the anterior superior mediastinum. The majority of thymomas are completely encapsulated, but in one third of cases there may be invasion of the tumor capsule and/or the surrounding structure (invasive thymoma or malignant thymoma).

MG is common in thymoma (T-MG), occurring in approximately 44% of thymoma patients. Conversely, 10%–15% of MG patients have thymoma. Thymoma occurs in MG at any age. However, it is much more common among middle-aged and older patients. MG tends to be more severe in patients with thymoma than those with early-onset MG. The MG subgroup has a poorer prognosis than the group with MG without thymoma, requiring long-term immunotherapy with prednisone, AZA, or other immunosuppressive drugs.

When the diagnosis of T-MG is established, thymoma should be removed surgically, ensuring radical excision. The removal of thymoma does cure the thymic neoplasia in most cases, but MG symptoms usually continue after thymectomy.

The pharmacological treatment of T-MG is not different from that for nonparaneoplastic MG, except for tacrolimus that should be considered in difficult cases. Tacrolimus, an immunosuppressant and enhancer of ryanodine receptor (RyR)–related sarcoplasmic calcium release, is beneficial in MG patients with RyR antibodies that in theory might block the RyR. It seems to have a purely symptomatic effect in addition to its immunosuppressive effects. Since most patients with T-MG have RyR antibodies, tacrolimus may be of more value specifically in T-MG patients.

The first antibodies described in MG in 1960 were the striational muscle (SM) antibodies, and the main antigens were later identified as titin and RyR. SM antibodies were present in 24% of patients with thymoma alone, in 38% of patients with MG without tumor, and in 80%–90% of T-MG patients (Rivner & Swift, 1990). There is a correlation between the titer of SM antibody and the likelihood of a thymoma. The appearance of thymic enlargement on computed tomography (CT) scan and a high titer of antistriational antibody make the diagnosis of thymoma virtually certain. More specific SM antibody tests against titin and RyR have become available in recent years. Titin and RyR antibodies have been found in 95% and 70% of thymoma MG patients, respectively (Skeie & Romi, 2008), and 58% and 6% of late-onset MG patients have titin and RyR antibodies, respectively. Titin and RyR antibody tests and CT scan of the mediastinum share similar sensitivities for thymoma in MG. Skeie and Romi (2008) claimed that the presence of titin and RyR antibodies in an MG patient younger than 60 years strongly suggests a thymoma, while the absence of such antibodies at any age strongly excludes thymoma.

The treatment of thymomas is determined after the lesion has been staged (class III). In general, complete surgical resection of tumor is the preferred treatment. This is the treatment of choice in stage I tumor (noninvasive thymoma), given the very low recurrence rate. In invasive thymoma (stages II, III, and IV), adjuvant radiation therapy is recommended because of the recurrence of tumor.

RADIATION THERAPY

Mediastinal irradiation at a dose ranging from 45 to 55 Gy was performed postoperatively in patients with invasive thymoma. This therapy has been used for a long period, and most experts agree that adjuvant radiotherapy (presurgical, postsurgical, or both) may improve the prognosis of these patients.

Chemotherapy was carried out according to standard cisplatin-based protocols consisting of doxorubicin (50 mg/m^2 IV day 1)/cyclophosphamide (500 mg/m^2 IV day 1)/cisplatin (50 mg/m^2 IV day 1) or etoposide (100 mg/m^2 IV day 1–3)/cisplatin (80 mg/m^2 IV day 1); cycles were repeated every 3 weeks. At this time, controversy remains on whether this chemotherapy regimen is superior alone or in combination with radiation therapy.

Tumor surveillance should be performed with CT scan every 1 to 2 years, as well as periodic tests of serologic marker for thymoma, antibody to striated muscle.

PREOPERATIVE THERAPY FOR THYMOMA SURGERY

Unless there is a compelling medical indication, there is no reason to rush to the surgery. My recommendation is to stabilize MG status first with aggressive therapy, including steroids, PE, and IVIg, and then subject patients to surgery.

DRUGS AND AGENTS UNMASKING OR AGGRAVATING MYASTHENIA GRAVIS

There are many drugs and agents known to unmask MG or aggravate MG symptoms. Except for penicillamine, there are no drugs that are absolutely contraindicated in patients with MG or LEMS. Drugs and agents are listed in Box 19.1 as definite, probable, and possible in the order of probability of cause (Howard, 1990; Wittbrodt, 1997).

In view of the widespread use of statins for the control of cholesterol and cardiovascular diseases in recent years, special notice is made here that statins may induce, unmask, or aggravate MG. The Oh study showed that in 11% of MG patients on statin. MG worsening occurred without regard to type of MG or brand of statin (Oh et al., 2008). According to the World Health Organization (WHO) VigiBase pharmacovigilance database, among a total of 3967 reports that mentioned MG, 169 (4%) were suspected to be statin induced (Gras-Champel, Batteux, Masmoudi, & Liabeuf, 2019). There is one case report of red yeast rice dietary supplement (predominantly lovastatin) worsening MG (Dobremez et al., 2018).

GENERAL GUIDELINE OF THERAPEUTIC MANAGEMENT OF MYASTHENIA GRAVIS

There are many regimens for therapeutic management of MG. Treatment regimens vary among physicians from different parts of the world and even among different centers from the same country. Steroids are popular in the United States, while AZA is preferred in Europe and tacrolimus is preferred in Japan (Table 19.5).

The guidelines presented here are the University of Alabama at Birmingham (UAB) protocol based on the general consensus, best knowledge, and UAB experiences and should be used as general rather than as strict guidelines (Fig. 19.3).

Once the diagnosis of MG is established, AChEIs are used for the symptomatic treatment in all MG patients, and thymoma, when found, should be removed by thymectomy. CT scan of the mediastinum without contrast is the image of choice for thymoma. When MG symptoms are not well controlled with AChEIs alone with the maximal daily recommended dose (<1 gm/day), steroids are chosen as the first-line immunosuppressive therapy, mainly for short-term immunotherapy. However, steroids may be used as long-term therapy if pharmacological remission can be achieved with minimal dose (less than 10 mg of prednisone a day) without undue

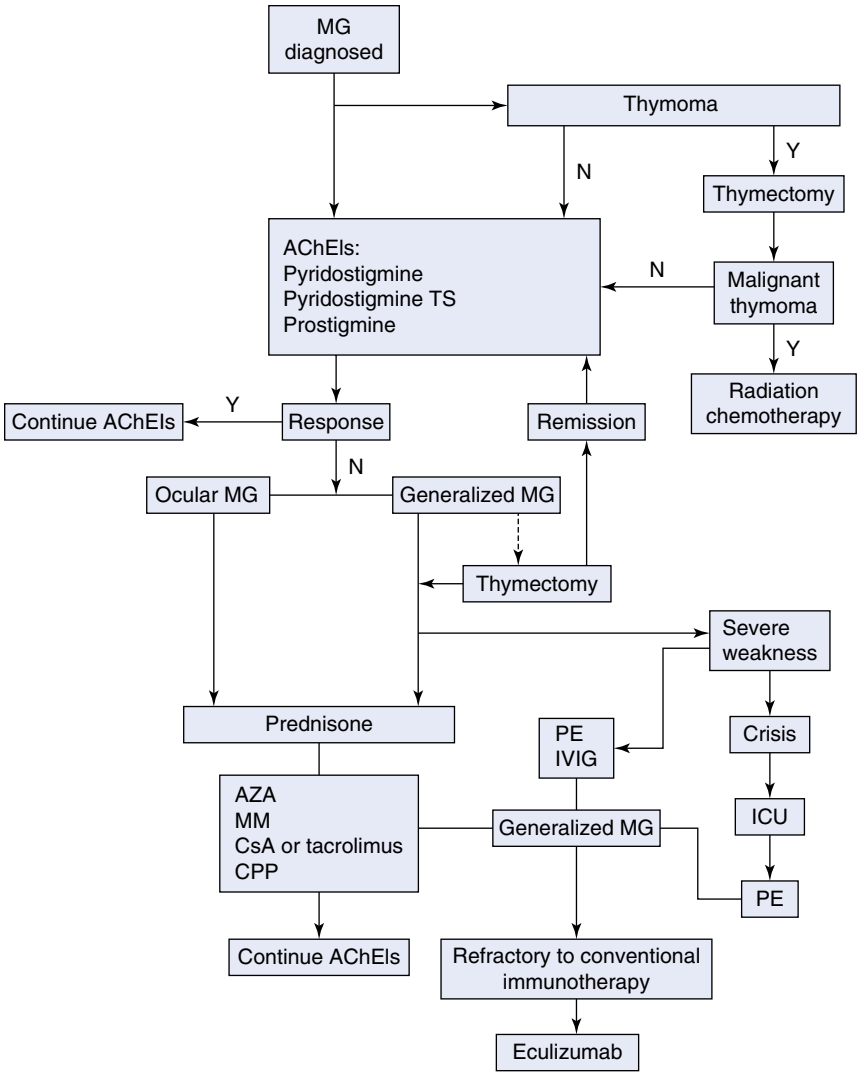


Fig. 19.3 Treatment algorithm in myasthenia gravis (MG). *AChEIs*, Acetylcholineesterase inhibitors; *AZA*, azathioprine; *CPP*, cyclophosphamide; *CsA*, cyclosporine A; *ICU*, intensive care unit; *IVIg*, intravenous immunoglobulin; *MM*, mycophenolate mofetil; *N*, no; *PE*, plasma exchange; *TS*, time span; *Y*, yes.

side reaction. If MG symptoms are not well controlled with AChEIs and steroids within a reasonable time (6 months), AZA is chosen as the second-line immunosuppressive therapy, mainly for long-term therapy or to spare the dose of steroids. CsA and tacrolimus are the third-line immunotherapy. The choice between CsA and tacrolimus depends on one's experience. CPP is the last-line immunosuppressive therapy because of serious potential side reactions, not based on the best evidence. We prefer MM as an adjunct agent to any long-term immunosuppressant because of its minimal side reaction profile, not based on the best evidence.

We believe that thymectomy is indicated in any early-onset MG (<65 years of age) patients in whom GMG is not satisfactorily controlled with AChEIs and initial immunotherapy (class I recommendation for AChR-Ab-positive MG). This is done with the understanding that thymectomy induces long-term improvement and remission. Thymectomy should be done when MG is stable.

PE is the treatment of choice for MG crisis. PE and IVIg are recommended for rapidly worsening MG patients for short-term improvement (class III for PE and class I for IVIg). Intermittent IVIg can also be used as the adjuvant to long-term immunosuppressive therapy (class IV), a definite advantage of IVIg over the PE.

Ecluzumab is indicated in moderate/severe AChR-Ab-positive GMG patients who are refractory to adequate trials with existing immunotherapy.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is an autoimmune disease clinically characterized by easy fatigability, proximal leg weakness, paucity of oculobulbar symptoms, and hyporeflexia. The main defect in this disorder is the insufficient release of ACh at the presynaptic membrane induced by the antibodies against voltage-gated calcium channels (VGCCs). A recent study showed that this antibody was found in 52% of LEMS patients for the N type and in 90% of LEMS patients for the P/Q type (Lennon & Lambert, 1989).

The clinical, electrophysiological, and pharmacological differences between MG and LEMS are given in Table 19.6 (Oh, Kurokawa, Claussen, & Ryan, 2005). The clinical diagnosis of LEMS is almost always elusive. According to our experience, LEMS can mimic MG, myopathy, motor neuropathy, conversion reaction, or lumbar radiculopathy. Clinical suspicion is the key for the diagnosis of LEMS. The most

Table 19.6 Differences Between Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome

	Myasthenia Gravis	Lambert-Eaton Myasthenic Syndrome
Basic defect	Postsynaptic	Presynaptic
Sex	F:M = 2:1	F:M = 2:3
Age	Peaks at 20s and 60s–70s	Peak at old age
Presenting symptoms and signs	Weakness of ocular, bulbar, and facial muscles	Weakness of proximal leg muscles
Exertion	Exertional weakness	Transient improvement after a brief exercise followed by weakness
Reflexes	Normal	Reduced or absent
Tumor	Thymoma in 16% of cases	Small cell carcinoma of the lung in 50% of cases
Edrophonium test	(+) in 90%	(+) in 37%
RNS test		
CMAP at rest	Normal	Low
After 10-second exercise	No change	Marked increase
Low-rate stimulation	Decremental response	Decremental response
High-rate stimulation	Normal or decrement	Incremental response
Antibodies	AChR-Ab (+) in 85%	VGCC-Ab (+) in 90%
Symptomatic drugs	AChEIs	Amifampridine
Immunotherapies	Steroids, immunosuppressants, plasmapheresis, IVIg, and ecluzumab	Steroid, immunosuppressants, plasmapheresis, and IVIg
Thymectomy	Effective	Not indicated

AChR, Acetylcholine receptor; *CMAP*, compound muscle action potential; *IVIg*, intravenous immunoglobulin; *RNS*, repetitive nerve stimulation; *VGCC*, voltage-gated calcium channel.

common symptoms are easy fatigability and proximal leg weakness. The classic clinical triad of LEMS includes proximal leg weakness, hyporeflexia or areflexia, and cholinergic dysautonomia (dry mouth, impotence, and orthostatic hypotension). A transient improvement in muscle strength and muscle stretch reflexes immediately after brief exercise is classically observed in LEMS. These findings, if observed, are pathognomonic of LEMS. This facilitation is most easily detected in moderately affected muscles, often the deltoid or iliopsoas muscles. This is the clinical counterpart of PEF on the RNS test. Unfortunately, these are not common observations, being noted in one of three cases, according to our experience (Odabasi et al., 2002; Oh 2017). Thus, when LEMS is suspected, these simple bedside tests are extremely helpful for confirmation of the disease. In this connection, in LEMS patients, it is important to assess muscle strength on the first effort made by the patient after rest, before facilitation has increased the force of the contraction. With brief exercise and tetanic nerve stimulation, more calcium is available at the presynaptic membrane, which increases ACh release, subsequently improving NMT. This is an explanation for the postexercise improvement of muscle strength or reflexes.

LEMS is a pivotal example of a paraneoplastic neurological syndrome. From the first description of LEMS, its association with small cell lung cancer (SCLC) has been well known. As noted previously, an earlier study showed that 75% of LEMS patients had SCLC, whereas a more recent study showed this association in only 50% of cases, suggesting a trend toward a lower tumor frequency in recent years (Lambert, Rooke, Eaton, & Hodgson, 1961; Titulaer et al., 2008). Certainly, having a history of smoking is a risk factor for LEMS because it is a risk factor for SCLC. It is estimated that LEMS occurs in about 3% of patients with SCLC. Although other tumors have been reported to be associated with LEMS, most cancer-associated LEMS is due to SCLC. A recent study suggested that lymphoproliferative disorders may constitute another risk group for LEMS.

LEMS is a disease of the elderly, with the most common age of onset of symptoms being about 60 years of age. Paraneoplastic LEMS typically develops in middle-aged to elderly individuals and was originally seen more commonly in men. However, more recent studies have shown less male predominance. Our latest series showed a 1:1 ratio. Paraneoplastic LEMS was clearly more common in males, whereas autoimmune (nonparaneoplastic) LEMS was more frequent in females. In subjects younger than 30 years, the chance of cancer association is small. Usually, the discovery of LEMS precedes that of cancer by several months to years. In all cases, cancer develops within 2 years following the diagnosis of LEMS (Titulaer et al., 2008). Thus, it is important to do a workup for occult cancer, especially SCLC, at the time of diagnosis of LEMS and serially thereafter, as noted. There are no clinical and electrophysiological differences that

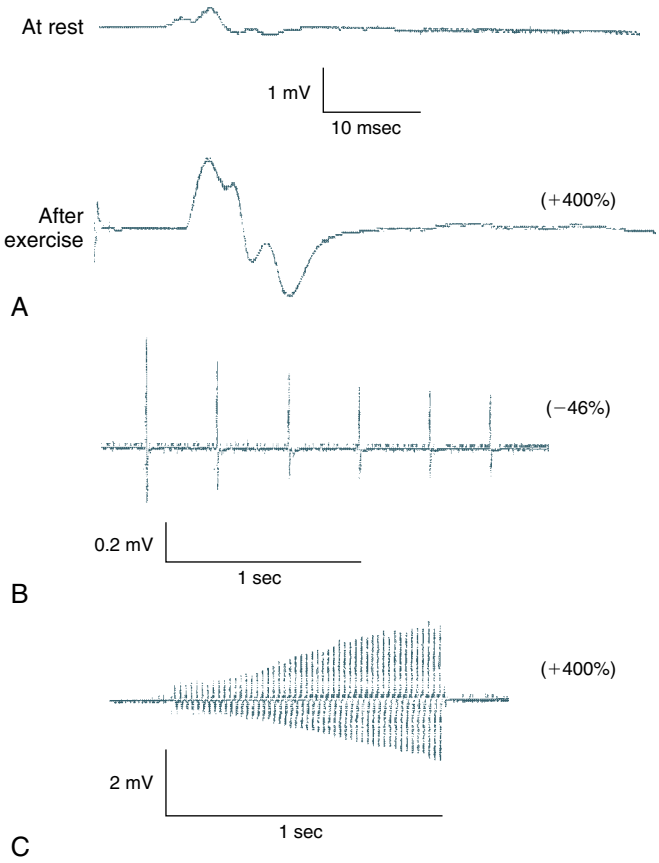


Fig. 19.4 Typical repetitive nerve stimulation pattern in the abductor digiti quinti muscle in Lambert-Eaton myasthenic syndrome. (A) Low compound muscle action potential amplitude at rest. Marked incremental response (+400%) after 30 seconds of exercise. (B) Decremental response (-46%) at low-rate stimulation (3 Hz). (C) Marked incremental response (+400%) at high-rate stimulation (50 Hz).

separate paraneoplastic LEMS from autoimmune LEMS. According to our experience, cancer is less likely associated with LEMS if the patient is a young woman and if cancer is not found within 4 years after the diagnosis of LEMS is made.

DIAGNOSIS AND EVALUATION

The diagnosis of LEMS can be confirmed only by the RNS test (Oh, 2017). The RNS test is essential in confirming the diagnosis of this disease.

The RNS test in LEMS is characterized by a presynaptic NMT block: (1) low CMAP, (2) dramatic PEF, (3) decremental response at LRS, (4) marked incremental response at HRS, and (5) prominent PTF but less prominent PTE (Oh, 1998, 2005, 2017) (Fig. 19.4, Table 19.6). Low CMAP has been noted in 88% of cases in this disorder. For brief exercise testing, a 10-second exercise is critical (Hatanaka & Oh, 2008). A more than 100% incremental response at PEF or at HRS is almost pathognomonic of LEMS (Lambert et al., 1961). Our study showed that a more than 60% response in PEF or at HRS is sufficient for the diagnosis of LEMS (Oh et al., 2005). In almost all cases, a decremental response has been noted at LRS. In our series, a decremental response was present in 97% of cases. The most dramatic facilitation at HRS was seen in this disease. In all cases, there was an incremental response at HRS, ranging from 100% to 4000%. A more than 100% incremental response at HRS is almost pathognomonic of LEMS (Oh, 1989). Our recent study showed that the RNS test is more typical of LEMS and more severe in the seropositive LEMS group and the classic triad (low CMAP amplitude, decrement at LRS, and increment at PEF or HRS) is rare in the seronegative group (Oh, Hatanaka, Claussen, & Sher, 2007).

Testing for P/Q-type VGCC antibody is positive in 90% of LEMS patients (Oh, 1989). Thus, the diagnosis of LEMS may be confirmed by radioimmunoassay of VGCC antibodies. However, cautious interpretation of positive VGCC antibody test in LEMS diagnosis is advised in view of low specificity: 3% (6/236) in recent studies (Zalewski et al., 2016). The workup should also include a CT scan of the chest for small cell carcinoma of the lung and, possibly, also bronchoscopy and 18F-fluorodeoxyglucose positron emission tomography (PET) scan if the CT scan is negative. Screening detected 96% of SCLC within 1 year of diagnosis of LEMS (Titulaer et al., 2008). Follow-up should be continued with a CT scan every 6 months for at least 2 years. If cancer is not found, an autoimmune etiology should be considered and patients should be studied for other autoimmune disorders.

TREATMENT AND MANAGEMENT

SYMPTOMATIC TREATMENT

In contrast to MG, in which symptomatic improvement is achieved by AChEIs, which increases the availability of ACh at the postsynaptic membrane, in LEMS symptomatic improvement is achieved by two potassium channel blockers, which increases the release of ACh at the presynaptic membrane: guanidine and aminopyridines.

Guanidine Hydrochloride

Guanidine hydrochloride acts on the presynaptic neuromuscular junction by increasing the number of ACh quanta released from the immediately available pool on nerve impulse by blocking potassium channels and thus prolonging the nerve terminal action potential or by facilitating an effect on the nerve terminal calcium channels (Verschuuren, Wirtz, Titulaer, Willems, & van Gerven, 2006). Thus, this drug is ideal for symptomatic treatment of LEMS and has been used since 1966. It was mostly studied in case reports and has not been studied in randomized trials. Guanidine was used in 47 LEMS cases, and clinical improvement was reported in most cases (Verschuuren et al., 2006). Two papers described a larger series, both of nine patients. Improvement ranged from "slight to dramatic" (Oh, Kim, Head, & Claussen, 1997; Tim, Massey, & Sanders, 2000). Electrophysiological improvement was also reported in two studies. In the RNS test, all parameters improved in all tested cases. However, the most definite improvement was in the CMAP amplitude. In SFEMG, there was an improvement in two of three tested cases (Oh et al., 1997).

The most common side reactions are GI symptoms and distal paresthesia. Such reactions are known to occur even at very low doses and are usually mild and transient. Moreover, GI troubles induced by guanidine are easily controlled by antacids or atropine. Thus, these alone are not an indication for discontinuation of treatment. In one series, GI symptoms

were the most common side reactions, as observed in 50% of cases, and medications had to be discontinued in a few cases (Oh et al., 1997).

The most serious side reactions of guanidine are hematologic abnormalities and renal insufficiency. In most reported cases, hematologic abnormalities developed in the early course of the high-dose therapy and were reversible. In the study of Norris, Calanchini, Fallat, Panchari, and Jewett (1974) on motor neuron disease, which is probably the largest series of guanidine trial, they reported five cases (2.5%) of bone marrow suppression among 200 patients. This finding emphasizes the importance of routine monthly blood tests during the first few months in guanidine-treated patients until a safe dose level is established.

In contrast, less commonly reported guanidine-induced renal insufficiency tended to develop after longer use (mean duration, 26 months) and with doses higher than 1000 mg/day in three cases. It is most likely to be irreversible. Up to this time, there is no reported case of guanidine-induced renal insufficiency with the total daily dose of guanidine less than 1000 mg/day.

Low-dose guanidine (less than 1000 mg/day) was used in conjunction with pyridostigmine in nine participants with LEMS in an open trial (Oh et al., 1997). The mean treatment duration was 3 years, during which time three participants stopped taking guanidine due to persistent GI side effects. Combination treatment was beneficial in terms of muscle strength and electrophysiological CMAP amplitude measurements in all nine participants. There were no reported serious side effects. Another study described the successful change of daily low-dose guanidine therapy (10 mg/kg) into an alternate-day regimen after the patient had developed a neutropenia on the daily dose. These observations suggest that the effect of guanidine is dose dependent, with minor side reaction at 5–10 mg/kg per day and at a ceiling does of 30 mg/kg per day. Thus, combination therapy of low-dose guanidine and pyridostigmine can be used as an alternative therapy for LEMS when 3,4-DAP or 3,4-DAPP is not readily available or patients are allergic to ir.

Aminopyridine

Aminopyridines, which are potassium channel blockers, increase ACh release at the presynaptic level by prolonging the duration of nerve action potential at central, autonomic, and neuromuscular synapses.

4-Aminopyridine (4-AP) was used for the symptomatic treatment of LEMS in open trials in nine cases (Verschuuren et al., 2006). There was clinical improvement and electrophysiological improvement. However, seizures occurred in four patients. The threat of serious central nervous system (CNS) side effects has thus limited the use of 4-AP in LEMS. 4-AP is known to cross the blood-brain barrier and result in epileptogenic effects in animals.

3,4-Diaminopyridine and 3,4-Diaminopyridine Phosphate

3,4-DAP and 3,4-DAPP are now approved by the FDA as agents for symptomatic treatment for LEMS after four randomized placebo-controlled trials for 3,4-DAP and two randomized placebo-controlled trials for 3,4-DAPP (Oh, 2019).

3,4-DAP has been shown in animals to be more potent in improving NMT and less convulsing than 4-AP. In addition, it has an advantage over 4-AP because it crosses the blood-brain barrier less readily, resulting in fewer CNS side effects. The first use of 3,4-DAP was in three patients with LEMS without lung cancer, and clinical and electrophysiological improvement was noted in all three patients (Lundh, Nilsson, Rosén, & Johansson, 1993). Since then, the clinical effectiveness of 3,4-DAP in LEMS has been consistently well documented in repeated case reports and one open trial in more than 128 cases (Oh, 2019).

So far, there have been six randomized placebo-controlled trials of 3,4-DAP in patients with LEMS. McEvoy et al. found a significant dose-related improvement with 3,4-DAP in three independent measurements (neurological disability score, isometric strength testing, and CMAP amplitude) in 12 patients in a randomized, double-blind, crossover study (Sanders et al., 2018). Sanders et al. found a significantly greater improvement in two measurements (QMG score and the summated CMAP) in 12 DAP patients in comparison with 14 placebo patients in a prospective randomized study (Sanders, Howard, & Massey, 1993; Sanders, Massey, Sanders, & Edwards, 2000). Oh, Hatanaka, Claussen, and Morgan (2009) reported a signficant improvement in all listed primary endpoints (subjective symptoms, LEMS classification, muscle strength score, QMG score, and CMAP) in a double-blind, placebo-controlled, crossover trial of 3,4-DAP compared with placebo. Sanders et al. (2018) used the three times up-and-go test and W-SAS (self-assessment of LEMS weakness) in a multicenter 7-day study and found a signficant improvement in 3,4-DAP versus placebo in both end points.

3,4-DAPP is a phosphate salt form of 3,4-DAP base. The major difference between the two compounds is the higher stability of 3,4-DAPP (Oh, 2019). Only eight cases of 3,4-DAPP have been reported in open-label studies, with clinical improvement in all cases. In two multicenter randomized double-blind placebo-controlled studies (38 patients in the first study and 26 patients in the second study), all primary end points were met in favor of 3,4-DAPP compared with placebo (Oh et al., 2016; Shieh, Sharma, Kohrman, & Oh, 2019).

The usual effective dose of 3,4-DAP and 3,4-DAPP in LEMS is 20–80 mg/day, and the ceiling dose is 80 mg/day (Oh, 2019). The drug is well tolerated, with only mild side effects, as long as the dose is kept below 80 mg/day. Patients notice the onset of effect less than 30 minutes after taking a dose, and benefit from a single dose lasts for 2.5 to 4 hours. Many patients notice an accumulative effect of fixed doses, with the maximum response occurring 3 to 4 days after a dose change. DAP effects begin to wear off after less than 8 hours following the last dose and clear entirely in less than 2 days. Mild side reactions include perioral or sacral paresthesia, light headache, epigastric distress, nausea, anxiety, and insomnia. The only major side reactions reported so far have been seizures in four patients: three while on a dose of 100 mg/day and one while on a dose of 60 mg/day (Oh, 2019). One patient had brain metastases. Another side reaction was death from myocardial infarction a few weeks after starting 3,4-DAP, possibly as a result of the sudden increase in physical activity. One patient had cardiac arrest from iatrogenic overdose (360 mg/day) of medication but recovered with appropriate treatment. No major cardiac complication including the prolongation of Q-T interval was reported.

3,4-DAP and 3,4-DAPP are the most studied drugs in neuromuscular diseases and are now preferred for treatment in LEMS and have become the mainstay of symptomatic treatment of LEMS.

Acetylcholinesterase Inhibitors

Pyridostgmine has been used for symptomatic treatment in more than 80 cases from 1953 when the first case of LEMS was reported (Verschuuren et al., 2006). This is understandable in view of the clinical similarity in MG and LEMS. The edrophonium test was reported to be positive in 37% of tested cases in LEMS. As in MG, repeated doses at every 4-hour intervals are used. A double-blind, placebo-controlled, crossover study found a significant improvement in CMAP amplitude and muscle strength by IV administration of 3,4-DAP, but not of pyridostigmine (Wirtz et al., 2009). In an extensive review (Verschuuren et al., 2006), minimal to moderate response was reported in 5 cases among more than 80 treated cases. Thus, there seems to be consensus in the available literature that AChEI alone is ineffective in LEMS. On the other hand, two studies from centers with extensive experience in LEMS treatment showed that pyridostigmine alone can be effective in mild LEMS cases. In the Oh study with 14 patients who had symptomatic treatment longer than 3 months, pyridostigmine alone (180–1200 mg/day) was tested to maximize benefit in six patients, including two who could not take guanidine because of adverse side reactions (Oh et al., 1998). They found that, in some mild LEMS cases, pyridostigmine alone is enough to induce a satisfactory symptomatic treatment when LEMS is stable with immunotherapy or anticancer therapy. Lundh et al. (1993) tested the oral administration of pyridostigmine, 3,4-DAP, and combinations of both drugs on consecutive days as the test protocol. They found only slight improvement at 60 mg and a more clear-cut effect at 120 mg on the clinical tests as well as on CMAP in the test protocol. They reported that few of the 19 LEMS patients did well on pyridostigmine alone.

The combined therapy of pyridostigmine and guanidine or 3,4-DAP seems to be the favored treatment at many centers. As discussed earlier, Oh preferred liberal use of pyridostigmine and low-dose guanidine (less than 1000 mg/day) for LEMS (Oh et al., 1997). Several reports suggest a potentiation of the therapeutic effect of 3,4-DAP. Lundh et al. (1993) reported that the addition of pyridostigmine to 3,4-DAP improved the step test performance but did not significantly improve limb elevation tests or CMAP and many patients benefitted from combined treatment of both drugs. In the McEvoy study, 4 of 12 patients had pyridostigmine added to DAP during the follow-up period (McEvoy, Windebank, Daube, & Low, 1989). In Sanders et al.'s (2000) study, 25 patients participated in an open-label DAP trial. All but three improved by at least 2 QMG score points, usually with pyridostigmine. In Tim's study, 53 patients were treated with 3,4-DAP and pyridostgmine, and 79% had functional improvement (Tim et al., 2000). These indicate that, in practice, many patients on 3,4-DAP need additional pyridostigmine to maintain an improved status in LEMS.

IMMUNOTHERAPY

Considering that LEMS is an autoimmune disorder, immunotherapy should be the mainstay of treatment in patients. IVIg is the only therapy in which a rigorous controlled study showed effectiveness (Bain et al., 1996).

Immunosuppressive Therapy

Clinical improvement with steroids was first reported in 1969 in one case after 2 weeks of treatment with prednisone. Three cases were reported to show clinical improvement with a high dose of prednisone: The onset of improvement was within 2 weeks, and maximal improvement was seen in 3–4 months (Newsom-Davis & Murray, 1984). In Tim's study, 9 (28%) of 32 patients showed moderate improvement with prednisone (Tim et al., 2000). A combination of steroid therapy with AZA has been described to be more effective than prednisone monotherapy (Newsom-Davis & Murray, 1984). Three of six noncancer LEMS patients achieved almost complete remission of symptoms within a year after beginning treatment with prednisolone and AZA. The remaining three patients also improved, but to a lesser degree (two patients were intolerant of AZA and received prednisone alone). Similar improvement was seen in resting CMAP amplitudes.

So far, there is no trial with other immunosuppressants in LEMS. Most experts recommend immunosuppressive treatment in patients who are unresponsive to symptomatic treatment and specific tumor therapy. Newsom-Davis (1998) prefers prednisone for paraneoplastic LEMS and prednisone combined with AZA for nonparaneoplastic LEMS because of concerns regarding the carcinogenic properties of AZA. There are isolated reports of favorable response to rituximab in nonparaneoplastic LEMS (Boutin, Rey, Romeu, Pouget, & Franques, 2013).

Immunomodulating Therapy

One randomized, double-blind, placebo-controlled study with IVIg showed a signficant improvement in myometric strength measurement and a signficant decline in serum VGCC antibody titers in nine patients compared with placebo (Bain et al., 1996). One gram of IVIg was given during two consecutive days. There was a signficant improvement in strength and in decline of antibodies. The beneficial effect on strength was maximal 2–4 weeks after treatment. VGCC titers decreased rapidly in the first week and became normal after 3 weeks.

Several studies have reported a marked clinical improvement in LEMS patients after treatment with either PE or IVIg: four studies dealing with one to nine patients in PE and five studies dealing with three patients in IVIg (Verschuuren et al., 2006). In Tim's studies, marked improvement was reported in 2 (11%) of 19 patients on PE and in 7 (41%) of 17 patients on IVIg (Tim et al., 2000). They stated that the benefit was transient with PE or IVIg.

In the best open trial study on PE, serial clinical and CMAP amplitude assessment was done in nine patients over 0.5 to 2.5 years (Chalk, Murray, Newsom-Davis, O'Neill, & Spiro, 1990). Eight of the nine patients showed a short-term clinical and electromyographic (EMG) response to PE. The improvement in muscle strength develops after a longer time interval (about 10 days) than in MG, where the response is typically evident within 2 days (Chalk et al., 1990). This suggests a slower turnover rate of VGCCs as compared with AChR-Ab. Improvement peaked at 2 weeks and subsided by 6 weeks. PE and IVIg are indicated in severely weak patients.

TUMOR TREATMENT IN LAMBERT-EATON MYASTHENIC SYNDROME

Unlike other paraneoplastic neurological syndromes that are usually resistant to any therapy, LEMS is known to be consistently responsive to immunotherapy or anticancer therapy (Chalk et al., 1990). Thus, treatment of cancer is of paramount importance in paraneoplastic LEMS. Successful cancer treatment may result in remission or otherwise usually in improvement, as noted in several case reports and two small series with anticancer treatment (Verschuuren et al., 2006). Tumor is implicated as the initial site of VGCC antibody production in paraneoplastic LEMS. Therefore, treatment of the tumor, especially its surgical removal, would presumably reduce or even eliminate antigenic driving of the autoantibody response. Aggressive therapy for cancer is recommended. A small retrospective study showed that 7 of 11 paraneoplastic LEMS cases survived specific tumor therapy by more than 2 months and subsequently showed progressive improvement in their neurological symptoms; in the other three patients, improvement was followed by a relapse. Specific tumor therapy in a small retrospective series resulted in recovery from LEMS within 6–12 months (Chalk et al., 1990). This was confirmed by the parallel recovery in the CMAP amplitudes, which in all patient studies had returned to the normal range within 6–12 months of starting therapy. The specific tumor therapy included chemotherapy, surgical resection, and local radiotherapy. Chemotherapy is the first choice in SCLC, and this will have an additional immunosuppressive effect. The standard regimen for the treatment of SCLC is combination chemotherapy with cisplatin, etoposide, carboplatin, and irinotecan. Thoracic radiation therapy and prophylactic cranial radiation therapy are also offered to patients with limited-stage disease who respond to chemotherapy. Despite a high chemosensitivity and trials with different combinations of therapy, SCLC remains associated with a poor long-term survival. Fewer than 10% of the patients survive longer than 2 years. A recent study showed a signficant prolonged survival in 15 SCLC LEMS patients compared to matched SCLC patients without LEMS (Maddison, Newsom-Davis, Mills, & Souhami, 1999). These findings suggest that the autoimmune response elicited by the tumor might help to slow down the growth of the SCLC.

SYMPTOMATIC TREATMENT FOR MYASTHENIA GRAVIS–LAMBERT-EATON MYASTHENIC SYNDROME OVERLAP SYNDROME

Recently, 39 cases of combined MG-LEMS cases were reviewed under the name of MLOS (MG-LEMS overlap syndrome) (Oh, 2016). All MLOS cases have typical features of MG and classical LEMS pattern in the RNS test. By definition, all MLOS cases have a good response to AChEIs, edrophonium, neostigmine, or pyridostigmine. Good response was reported with 3,4-DAP in four of five treated patients (Oh, 2019). Good response was reported with guanidine in six patients. Among 22 patients treated with pyridostigmine, "good and dramatic improvement" was reported in 4, "improvement" in 16, and no response in 2. In eight patients with MLOS, Lee, Sunwoo, and Kim (2018) compared the treatment of 3,4-DAP (average 50 mg/day) for 2 days with combined treatment of 3,4-DAP and pyridostigmine (420 mg average) for 2 days and found that the combined treatment showed the best outcome.

DRUGS AGGRAVATING LAMBERT-EATON MYASTHENIC SYNDROME

Competitive neuromuscular blocking agents such as d-tubocurarine and pancuronium, magnesium agents, diltiazem, verapamil, ofloxacin, botulinum toxin, and muscle relaxant are reported to aggravate LEMS in isolated cases (Verschuuren et al., 2006). Varenicline (Chantix) unmasked LEMS in one case (Abou-Zeid, Rudnicki, & Keyrouz, 2009). Many drugs that induce or aggravate MG may aggravate LEMS.

GENERAL GUIDELINES OF THERAPEUTIC MANAGEMENT OF LAMBERT-EATON MYASTHENIC SYNDROME

The guidelines presented here are the UAB protocol based on the general consensus, best knowledge, and UAB experiences and should be used as general rather than as strict guidelines (Fig. 19.5).

Once the diagnosis of LEMS is established, 3,4-DAP and 3,4-DAPP are the drugs of choice for symptomatic treatment (class I) (Oh, 2019). This will virtually always produce symptomatic improvement. If one is allergic to 3,4-DAP or 3,4-DAPP, certainly, guanidine HCl is an alternative choice of drug, usually with a liberal dose of pyridostigmine (class VI; label B). Some LEMS patients find that the addition of pyridostigmine to 3,4-DAP or 3,4-DAPP treatment is beneficial.

The next important workup at the time of diagnosis of LEMS is to test for SCLC because it is found in half of LEMS patients and SCLC is found at the time or within 2 years of diagnosis. The best diagnostic test for SCLC is a high-resolution chest CT scan and, possibly, bronchoscopy, and 18-fluorine fluro-2-deoxyglucose positron emission tomography (FDG-PET) scan if the CT scan is negative. This is especially important for patients with a high risk of SCLC (smoking and older patients). Follow-up should be continued with CT scan every 6 months for at least 2 years.

Once the diagnosis of SCLC is established, treatment of cancer will be implemented in its own right, but an added benefit is that it induces an improvement of LEMS symptoms. Chemotherapy is the first choice in SCLC because it has an additional immunosuppressive effect. The presence of LEMS in a patient with SCLC is known to improve survival.

If symptomatic treatment is insufficient, the next step is immunosuppressive therapy usually with high-dose steroid (class IV) regardless of whether one has SCLC. When remission has been obtained in LEMS, the prednisone dose should be tapered to the minimum required to maintain remission. For the long-term immunosuppressive medications, AZA is the first-line choice (class IV).

For the second-line choice for long-term immunosuppressive medication, one can choose IVIg (intermittent use) (class I). CsA or MM is another alternative. However, this recommendation is based on MG, not on LEMS. Personally, none of my patients needed CsA or MM for long-term immunosuppressants.

For severe LEMS patients, IVIg is the treatment of choice since it has been shown to be beneficial in the short term in LEMS (class I). PE may be an alternative treatment if IVIg is not effective (class IV).

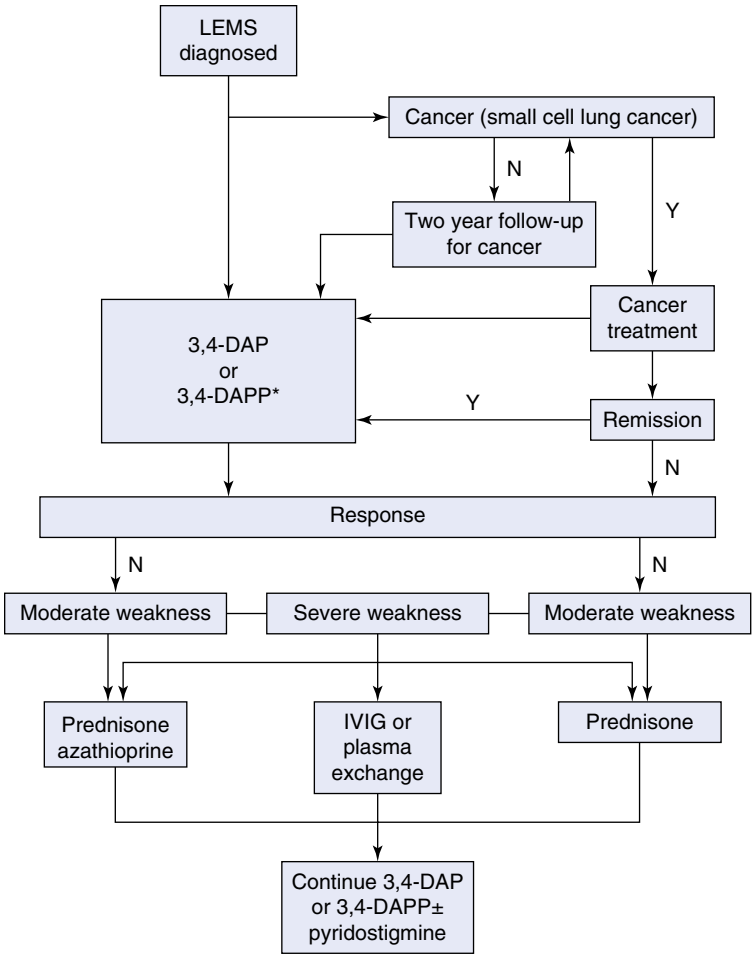


Fig. 19.5 Treatment algorithm in Lambert-Eaton myasthenic syndrome (LEMS). *3,4-DAP*, 3,4-diaminopyridine; *3,4-DAPP*, 3,4-diaminopyridine phosphate; *IVIg*, intravenous immunoglobulin; *N*, no; *Y*, yes.

Respiratory weakness and bulbar muscle weakness, which are rare in LEMS, can occasionally be life-threatening. There were two case reports of patients with LEMS crisis with a good response to 3,4-DAP: one who received 8 mg of IV injection of 3,4-DAP and one who received 20–40 mg of 3,4-DAP a day (Oh, 2019).

BOTULISM

Botulism is an uncommon, but potentially life-threatening, neuroparalytic syndrome caused by a potent neurotoxin produced by *Clostridium botulinum*. Botulism is both an old and an emerging disease. The classic foodborne botulism was first reported over 100 years ago, and new forms of botulism were added in the 20th century with the newest addition of Botox-induced botulism.

C. botulinum is a gram-positive spore-forming anaerobic bacteria found in soil throughout world. Spores of *C. botulinum* are ubiquitous and not dangerous in themselves when ingested. When spores germinate in an anaerobic environment, they produce botulinum toxin, one of the most potent neurotoxins in humans. It has been estimated that doses as small as 0.05 to 0.1 μg can cause death in humans. Unlike the toxin, which is heat labile, the spores are relatively heat resistant. A temperature of 120°C may be required to kill the spores, although heating at 85°C inactivates the toxin.

There are eight strains of *C. botulinum* that are known to produce antigenically distinct toxins (A, B, C1, C2, D, E, F, and G). In humans, the A, B, and E strains are almost always involved, and the F strain extremely rarely. Recovery times from paralysis type A poisoning are longer than from type E (Cherington, 2004).

Six distinct clinical syndromes have been described: (1) foodborne botulism, (2) infant botulism, (3) wound botulism, (4) adult variant of "infant botulism," (5) Botox induced botulism and (6) inhalational botulism.

Among these, the first three syndromes are clinically important because the latter three syndromes are rare (Table 19.7).

TYPES OF BOTULISM

FOODBORNE BOTULISM

Foodborne botulism is due to ingestion of preformed toxin in foods that have not been canned or preserved properly. While European cases most commonly are associated with type B contamination of home-processed meats, Alaskan, Canadian, and Japanese outbreaks often involve type E toxin in preserved seafood (Talliac, Kim, & Bessman, 2008). By far, home-processed foods are responsible for most (94%) outbreaks of foodborne botulism in the United States. In the United States, vegetables are the most commonly implicated foods in types A and B outbreaks, while fish or fish products are responsible in type E outbreaks. The toxin type

Table 19.7 Clinical, Diagnostic, and Therapeutic Features of Subtypes of Botulism

	Food Botulism	Wound Botulism	Infant Botulism
Prevalence	Rare	Mainly in IV drug users The most common in California	The most common form in the United States Infants <6 months of age
Source of infection	Ingestion of preformed toxin in the ingested food	Toxin from organisms in the wound	Toxin from organisms in the infant intestine
Fever	Absent	May be present if other infections are present	Absent
Incubation	6 hours to 8 days	4 to 14 days	3–30 days
GI symptoms	May be present: nausea and vomiting	Absent	Almost always: constipation
Sensory deficit	Absent	Unilateral sensory deficits may be present	Absent
Botulinum toxin in serum	Present	Present	Rarely present
Diagnosis	Toxin in serum; toxin and *C. botulinum* in food and its container, gastric contents, vomitus and feces	Toxin in serum. Toxin and *C. botulinum* in wound	Toxin or *C. botulinum* in feces
Treatment	Trivalent antitoxin Laxative or enema	Wound debridement. Antibiotics for other bacteria. Trivalent antitoxin	Intravenous botulinum immunoglobulin (BIG-IV)

most often responsible for foodborne botulism corresponds well with the geographic distribution of the toxigenic species. Most of the type A outbreaks occurred west of the Mississippi River, while most of the type B outbreaks occurred east of the Mississippi River. Most cases of type E poisoning were distributed around the Great Lakes and in Alaska. Toxin A produces a more severe illness than type B does, and type E is least severe.

Botulinum toxin is primarily absorbed from the upper GI tract, but toxin reaching the lower small bowel and colon may be slowly absorbed, thus perhaps accounting for the delayed onset and prolonged duration of symptoms seen in many patients with clinical botulism. Mortality rate is around 3%–5% at present.

INFANT BOTULISM

Infant botulism was first described in 1976 and is the most common form of botulism in the United States at this time, exceeding foodborne botulism. Infant botulism results from toxin produced in vivo from the intestinal colonization of *C. botulinum* in infants younger than 6 months in 95% of cases (Carrillo-Marquez, 2019). The infant intestinal tract often lacks both the protective bacterial flora and the clostridium-inhibiting bile acids found in the normal adult intestinal tract. There are more type B than type A cases in infant botulism. Clinical features in these infants include acute onset of constipation, poor sucking, weak cry, hypotonia, and muscle weakness. Loss of head control is particularly striking. Ophthalmoplegia, ptosis, flaccid facial expression, pooled oral secretions, dysphagia, and a weak gag reflex are frequent. With adequate supportive care, most infants recover in weeks or months without sequelae. Mortality rate (1%) is low compared to foodborne botulism (5%). On rare occasions (5%), infants may show a recurrence of symptoms.

WOUND BOTULISM

This is caused by the systemic spread of toxin produced by *C. botulinum* inhabiting in anaerobic wounds and is associated with trauma, surgery, subcutaneous heroin injection (black tar injection), and sinusitis from intranasal cocaine abuse. Through 1992, only one to three cases of wound botulism were reported in the United States each year. Since 1992, the number of cases of wound botulism has increased dramatically. During 2001–2016 in the United States, 353 cases were reported to the Centers for Disease Control and Prevention (CDC, 2018). Nearly all of these new cases occurred in heroin-injection drug users. Most of these cases are from California. Two thirds of cases were type A and almost one third were type B. Mortality rate is about 10%.

ADULT VARIANT OF "INFANT BOTULISM"

Similar in pathogenesis to infant botulism, this form occurs in older children and adults with abnormal bowel, such as colitis, having had intestinal bypass procedures, or in association with other conditions that may create local or widespread disruption in the normal intestinal flora. These cases were associated with a prolonged latent period of up to 47 days postingestion before the onset of symptoms. A diagnostic clue is abnormality in the GI tract as described previously. The findings of *C. botulinum* in the feces of adult patients are almost always associated with clinical botulism.

IATROGENIC BOTULISM

Subclinical NMT abnormality was reported via SFEMG in distant muscles in patients with cervical dystonia who received Botox treatment. Dysphagia is the most common complication of Botox injection. A case of brachial plexus neuropathy was reported following Botox injection. Sixteen cases of frank but mild botulism were reported following

medical treatment with botulinum toxin. Nine cases were from 250–1400 units of Dysport (British) botulism toxin and seven were from 30–750 units of Botox (Leonardi, Haggiag, Petrucci, & Lispi, 2019).

INHALATION BOTULISM

To date, three human cases have been the result of inadvertent inhalation of toxin by laboratory workers.

PATHOPHYSIOLOGY

Botulinum toxins interfere with the release of ACh at the cholinergic transmission sites of the peripheral nervous system. As a rule, neuromuscular block is most prominent at these sites, producing paralysis of extraocular, bulbar, and limb muscles. Because of the involvement of the parasympathetic system, autonomic dysfunction is common but less prominent and includes pupillary abnormality, paralytic ileus, urinary retention, diminution of secretions, and orthostatic hypotension. Dysautonomia is more commonly observed in type B botulism, and neuromuscular block in type A.

DIAGNOSIS AND EVALUATION

CLINICAL MANIFESTATIONS

The hallmark of botulism is an acute descending symmetrical motor paralysis first affecting the muscles supplied by the cranial nerves (Carrillo-Marquez, 2019). Presenting complaints generally consist of oculobulbar symptoms: ptosis, blurred or double vision, dysphagia, or dysarthria. These are usually followed by descending weakness and dyspnea. Dyspnea should be regarded as a warning sign of impending respiratory failure that may require ventilatory support. Dysautonomic symptoms, including dryness of the mouth, pupillary abnormalities, and ileus, are frequently seen. Dilatation of the pupils is found in fewer than 50% of patients. Deep tendon reflexes are frequently depressed symmetrically or absent. Conspicuously absent is any objective sensory disturbance despite profound motor abnormalities. Thus, the clinical features mimic those of MG and the descending form of Guillain-Bàrre syndrome (GBS). In MG, dysautonomic findings are lacking and reflexes are preserved. In GBS, ascending weakness is the classic presentation and the spinal fluid protein is invariably high. In botulism, the spinal fluid protein is normal. In Miller-Fisher syndrome, a variant of the descending form of GBS, 90% has autoantibodies to GQ1b antibody in acute phase sera.

ELECTRODIAGNOSTIC FEATURES

Electrophysiological studies are extremely helpful in the diagnosis of botulism. Since the RNS test provides the only relatively specific responses in botulism, this test has been found to be the most convincing objective evidence of botulism until microbiological confirmation is achieved. In all cases of botulism showing neuromuscular weakness, the RNS test shows some abnormalities. The most characteristic RNS abnormalities are those of presynaptic NMT blocks: (1) low CMAP amplitude, (2) decremental response at the LRS, and (3) incremental response at a high rate of stimulation (Fig. 19.6). The most consistent electrophysiological abnormality is an incremental response at a high rate of stimulation, and

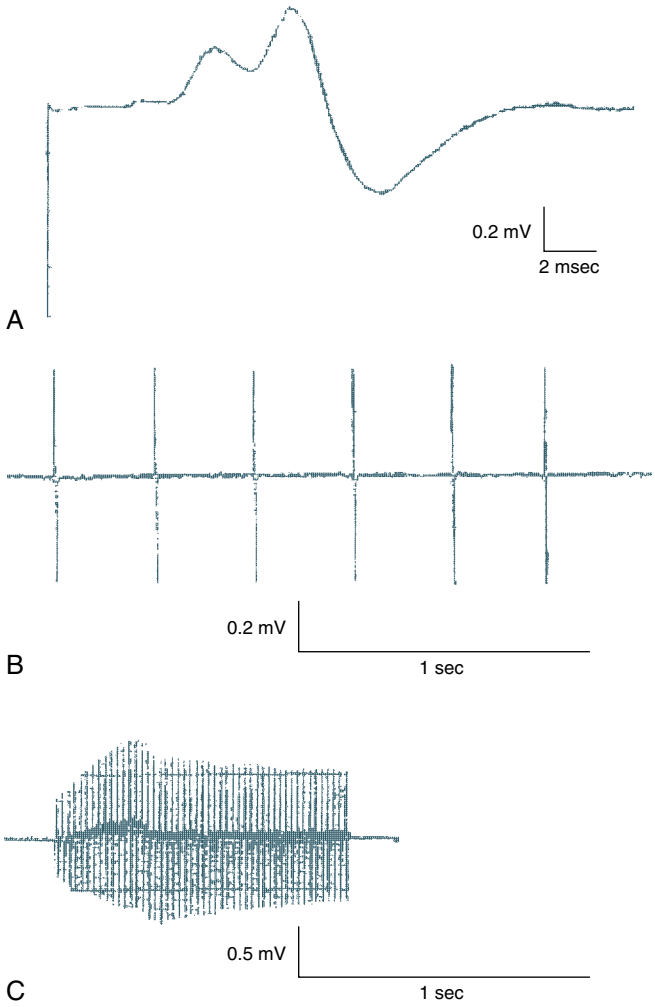


Fig. 19.6 Typical repetitive nerve stimulation pattern in the abductor digiti quinti muscle in infant botulism. (A) Low compound muscle action potential amplitude. (B) Normal response at low-rate stimulation (3 Hz). (C) Incremental response (+114%) at high-rate stimulation (50 Hz).

the next common abnormality is a low CMAP amplitude to a single stimulation in a clinically affected muscle. Witoonpanich, Vichayanrat, Tantisiriwit, Rattanasiri, and Ingsathit (2009) studied the CMAP at rest and incremental response after a 10-second exercise in 63 cases of food botulism. The CMAP at rest below 5 mV was observed in 56 (92%) patients. Postexercise facilitation (>40% increment) was observed in 55 (87%) patients, with >100% facilitation in half (49.2%) of the patients. There was an inverse correlation between the CMAP amplitude and degree of PEF. They concluded that preexercise and postexercise single supramaximal stimulations were sensitive for the diagnosis of botulism. A decremental response at the LRS is infrequent. Small-amplitude, short-duration motor unit action potentials (MUPs) typical of myopathy have been characteristic findings in needle EMGs. Fibrillations are observed in about 50% of cases. SFEMG shows typically increased jitter and blocking, which become less marked at the higher rate of discharge.

DIAGNOSIS

The most important clue in the diagnosis of botulism is the high index of suspicion on the basis of history and

Box 19.3 Protocols for Clinicians Evaluating Suspected Cases of Botulism

Clinicians evaluating a suspected case of botulism should immediately seek clinical consultation and should administer antitoxin as follows:

- For suspected foodborne botulism or botulism of unknown source, the state health department should be contacted via its 24-hour emergency telephone number. If there is no response, then the Centers for Disease Control and Prevention Director's Emergency Operations Center should be contacted at 770-488-7100.
- For suspected infant botulism occurring in any state, the California Department of Health Services Infant Botulism Treatment and Prevention Program should be contacted at 510-540-2646.

examination. A cluster of two or more with compatible symptoms of botulism is essentially pathognomonic of foodborne botulism, because the illnesses that resemble botulism do not produce outbreaks. Every case of botulism is a public health emergency, and the clinician should report the suspected case to the 24-hour emergency telephone number of the state health department or the CDC 24-hour botulism consultancy service (770-488-7100, the CDC Emergency Operations Center) (Box 19.3).

The diagnosis of botulism is confirmed by either detection of the toxin in the serum or identification of *C. botulinum* organism or toxin in food and container (foodborne botulism), in tissue (wound botulism), and any GI fluid or excretes (infant botulism or foodborne botulism). Confirmation of the diagnosis is made in almost 75% of cases (Talliac et al., 2008). Early cases are more likely to be diagnosed by toxin assays, whereas late-onset cases are more likely to have positive culture. If the delay in securing the serum samples is more than 2 days after ingestion of the toxin, the chance of obtaining a positive test is less than 30% (Cherington, 2004). Only 36% of stool cultures are positive after 3 days. Laboratory confirmation of toxin presence is via a mouse bioassay, and identification of the toxin type is performed by a mouse toxin neutralization test. From the time that mice are injected, final results may not be available for 24 hours or even 48 hours. In foodborne botulism, toxin is found in serum in 39% of cases and in stool in 24% of cases, and organisms are found in cultures of stool in 55% of cases. In infant botulism, stools or enema fluids are the specimen of diagnostic choice, as serum is only rarely toxin positive. In wound botulism, the diagnosis is confirmed by the presence of toxin in serum or by toxin or *C. botulinum* organisms in wound specimens. In the adult variant of infant botulism, the organism may be detected in stool and toxin in serum for up to 119 days following the onset of symptoms.

TREATMENT AND MANAGEMENT

INTENSIVE SUPPORTIVE CARE

The most important treatment for severe botulism is an intensive supportive care with special attention to respiratory status (good practice). During the first half of the 20th century in the United States, the mortality rate among patients with botulism was 60%–70%, even when equine antitoxin was administered in heroic doses (Sobel, 2005). Since then, the mortality rate decreased precipitously, until it reached the current rate of 3%–5%. This is largely due to the modern intensive supportive care, principally mechanical ventilation. Thus, any patient with clinical findings or history suggestive of botulism should be hospitalized immediately and meticulously monitored for signs of respiratory failure and mechanical ventilation should be instituted at the earliest sign of respiratory failure. Paralysis due to botulism can be protracted, lasting weeks to months, and meticulous intensive care is required during this period of recovery.

TRIVALENT EQUINE BOTULISM ANTITOXIN

Trivalent equine botulism antitoxin has been available in the United States since 1940. Its efficacy has never been evaluated in a controlled trial. The best data in this regard are from two retrospective case studies (Tacket, Shandera, Mann, Hargrett, & Blake, 1984; Sandrock & Murin, 2001).

Tacket et al. (1984) analyzed the clinical data on 132 cases of type A foodborne botulism reported to the CDC between 1973 and 1980. The clinical data were collected from the patients' clinicians by completing the questionnaires. Eighty-seven percent of the patients received antitoxin sometime during their course. The fatality was 19%. They observed that patients who had received trivalent equine antitoxin had a lower fatality rate (10%–15% vs. 46%) and a shorter hospital course (10–41 vs. 56 days) than those who did not receive antitoxin; and patients who received antitoxin in the first 24 hours after onset had a shorter hospital course (median, 10 vs. 41 days) but about the same fatality rate (10% vs. 15%) as those who received antitoxin later (class III).

In type A wound botulism, Sandrock and Murin analyzed the long-term outcome in 20 consecutive patients from 1991 to 1998 in one university hospital and showed that prompt (<12 hours after presentation) antitoxin administration is associated with a decreased likelihood of developing respiratory failure (57% vs. 85%; not statistically significant), while neither antibiotic administration nor surgical debridement appears to affect the course of the disease (class IV). Their data were not statistically significant (Sandrock & Murin, 2001).

Thus, these studies suggest that, at best, early administration (<24 hours after onset) of equine trivalent antitoxin to adult patients with foodborne and wound botulism was associated with improved outcomes. This is because antitoxin neutralizes only toxin molecules that are yet unbound to nerve endings. Approximately 6% of adults with foodborne botulism had anaphylaxis or serum sickness when treated with one or two vials of equine botulism antitoxin, and thus such treatment is not suitable for infants.

HUMAN BOTULISM IMMUNE GLOBULIN (BIG):

Botulism immune globulin (BIG-IV) has been available in the United States since 2006, and its efficacy was proven by the randomized, double-blind, placebo-controlled trial and later open-label study on infant botulism (Arnon, Schechter, Maslanka, Jewell, & Hatheway, 2006).

Arnon et al. (2006) performed a 5-year, randomized, double-blind, placebo-controlled trial in California of BIG-IV in 122 infants with suspected (and subsequently

laboratory-confirmed) infant botulism (74 caused by type A *C. botulinum* toxin and 47 by type B toxin); a single IV infusion of BIG-IV (50 mg/kg of body weight [1 mL/kg]) was given within 3 days after hospital admission. This was tested against placebo immune globulin. Sixty-three patients received the placebo immune globulin, and 59 patients received BIG-IV. They found that, as compared with the control group in the randomized trial, infants treated with BIG-IV had a reduction in the mean length of hospital stay, the primary efficacy outcome measure, by 3.1 weeks. BIG-IV treatment also reduced the mean duration of intensive care by 3.2 weeks, the mean duration of mechanical ventilation by 2.6 weeks, and the mean duration of tube or IV feeding by 6.4 weeks, and the mean hospital charge per patient day by $88,600. The efficacy was statistically significant (class I).

In an open-label study on 382 patients with laboratory-confirmed infant botulism, infants treated with BIG-IV within 7 days of admission had a mean length of hospital stay of 2.2 weeks, and early treatment within 3 days of admission shortened the mean length of stay significantly more than did treatment provided later (4–7 days) (class I). The only adverse effect perhaps related to BIG-IV was a transient, blush-like erythematous rash. Another advantage of BIG-IV is a longer half-life (28 days in vivo compared with 6 days in trivalent botulinum toxin) and thus having a large capacity to neutralize botulinum toxin. A single infusion will neutralize for at least 6 months all the botulinum toxin that may be absorbed from the colon of an infant.

BIG-IV is a safe and effective treatment for infant botulism type A and type B. Treatment should be given as soon as possible after hospital admission and should not be delayed for confirmatory testing of feces or enema. Baby BIG is available as public-service orphan drug in the United States. (Information on this drug may be obtained at www.infantbotulism.org and by telephone from the California Department of Human Service Infant Botulism Treatment and Prevention Program at 510-231-7600; www.infantbotulism.org.)

GUANIDINE AND 3,4-DIAMINOPYRIDINE

These drugs increase the release of ACh from the nerve terminal. Theoretically, they should improve muscle strength. In one study, more than 20 cases were treated with guanidine hydrochloride (Cherington, 2004). Varying degrees of clinical improvement were reported. It has been most effective in overcoming the paralysis of limbs and extraocular muscles and less effective for respiratory paralysis and autonomic dysfunction. DAP was tried in three patients, with improvement in one (Oh, 2019). Thus, in view of the mixed results of improvement and lower effectiveness in respiratory paralysis, they are not substitute for medical management in an ICU.

ANTIBIOTICS

Antibiotic therapy is unproved by clinical trial but is widely used and recommended for wound botulism because of the risk of polymicrobial infection in cases of wound botulism. In leukocytosis, fever, and abscess, or when cellulitis is present, it is a good practice to treat the patient with antibiotics. One study showed that the final outcome was not affected by antibiotic treatment (Sandrock & Murin, 2001). Penicillin G (3 million units IV every 4 hours in adults) or metronidazole (500 mg IV every eight hours) in penicillin-allergic patients is usually recommended. The use of aminoglycosides is contraindicated, since they have been reported to induce neuromuscular blockade, potentiating the effects of the toxin in these patients.

TOXIN REMOVAL TREATMENT

This is mainly aimed to remove unabsorbed toxin from the GI tract in foodborne botulism or from the wound in wound botulism (good practice point). In foodborne botulism, laxatives, enemas, or other cathartics may be given, provided no signficant ileus is present. Magnesium salt containing cathartics is not recommended because slowly absorbed ion will potentially aggravate the neuromuscular block in botulism because magnesium is known to reduce the release of ACh from the presynaptic membrane. Patients presenting with wound botulism should undergo an extensive debridement, even if the wound appears unimpressive, to remove the source of toxin (good practice). In one study, surgical debridement did not affect the course of disease (Sandrock & Murin, 2001).

GUIDELINES ON THERAPEUTIC MANAGEMENT

Any patient with history, symptoms, and clinical signs suspicious of botulism should be hospitalized immediately and closely monitored for signs of respiratory failure. If needed, ventilatory support should be provided (Fig. 19.7).

Once the diagnosis of botulism is clinically suspected, one should call the state health department's emergency 24-hour telephone or the CDC to report suspected botulism cases, arrange for a clinical consultation, and, if indicated, request release of botulism antitoxin.

The only specific treatment for botulism is administration of botulinum antitoxin. Antitoxin should be given early in the course of illness, ideally <24 hours after the onset of symptoms, because antitoxin neutralizes only toxin molecules that are yet unbound to nerve bending. This is the best method to prevent respiratory failure and the need for mechanical ventilation.

Before treatment with antitoxin, one has to obtain 10–15 mL of serum, 25–50 g of feces, and possibly 25–50 mL of fluid from gastric aspiration. Also, one has to collect and refrigerate similar quantities of suspected food samples for testing. In constipated patients, a gentle saline enema may be required to obtain fecal specimens. In wound botulism, wound tissue is obtained for culture and toxin assessment.

There are two botulism antitoxin therapies available in the United States. Trivalent equine botulism antitoxin is used to treat children older than 1 year and adults; BIG-IV is used for infants less than 1 year of age. In food and wound botulism, trivalent botulism antitoxin (one vial [10,000 IU of antibodies against toxin types A, B, and E]) is diluted 1:10 with saline and administered IV over 30–60 minutes. Skin test for hypersensitivity should be done before the antitoxin injection as per the CDC guideline. In infant botulism, BIG-IV should be given (50 mg/kg [1 mL/kg] IV infusion) at an initial infusion rate of 25 mg/kg/hour IV (0.5 mL/kg/hour) (0–15 minutes), not exceeding an infusion rate of 50 mg/kg/hour (1 mL/kg/hour). This is obtained from the California Department of Health Services (24-hour telephone: 510-540-2646).

In foodborne botulism, laxatives, enemas, and other cathartics may be given to remove the toxin from the gut. In

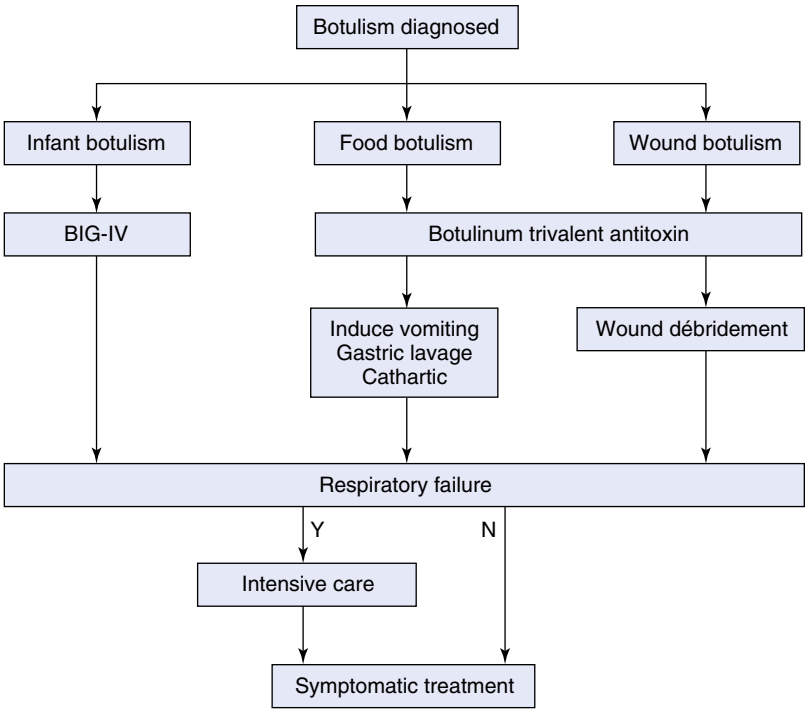


Fig. 19.7 Treatment algorithm in botulism. *BIG-IV*, Intravenous botulinum immunoglobulin; *N*, no; *Y*, yes.

wound botulism, wound debridement is recommended and antibiotics are widely used (good practice).

CONGENITAL MYASTHENIC SYNDROME

CMS refers to the heterogeneous group of hereditary congenital disorders of the neuromuscular junctions. Thirty-two forms of CMS have been described up to 2019, and new syndromes are added almost every year (Finsterer, 2019) (Table 19.8). Recent studies showed that many CMSs are now known to be due to mutations in presynaptic membrane, synaptic basal lamina, and postsynaptic proteins.

DIAGNOSIS AND EVALUATION

CLINICAL MANIFESTATION

These disorders are present at birth by definition, but some patients are not evaluated until later in childhood or adulthood because the symptoms are mild or not recognized (Engel, Ohno, & Sine, 2003). A positive family history is consistent with the diagnosis of CMS, but a negative family history does not exclude autosomal recessive inheritance. Most cases of CMS are inherited by an autosomal recessive pattern except one. The classic slow-channel syndrome has an autosomal dominant inheritance. On examination, the most important clue to an NMT disorder is increasing weakness on sustained exertion (myasthenic weakness) involving ocular, bulbar, and limb muscles. There are some findings suggestive of the specific forms of CMS: delayed or absent pupillary light reflex in AChE deficiency, selective severe weakness of cervical muscles and of wrist and finger extensor muscles in endplate AChE deficiency and slow-channel syndrome, lack of ocular muscle involvement in AChE deficiency, slow-channel syndrome, familial limb-girdle myasthenia (ChAT), DOK7 myasthenia, and hyporeflexia in congenital LEMS. A positive Tensilon test is consistent with the diagnosis of CMS, but a negative test does not rule out CMS because this test is negative in patients with endplate AChE deficiency, DOK7, slow channel syndrome (SCS), LRP4 deficiency, and MuSK deficiency. Responsiveness to AChEIs is present in many CMSs, including the most common AChR deficiency, but not in endplate AChE deficiency, SCS, and DOK7 myasthenia (Lee, Beeson, & Palace, 2018).

ELECTRODIAGNOSTIC TEST

The diagnosis must be supported by a decremental response at LRS in at least one muscle or by abnormal jitter and blocking on SFEMG, according to Engel (1994). The decremental response may be absent in familial infantile myasthenia (ChAT deficiency) between attacks; a decremental response can be elicited by prolonged 10-Hz stimulation or by exercise for several minutes before 2-Hz stimulation. Repetitive discharges are typically observed in two forms: endplate AChE deficiency and slow-channel syndrome due to "prolonged activation of postsynaptic membrane" (too much ACh) (Shieh & Oh, 2018) (Fig. 19.8). The LEMS pattern was reported in congenital LEMS and synaptotagmin 2 (SYT2) (Whittaker et al., 2015).

DIAGNOSIS

The diagnosis of CMS can be made on the basis of the tetrad of myasthenic symptoms since birth, exertional weakness on examination, negative AChR-Ab and MuSK-Ab, and decremental response at LRS. The clinical history and examination, Tensilon response, and RNS test findings can provide sufficient information for a specific diagnosis of CMS in some cases (Table 19.8), but detailed microphysiological, ultrastructural, and histochemical studies are required for accurate diagnosis and classification in most

Table 19.8 The Most Common and Well-known Types of Congenital Myasthenic Syndrome

Type	Clinical Features	Electrophysiology	Genetics	Endplate Defects	Treatment of Choice
Presynaptic defects	The least common				
ChAT deficiency (CMS-EA) (familial infantile myasthenia) (5%)[a]	Hypotonia, respiratory failure at birth, episodic apnea and crisis, improvement with age	Decrement at LRS after prolonged exercise or continuous repetitive stimulation at moderate stimulation rate (10–15 Hz)	ChAT	Normal	AChEI
Synaptic defects					
Endplate AChE deficiency (13%)	Early onset; variable severity; general muscle weakness/severe axial muscle involvement Absent pupillary response	**Repetitive discharge** in CMAP Decremental response at LRS and HRS	COLQ	Small nerve terminals; degenerated junctional fold	Ephedrine/Albuterol **AChEI/3,4-DAP: avoid**
Postsynaptic defects					
AChR deficiency (50%)	Early onset, variable severity; fatigue; typical MG features	Decremental response at LRS	Autosomal recessive. Epsilon subunit mutation is most common. Many different mutations	Increased length of end plates; variable synaptic folds	AChEI/3,4-DAP
Rapsyn deficiency (15%)	Early onset: arthrogryposis; episodic apnea and crisis, hypotonia Late onset: typical MG features	Decremental response at LRS	RAPSN; N88K mutation is common.		AChEI/3,4-DAP
DOK 7 (10%)	Limb-girdle weakness	Decremental response at LRS	Exon 7 of the DOK7 in some cases	CK may be elevated	Albuterol/Ephedrine **AChEI: avoid**
Glycolation defect (3%)	Limb-girdle weakness		Defects in 4 enzymes CHFPT1. DPAGT1, ALG2, ALG 14		AChEI
Slow channel syndrome (SCS)	Most common; forearm extensor weakness; onset second to third decades; variable severity	**Repetitive discharge; decrement at LRS** and **HRS**	**Autosomal dominant.** Alpha, beta, epsilon AChR mutations	Excitotoxic endplate myopathy; decreased AChRs	Quinidine/quinine Fluoxetine **AChEI/3,4-DAP: avoid**
Fast channel syndrome	Early onset; moderately severe; typical MG feature	Decremental response at LRS	Autosomal recessive	Normal endplate	AChEI **Quinidine/quinine/fluoxetine: avoid**
MuSK deficiency	Ptosis and respiratory distress since birth		MuSK mutation		3,4-DAP improved
Pectin deficiency	Progressive myopathy in ocular, facial, and limb muscles	Decrement response at LRS		No specific myopathy	3,4-DAP improved

% represent the percentage of patients among 356 patients at Mayo Clinic between 1988 and 2014 (Engel, A. G., Shen, X., Selcen, D., & Sine, S. M. (2015). Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *Lancet Neurology, 14,* 420-434.)

AChE, Acetylcholinesterase. *AChEI*, acetylcholinesterase inhibitor; *AChR*, acetylcholine receptor; *ChAT,* choline acetyltransferase; *CK,* creatinine kinase; *CMAP*, compound muscle action potential; *CMS*, congenital myasthenic syndrome; *CMS-EA*, congenital myasthenic syndrome with episodic apnea; COLQ, collagen-like subunit gene; *3,4-DAP*, 3.4-diaminopyridine; *HRS,* high-rate stimulation; *LRS*, low-rate stimulation; *MG,* myasthenia gravis; *MuSK*, muscle-specific kinase.

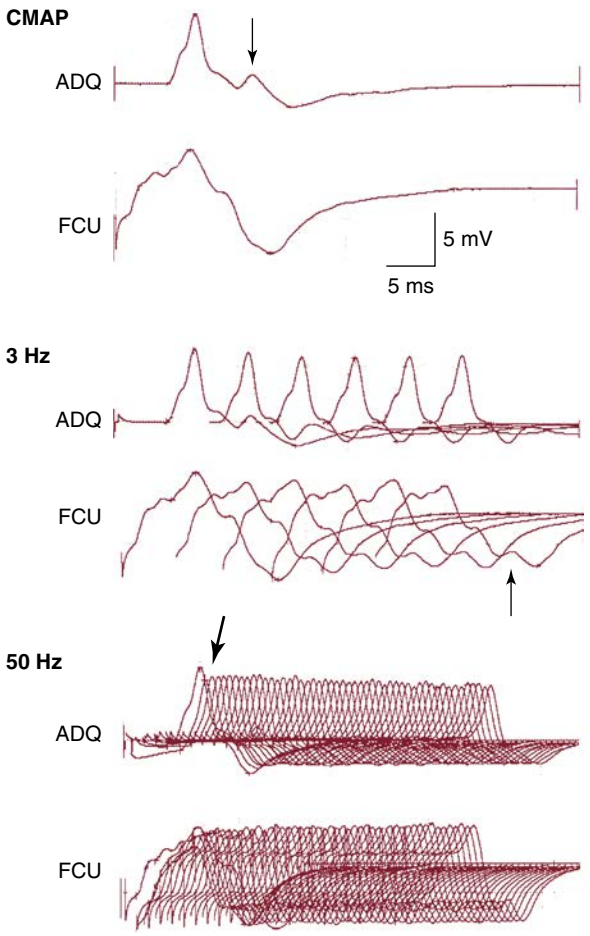


Fig. 19.8 Repetitive nerve stimulation response in the abductor digiti quinti (ADQ) muscle and flexor carpi ulnaris (FCU) muscles in a case of slow channel syndrome. Repetitive discharge (*thin arrow*) in the compound muscle action potential. Decremental response at low-rate stimulation (3 Hz). Dip phenomenon (*thick arrow*) at high-rate stimulation (50 Hz). (From Shieh, P. B., & Oh, S. J. (2018). Congenital myasthenic syndromes. *Neurologic Clinics, 36*, 371. With permission.)

cases in the past. These latter studies can be performed in only a few centers in the world. Fortunately, specific genes are identified in many CMSs, and such a test is now commercially available, making the diagnosis of CMS much easier and faster without sending the patients to the special centers. Thus, once CMS is clinically suspected, the best next step is to request genetic testing for CMS. Conventional muscle biopsy and routine histochemical studies show no major abnormalities except for a type I fiber predominance and occasional minor nonspecific myopathic changes. Serum creatinine kinase (CK) is normal or slightly elevated (Abicht & Lochmüller, 2016).

TREATMENT AND MANAGEMENT

At this time, there is no approved drug for CMS. There are three basic classes of drugs for treatment: (1) cholinergic agonists, which increase the amount of ACh at the neuromuscular junction: AChEIs and 3,4-DAP; (2) open channel blockers, fluoxetine, and quinidine; and (3) two adrenergic agonists: ephedrine and albuterol (Finsterer, 2019; Lee et al., 2018) (Fig. 19.9).

CHOLINERGIC AGONISTS: ACETYLCHOLINESTERASE INHIBITOR AND 3,4-DIAMINOPYRIDINE

AChEIs prolong the activity of ACh by inhibiting ACh breakdown at the synapse. 3,4-DAP is a potassium channel blocker working on the presynaptic nerve terminal by prolonging the motor nerve potential and consequently augmenting the quantal release of ACh at the synaptic cleft.

Acetylcholinesterase Inhibitors

There has not been any systematic study of the benefits of AChEIs. Clinical improvement was documented in case studies. AChEI, mainly pyridostigmine, has been used as the first drug of choice in CMS historically because of the similarity between MG and CMS. It has been effective in most CMSs, except a few CMSs: SCS, endplate AChE deficiency, DOK7, and LRP4, MuSK, and Lamin B2 related CMSs (Finsterer, 2019). In fact, AChEIs worsen symptoms in these CMSs. CMSs that respond to pyridostigmine are CMS due to ChAT deficiency, paucity of the synaptic vesicles and decreased quantal release, the fast channel syndrome, rapsyn mutation, AChR deficiency, and sodium channel syndrome.

Potassium Channel Blocker: 3,4-Diaminopyridine and 3,4-Diaminopyridine Phosphate

In the 1990s, there were two randomized controlled studies on CMS (Anlar, Varli, Ozdirim, & Ertan, 1996; Palace, Wiles, & Newsom-Davis, 1991). Conflicting results were observed. Both studies used the same diagnostic criteria of CMS: fatigable muscle weakness, EMG evidence of abnormal NMT (decrement >10% at 3 Hz stimulation or jitter >53 μs on SFEMG), and absence of AChR-Ab. With 3,4-DAP 15–80 mg/day, the Palace study showed a significant improvement in 10 patients in the open prospective study and in 4 patients on placebo in the double-blind, crossover study (Palace et al., 1991).

On the other hand, the Anlar study did not show any significant difference between the 3,4-DAP group (significant improvement in 5/11) and the placebo group (signficant improvement in 3/11) in 11 patients in the double-blind, placebo-controlled, crossover study (Anlar et al., 1996).

Since 2000, 3,4-DAP has been tried in an open-label study in 21 patients whose gene defects were identified (Oh, 2019). Except for two patients with presynaptic protein mutation (SYT2), 21 patients represented postsynaptic protein mutation (RAPSN mutation, 7; fast channel syndrome, 7; CHRNE mutation, 5; DPAGT, 3; and DOK, 1). "Improvement" was recorded in 20 patients, together with pyridostigmine in 15 patients. One patient with DPAGT1 mutation was not able to take the drug due to side effects. With 3,4-DAPP, clinical improvement, together with jitter improvement, was reported in two patients with CHRNE mutations (Verma, Mazell, & Shah, 2016). Thus, one can conclude that 3,4-DAP alone is not effective but may have an added benefit to AChEIs in many CMS patients with "underactive synaptic activity."

TWO ADRENERGIC AGONISTS: EPHEDRINE AND ALBUTEROL

Two adrenergic agonists are thought to stabilize the neuromuscular junction and reduce the dispersion of AChR (Lee et al., 2018). It is important to recognize that the response is seen over months and in some cases may go on improving beyond 1 year. Ephedrine, which was used for MG treatment

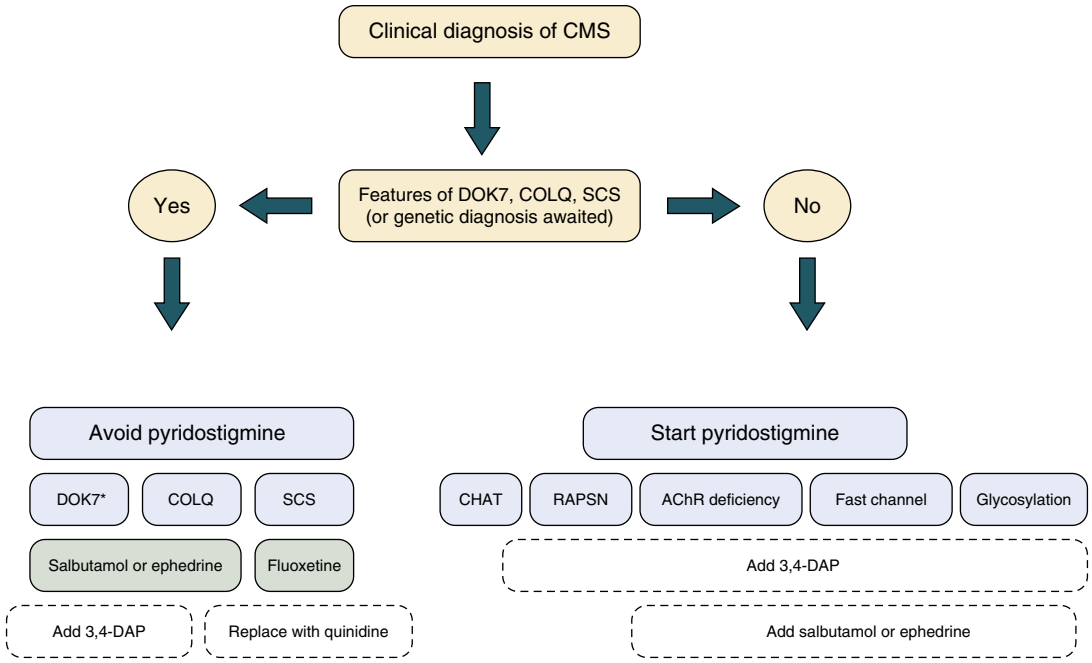


Fig. 19.9 Treatment algorithm for the main congenital myasthenic syndrome subtypes, with second- and third-line treatments shown as *dotted lines*. * Applies to all members of the acetylcholine receptor–clustering complex. (From Lee, M., Beeson, D., & Palace, J. (2018). Therapeutic strategies for congenital myasthenic syndromes. *Annals of the New York Academy of Sciences, 1412*, 132. With permission.)

before AChEIs were introduced, was found to be beneficial in occasional patients with CMS. Felice and Relva (1996) tried ephedrine 25 mg twice a day in three CMS patients: All three patients had long-standing and variable weakness, substantial decremental responses in the RNS test, positive family history, absent AChR antibody, clinical worsening on oral AChEI, and subjective improvement on ephedrine 25 mg/day. In an open study in three patients, all patients admitted to mild improvement in strength and stamina while on ephedrine but failed to show any signficant improvement in forced vital capacity (FVC), muscle strength, hand dynamometer, and RNS test. Subtype of CMS was not identified (Felice & Relva, 1996). With an identification of the specific subtypes of CMS, it became apparent that responsiveness was associated with certain CMS genotypes, namely, COLQ and DOK7 CMS (Lee et al., 2018). Albuterol/salbutamol has been used for ephedrine since the US FDA ban of ephedrine in 2004. According to Lee et al.'s (2018) summary, 32 of 33 DOK7 patients, 6 of 6 COLQ patients, and 3 MuSK, 2 AGRIN, and 2 LRP4 patients showed a clinical improvement with albuterol/salbutamol.

QUINIDINE AND FLUOXETINE (PROZAC)

Quinidine and fluoxetine are long-lived channel blockers of the AChR channel, thereby reducing channel opening time. These drugs provide symptomatic relief in SCS. Fluoxetine is used at doses up to 100 mg daily, and quinidine, at doses of 600–1700 mg.

Harper and Engel (1998) treated six SCS patients with quinidine sulfate in an open-label trial using objective clinical measurement of muscle strength and RNS test as end points. Four patients tolerated the drug well and after 30 days of continuous therapy showed statistically signficant improvement in muscle strength and in decrement of the CMAP at HRS. They concluded that quinidine sulfate appears to be a safe and effective treatment in most patients with SCS, but it should be used with caution because of potential adverse effects such as drug allergy.

Harper, Fukodome, and Engel (2003) studied the effects of fluoxetine in two patients who were allergic to quinidine, with up to 80 to 120 mg of fluoxetine per day over 3 years. Both patients showed subjective and objective improvement by quantitative muscle strength testing using the neuropathy impairment score and EMG. The CMAP increased by 58%–120%, and the decrement improved dramatically at 50-Hz stimulation, decreasing from 72% to 4% in one case and from 67% to 28% in the other. In one case, the repetitive CMAP was less prominent with treatment. These authors interpreted that the progressive improvement on fluoxetine was similar to that observed in SCS patients treated with quinidine and likely corresponds to gradual repair of the endplate myopathy. Chaouch et al. (2012) analyzed their experience on quinidine and fluoxetine in 15 patients with SCS. Quinidine was tried in four patients. Quinidine was tolerated well in all patients and showed a clear benefit in two. Fluoxetine was tried in 10 patients. Three suffered signficant adverse reaction and seven patients exhibited marked to moderate increase in muscle strength, although all patients showed clear improvement in endurability. On the basis of these studies, quinidine and fluoxetine became the drugs of choice for SCS. Quinidine is more likely to cause cardiac conduction defect. Thus, in practice, fluoxetine, a familiar drug to most physicians, is more commonly prescribed (Lee et al., 2018).

PREGNANCY

There is only one report to date on CMS in pregnancy. Servais et al. (2013) analyzed the data on 17 pregnancies in 8 patients with CMS. They concluded that pregnancy deteriorated the clinical manifestations of CMS; affected females recovered within 6 months postnatally, and the outcome of neonates born to females with CMS was fair.

GUIDELINES OF THERAPEUTIC MANAGEMENT

In principle, CMSs that decrease the synaptic response to ACh are best treated with cholinergic agonists that augment cholinergic response, namely, AChEIs (pyridostigmine) and, in some cases, 3,4-DAP. AChEIs increase the number of AChRs activated by each quantum by inhibiting ACh breakdown. 3,4-DAP increases the number of quanta release by nerve impulses. In contrast, CMSs that increase the synaptic response, that is, SCS, are treated with long-lived open-channel blockers of AChR, namely, quinidine and fluoxetine. Thus, theoretically, pyridostigmine should be effective in most CMSs because most patients have CMSs that decrease the synaptic response to ACh.

With the availability of genetic testing, it is much easier for the clinician to decide which treatment mode is best for the CMS patients. Molecular diagnosis should inform the choice of therapy. The following guidelines are based on the most recent reviews on CMS (Engel & Sine, 2005; Lee et al., 2018; Ranawaka, Lalloo, & de Silva, 2013):

1. If the genetic test is not available, pyridostigmine should be tried first in all CMS patients, except in those with DOK7, COLQ, and SCS, in which it is known to worsen symptoms. Typical clinical and electrophysiological features are helpful for the identification of these CMSs: limb-girdle weakness in DOK7, absent pupillary response in COLQ, forearm extensor weakness in SCS, and repetitive discharge in COLQ and SCS (Fig. 19.7).
2. Fluoxetine and quinidine sulfate are the drugs of choice in SCCMS. Both medications act as long-lived open-channel blockers of AChR and gradually improve symptoms over days, weeks, or months.
3. Pyridostigmine should be avoided in the following CMSs because it is reported to worsen symptoms: DOK7, COLQ, SCS, and LRP4, MuSK, and Lamin B2 related CMSs.
4. In endplate AChE deficiency (COLQ) and DOK7, albuterol and ephedrine are known to mitigate their symptoms.
5. ChAT deficiency is treated prophylactically with oral pyridostigmine to prevent respiratory crisis and with parenteral prostigmine methylsulfate during respiratory crisis.
6. Fast-channel syndrome patients, and especially those without AChR deficiency, respond well to combined therapy with pyridostigmine and 3,4-DAP.
7. Patients with rapsyn deficiency respond to pyridostigmine, and some derive a further striking benefit from the use of 3,4-DAP.
8. A patient with sodium channel myasthenia showed improved endurance on treatment with pyridostigmine; additional therapy with acetazolamide, which is known to mitigate periodic paralysis attributed to Nav1.4 mutations, prevented further attacks of respiratory and bulbar weakness.

SNAKEBITE MYASTHENIC SYNDROME

Snakebite is classified by the WHO as a neglected tropical disease (Minton, 1990). Victims of snakebites are mainly from rural population who are bitten during field work and when sleeping outdoors. Most snakes are not venomous and are harmless. Some venomous snakes rarely bite and many venomous snakes make a dry bite. Neurotoxic envenomation by snakes is common in some parts of the world and may lead to fatal respiratory failure. Four families of poisonous snakes (Elapidae, Atractaspididae, Colubridae, and Viperidae) are responsible for most envenomations. Cobras, vipers, and kraits are the principle causes of snakebite deaths in India, Sri Lanka, and Southeast Asia. Thus, most research on this subject are from these countries.

Snake venoms contain complex mixtures of enzymes, polypeptide toxins including neurotoxins, procoagulants, and hemorrhagins producing several organ failures (Menon et al., 2016). The degree of combined organ failures varies depending on the family of poisonous snakes. Among these, neurotoxicity and blood coagulability are two major problems in snake envenomation.

Thus, snakebites are classified into two major categories: hematotoxic snakebites and neurotoxic snakebites. A hematotoxic snakebite is diagnosed from systemic envenomation and prima facie evidence of viperidal bite. Neurotoxic snakebites are made by elapid snakes, such as cobra and krait, which lead to neurotoxic symptoms (Menon et al., 2016).

Envenomed patients usually have fang marks at the site of the bite, local pain, swelling, and discoloration of bite site and develop local tender lymphadenopathy and abdominal pain (Sanmuganathan, 1998; Seneviratne & Dissanayake, 2002). A systemic consumption coagulopathy may develop within 1 to 2 hours of the bite in many patients. Renal failure may ensue in some patients and requires peritoneal dialysis.

CLINICAL MANIFESTATION

Snakebite myasthenic syndrome (SMS) is a reversible syndrome characterized by descending paralysis as noted in MG. SBMS is common in endemic areas such as Southeast Asia but rare in the United States (Sanmuganathan, 1998). Neuromuscular paralysis may set within an hour after the bite. In one series, the onset of neuromuscular paralysis occurred between 30 minutes and 4 hours (Seneviratne & Dissanayake, 2002). Neuromuscular paralysis lasts up to 10 days, with fatigability lasting for 12 days (Seneviratne & Dissanayake, 2002). Fatigability, ptosis, double vision, and external ophthalmoplegia are common findings. These are followed by facial and bulbar palsy producing dysphagia and dysphonia and by proximal muscle weakness. Respiratory failure was seen in severe cases, necessitating mechanical ventilation, and reported in 2%–18% of cases in two series (Anadure, Narayanan, Hande, Singhal, & Varadaraj, 2018; Seneviratne & Dissanayake, 2002). The majority of these patients were bitten by a cobra and krait (Sanmuganathan, 1998). Assisted ventilation with intermittent positive pressure is required usually for 18 and 48 hours. Pupils are spared. Reflexes are normal, and sensory function is preserved. Death from a snakebite is extremely rare, usually due to consumption coagulopathy. Early-morning neuroparalytic syndrome in the tropics is an example of neurotoxic syndrome due to neurotoxic snakebites (Singh, Pannu, Chawla, & Malhotra, 1999).

PATHOPHYSIOLOGY

Historically, snake-venom neurotoxins have been known to produce effects similar to those of curare and MG. SBMS results from the action of two major groups of toxins: presynaptic neurotoxins and postsynaptic neurotoxins (Box 19.4).

Box 19.4 Toxin in Snakebite Myasthenic Syndromes

Presynaptic Toxin[a]	Postsynaptic Toxin
Binds to motor nerve terminals, causing an early depletion of synaptic vesicle and delayed degeneration of the motor nerve terminal	Irreversible binding to the alpha subunit of the acetylcholine receptor
Presynaptic block	Postsynaptic block
Beta-bungarotoxin (krait) Notexin (tiger snake) Taipoxin (Taipan) Crotoxin (Brazilian rattlesnake) Gamma-bungarotoxin (krait)	Alpha-bungarotoxin (Elapidae family): producing irreversible block Cobra toxin: producing reversible block
Tensilon test result: negative	Tensilon test result: positive
More lethal than postsynaptic toxins	Antivenin is effective AChEI: effective if Tensilon test result is positive

AChEI, Anticholinesterase inhibitor
[a] Usually contains phospholipase A2 activity responsible for myotoxicity.

The best known presynaptic toxins are beta-bungarotoxin, taipoxin, and crotoxin. In postsynaptic toxins, the best known toxin is alpha-bungarotoxin. Although there might be some differences in the degree depending on the species of the snake, SBMS is due to the combined presynaptic and postsynaptic neuromuscular blocks. This explains conflicting observations on the edrophonium test and anticholinesterase benefit in this disorder. The edrophonium test showed no positive response (Anadure et al., 2018; Watt et al., 1986), positive response in seven of eight tested cases, and positive response in the placebo-controlled study in eight patients with cobra bite (Connolly et al., 1995). Clinical trials testing anticholinesterase drugs have demonstrated both favorable and unfavorable results (Seneviratne & Dissanayake, 2002). Considering all of the data available, it appears that the presynaptic block is more influential in SMS.

As a rare neurotoxic syndrome, myokymia in timber rattle snake (*Crotalus horridus*), rhabdomyolysis from Russell's viper, and dysautonomia from Malayan krait have been reported.

DIAGNOSIS AND EVALUATION

ELECTROPHYSIOLOGICAL FINDINGS

Nerve conduction study (NCS): Sensory nerve conduction is completely normal. In motor nerve conduction, terminal latencies, nerve conduction velocity (NCV), and F-wave latencies are all normal. Low CMAP was observed in severe cases. There may be a progressive decrease in the CMAP in the first 2–4 days after envenomation, paralleling clinical deterioration.

Needle EMG: MUPs are normal. Fibrillation was detected in all four severe cases but not in milder cases. SFEMG during the recovery phase of the illness revealed markedly increased jitter and blocking in all three tested cases (Connolly et al., 1995). In the RNS test, the CMAP amplitude is normal and low in severe cases (Watt et al., 1986). A decremental response at the LRS is rare and reported in severe cases. In contrast, a decremental response at HRS (30–50 Hz) is common, most marked around 6 days after the bite and more often in milder cases. Sanmuganathan claimed that this is the distinct pattern for SBMS (Seneviratne & Dissanayake, 2002). Connolly observed that the decrement, which was never more than mild at rest, was enhanced dramatically 5 to 30 seconds following exercise or tetanic stimulation. These effects lasted up to 30 minutes (Sundar et al., 2017). This pattern is distinctive and probably reflects the severely depleted numbers of vesicle seen in the motor terminals on electron microscope.

DIAGNOSIS

The diagnosis of SBMS is not that difficult in endemic areas such as Southeast Asia. Extensive diagnostic workup is generally unnecessary, since most patients are fully aware of the snakebite. Differentiation of nonvenomous and venomous snakebites is beyond the scope of this chapter. In general, the presence of local pain, swelling, and discoloration and regional lymphadenopathy permits early recognition of a venomous snakebite. Ptosis, double vision, and difficulty in opening the mouth and protruding the tongue are usual early sign of SBMS. Enzyme-linked immunosorbent assay for the detection of snake venoms is generally available in Australia and other nations to aid in determining the specific snake species involved in a bite. These kits identify venom in the victim's blood, urine, and wound aspirate (Menon et al., 2016).

In view of the clinical similarity between snakebite myasthenic syndrome and MG, including myasthenic crisis, serum AChR-Ab was tested in some patients. False-positive results were reported in two patients who received antisnake venom before the blood was drawn for the test for AChR-Ab. In the third patient, the blood was drawn for AChR-Ab before and after antisnake venom treatment. AChR-Ab was negative in the blood drawn before antisnake venom treatment but positive in the blood drawn after antisnake venom treatment, confirming that the antisnake venom was responsible for the false-positive AChR-Ab result (Harris & Goonetilleke, 2004).

TREATMENT AND MANAGEMENT

Specific antivenom treatment is the mainstay of hospital treatment for venomous snakebite. There is no universal consensus with regard to AChEI usage in SBMS. In case of respiratory failure, supportive ventilatory care should be provided. In addition to SBMS, there are other life-threatening complications of snake envenomation: hypovolemic shock, coagulopathy, and acute renal failure. These have to be diagnosed and treated accordingly medically. Often, these other complications are the cause of death in venomous snakebite.

ANTIVENOMS

Specific antivenoms should be used in accordance with local national protocol as soon as systemic poisoning including neurotoxicity is apparent but should be administered in a

medical facility (good practice) (Sanmuganathan, 1998), although the evidence for antivenom treatment is not strong (Minton, 1990). Some antivenoms are specific for venom of one snake species, whereas others are polyvalent against venoms of all snakes of a particular geographic area (in the United States, antivenin Crotalidae polyvalent [ACP]; in Australia, tiger snake antivenom). Antivenoms used in the past 35 years have been equine derived. Antivenom is administered intravenously but should be administered in a facility where acute anaphylaxis and serum sickness can be treated. Physicians should be present for antivenom administration, and epinephrine and an antihistamine should be at the bedside. In a retrospective study, rates for acute allergic reaction with ACP administration range from 23% to 56%, with even higher rates for delayed serum sickness. Ideally, antivenom is administered within 4 hours of snakebite, but it is effective for at least the first 24 hours. Antivenom is known to be effective in postsynaptic neurotoxins (Juckett & Hancox, 2002). It accelerates dissociation of the toxin from the postsynaptic receptor. Presynaptic toxins have no response to antivenoms. In recent years, the ovine (sheep-derived) antivenom has been approved. A prospective study showed that the ovine antivenom showed a significantly lower incidence of adverse reactions and nearly all events are mild to moderate (Ariaratnam et al., 2001; Gerardo et al., 2017). A randomized, double-blind, placebo-controlled clinical trial on the basis of 74 patients (45 ovine, 29 placebo) concluded that treatment with ovine antivenom reduces limb disability measured by the patient-specific functional scale 14 days after copperhead envenomation (Watt, Smith, Kaewsupo, & Davisi, 1994).

ACETYLCHOLINESTERASE INHIBITORS

Experimentally, the neuromuscular blocking activity of snake-venom fractions can sometimes be reversed by AChEIs (Rusyniak & Nañagas, 2004), but clinical trials have demonstrated conflicting results: both favorable and unfavorable results. Unfortunately, these trials have been uncontrolled, and most have lacked objective data. Watt et al. conducted a placebo-controlled, double-blind, crossover trial of IV edrophonium in 10 SBMS patients by cobra bites and found significantly more improvement in ptosis and endurance of upward gaze after edrophonium than after placebo (class II) (Connolly et al., 1995). Further, they also found that this test accurately predicted the eventual response to neostigmine. They controlled neurological signs and symptoms by careful titration of the amount of neostigmine for each patient, beginning with 25 μg per kilogram of body weight per hour delivered by continuous infusion. No additional antivenom was given to any patient. No severe reactions were observed. Abdominal pain was the most frequent side effect and was easily controlled with atropine. Watt et al.'s dramatic experience with the edrophonium test and a subsequent good response with neostigmine is most likely due to the selection of patients with cobra bite. Cobra toxin is known to be a postsynaptic blocker. The edrophonium test has been used by some to identify SBMS patients who will respond to anticholinesterase medications (Connolly et al., 1995) (class IV). Six out of seven patients with a positive response to the edrophonium test who were treated with oral neostigmine made a full recovery within 8 days. In India, the neostigmine test is usually used because of easy availability of the drug (Sanmuganathan, 1998). If the neostigmine test is positive, 0.5 mg of neostigmine is injected intravenously with 0.6 mg of atropine. The same is repeated at half hourly intervals to a total of five doses. This is followed up by repeat injections at increasing intervals of 2–12 hours. If there is no improvement in symptoms after 1 hour, neostigmine should be stopped.

SUPPORTIVE TREATMENT

Artificial respiratory support is mandatory and life-saving if respiratory failure occurs (good practice point). The respiratory failure caused by venom neurotoxins may be difficult to reverse with antivenom. This may be because antivenom is known to be more effective on postsynaptic neurotoxins (Juckett & Hancox, 2002). It accelerates dissociation of the toxins from the postsynaptic receptor. Intermittent positive pressure ventilation with or without tracheostomy is often needed. It may be used alone or combined with antivenom and neostigmine-atropine. Artificial respiratory support often is needed for 14 to 48 hours in cases of krait and cobra bites and was required for more than 10 weeks in an Australian snakebite case (Menon et al., 2016). The patient eventually recovered.

ORGANOPHOSPHATE INTOXICATION

Orgnophosphate poisoning (OPP) is a major global health problem, with 1 million serious accidental and 2 million suicidal poisonings due to insecticides worldwide, every year, of which 200,000 die; most of these deaths occur in developing countries including India and Sri Lanka. OPP is the most common mode of suicidal poisoning in India. Thus, most work is from these countries. Although its possibility is small, the potential use of organophosphous "nerve gas" (e.g., tabun [GA], sarin [GB], soman [GD]) in chemical warfare continues to be a serious concern.

PATHOPHYSIOLOGY

Organophosphates (OP) are a class of compounds that inhibit cholinesterases, including AChE. Organophosphates cause toxicity after their absorption from the skin, mucous membranes and respiratory tract following accidental exposure, or from the GI tract following suicidal ingestion (Singh & Sharma, 2000).

Following the release of ACh in response to a nerve impulse and subsequent depolarization of ACh receptor at the postsynaptic membrane, ACh is quickly hydrolyzed by AChE, allowing for the repolarization of the postsynaptic membrane. OP, by inhibiting AChE, results in excessive accumulation of ACh at the various cholinergic receptors: the preganglionic and postganglionic parasympathetic and sympathetic nervous system, CNS, and neuromuscular junctions. Excess of ACh stimulates muscarinic and nicotinic receptors, resulting in an acute cholinergic syndrome, including excessive pulmonary secretions, muscle weakness, and CNS depression. Binding of OP with AChE is initially reversible, but after the passage of time, this binding becomes irreversible due to aging of AChE. Following inhibition, recovery of this enzyme occurs slowly at a rate of about 1% per day (Wadia, Sadagopan, Amin,

& Sardesai, 1974). Restoration of AChE occurs by spontaneous rephosphorylation of the enzyme and by new enzyme synthesis.

CLINICAL MANIFESTATION

OPP leads to three distinct main syndromes: acute cholinergic crisis, intermediate myasthenic syndrome (IMS), and OP-induced delayed polyneuropathy (OPIDPN) (Table 19.9).

ACUTE CHOLINERGIC CRISIS

OP being an inhibitor of esterases, particularly AChE, leads to acute cholinergic syndrome. The clinical effects from an acute poisoning can be separated into autonomic nervous system, neuromuscular junction, and CNS categories. Increased parasympathetic muscarinic activity results in the classic SLUDGE (salivation, lacrimation, urination, defecation, gastric secretions, and emesis) or DUMBBELS (defecation, urination, miosis, bronchorrhea, bradycardia, emesis, lacrimation, salivation) syndrome. Miosis is a commonly recognized feature of OPP and is reported to be present in 65% to 95% of cases (Singh & Sharma, 2000). Excess nicotinic stimulation at the neuromuscular junction is responsible for rapid depolarization with muscle fasciculations, followed by receptor blockade manifesting as weakness and/or paralysis. Paralysis can occur both during acute cholinergic syndrome and several days after acute cholinergic syndrome. Paralysis may lead to respiratory failure, requiring mechanical ventilation, and is thought to be the most common cause of death in acute poisoning. Paralysis usually passes off within 48–72 hours, but complete clinical recovery may take up to a week after exposure to OP. CNS effects are from excessive nicotinic and muscarinic stimulation in the brain. Commonly reported symptoms are agitation, depressed mental status, coma, and seizures. Seizures are more commonly associated with the chemical nerve agents (Singh & Sharma, 2000).

INTERMEDIATE MYASTHENIC SYNDROME

After the resolution of cholinergic effects in acute cholinergic crisis, but before the onset of OPIDPN, a myasthenia-like syndrome can occur due to a prolonged action of ACh on the nicotinic receptors. This is termed *intermediate myasthenic syndrome* (IMS). The incidence of IMS was reported to be between 5% and 65% of patients of OPP. Symptoms typically occur 1 to 3 days after the acute cholinergic crisis and are characterized by weakness in the neck and proximal muscles, less often in the ocular, bulbar, and respiratory muscles. Reflexes are absent in 50% cases in one series (Wadia, Chitra, Amin, Kiwalkar, & Sardesai, 1987). IMS is distinguished from acute cholinergic crisis by the lack of other muscarinic symptoms and lack of response to atropine. It is also distinguished from OPIDP in that the latter affects distal muscles and spares the cranial nerves and respiratory muscles. Prolonged suppression of the AChE is seen during this stage. Full recovery eventually occurs in 4–18 days. No specific therapy has been shown to be beneficial in the treatment or prevention of IMS. Recognition of IMS, however, is critically important as respiratory failure is fatal without adequate ventilatory care. The mainstay of treatment is to provide respiratory support in the form of mechanical ventilation. Atropine is not effective in this syndrome.

ORGANOPHOSPHATE-INDUCED DELAYED POLYNEUROPATHY

OPIDPN is common following exposure to OP that have weak AChE activity, e.g., triorthocresyl phosphate. However, exposure to commonly available OP that have a strong AChE activity is distinctly uncommon (Wadia et al., 1987).

Table 19.9 Pathophysiology and Clinical Features of Various Syndromes in Organophosphate Poisoning

	Acute Cholinergic Crisis	Intermediate Myasthenic Syndrome	OPIDP
Frequency		11%–68%	1.5%
Pathophysiology	Excessive ACh at the CNS, ANS, and neuromuscular junction (muscarinic syndrome)	Excessive ACh at neuromuscular junction (nicotinic syndrome)	Phosphorylation and aging of neuropathy target esterase in the nervous system
Time to onset		1 to 3 days after acute cholinergic crisis	1 to 4 weeks after exposure
Clinical features	SLUDGE Neuromuscular paralysis CNS symptoms: agitation, decreased mental status, coma, and seizure	Myasthenic syndrome: weakness of the proximal and neck muscle followed by cranial nerve palsy and rarely respiratory failure	Predominantly motor polyneuropathy followed by spastic myelopathy
Electrophysiology	Repetitive discharge Decrement-increment at 30–50 Hz stimulation	Repetitive discharge Decrement or decrement-increment at 30–50 Hz stimulation	Axonal motor neuropathy Needle EMG: fibrillation/PSW
Recovery	Typically in 2–3 days	Typically occurs in 4–18 days	Slow recovery
Treatment	Atropine Diazepam for seizure Oximetherapy	Typically occurs in 4–18 days Respiratory care	Physical therapy

ACh, Acetylcholine; *ANS*, autonomic nervous system; *CNS*, central nervous system; *EMG*, electromyography; *OPIDP*, organophosphate-induced delayed polyneuropathy; *PSW*, positive sharp wave; *SLUDGE*, salivation, lacrimation, urination, defecation, gastric emesis, emesis.

OPIDP is the result of the phosphorylation and aging of a protein found in nervous tissue known as neuropathy target esterase, which is present in the brain, spinal cord, and peripheral nerves (Watt et al., 1994). The symptoms of OPIDPN begin 1 to 4 weeks after exposure, long after cholinergic signs have worn off. The earliest symptoms are paresthesias and calf pain. This is soon followed by weakness in the distal muscles of the legs over a 2-week period. Examination showed a predominately motor length–dependent polyneuropathy with weakness of the distal limb muscles. Clinical involvement of the corticospinal tracts and the dorsal columns becomes apparent when the peripheral neuropathy improves. No treatment is currently available for OPIDP. Over time, patients may regain some function. Other neurobehavioral changes and some extrapyramidal symptoms were also reported as a chronic neurological sequelae persisting after cessation of exposure.

DIAGNOSIS AND EVALUATION

ELECTROPHYSIOLOGIC FINDINGS

Motor NCV and distal latencies are normal even in a severely paralyzed patient.

Needle EMG was done in 18 cases in IMS. No case showed fibrillation or positive sharp waves (PSW). MUPs were normal (Gutmann & Besser, 1990). In OPIDP, axonal motor neuropathy was found in NCS and needle EMG showed fibrillations and PSW.

The RNS test shows a rather distinct pattern indicative of an excessive cholinergic state: (1) the repetitive discharges in the CMAP with a single stimulation and (2) decrement-increment phenomenon with a high rate of stimulation (10–50 Hz). (Fig. 19.8 shows the repetitive discharges seen in some CMS that are similar of what is seen in OPP.) These are due to depolarization block due to an excess of ACh. The CMAP with repetitive discharges is the earliest and most frequent abnormality of excessive ACh regardless of severity of poisoning. Therefore, this is the most sensitive indicator of the action of AChEIs at the endplate. The repetitive discharges are also seen in pyridostigmine intoxication such as cholinergic crisis in MG and two congenital myasthenic syndromes: slow channel myasthenic syndrome and AChE deficiency. With the progression of weakness, the decrement-increment response, a unique abnormality seen only in the excessive cholinergic state follows. Unlike MG, the decrement is maximal by the second stimulus, and this is followed by a gradual increment.

These various RNS abnormalities are useful in staging the severity of OPP and following its progress (Eddleston, Szinicz, Eyer, & Buckley, 2002; Jayawardane et al., 2008). The CMAP with repetitive discharges is seen early and virtually always present. The decrement-increment phenomenon occurs next in the course of intoxication and may be associated with minimal or no clinical weakness. The decrement response occurs with more severe intoxication. The degree of the decrement response may reflect the severity of weakness, and the subsequent improvement in the decrement heralds the onset of clinical recovery (Jayawardane et al., 2008).

DIAGNOSIS

The diagnosis of OPP is made on clinical grounds: history of exposure with OP and the clinical features of cholinergic excess. Confirmation of OPP is based on the measurement of cholinesterase activity. Typically, these results are not readily available. Although erythrocyte and plasma (pseudo) cholinesterase levels can both be used, the erythrocyte cholinesterase test is more accurate of the two measurements because it reflects better the AChE found in neural synapses. On the other hand, plasma cholinesterase is easier to assay and is more readily available. The usefulness of these tests is further limited by the lack of good correlation with severity of clinical illness, the considerable interindividual variation, and the effects by other disease states. Thus, it appears that, at best, the tests can be useful as a marker of OP exposure (Singh & Sharma, 2000). Field and fast methods using paper strips are also available in India (Wadia et al., 1974).

TREATMENT AND MANAGEMENT

The WHO and Eddleston et al. (Wadia, 2003) urge the restriction of use of class I pesticides (extremely toxic). They urge a ban or major restriction of use of class 1 pesticides and reduction of pesticide use to a minimal number of less hazardous compounds (Aggarwal & Jamshed, 2008). In 1981, Jordan banned parathion use, and poisoning autopsies in Amman fell from 50 a year in 1981 to below 10 in 1983 to 1985 (Aggarwal & Jamshed, 2008). In Samoa, the same finding occurred after banning paraquat. Wadia recommended banning of aluminum phosphide and high concentration formulations as the first goal in preventing the mortality of OPP in India (Aggarwal & Jamshed, 2008).

ACUTE MANAGEMENT

During acute cholinergic crisis, the mainstay of medical therapy includes atropine, pralidoxime (2-PAM), and benzodiazepines.

During acute cholinergic crisis, the initial therapy should be immediate removal of patients from further OP exposure and aggressive use of atropine as an antidote to counter the muscarinic effects of ACh. All cases require an aggressive decontamination with complete removal of the patient's cloths and vigorous irrigation of the affected area. In OP ingestion, the position statement by the American Academy of Clinical Toxicology and European Association of Poison Centers and Clinical Toxicologists states that gastric lavage should be considered only if a poisoned patient presents within 1 hour of ingestion of a potential toxic amount. However, gastric lavage is routinely used, particularly in developing countries (Buckley, Eddleston, & Szinicz, 2005; Peter et al. 2006). Apparently this is due to the lack of any good studies to settle this issue. In warfare, potential use of OP requires the availability of gas masks. For practical guide for the current pharmacological treatment for OPP, I provide Eddleston and Chowdhury's recommendation (Table 19.10) (Connors, Harnett, & Hoffman, 2014).

ATROPINE

Atropine is primarily effective in treating the muscarinic effects of OPP, especially in its effects on bronchial secretion. It has no effects on the neuromuscular junctions. Atropine crosses the blood-brain barrier and counters the effects of excess ACh on the extrapyramidal system. Thus, atropinization is the most important mode of treatment during acute cholinergic crisis and can be achieved with the judicious

Table 19.10 Eddleton and Chowdhury Recommendations on Pharmacological Treatment for Organophosphorus (OP) Poisoning

Drug Name	Type	Dose
Atropine	Antimuscarinic	• Give a bolus loading dose of 0.6 to 3 mg, rapidly IV. • Then administer doubling doses every 5 minutes until the patient is a tropinized (HR >80 bpm, SBP >80 mm Hg, clear lung). • Once the patient is atropinized, give an infusion of 10%–20% of the total dose required to atropinize the patient each hour in 0.9% saline chloride. • Watch the patient carefully for recurrent cholinergic toxicity or onset of atropine toxicity (see later). • If cholinergic toxicity recurs at any point, restart the bolus doses until the patient is atropinized again and increase the infusion rate by 20% per hour. • If the patient becomes atropine toxic (tachycardia, absent bowel sounds, hyperthermia, delirium, urinary retention), stop the infusion for 30 minutes and then start again at a 20% lower dose.
Pralidoxime	Oxime AChE reactivator	• Give a loading dose of 20–30 mg kg^{-1} over 30 minutes. • This dose can be repeated at 6–8-hour intervals. • Alternatively, a continuous infusion of 5–10 mg kg^{-1} h^{-1} can be given in 0.9% sodium chloride. • The duration of treatment is uncertain. Treatment can be stopped at 48 hours and then restarted if clinical or electrophysiological deterioration occurs. • Monitoring of red cell AChE activity can be helpful.
Obidoxime	Oxime AChE Reactivator	• Give a loading dose of 250 mg over 30 minutes. • Then give a continuous infusion of 750 mg every 24 hours until clinical recovery.
Diazepam	GABA-A agonist	• Give 10–20 mg IV to agitated patients or patients with impaired respiration for whom intubation and ventilation are available.

Doses are given for the antidotes widely used for OP insecticide poisoning. The evidence for these doses is generally weak.
From Eddleston & Chowdhury *British Journal of Clinical Pharmacology*, 2015, 81, 463.
AChE, Acetylcholinesterase; *bpm*, beats per minute; *GABA*, gamma-aminobutyric acid; *HR*, heart rate; *IV*, intravenous; *SBP*, systolic blood pressure.

use of atropine. As many as 38 dose schedules of atropine have been cited by different authors. Atropinization, once achieved, should be maintained for 3–5 days, depending upon the compound involved. The end point of atropinization is clearing of lung, heart rate >80 beat per minutes, and systolic blood pressure >80 mm Hg. Tachycardia and mydriasis must not be used to limit or to stop subsequent doses of atropine. According to the most cited schedule, the initial recommended dose of atropine is to begin IV administration at 2 to 5 mg in adults or 0.05 mg/kg in children and should be given 3 to 5 minutes until pulmonary secretions clear (Singh & Sharma, 2000). The current recommendation is to achieve atropinization within 1 hour (Connors et al., 2014). This new regimen reduces the mean time or atropinization from 152 minutes to 24 minutes and was associated with a reduction in mortality from 22.5% to 8%. An alternative to repeated doses of atropine is a continuous infusion (0.02 to 0.08 mg/kg/hour) after the initial bolus has been given (Singh & Sharma, 2000). Glycopyrrolate (Robinul) may be considered as an alternative to atropine when the patient develops too much central anticholinergic delirium or agitation. Glycopyrrolate does not enter the brain and so will not cause toxic delirium, but it does not dry up secretions as much as atropine does.

OXIMES

Cholinesterase reactivators (oximes) should be theoretically effective as an antidote for OPP. Oximes work by removal of the phosphoryl group from the inhibited AChE enzyme, resulting in enzyme reactivation. When given before aging (permanent inhibition of the cholinesterase enzyme), oximes are generally regarded as effective treatments in reversing nicotinic sign. Pralidoxime is the most commonly used oxime worldwide. However, a meta-analysis of various trials did not conclusively prove the efficacy of PAM (Buckley et al., 2005; Pawar et al., 2006). Unfortunately, in the trials that were analyzed, PAM was used in doses lower than that recommended by the WHO (Eddleston & Chowdhury, 2015). A recent trial reported from India showed beneficial effects with high doses of PAM in patients with moderately severe OPP, particularly when it is given within 2.5 hours of exposure (Rusyniak & Nañagas, 2004). This study showed reduced mortality, from 8% to 1%, as well as a reduced incidence of pneumonia and intubation, and a reduced need for atropine and ventilation. The initial dose was 2 gm of PAM (as the iodized salt), followed by 1 gm every hour as an infusion for 48 hours, and then 1 gm every 4 hours until recovery. A second oxime, obidoxime, is also available. In vitro tests of human red cell AChE reactivation showed that it is significantly more potent than PAM. There has been no formal comparative randomized control study of obidoxime as yet (Connors et al., 2014).

DIAZEPAM

Seizures from OPP are rare. Although seizures are more commonly associated with the chemical nerve agents, in

one case series of pesticide poisoning, seizures occurred in as many as 13% of patients (Krendel, 1990). Seizures from OPP are thought to be initiated from increased ACh levels and atropine response. Ongoing seizure activity is due to subsequent glutamate release and is not responsive to atropine. Diazepam, which is known to potentiate the effects of gamma-aminobutyric acid (GABA) and facilitate inhibitory GABA neurotransmission, has been effectively used for control of OPP. It now appears that diazepam may also be beneficial in patients without seizures, in whom it may protect the CNS and reduce mortality (Aggarwal & Jamshed, 2008). For seizure control, the usual dose is 5–15 mg IV every 5–10 minutes as needed.

HYPERMAGNESEMIA-INDUCED PARALYSIS

Hypermagnesemia is an uncommon clinical finding, and symptomatic hypermagnesemia is even less common. This disorder is rare because the normal kidney is able to eliminate excess magnesium by rapidly reducing its tubular reabsorption to almost negligible amounts (Sghirlanzoni, Peluchetti, Mantegazza, Fiacchino, & Cornelio, 1984).

The most common cause of hypermagnesemia is renal failure. The ingestion of magnesium-containing medications (e.g., antacids, cathartics) can exacerbate the condition. In the treatment of eclampsia, hypermagnesemia is induced deliberately and sometimes can be symptomatic.

Normally, the serum magnesium level is 1.5 to 2.5 mEq/L. Above 5 mEq/L, deep tendon reflexes are depressed. Reflexes are usually absent at levels of 9 to 10 mEq/L, and weakness is usually seen in that range. At levels greater than 14 mEq/L, there may be severe cardiac arrhythmias or respiratory failure.

Magnesium impairs NMT primarily by reducing ACh release. Calcium entry into the presynaptic terminal is necessary for ACh release, and magnesium competitively blocks calcium entry. Thus, hypermagnesium produces presynaptic block.

DIAGNOSIS AND EVALUATION

Muscle weakness in hypermagnesemia resembles LEMS, hyporeflexia, and limb weakness, usually sparing the extraocular muscles.

In two reported cases of weakness due to hypermagnesemia, electrophysiological findings resembled those of LEMS: low CMAP amplitude, incremental response (186%–300%) after exercise, decremental response at low rate of stimulation, and incremental response (254%) at HRS.

A diagnosis of hypermagnesemia is suspected in the right clinical set-ups, confirmed by the serum level of magnesium.

TREATMENT AND MANAGEMENT

Because magnesium-induced weakness is almost always iatrogenic, prevention is usually possible. Avoidance of magnesium-containing compounds in patients with renal failure is the most important preventive measure. Treatment of hypermagnesemia depends on the severity of the clinical manifestations. In mild cases, discontinuation of magnesium or furosemide 20–80 mg/daily PO may be all that is required. In serious weakness, IV calcium gluconate (100–300 mg calcium IV diluted in 150 mL D5W over 10 minutes) will usually produce prompt improvement.

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20 Treatment and Management of Muscular Dystrophies[1]

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Muscular dystrophies have long been recognized as heterogeneous inherited disorders, characterized by progressive skeletal muscle degeneration, weakness, and dystrophic changes in muscle biopsy. These diseases are known to have autosomal dominant, recessive, or X-linked inheritance. Clinical observations initially led to classification into six groups: Duchenne like, Emery-Dreifuss type, limb-girdle type, facioscapulohumeral peroneal type, distal myopathies, and oculopharyngeal type (Emery, 2002). The expanding genetic and molecular understanding of the muscular dystrophies has further complicated their classification. An updated classification system for these disorders is shown in Table 20.1.

The underlying molecular defects responsible for these disorders are found throughout the cellular structure, including extracellular matrix (ECM) structural proteins and glycosylation enzymes, transmembrane- and sarcolemma-associated proteins, cytoplasmatic proteases, and cytoplasmic proteins associated with organelles and sarcomeres and nuclear membrane proteins. These diseases have provided a window to a better understanding of sarcolemmal organization and the underlying muscle biology responsible for the structure and maintenance of normal muscle cell function. The relationships between these proteins are complex; the function of each of the defective proteins, including the most investigated one, dystrophin, is not entirely known. Structural, enzymatic, and signaling dysfunctions provide the basis for the pathophysiology that has been associated with these disorders. Fig. 20.1 shows a current depiction of the muscle membrane as well as other areas of the muscle fiber associated with muscular dystrophies.

DYSTROPHINOPATHIES

Dystrophinopathies are a group of dystrophies resulting from mutations in the dystrophin (*DMD*) gene, located on the short arm of the X chromosome in the Xp21 region (Baumbach, Chamberlain, Ward, Farewell, & Caskey, 1989). Duchenne muscular dystrophy (DMD) is the most common dystrophinopathy and represents a complete absence of the subsarcolemmal protein dystrophin. Becker muscular dystrophy (BMD), which is rarer, involves a decrease in the quantity or quality of the dystrophin protein. This gives rise to a milder disease with variable severity and time of clinical onset. Other phenotypes associated with mutations in the dystrophin gene include *DMD*-associated dilated cardiomyopathy and in the milder spectrum of the disease asymptomatic elevation of creatine phosphokinase (CK), muscle cramps, and myoglobinuria (Aartsma-Rus, Ginjaar, & Bushby, 2016).

DUCHENNE AND BECKER MUSCULAR DYSTROPHIES

The clinical and pathologic features of DMD were first described in 1851 by Edward Meryon, an English physician, in a communication about eight boys in three British families who had the disease. Several years later, in 1868, the French neurologist Guillaume-Benjamin Duchenne described the same syndrome in detail, and it ultimately would bear his name. Several other meticulous descriptions of the disease can be found in the early literature.

The incidence of DMD has been estimated at approximately in 3300 male births (Brooks & Emery, 1977; Jeppesen, Green, Steffensen, & Rahbek, 2003). The most common mode of inheritance is X-linked recessive, but approximately 30% of cases are spontaneous mutations with no demonstrable family history (Brooks & Emery, 1977; Moser, 1984; Scheuerbrandt, Lundin, Lövgren, & Mortier, 1986; van Essen, Busch, te Meerman, & ten Kate, 1992). Males are primarily affected, but females may manifest symptoms of DMD if they also exhibit skewed X-inactivation, wherein the abnormal X chromosome is expressed in an excessively abnormal proportion (Kinoshita, Ikeda, Yoshimura, Saku, & Watanabe, 1990; Lesca et al., 2003; Pena, Karpati, Carpenter, & Fraser, 1987; Yoshioka, Itagaki, Saida, & Nishitani, 1986).

MOLECULAR PATHOGENESIS

The *DMD* gene, located in chromosome Xp21.2-p21.1, consists of 86 exons (including seven promoters linked to unique first exons). The gene, which spans a genetic distance of more than 2.5 million base pairs (Burmeister & Lehrach, 1986), is the largest isolated human gene. The most common mutation responsible for DMD and BMD is a deletion spanning one or multiple exons. Such deletions account for 60%–70% of all DMD cases and 80%–85% of BMD cases. Point mutations are responsible for around 26% of DMD cases and 13% of BMD cases. Exonic duplications account for 10% to 15% of all DMD cases and 5% to 10% of BMD cases. Subexonic insertions, deletions, splice mutations, and missense mutations account for the rest of the cases (Flanigan et al., 2009; Tuffery-Giraud et al., 2009).

[1]The authors wish to acknowledge previous edition contributors to this chapter, including Peter O'Carroll, MD, and Robert Leshner, MD.

Table 20.1 Pathophysiological Classification of Muscular Dystrophies

Disease	Locus	Gene	Mode of Inheritance
Limb-girdle muscular dystrophy (LGMD) caused by sarcolemma or cytosolic protein defects			
Duchenne/Becker MD	Xp21	Dystrophin	XR
LGMD 1A (myofibrillar myopathy)	5q31	Myotilin	AD
LGMD 1B (Emery-Dreifuss muscular dystrophy)	1q21	Lamin A/C	AD
LGMD 1C (rippling muscle disease)	3p25	Caveolin	AD
LGMD 1D (D1 DNAJB6-related LGMD)	7q36	DNAJB6	AD
LGMD 1E (myofibrillar myopathy)	6q23	Desmin	AD
LGMD 1F (D2 TNP03-related LGMD)	7q32	Transportin-3	AD
LGMD 1G (D3 HNRNPDL-related LGMD)	2q37	HNRDL	AD
LGMD 1H LGMD 1L (D4 calpain-3–related LGMD)	3p23-25 15q15.1	Unknown—not confirmed Calpain-3	AD
LGMD 2A (R1 calpain-3–related LGMD)	15q15.1	Calpain-3	AR
LGMD 2B (R2 dysferlin–related LGMD)	2p13.1	Dysferlin	AR
LGMD 2C (R5 γ-sarcoglycan–related LGMD)	13q12	Gamma-sarcoglycan	AR
LGMD 2D (R3 α-sarcoglycan–related LGMD)	17q21	Alpha-sarcoglycan	AR
LGMD 2E (R4 β-sarcoglycan–related LGMD)	4q12	Beta-sarcoglycan	AR
LGMD 2F (R6 δ-sarcoglycan–related LGMD	5q33	Delta-sarcoglycan	AR
LGMD 2G (R7-telethonin–related LGMD)	17q11.2	Telethonin (TCAP)	AR
LGMD 2H (R8 TRIM 32– related LGMD)	9q31-q33	Tripartite motif-containing 32 (TRIM32)	AR
LGMD 2I (R9-FKRP–related LGMD)	13q13.3	Fukutin-related protein (FKRP)	AR
LGMD 2J (R10-Titin–related LGMD)	2q31	Titin	AR/AD
LGMD 2K (R11-POMT1–related LGMD)	9q34.1	Protein-O-mannosyl-transeferase (POMT1)	AR
LGMD 2L (R12-anoctamin 5–related LGMD)	11p14.3	ANO5	AR
LGMD 2M (R13-fukutin–related LGMD)	9q31	Fukutin	AR
LGMD 2N (R14 POMT2–related LGMD) LGMD 2O (R15 POMGNT1–related LGMD) LGMD 2P (R16 α-dystrolycan–related LGMD) LGMD 2Q (R17 plectin–related LGMD) LGMD 2R (myofibrillar myopathy) LGMD 2S (R18 TRAPPC11–related LGMD) LGMD 2T (R19 GMPPB–related LGMD) LGMD 2U (R20 ISPD–related LGMD) LGMD 2V (Pompe disease) LGMD 2W (PINCH-2–related myopathy) LGMD 2X (BVES-related myopathy) LGMD 2Y (TOR1AIP1-related myopathy) LGMD 2Z	14q24 1p32 3p21 8q24 2q35 4q35 3p21 7p21 17q25 2q14 6p21 3q13,33 6q21	POMT2 POMGnT1 DAG1 Plectin 1f Desmin TRAPPC11 GMPPB ISPD GAA LIMS2 BVES POGLUT1 POPDC1	AR AR AR AR AR AR AR AR AR AR AR AR
Congenital muscular dystrophy (CMD) secondary to glycosylation disorder			
Fukuyama MD (syndromic)	9q31	Fukutin	AR
Muscle-eye-brain disease (syndromic)	1p34.1	Protein O-linked mannose b1,2-Nacetylglucosamin-yltransferase (POMGnT1)	AR
Walker-Warburg syndrome (syndromic)	9q34.1	Protein-O-mannosyl-transeferase (POMT1)	AR
MDC 1A (merosin-negative CMD)	6q22-23	Laminin-a2 (merosin)	
MDC 1B (merosin-positive CMD)	1q42	?	AR
MDC 1C	19q13.3	Fukutin-related protein (FKRP)	AR
MDC 1D	22q12.3-q13.1	LARGE	AR

Continued

Table 20.1 Pathophysiological Classification of Muscular Dystrophies—cont'd

Disease	Locus	Gene	Mode of Inheritance
Other congenital muscular dystrophies			
CMD with early rigid spine (RSS)	1p36	Selenoprotein N-1	AR
CMD with ITGA7 mutations	12q	Integrin α7	AR
Ullrich syndrome/Bethlem myopathy	21q22.3 (A1, A2) 2q37 (A3)	Collagen VI α1, α2, and α3	AD
Muscular dystrophies secondary to nuclear envelope defects			
Emery-Dreifuss MD X1	Xq28	Emerin	XR
Emery-Dreifuss MD X2	q21.2	Lamin A/C	AD
Emery-Dreifuss MD X3	1q21.2	Lamin A/C	AR
Emery-Dreifuss MD X4	6q25	Synaptic nuclear envelope protein 1 (SYNE1; Nesprin-1)	AD
Emery-Dreifuss MD X5	14q23	SYNE2	AD
Emery-Dreifuss MD X6 Emery-Dreifuss MD X7?	Xq26 3p25.1	Four-and-a-half-LIM protein 1 (FHL1) LUMA (transmembrane protein 43)	XR AR
Muscular dystrophies secondary to RNA metabolism defects			
Myotonic dystrophy 1 (DM1)	19q13.3	Myotonic dystrophy-associated protein kinase (DMPK)	AD
Myotonic dystrophy 2 (DM2)	3q21	Zinc finger, nucleic acid binding protein (ZNF9)	AD
Other muscular dystrophies of unknown mechanism			
Facioscapulohumeral dystrophy (FSHD)	3q21	FRG-1 (FSH region gene 1)	AD
Oculopharyngeal MD	14q11.2-q13	PABPN1	AD

LGMD table: Disease names in parentheses: New nomenclature proposed from 2018 European Neuromuscular Centre Workshop.
AD, Autosomal dominant; AR, autosomal recessive; *MD*, muscular dystrophy; *MDC*, muscular dystrophy congenita; *X*, X-linked recessive.

Deletions can occur almost anywhere in the *DMD* gene, but two hotspots have been identified. The most commonly mutated region includes exons 45–55, with the genomic breakpoint (i.e., the endpoint of where the deletions actually occurs) lying within intron 44. The second region includes exons 2–19, with genomic breakpoints commonly found in introns 2 and 7 (Beggs, Koenig, Boyce, & Kunkel, 1990; den Dunnen et al., 1989; Nobile, Galvagni, Marchi, Roberts, & Vitiello, 1995; Oudet, Hanauer, Clemens, Caskey, & Mandel, 1992). The other 40% of cases result from small mutations (point mutations resulting in frame-shift or nonsense mutations) or duplications. There is a great deal of variability between the size and type of mutations, how they affect transcription, and the clinical phenotype of the disease. The Leiden database (http://www.dmd.nl/) Clinvar and OMIN (ncbi.nlm.nih.gov) are useful resources for phenotype/genotype correlation in cases in which genetic testing and phenotype do not appear to be clearly correlated.

More than 90% of boys with DMD have an absence of dystrophin corresponding to an "out-of-frame" mutation that disrupts normal dystrophin transcription (Gillard et al., 1989). These mutations cause a premature stop codon and early termination of mRNA transcription. As a result, an unstable RNA is produced that undergoes rapid decay, leading to the production of nearly undetectable concentrations of truncated protein. If the mutation is one that does not stop transcription, an "in-frame" deletion, the BMD phenotype occurs, with abnormal dystrophin protein (Hoffman et al., 1988). This reading frame hypothesis holds for more than 90% of cases and is commonly used both to confirm diagnosis of dystrophinopathies and to differentiate between DMD and BMD. Exceptions occur in approximately 10% of patients and might be higher in patients with BMD (Kesari et al., 2008).

Out-of-frame deletions affecting exons 3–7, 5–7, or 3–6 or downstream at exons 51, 49–50, 47–52, 44, or 45 can result in a milder BMD phenotype. The most common underlying explanation for the presence of at least some dystrophin in these patients is a process called *exon skipping*, which occurs via alternative splicing (Nicholson et al., 1992; Patria et al., 1996). In these BMD patients, the carboxy-terminus is always preserved (Arahata et al., 1991). The involved exons are generally thought to encode noncritical areas of the protein so that when they are skipped, a shortened but still functional dystrophin protein is produced. Exon skipping is also the underlying mechanism for the revertant fibers (a few scattered muscle fibers showing dystrophin staining in

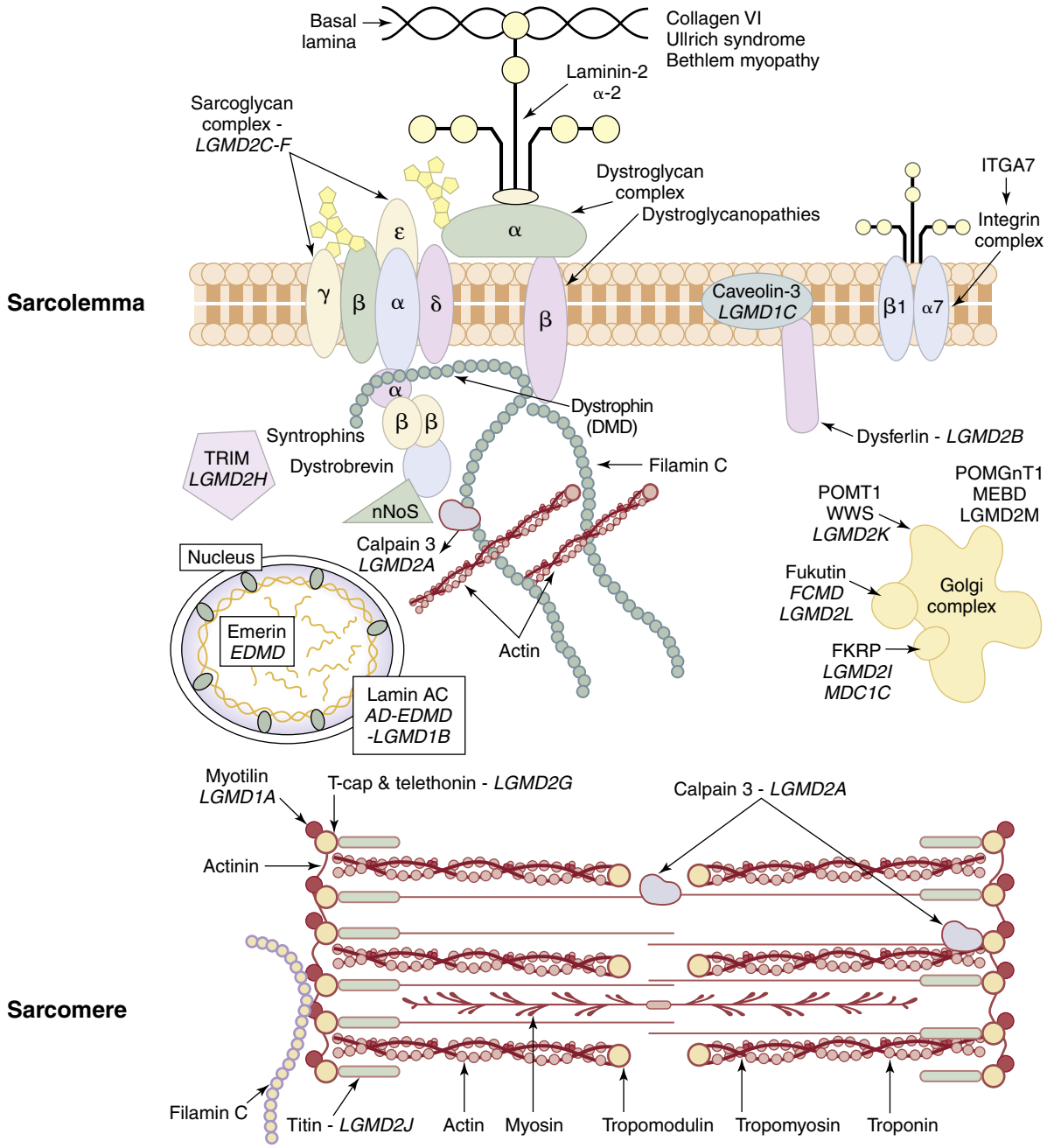


Fig. 20.1 Different proteins of sarcolemma and other areas of the muscle fiber associated with muscular dystrophy. *EDMD*, Emery-Dreifuss muscular dystrophy; *FCMD*, Fukuyama congenital muscular dystrophy; *FKRP*, fukutin-related protein; *ITGA7*, integrin, alpha7; *LGMD*, limb-girdle muscular dystrophy; *LGMD2M*, limb-girdle muscular dystrophy 2M; *MEBD*, muscle-eye-brain disease; *nNOS*, neuronal nitric oxide synthase; *POMGnT1*, protein O–linked mannose β1,2-*N*-acetylglucosaminyltransferase; *POMT*, protein O–mannosyltransferase; *TRIM*, tripartite motif; *WWS*, Walker-Warburg syndrome.

muscle biopsies) seen in approximately 50% of DMD boys (Winnard, Mendell, Prior, Florence, & Burghes, 1995). The limited expression of dystrophin results in a slower progression of muscle weakness compared with the usual Duchenne phenotype (Arahata et al., 1989; Baumbach et al., 1989; Koenig et al., 1989; Malhotra et al., 1988). This process has been therefore an appealing target for therapy in dystrophinopathies, because pharmacologic induction of exon skipping in DMD patients should produce some quantity of dystrophin and may alleviate the severity of the disease (see discussion of Treatment and Management in this chapter).

Pathophysiology

Dystrophin Protein. The normal *DMD* gene creates a 14-kb dystrophin mRNA that encodes dystrophin, a 427-kDa protein. Dystrophin localizes to the subsarcolemmal region in skeletal and cardiac muscle and composes 0.002% of total muscle protein (Hoffman, Brown, & Kunkel, 1987; Hoffman, Knudson, Campbell, & Kunkel, 1987; Knudson, Hoffman, Kahl, Kunkel, & Campbell, 1988). Dystrophin binds to the cytoskeletal actin and to the cytoplasmic tail of the transmembrane dystrophin-glycoprotein complex (DGC) protein β-dystroglycan, and through this to α-sarcoglycan,

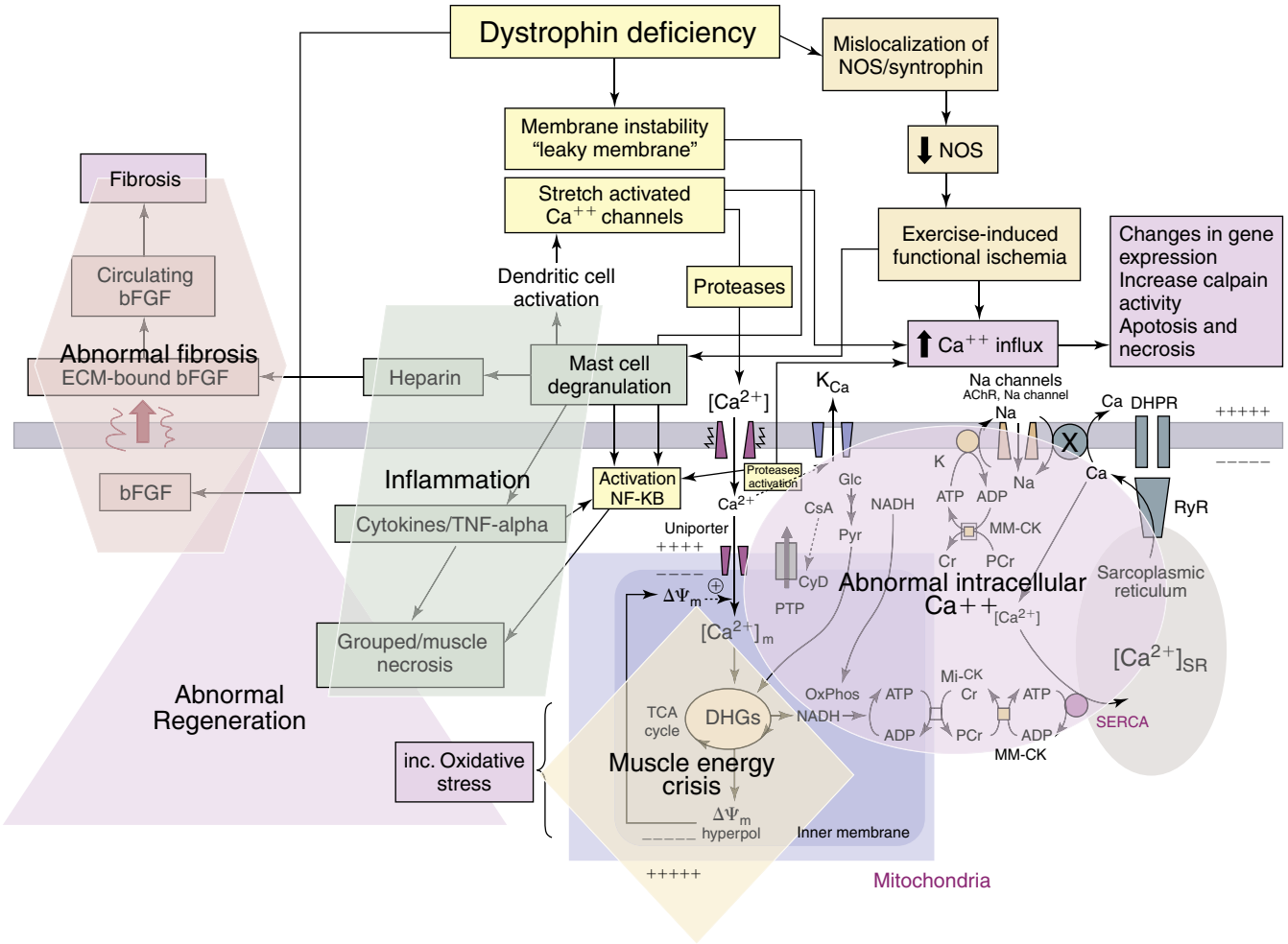


Fig. 20.2 Events in the pathogenesis of muscle necrosis in Duchenne muscular dystrophy. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *bFGF*, basic fibroblast growth factor; *DHGs*, dehydrogenases; *DHPR*, dihydropyridine receptor; *ECM*, extracellular matrix; *MM-CK*, MM fraction of creatine kinase; *NADH*, nicotinamide adenosine dinucelotide (reduced); *NOS*, nitric oxide synthase; *SERCA*, sarcoplasmic/endoplasmic Ca2+ ATPase; *SR*, sarcoplasmic reticulum; *TCA*, tricarboxylic acid cycle; *TNF*, tumor necrosis factor.

thus forming a link from the cytoskeleton to the ECM (see Fig. 20.1). The dystrophin protein is also found in brain, smooth muscle, and retina.

Primary and Secondary (Downstream) Events. Muscle cell death (by apoptosis and necrosis) in the muscular dystrophies is conditional on endogenous biochemical mechanisms and reflects a propensity that varies between muscles and changes with age (Fig. 20.2) (Rando, 2001a). Although dystrophin deficiency is the primary cause of DMD, multiple secondary pathways are responsible for the progression of muscle necrosis, the abnormal fibrosis, and the failure of regeneration that results in a progressively worsening clinical status. The literature is rich in evidence supporting oxidative radical damage to myofibers (Baker & Austin, 1989; Haycock, MacNeil, Jones, Harris, & Mantle, 1996; Murphy & Kehrer, 1986; Williams & Allen, 2007), inflammation (Cai, Spencer, Nakamura, Tseng-Ong, & Tidball, 2000; Kissel et al., 1993; Lagrota-Candido et al., 2002; Li, Mittal, Makonchuk, Bhatnagar, & Kumar, 2009; McDouall, Dunn, & Dubowitz, 1990; Porter et al., 2002; Rosemberg et al., 2015; Spencer & Tidball, 2001), abnormal calcium homeostasis (Baker & Austin, 1989; Gervásio, Whitehead, Yeung, Phillips, & Allen, 2008; Iwata, Katanosaka, Arai, Shigekawa, & Wakabayashi, 2009; Suchyna, & Sachs, 2007; Wrogemann & Pena, 1976; Yeung & Allen, 2004), myonuclear apoptosis (Adams, Gielen, Hambrecht, & Schuler, 2001; Sandri et al., 1995, 2001; Smith, Goldsmith, Ward, & LeDieu, 2000; Spencer, Walsh, Dorshkind, Rodriguez, & Tidball, 1997; Tews, 2002; Tindall et al., 1987), abnormal fibrosis, and failure of regeneration (Bernasconi et al., 1995; D'Amore et al., 1994; Iannaccone et al., 1995; Luz, Marques, & Santo Neto, 2002; Melone, Peluso, Galderisi, Petillo, & Cotrufo, 2000; Passerini et al., 2002; Spurney et al., 2008; Wehling-Henricks et al., 2008; Yamazaki et al., 1994). The following is a brief summary of the current understanding of how these processes occur.

Mechanical Membrane Fragility. Dystrophin is a link between the intracellular cytoskeleton and the ECM. The carboxy-terminal of dystrophin is attached to the sarcolemma, the surface membrane of striated muscle cells (Arahata et al., 1988; Bonilla et al., 1988; Watkins, Hoffman, Slayter, & Kunkel, 1988; Zubrzycka-Gaarn et al., 1988), binding to β-dystroglycan (Jung, Yang, Meyer, Chamberlain, & Campbell, 1995) and through this to other dystrophin-associated

glycoproteins and to α-dystroglycan, which links the sarcolemma to the ECM (Ervasti & Campbell, 1991). When dystrophin is not present, the disconnection of contractile proteins from β-dystroglycan results in loss of β- and α-dystroglycan and the DGC from the sarcolemma. This disruption results in membrane fragility and abnormal permeability, particularly to calcium ions.

Abnormal Permeability to Calcium and Chronic Increase in Intracellular Calcium. Cumulative evidence points to elevated intracellular Ca^{2+} homeostasis being a cause or facilitator to the development of muscle weakness in muscular dystrophies (Andersson et al., 2012; Goonasekera et al., 2011; Pal et al., 2014). Abnormal Ca^{2+} handling may be related to direct dystrophin regulation of mechanosensitive transient receptor potential (TRP) channels (Vandebrouck, Martin, Colson-Van Schoor, Debaix, & Gailly, 2002; Yeung & Allen, 2004), as well as abnormal intracellular Ca^{2+} cycling (Doran et al., 2004; Dowling, Doran, & Ohlendieck, 2004; Woods, Novo, DiFranco, & Vergara, 2004).

The deregulation of Ca^{2+} channels is seen in abnormal function of voltage-insensitive or "stretch-activated" Ca^{2+} channels, a subfamily of the TRP channels (Clapham, 2003). These stretch-activated channels are abnormally active under mechanical stimulation in myotubes of *mdx* mice (murine model of DMD), resulting in an increase in intracellular calcium (Mallouk & Allard, 2000; Vandebrouck, Duport, Raymond, & Cognard, 2002; Vandebrouck, Martin, et al., 2002).

The L-type, voltage-gated Ca^{2+} channels also appear to be abnormal in the absence of dystrophin; it has been shown that the Ca^{2+} currents in response to an action potential are much smaller in *mdx* mice than in normal controls. A disrupted direct or indirect linkage of dystrophin with these channels may be crucial for proper excitation-contraction coupling, initiating Ca^{2+} release from the sarcoplasmic reticulum.

The abnormal intracellular Ca^{2+} levels result in abnormal activation of Ca^{2+}-activated proteases (i.e., calpain) with subsequent abnormal degradation of intracellular proteins, which probably contributes to the abnormal functioning of the calcium leak channels (Turner, Schultz, Ganguly, & Steinhardt, 1993). Cumulative preclinical evidence shows that chronic eccentric exercise worsens the abnormalities in calcium homeostasis in *mdx* mice (Fraysse et al., 2004), which supports the clinical observation that eccentric exercises in DMD are deleterious and exacerbate muscle weakness (Allen, 2004; Ansved, 2003). Calcium also accumulates in mitochondria, contributing to cell dysfunction by affecting energy production (Dubinin et al., 2020; Wrogemann & Pena, 1976).

Abnormal Immunologic Response. Dystrophic skeletal muscle is characterized by a persistent inflammatory response, with muscle degeneration, regeneration, and fibrosis. The lack of dystrophin in myofibers leads to contraction-induced membrane damage with release of cytoplasmic contents and self-sustaining stimulation of innate immunity. Proinflammatory cytokines induce recruitment of T and B cells and generation of an adaptive immune response in the muscle milieu. This proinflammatory microenvironment is often superimposed on the neutrophil and macrophage infiltrations induced by successive courses of myofiber degeneration and regeneration. In contrast to the full resolution of a single bout of inflammation and repair of normal muscle, dystrophin-deficient muscle loses the bout effect. Neighboring fibers or groups of fibers enter the necrotic stage at different times in the 2-week degeneration/regeneration cycle (asynchronous regeneration), thus sustaining a chronic inflammatory state, which, in turn, creates a more proinflammatory environment with activation of innate immune pathways, and evidence of increased antigen presentation (Dadgar et al., 2014; Rosemberg et al., 2015).

Many of these immune response pathways are known to be blocked by the glucocorticoids prednisone and deflazacort, drugs that have been shown to slow progression of the disease, improve muscle strength and motor function, and prolong survival. Other therapeutic immunomodulatory approaches are being developed to alter the natural course of the disease and could be an adjunct treatment for other therapies such as gene and exon skipping therapies.

Abnormal Signaling Functions. Mounting evidence shows that the dystroglycan complex has important muscle cell signaling functions, and its integrity is essential for muscle cell viability (Rando, 2001b). These functions include transmembrane signaling (through β-dystroglycan), docking of signal transduction molecules (i.e., caveolin-3), and interaction with or regulation of other transmembrane complexes (i.e., integrins). When the dystroglycan complex is disassociated from the sarcolemma, there is a disruption of the cell signaling involved in regulating apoptosis (Rando, 2001b) and in the metabolism of reactive oxygen species (Baker & Austin, 1989; Haycock et al., 1996; Kumar & Boriek, 2003; Ragusa, Chow, & Porter, 1997; Rando, 2002; Spencer, Montecino-Rodriguez, Dorshkind, & Tidball, 2001).

Another abnormality of cell signaling is likely the underlying explanation for the "vascular" theory of DMD pathogenesis, supported in the past by morphologic evidence of muscle fiber group necrosis occurring very early in the disease, presumably secondary to ischemia. Dystrophin absence results in mislocalization and reduction of neuronal nitric oxide synthase (nNOS) in dystrophic muscle, affecting smooth vessel vasodilation in response to alpha-adrenergic stimuli in exercise (Thomas, Shaul, Yuhanna, Froehner, & Adams, 2003), resulting in muscle ischemia (Sander et al., 2000). Dystrophin-associated α-syntrophin appears to be essential for the membrane localization of nNOS (Thomas et al., 2003).

Abnormal Fibrosis and Muscle Regeneration. The chronic inflammation in DMD leads to a shift in balance from myogenic pathways resulting in successful muscle regeneration toward fibrogenic pathways, culminating in the loss of muscle fibers and their replacement with fatty-fibrotic matrix. The gradual accumulation of fibrosis in skeletal muscle dysregulates contractile function and is directly related to loss of motor function in DMD. Fibrosis also becomes a physical barrier that prevents normal blood flow to the muscle and the delivery of gene therapy or antisense-oligonucleotides to the muscle fiber. Thus, understanding the fibrotic process in DMD has become important to identify new therapeutic targets that could complement anti-inflammatory as well as dystrophin delivery therapies (Smith et al., 2018).

Fibrosis (the excessive deposition of endomysial and perimysial ECM) is a known secondary phenomenon to chronic muscle inflammation and fiber degeneration in DMD (Porter et al., 2002). Many signaling pathways modulate fibrotic progression in dystrophic skeletal muscle, and these provide important therapeutic targets to reduce fibrosis in DMD and other muscular dystrophies. The primary profibrotic signal is transforming growth factor-beta (TGFβ) (Ceco et al., 2013). High expression of TGFβ is evident in dystrophic muscle (Bernasconi et al., 1995) and in serum samples of individuals with DMD (Bernasconi et al., 1999). TGFβ is stored in the ECM as a complex with latent TGFβ-binding proteins (LTBPs). Activation of TGFβ requires its release from the complex by proteases into the ECM. Polymorphisms in the LTBPs have been associated with worse prognosis and increased fibrosis in DMD (Flanigan et al., 2013). Thus, blocking the cleavage of LTBP4 is a potential therapeutic target for preventing the excessive release of active TGFβ (Smith et al., 2018). Once TGFβ is released, it can act through its canonical pathway of binding to the TGFβ receptor to mediate SMAD signaling, which upon nuclear entry leads to activation of a profibrotic transcriptional program that includes the production of collagen I (Ceco et al., 2013). Noncanonical pathways are also activated, including mitogen-activated protein kinase (MAPK) pathways and c-abl that, in turn, enhance transcription of profibrotic signals, including TGFβ itself, as part of the positive feedback in fibrosis (Smith et al., 2018). Other identified therapeutic targets include TGFβ downstream profibrotic pathways, like the renin-angiotensin system (Sun et al., 2009) and growth factors, like CTGC, found to be upregulated in dystrophic animal models and patients (Sun et al., 2008).

Interestingly, the amount of fibrosis in DMD seems disproportionate to the clinical severity in the earlier stages of the disease. Observation of this fact spurred the idea that fibrosis may also occur independent from muscle necrosis, degeneration, and failed regeneration. Evidence suggests that both enhanced fibrinogenesis and decreased fibrinolysis (von Moers et al., 2004) are implicated in the development of muscle fibrosis in DMD. Serum from DMD patients also have increase basic fibroblast growth factor, a skeletal muscle cytoplasmic polypeptide that colocalized with dystrophin in the muscle membrane. Leaking of this growth regulator that stimulates connective tissue synthesis, induces satellite cell (SC) proliferation, and suppresses myogenic differentiation could contribute to early fibrogenesis (D'Amore et al., 1994).

Dystrophin and Its Role in Satellite Cells. The cycles of segmental degeneration and regeneration of the dystrophin-deficient muscle fibers trigger SC recruitment for regeneration. During regeneration of dystrophic muscles, decisions regarding SC fate are regulated by intrinsic mechanisms and extrinsic signals (Almada et al., 2016). Dystrophin deficiency in SCs affects cell polarity and self-renewal. This results in asymmetric cell division, which in turn alters normal muscle repair mechanisms (Chang, Chevalier, & Rudniki, 2016). Exhaustion of SC pool has been a concern in DMD, as it was thought that the chronicity of this degeneration-regeneration process would result in SC pool depletion over time and result in failed regeneration (Heslop et al., 2000). However, it is known that dystrophic SCs are initially increased in muscle biopsies of young DMD patients when compared with matched normal controls (Bankole et al., 2013). Recent preclinical studies in different murine models of muscular dystrophy have shown that dystrophic mice retain their SC pool. Furthermore, the number of activated SCs is elevated and the dystrophic muscle retains its ability to form new muscle fibers, compatible with active regeneration and pool maintenance. However, this regenerative process is incomplete, with a possible defect in the maturation characteristics that could be determinant to the dysfunction of these fibers (Ribeiro et al., 2019). These new findings support efforts to improve late muscle regeneration as therapeutic approaches, even in advance disease.

DIAGNOSIS AND EVALUATION

Clinical Characteristics

Duchenne Muscular Dystrophy

Neuromuscular Involvement. Muscle fiber necrosis with elevated muscle calcium levels and a high serum creatine kinase (CK) enzyme level can be found in infancy in patients with DMD (Bertorini et al., 1986), but the clinical manifestations are typically not recognized until at least age 3 years. This discrepancy represents a potential therapeutic window in which early interventions could theoretically prevent or delay the onset of symptoms. Walking often begins later than in normal children, and affected boys experience more falling than expected. Gait abnormality often becomes apparent by age 3 to 4 years, leading to clinical evaluation. Muscle weakness presents initially in neck flexor muscles, with power being less than antigravity. As a result, the child turns on his or her side when getting up from a supine position on the floor, which is the initial sign of the Gowers maneuver. Hypertrophy of calf muscles becomes prominent by age 3 or 4 years (Fig. 20.3). Hypertrophy of other muscles, including the vastus lateralis, infraspinatus, deltoid, and less frequently the gluteus maximus, triceps, and masseter muscles, may also develop. Muscle mass is usually decreased in later stages in the pectoral, peroneal, and anterior tibial muscles.

Because of hip girdle weakness, untreated patients exhibit the Gowers sign by age 5 or 6 years. The patient assumes a locked-leg, buttocks-first position followed by pushing off the floor with the hands, literally pushing the trunk erect by bracing the arms against the anterior thighs. Patients also tend to rock from side to side when walking, producing the waddling gait that is typical in older boys with the disease. Climbing stairs also becomes difficult with disease progression, and eventually distal muscles of the arms and legs become weak.

Accelerated deterioration in strength and balance often results from intercurrent disease or surgically induced immobilization. A wheelchair is required when ambulation is no longer possible, typically near the end of the first decade in untreated DMD and about 3 to 10 years later in steroid-treated DMD. After loss of ambulation, contractures become more pronounced in the lower extremities; they also soon involve the shoulders, and kyphoscoliosis may develop. Cardiac and respiratory involvement often occurs in this later disease stage as well.

Adolescent patients manifest increasing weakness and are unable to perform routine daily tasks with their arms,

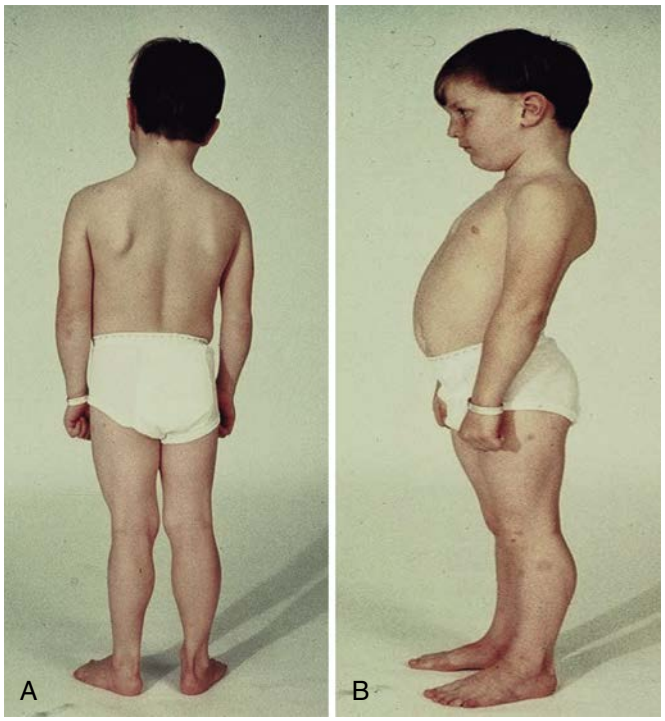


Fig. 20.3 A child with Duchenne muscular dystrophy. Notice winging of the scapulae (A), hypertrophy of the calf muscles, and prominent lordosis (B).



Fig. 20.4 An adult patient with Becker muscular dystrophy. (A) Patient's front; (B) patient's back. Notice the prominent calf muscles.

hands, and fingers. The head may progressively flex forward as extensor neck muscles lose strength. Lower facial muscles may be involved in the advanced phase.

Respiratory Involvement. Pulmonary function becomes compromised because of weakness of intercostal and diaphragmatic muscles and severe scoliosis. It occurs later in the disease in nonambulatory boys and is the primary cause of mortality in DMD. Muscle weakness affects all aspects of lung function, including mucociliary clearance, gas exchange at rest and during exercise, and respiratory control during wakefulness and sleep (Gozal, 2000). It is important to recognize that DMD is often associated with sleep disordered breathing, which could be asymptomatic or only mildly symptomatic. Respiratory complications and their treatment are discussed in greater detail in Chapter 2.

Cardiac Involvement. Boys with DMD are at risk for cardiomyopathy, especially if they have deletion of exons 48 to 53 (Nigro, Politano, Nigro, Petretta, & Comi, 1994). Mild degrees of cardiac compromise in DMD may occur in up to 95% of boys (Melacini et al., 1996). Chronic heart failure may affect up to 50% (Melacini et al., 1996; Wahi, Bhargava, & Mohindra, 1971). Sudden cardiac failure can occur, especially during adolescence. In one series of 19 patients, autopsies revealed that 84% had demonstrable cardiac involvement (Leth & Wulff, 1976). Cardiac complications and their management are discussed further in Chapter 3.

Neuropsychological Involvement. Overall, the IQ curve in boys with DMD is shifted to the left (Ogasawara, 1989). The mean IQ score in one study was 83 (range, 46 to 134). Other studies have not been able to prove a difference in overall IQ (Bushby et al., 1995; Felisari et al., 2000; Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000; Roccella, Pace, & De Gregorio, 2003). Recently, it has become evident that certain cognitive areas (i.e., verbal memory and executive function) are more affected than others in DMD (Hinton et al., 2000). The severity of central nervous system impairment increases with mutations at the 3′ end of the gene, which lead to cumulative loss of several dystrophin-gene products (Dp260, Dp140, Dp116, and Dp71) encoded by distinct internal promoters and normally expressed in the nervous system in a cell-specific manner (Ricotti et al., 2016; Taylor et al., 2010).

Other Organ Involvement. Rarely, gastrointestinal tract involvement associated with smooth muscle dysfunction causes megacolon, volvulus, abdominal cramping, and malabsorption (Borrelli et al., 2005).

Clinical Characteristics of Becker Muscular Dystrophy. BMD is present in 3 to 6 per 100,000 male births (Gardner-Medwin, 1970). The onset of weakness is later than in the Duchenne type, usually seen after age 7 years and often in the second decade; the disease is also marked by lordosis, calf hypertrophy, and other features of DMD of a milder phenotype (Fig. 20.4). The course is prolonged into adulthood, often with a normal life span. Ambulation is typically maintained beyond age 30 years. CK level is usually between 2000 and 20,000 U/L but may be in the normal range for mildly affected males. Because these patients can be asymptomatic for decades, they commonly are misdiagnosed as having liver disorder when routine laboratory values show elevated transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), which are elevated in parallel with serum CK levels. At times, the BMD diagnosis is made after many years of gastrointestinal follow-up for elevated transaminases, until someone thinks of measuring the CK, which comes back extremely elevated. Pseudohypertrophy, proximal hip weakness resulting in the Gowers sign, and electrocardiogram (ECG) abnormalities associated with DMD are also common to BMD.

Chromosome Xp21 Microdeletion Syndromes. The Xp21 microdeletion syndromes are a series of syndromes that include DMD, Aland Island eye disease, adrenal hypoplasia, glycerol kinase deficiency, retinitis pigmentosa (*RP3*), mental retardation (*MRX1*), and ornithine transcarbamylase deficiency. The combination of these conditions led to the discovery of the *DMD* gene on Xp21 (Francke et al., 1985).

Female Duchenne Muscular Dystrophy D Carriers and Manifesting Carriers. Carrier females are heterozygous with a normal *DMD* gene on one X chromosome and a mutant gene on the other. More than 90% of female carriers are asymptomatic. However, variable degrees of muscle weakness may be seen with skewed X-inactivation, in which more than half of the mutant X chromosomes are operant in muscle cells. Such cells are prone to degeneration. If a large number of abnormal muscle fibers are present in a given muscle, that muscle may display weakness. The degree of strength from one muscle to another may vary from normal strength to significant weakness.

Signs and symptoms of female dystrophinopathy include muscle weakness, myopathic findings on muscle biopsies, elevated CK levels, and partial absence of dystrophin in muscle (Hoffman, Arahata, Minetti, Bonilla, & Rowland, 1992). Symptoms manifest in about one fifth of DMD carriers (Hoogerwaard, Backer, et al., 1999). The diagnosis should be considered in women with elevated CK levels and muscle weakness, even in the absence of a positive family history for DMD (Hoffman, 1996).

DMD carriers appear to have an increased incidence of cardiomyopathy. Studies have shown an incidence of asymptomatic cardiomyopathy ranging from 8% to 48% in adult DMD carriers (Grain et al., 2001; Hoogerwaard, Backer, et al., 1999; Hoogerwaard, van der Wouw, et al., 1999) and from 0% to 15% in DMD carrier girls under age 16 years (Nolan, Jones, Pedersen, & Johnston, 2003).

Clinical Laboratory Tests

In DMD, serum CK is greatly elevated, typically from 10,000 to 30,000 U/L, early in the course of the disease. Gaps in the sarcolemma allow efflux of the enzyme into the circulation. Serum CK levels can vary greatly with activity and decrease as muscle mass is lost with disease progression. There is no correlation between the serum CK level and clinical severity in DMD and use of CK levels as a surrogate marker of treatment response is not well supported. Because of the leakage of intracellular muscle proteins, other muscle isoenzymes also increase in the circulation. These include aldolase, lactate dehydrogenase, ALT, and, to a lesser degree, AST.

Genetic Testing

Dystrophin gene deletion and duplication testing is usually the first confirmatory test given that approximately 70% of individuals with DMD have a single-exon or multiexon deletion or duplication in the dystrophin gene. The most cost-effective techniques currently used are multiplex ligation-dependent probe amplification or array comparative genome hybridization, which are followed by full gene sequencing if the initial results are negative. In many countries, these techniques are being replaced by next generation sequencing (Aartsma-Rus et al., 2016). If genetic testing does not confirm the clinical diagnosis of DMD, then a muscle biopsy is recommended. Given that the genotype and phenotype correlation is approximately 89%, a muscle biopsy might also be necessary when the genetic findings predict a phenotype that is not consistent with the clinical presentation. Genetic testing is also important for genetic counseling, prenatal diagnosis, and eligibility for mutation specific therapies.

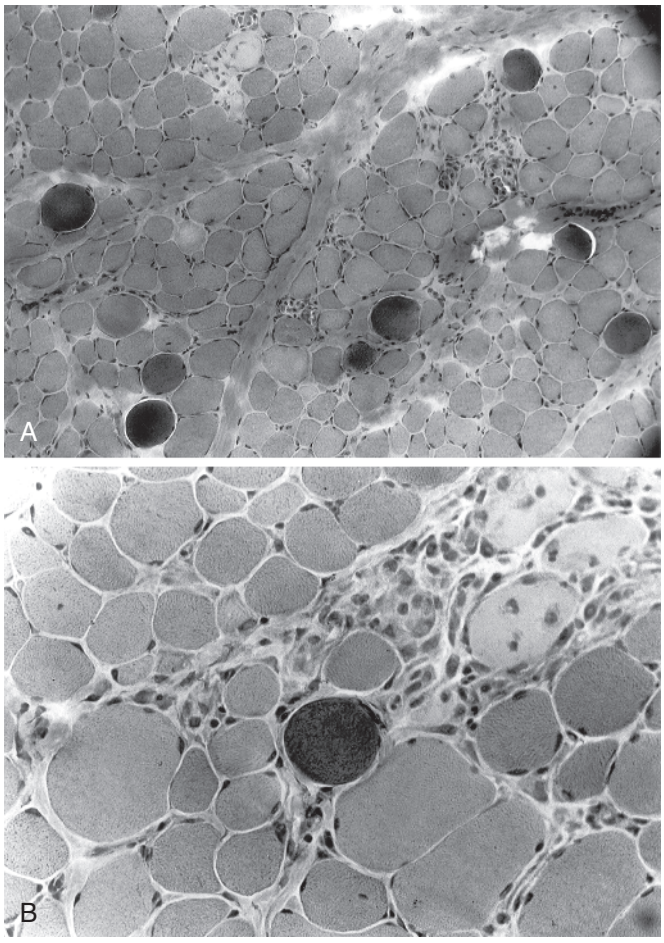


Fig. 20.5 (A) A trichrome-stained section of a muscle biopsy from a patient with Duchenne muscular dystrophy showing necrosis, opaque fibers, mildly increased endomysial connective tissue, and variation in muscle fiber size (×200). (B) Higher magnification (×400) showing fiber atrophy, hypertrophy and necrosis, and interstitial infiltrates of mononuclear cells. (Reproduced with permission from Bertorini, T. (2002). *"Muscular dystrophies" in Pourmond's neuromuscular diseases, expert clinicians' views*. Boston: Butterworth-Heinemann.)

Muscle Biopsy

Histology of DMD muscle demonstrates fiber size variation, degenerating and regenerating fibers, clusters of smaller fibers, endomysial fibrosis, and a few scattered lymphocytes. Large, opaque fibers are prominent on modified Gomori-Wheatley trichrome staining (Fig. 20.5). As the disease progresses, muscle fibers are lost and replaced with fat and connective tissue. Fiber typing with adenosine triphosphatase histochemistry is less distinct than expected. Oxidative histochemistry is maintained. On electron microscopy, gaps in the sarcolemma with preservation of the basement lamina are seen in nonnecrotic fibers (Fig. 20.6).

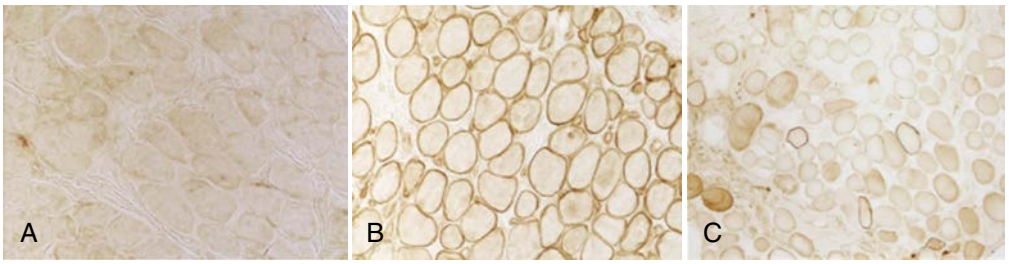


Fig. 20.6 Muscle biopsy of Duchenne muscular dystrophy showing staining for dystrophin with absence of the protein (A) compared with control muscle (B) showing normal staining for dystrophin and muscle atrophy. (C) An area of the muscle biopsy showing scattered revertant fibers that stain positive for dystrophin (×200).

Absence of immunoreactivity for dystrophin with monoclonal antibodies against the C-terminal, rod domain, and N-terminal is necessary for accurate diagnosis of DMD (Fig. 20.7). Quantitative dystrophin analysis by immunoblot is more accurate for diagnosis than immunostaining, with dystrophin value being less than 5% in DMD patients. Over the last decade, it has become crucial to accurately quantify dystrophin in muscle biopsies, as this is the primary biological endpoint of clinical trials aiming to induce functional dystrophin expression. Reliable and reproducible methods for quantification of dystrophin protein expression at the sarcolemma have been developed, including semiquantitative nested reverse-transcription polymerase chain reaction (RT-PCR), Taqman quantitative (q) RT-PCR assay (Anthony et al., 2012), high-throughput immunofluorescence analysis method (Sardone et al., 2018), as well as by mass spectroscopy (Brown et al., 2012).

Histologic findings in BMD are similar to but less pronounced than those in DMD. The sarcolemmal gaps are not as readily seen. Using monoclonal antibodies directed to separate regions of dystrophin, immunoreactivity over the sarcolemma shows a variety of staining patterns, ranging from intact to absent, with one or more antibodies (Jay, Becker, Ackerley, & Ray, 1993).

TREATMENT AND MANAGEMENT

In DMD and BMD, multidisciplinary care involving physicians (neurologists, physiatrists, orthopedic surgeons, endocrinologists, cardiologists, and pulmonary medicine specialists), physical and occupational therapists, nutritionists, exercise physiologists, genetic counselors, and social workers is important for the overall well-being of the child and the family.

Pharmacologic Treatment

Approved therapies

Corticosteroids. Corticosteroid treatment is considered standard of care in DMD (Gloss et al., 2016; Moxley et al., 2005). Different corticosteroids, regimens, and dosages have been used and compared in randomized clinical trials. Data from these studies have shown that prednisone at a dose of 0.75 mg/kg/day improves muscle strength, motor function, quality of life, and force vital capacity. Natural history studies also show that corticosteroid treatment prolongs ambulation (Bello et al., 2015; Fenichel et al., 1991). Evidence also exists that corticosteroid treatment decreases scoliosis, improves pulmonary function, and decreases cardiomyopathy (Gloss et al., 2016).

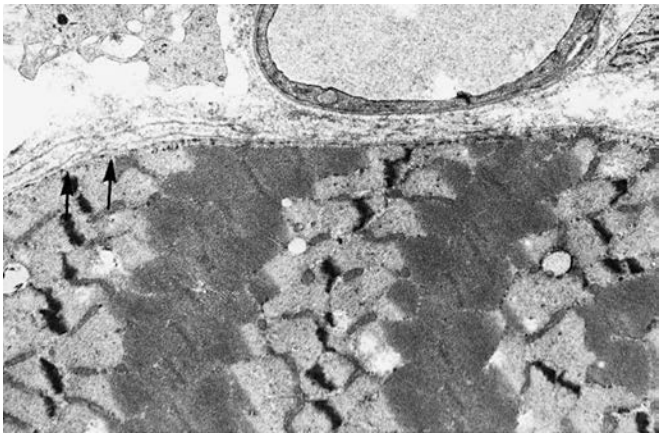


Fig. 20.7 Electromicrograph of a specimen from a 6-year-old child with Duchenne muscular dystrophy revealing sarcolemma (cell wall) disruption (*arrows*) with redundant membranes (×10,800). (Reprinted with permission from Escolar, D. (2006). *"Muscular dystrophies" in pediatric neurology principles & practice*. Philadelphia: Mosby.)

Standard daily vs. high-dose weekend-only prednisolone trials showed comparable efficacy in both pilot and randomized controlled studies (Connolly, Schierbecker, Renna, & Florence, 2002; Escolar et al., 2011), with the high-weekend dose boy retaining linear growth when compared with daily treatment. DMD boys treated with prednisone from an earlier age usually remain ambulatory into their teens, have less incidence of scoliosis (Alman, Raza, & Biggar, 2004; Biggar et al., 2004) and contractures (Yilmaz, Karaduman, & Topaloglu, 2004), and maintain normal or near-normal respiratory function (Angelini et al., 1994; Biggar et al., 2004; Campbell & Jacob, 2003; Merlini et al., 2003). Moreover, recent data showed that twice-weekly corticosteroids are well tolerated in infants and young boys with DMD and improves gross motor scaled score compared with the historical control cohort (Connolly et al., 2019) and that young boys treated with corticosteroids between the ages of 3 and 6 had better motor function at each time point than those who were corticosteroid-naive (Coratti et al., 2019).

Deflazacort has similar benefits to prednisone but causes less weight gain and Cushingoid features, although it appears to have an increased predisposition to asymptomatic cataract formation (Angelini et al., 1994; Biggar, Gingras, Fehlings, Harris, & Steele, 2001; Bonifati et al., 2000; Campbell & Jacob, 2003; Moxley et al., 2005; Mesa, Dubrovsky, Corderi, Marco, & Flores, 1991). Suggested dosage is 0.9 mg/kg/day. Lower-dose regimens, including alternate-day corticosteroids

and treatment for the first 10 days of the month, have not demonstrated sustained efficacy (Fenichel et al., 1991; Sansome, Royston, & Dubowitz, 1993). There is an ongoing randomized clinical trial (FOR-DMD) comparing different corticosteroids and regimens (daily prednisone 0.75 mg/kg/day, 10 days on and 10 days off vs. daily deflazacort 0.9 mg/kg/day) with a follow-up of 5 years, as the current data are not enough to draw conclusions about significant difference between all these regimens.

Despite the evidence in favor of use of steroids, a source of major concern for patients and physicians is the numerous potential side effects caused by this treatment. Therefore, timely monitoring and management of these adverse events are crucial. Side effects of chronic corticosteroid use in DMD commonly include increased appetite and weight gain, irritability, hirsutism, cushingoid features, delayed puberty, and decreased linear growth (Moxley et al., 2005). In this young population, common and serious side effects of corticosteroids like diabetes, hypertension, gastric ulcers, and infections are rare. Steroid-induced osteoporosis is difficult to assess in DMD because baseline osteoporosis might be present secondary to decreased activity (Aparicio, Jurkovic, & DeLullo, 2002; Bianchi et al., 2003; Larson & Henderson, 2000). Given these known side effects, current research is also looking at other steroid-like drugs with nuclear factor κB (NF-κB) inhibition, but without the metabolic effects, with the objective of maintaining the beneficial effects but decreasing or eliminating side effects. However, the mechanism of action of corticosteroids in DMD is still not fully understood, and the significant clinical benefit they confer might be due to a multitarget modulation of pathological pathways in DMD.

Stop Codon-Read-Through Mutation Suppression Approach

A small percentage of patients with DMD have nonsense mutations that promote premature translational termination of the dystrophin protein. The result is a small unstable protein that gets rapidly degraded. One pharmacologic approach to treat DMD aims to "skip" these premature stop codons. Gentamicin, an aminoglycoside antibiotic, has been investigated based on its binding of the ribosome causing "read-through" of premature stop codon (nonsense) mutations. It was tried first in the *mdx* model of DMD (Barton-Davis, Cordier, Shoturma, Leland, & Sweeney, 1999) and then in a clinical trial on four DMD/BMD patients (Wagner et al., 2001). Although the *mdx* experiments showed positive dystrophin in approximately 15% of previously negative muscle fibers (Barton-Davis et al., 1999), the human trial was unable to duplicate this finding.

An unrelated drug with a similar mechanism of action (forced read-through of premature stop codon mutations), Ataluren (Translarna™), has been conditionally approved in the European Zone, Israel, and South Korea and is currently under investigation in the United States in DMD boys. This oral medication can cause suppression of premature stop codons at much lower doses (from 10-fold to 100-fold lower) than gentamicin (Welch et al., 2007). This drug is recommended for ambulant boys with DMD nonsense mutations. A randomized multicenter study identified both clinical and statistical benefits in the subgroup of DMD patients in a specific ambulatory decline phase, with a 6-minute walk distance (6MWD) ranging from 300 m to less than 400 m (McDonald et al., 2017). A meta-analysis of patients pooled from the phase 2b and phase 3 studies with a baseline 6MWD of ≥150 m and ≤80% of predicted and ≥6 months of steroid treatment was performed and repeated using all patients from both studies. This analysis showed a clinical and statistical improvement in motor function in treated patients. Based on these suggestive data, the company has initiated efforts for approval in many other countries.

Exon Skipping Using Antisense Oligonucleotides

Approximately 70% of mutations in the *DMD* gene disrupt the open reading frame and result in incomplete translation of the dystrophin protein. The exon skipping approach is one method for gene repair, as it targets the pre-mRNA transcript introducing alternative splice sites resulting in "skipping" of one or more targeted exons. This leads to the restoration of the reading frame and expression of an "in-frame" semifunctional dystrophin protein (Errington, Mann, Fletcher, & Wilton, 2003; Gebski, Mann, Fletcher, & Wilton, 2003; Lu et al., 2003; Mann et al., 2001; Wells, Fletcher, Mann, Wilton, & Wells, 2003).

This approach was developed from in vitro and in vivo proof-of-concept studies (Aoki et al., 2005; Miyatake et al., 2018) to clinical trials in DMD targeting various single exons such as exon 51 (eteplirsen), exon 45 (casimersen), and exon 53 (NS-065/NCNP-01, golodirsen) (Dowling, 2016; Mendell et al., 2013).

Eteplirsen (brand name Exondys 51) was the first approved antisense therapy for DMD in the United States as a treatment option for DMD patients who are amenable to exon 51 skipping. Eteplirsen was granted accelerated approval and marketing authorization by the US Food and Drug Administration in 2016, on the condition that additional postapproval trials show clinical benefit (Mendell et al., 2016). More recently Golodirsen was also approved based on quantifiable and significant increases in dystrophin expression in muscle. Both Eteplirsen and Golodirsen medications are given intravenously once weekly at a dose of 30 mg/kg/dose and are well tolerated. These therapies apply to only 13%–14% of DMD patients. The approval of both drugs is contingent on successful completion of additional trials and other postmarketing commitments. Despite these advances in drug development using antisense oligonucleotides for DMD, it still remains unclear whether the low increases in dystrophin induced by these splice-switching oligonucleotides are sufficient to slow down disease progression.

Other antisense oligonucleotide targeting skipping of other exons is being tested in clinical trials and new ones are under development. However, for most exons, the applicability per exon is <1% of patients (e.g., exon 49 skipping would apply to only 0.02% of all patients), which poses challenges in their clinical development (Aartsma-Rus, Ferlini, Goemans, & Pasmooij, 2014; Guiraud et al., 2015; Hwang & Yokota, 2019).

Other Therapies in Development

Better understanding of the pathophysiology of dystrophinopathies has provided three main areas of interest for researchers in the development of new treatments for DMD over the past 20 years. Those include manipulation of the

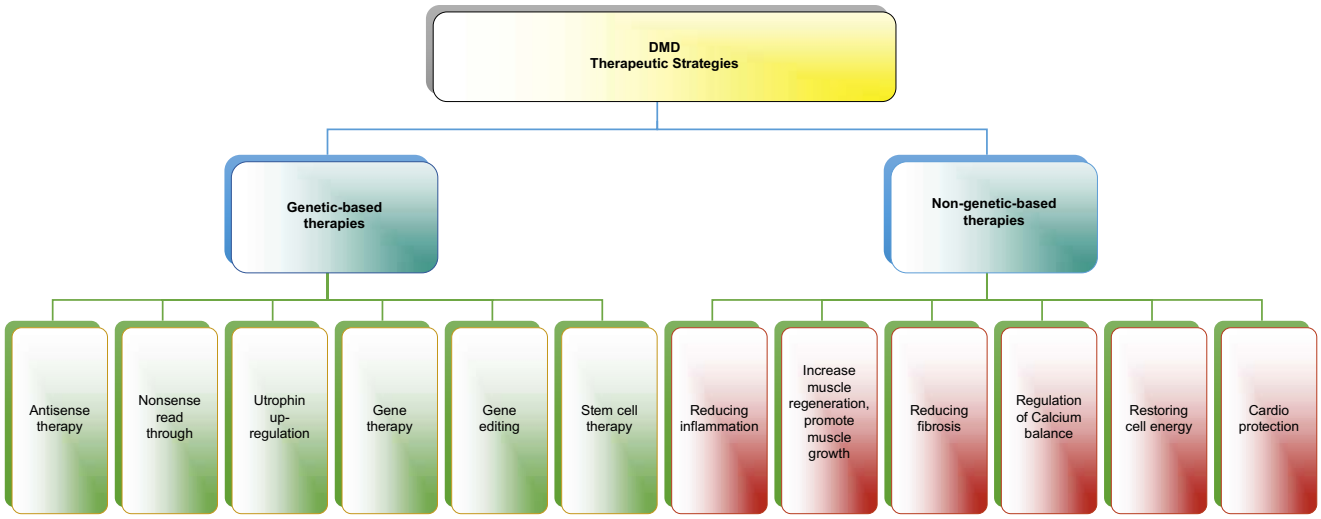


Fig. 20.8 Different treatment approaches in Duchenne muscular dystrophy, including gene repair, replacement, and upregulation of compensatory proteins and modification of downstream effects. *AAV*, Adeno-associated virus; *AG*, aminoglycosides; *AON*, antisense oligonucleotides; *PTC124*, (Ataluren); *ATb*, antibiotic; *CoQ10*, coenzyme Q10; *DNA*, deoxyribonucleic acid; *GALNAc*, N-acetylgalactosamine; *IGF*, insulin-like growth factor; *MYO-029*, NF-κB, nuclear factor κB; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *RNA*, ribonucleic acid; *TGF*, transforming growth factor; *TNF*, tumor necrosis factor.

DMD gene by substitution or correction of primary protein genetic defect; upregulation of proteins that may compensate for a lack of dystrophin and pharmacologic manipulation of the downstream events that occur when dystrophin is absent or reduced. These include inhibition of inflammation, promotion of muscle growth and regeneration, reduction of fibrosis, regulating calcium balance, and restoring cell energy (Fig. 20.8). Improving heart function has also been part of this effort and will be discussed on the cardiac management section.

Several approaches at these different levels have been investigated, and more are currently being evaluated. Most of the preclinical experiments have been performed in the mouse model of muscular dystrophy (*mdx*), but the mdx pharmacological trials have a poor predictive value for translation to humans. There are currently over 30 drugs in different stages of development. Later, we will describe mostly studies that have advanced to phase 2/3 stages of drug development.

Gene Therapy

Dystrophin Gene Substitution. Gene therapy in DMD has been studied for over 25 years. Dystrophin can be produced, the immune response can be prevented, and improved function and pathology in young and older animals have been achieved (DelloRusso et al., 2002; Hartigan-O'Connor, Kirk, Crawford, Mulé, & Chamberlain, 2001; Scott et al., 2002; Wang, Li, & Xiao, 2000). Given the large size of the dystrophin gene, reduced-size dystrophin (mini- or micro-dystrophin) constructions have been developed based on the observation that some large deletions of this gene were associated with extremely mild cases of BMD (England et al., 1990; McGreevy et al., 2015; Wang et al., 2008). More recently, given the successful development of better delivery methods of functional DMD gene to skeletal and cardiac muscle, the potential of restoring dystrophin protein has become promising.

Recombinant adeno-associated virus (AAV) is the preferred vehicle for delivery of the dystrophin construct due to the persistence of the injected AAV in striated muscles and the lack of pathogenicity. Several studies have now shown that newly developed AAV serotypes 6, 8, and 9 vectors achieve whole muscle gene transfer in rodent and dog models. With considerable advances in the types of AAV vectors available, but also better muscle-specific gene regulatory cassettes, and production/purification protocols, several academic groups and industry partners are conducting human clinical trials involving vascular delivery of AAV9 and AAVrh74/micro-dystrophin to young patients with DMD (Chamberlain et al., 2017).

Gene Editing. An alternative approach to increase dystrophin in muscle is by postnatal genome editing. Recent discovery of clustered regularly-interspaced short palindromic repeat (CRISPR) technology, in which an endonuclease called Cas 9 can cleave the genome in a precise manner when coupled with a strand of guide RNA (gRNA), offers a different method of correcting genomic alterations in the dystrophin gene (Cong, Ran, & Cox, 2013). Application of this technology to the mouse model of DMD is currently being explored by different groups with the goal of ameliorating muscle function (Long et al., 2016; Nelson et al., 2016; Tabebordbar et al., 2016). This type of intervention could potentially remove disease mutations in about 80% of patients with DMD, although it would have to be customized to each patient's specific mutation (Calos, 2016; Li Hongmei et al., 2015).

Cell Therapy. Finally, the transfer of myoblasts and other stem cells has been studied as an attempt to introduce the normal *DMD* gene, but these approaches have not yet been very encouraging (Wang et al., 2008). Myoblast transplants were tried in DMD boys, with no success (Miller et al., 1997; Munsat, 1990; Neumeyer et al., 1998; Partridge, 2002), although they were effective in *mdx* mice (Huard, Acsadi, Jani, Massie, & Karpati, 1994). New muscle cell precursor populations have since been identified, including the recently described "satellite side population (SP) cells" (Tanaka et al.,

2009), which may be the precursors of the muscle-repair "SCs." In *mdx* mice, these SP cells have been more efficient in engrafting into muscle fibers than the more mature cells used in previous trials, and the mice demonstrated extensive muscle regeneration and dystrophin production. In recent years, induced pluripotent stem cells (iPSCs) have attracted significant interest from many researchers and clinicians. iPSCs have been used as a gene editing technology as well as for discovery of new drugs and testing (Abujarour et al., 2014; Jeong et al., 2014).

Upregulation of Compensatory Proteins. Although the ultimate target for a cure in DMD is normalized expression of dystrophin, several other structural proteins have been proven to have at least a modifying effect on the disease. Utrophin is a sarcolemmal protein with a structure very similar to that of dystrophin. Transgenic overexpression of both truncated and full-length utrophin protein in *mdx* mice has demonstrated a significant improvement in phenotype (Deconinck et al., 1997; Tinsley et al., 1996, 1998). Upregulation of utrophin by pharmacologic means has been investigated. Prednisone is known to upregulate utrophin; arginine also has been shown to do the same (Barton, Morris, Kawana, Bish, & Toursel, 2005).

Currently, there are three drugs being developed upregulate utrophin. Unfortunately, Ezutromid, a utrophin modulator that was on phase 2 of development, was recently terminated based on the lack of efficacy (Ricotti et al., 2016). Other two drugs, TVN-102https://musculardystrophynews.com/biglycan-tv-102/, and rhLAM111, are currently in preclinical stages of development.

Another way to modulate utrophin expression is to overexpress *GALGT2*. Overexpression of *GALGT2* results in ectopic expression of synapse-associated proteins, including utrophin, away from the synaptic regions. Galgt2 normally acts at the synaptic regions by adding the terminal GalNAc to an O-linked carbohydrate antigen on the α-dystroglycan near the neuromuscular junctions (Nguyen et al., 2002). Overexpression of galgt2 protein in mdx mice prevents muscular dystrophy when the *GALGT2* gene is introduced transgenically (Nguyen et al., 2002), as well as through AAVrh74-mediated gene delivery (Martin et al., 2009).

Consequently, overexpression of *GALGT2* may ameliorate the phenotype of DMD by upregulating utrophin expression along the myofibers membrane. Currently, there is an AAVrh74-mediated GALGT2 study in early phases of clinical trial for ambulant boys with DMD (ClinicalTrials.gov Identifier: NCT03333590).

One of the limiting factors for successful upregulation of utrophin is the posttranscriptional repression mechanisms targeting the 5′ and 3′ untranslated regions (UTRs) of utrophin mRNA, which in turn significantly limit the magnitude of utrophin upregulation achievable by promoter activation. New approaches using small molecules capable of relieving utrophin posttranscriptional repression are under investigation at the preclinical level (Loro et al., 2020).

Inhibiting Inflammation/Fibrosis. A dissociative steroid Vamerolone has recently been shown in an open label study to be safe and well tolerated in oral administration, without evidence of most adverse effects seen with glucocorticoids (Hoffman et al., 2019).

Edasalonexent is an orally administered small molecule designed to inhibit NF-κB, which is activated in DMD since infancy and is central to causing muscle damage and preventing muscle regeneration. A phase 1 study was recently published showing good tolerability and a randomized clinical trial is currently ongoing (Finanger et al., 2019).

Other anti-inflammatory treatments such as Givinostat, a potent histone deacetylase inhibitor that has shown to reduce fibrosis and promote muscle regeneration in mdx, are currently being tested in a phase 2/3 clinical trial in DMD patients.

Another approach to ameliorate fibrosis is Pamrevlumab. This is a potent monoclonal antibody to connective tissue growth factor that acts as an antifibrotic drug, which is currently being investigated in nonambulant DMD patients (ClinicalTrials.gov Identifier: NCT02606136).

Regulating Calcium Balance. Rimeporide is a small molecule that inhibits Na^{+}/H^{+} exchange-1 and showed to be cardioprotective and to prolong survival in dystrophic hamsters with dilated cardiomyopathy (Thomé et al., 2017). Rimeporide also demonstrated promising data on skeletal muscle function of mdx mice, as well as reducing fibrosis and inflammation in skeletal, cardiac, and diaphragm muscles. A phase 1 study was recently completed (ClinicalTrials.gov Identifier: NCT02710591) and a phase 2 study is under preparation.

Promoting Muscle Growth and Regeneration. Several other types of proteins have shown the ability to compensate for the loss of dystrophin outside the arena of structural integrity. For instance, myostatin, the protein that negatively regulates muscle growth, has been targeted as a potential modulator of dystrophinopathies. Early studies on myostatin inhibition in mdx mouse model were encouraging, demonstrating that its inhibition caused increased in muscle strength and muscle mass (Bogdanovich et al., 2002). However, two large trials were terminated due to lack of efficacy: a phase 2 study of domagrozumab, a humanized monoclonal antibody against myostatin, administered intravenously monthly (ClinicalTrials.gov Identifier: NCT02310763), and a phase 2 study of Talditercept alfa, a weekly, subcutaneous human IgG1(Fc)–adnectin fusion antibody that binds myostatin (ClinicalTrials.gov Identifier: NCT03100630).

Restoring Cell Energy. Efforts to ameliorate the effects of reactive oxygen species are currently under investigation. One promising compound along these lines is idebenone, which incorporates into the mitochondrial membrane, improving respiratory chain function and inhibiting lipid peroxidation and thus decreasing oxidative stress. When given presymptomatically and long-term to *mdx* mice, it prevented cardiac diastolic dysfunction and the development of lethal acute heart failure (Buyse et al., 2009). In a recent phase 3 study in non-steroid-treated DMD patients, idebenone demonstrated improved pulmonary function when compared to placebo arm (Buyse et al., 2015).

Respiratory Care

Patients with DMD or BMD eventually progress to have ineffective cough and decreased ventilation, leading to pneumonia, atelectasis, and respiratory insufficiency in sleep and

while awake (Gozal, 2000). These complications are generally preventable with careful follow-up and assessments of respiratory function. Patients with DMD should have routine immunizations by a primary care physician as recommended for well children by the American Academy of Pediatrics. In addition, these patients should receive the pneumococcal vaccine and annual influenza vaccine.

A polysomnographic study with continuous CO_2 monitoring is the best way to assess the need for ventilatory support. Pulse oximetry, especially during the awake state, is suboptimal. The decisions regarding long-term ventilation, be it invasive or noninvasive, should involve the patient, caregivers, and medical teams. Physicians have a legal and ethical responsibility to disclose treatment options and must avoid using their own perceptions of quality of life as the main factor in deciding whether to offer this type of information (Do, 2002). End-of-life decision making should be discussed earlier based on all possible information available to the patient. Further details of respiratory management are provided in Chapter 2.

Cardiac Management

Although ECG abnormalities are common in DMD, the best correlation of cardiac involvement with prognosis is by measuring left ventricular dysfunction by echocardiography (Corrado et al., 2002). Recent guidelines for the study of cardiac involvement in DMD have been published (Bushby, Muntoni, & Bourke, 2003; Finsterer & Stollberger, 2003). These recommend that DMD patients have an ECG and echocardiography at the time of diagnosis, at every 2 years up to age 10 years, and subsequently every year. Use of cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement can accurately measure fibrosis in cardiac muscle, but this assessment is not widely used. Subepicardial fibrosis in the inferolateral wall is the typical CMR lesion in DMD/BMD (Mavrogeni et al., 2018). CMR is an accurate screening tool that can detect fibrosis without left ventricle volume changes and can potentially help with the decision of intensification of treatment (Magrath et al., 2018). The early, preventive use of ACE inhibitors and later β-blockers is recommended (Bushby et al., 2003; Finsterer & Stollberger, 2003). Cardiac management is discussed in more detail in Chapter 3.

Drug Precautions

Use of anticholinergic drugs and ganglionic blocking agents should be avoided because of their tendency to decrease muscle tone. Patients with DMD may be susceptible to malignant hyperthermia, and proper evaluation and preparation before administration of general anesthesia are recommended (Heiman-Patterson, Natter, Rosenberg, Fletcher, & Tahmoush, 1986). Cardiotoxic drugs, such as halothane, should not be used, and caution is advised in undertaking general anesthesia (Smith & Bush, 1985). Details are further discussed in Chapter 10.

Rehabilitation

No large prospective studies have been performed to evaluate the role of physical therapy, stretching exercises, use of braces, or type of physical activity in DMD. Thus, the evidence is lacking for solid recommendations. These approaches are described further in Chapter 8.

Contractures. Active range-of-motion exercises supplemented by passive stretching are important to prevent contractures. Nighttime stretching orthoses (similar to the static ankle-foot orthosis, but with a hinge at the ankle and adjustable straps) are useful and should be recommended at age 5 to 6 years. A standing board tilted up 20 degrees may be used for 20 minutes twice a day to provide constant stretching of the Achilles tendons. Keeping the heel cords stretched through vigorous passive stretching by parents and physical therapists helps maintain better gait mechanics. This program requires stretching of the tensor fascia lata, hamstrings, knee flexors, and ankle plantar flexors. If strenuous stretching is not effective, surgical release of tight heel cords may be beneficial (Do, 2002), even if the quadriceps and gastrocnemius muscle groups are both less than antigravity in strength. In the latter case, long leg bracing can be offered to keep some ambulation after contractures are corrected. Mobilization in a walking cast immediately after surgery is essential to prevent loss of strength. Temporary bracing after surgery is necessary for optimal results after tenotomy procedures. Hip flexion contractures may benefit from surgical release followed by application of long leg braces. Resection of the fascia lata (Rideau procedure) may be beneficial for some patients (Do, 2002).

Scoliosis. Nearly all patients with DMD develop scoliosis after losing independent ambulation. The use of solid seat and back inserts in properly fitted wheelchairs is helpful in preventing scoliosis by keeping truncal posture erect. For some boys, long leg braces can be fitted to allow braced upright daily standing to prevent curvature. Baseline back x-ray films to document the degree of curvature if scoliosis begins to develop should be obtained for comparison with future films. The use of steroids, perhaps because it prolongs ambulation beyond the growth spurt of the early teen years, delays or prevents scoliosis, even if the child is eventually wheelchair bound (Alman et al., 2004; Yilmaz et al., 2004). Surgical management of scoliosis and other orthopedic complications is discussed in Chapter 9.

Genetic Counseling

Duchenne and Becker muscular dystrophies are inherited in an X-linked recessive manner; the risk to the siblings of a proband depends on the carrier status of the mother. Carrier females have a 50% chance of transmitting the *DMD* mutation in each pregnancy. Sons who inherit the abnormal gene will be affected, whereas daughters will be carriers. Males with DMD do not reproduce. However, males with BMD and X-linked dilated cardiomyopathy may reproduce. All of their daughters will be carriers but none of the sons will inherit their father's *DMD* mutation. Prenatal testing for pregnancies at risk is possible. Until the molecular genetics of DMD and BMD were understood, the diagnosis of maternal and female sibling carriers was based on pedigree analysis and indirect assays. These included serum CK level determinations (Griggs et al., 1985; Milhorat & Goldstone, 1965), the occasional finding of histologic abnormalities in muscle obtained from carriers (Maunder-Sewry & Dubowitz, 1981), and in vitro muscle ribosomal protein synthesis (Ionasescu, Burmeister, & Hanson, 1980; Ionasescu, Zellweger, & Conway, 1971a, 1971b). Today, the specific molecular characterization of a proband makes genetic counseling much

easier. If a specific mutation is found in a boy with DMD or BMD, genetic testing of the mother or sister looking for the exact mutation will determine if she is a carrier, and appropriate counseling can be done for further pregnancies. When DNA analysis in the proband is not informative, muscle biopsy of the fetus can be used to make the diagnosis (Kuller, Hoffman, Fries, & Golbus, 1992). A study of muscle from male fetuses with DMD showed morphologic changes by the second trimester, especially greater muscle nuclear size when compared with fetuses of the same gestational age (Vassilopoulos & Emery, 1977). Immunoreaction for dystrophin is absent. When a deletion or specific mutation in the *DMD* gene has been demonstrated in another family member, the deletion may be looked for in fetal issue or earlier in chorionic villus. This means that intrauterine diagnosis is possible by 7 weeks' gestation in suspect male embryos.

Emotional and Behavioral Management

Dysthymic disorder and major depressive disorder can occur in DMD boys, especially in the adolescent (Fitzpatrick, Barry, & Garvey, 1986; Witte, 1985). An affected boy's preoccupation with self and subsequent withdrawal may lead many families to seek counseling. Depression may be seen in a boy who has lost an older brother or close friend to DMD. Depression is often associated with intellectual limitation, which may induce low tolerance for frustration and overstress other manifestations of emotional immaturity. Psychological evaluation and counseling may be necessary. Neuropsychological screening for intellectual deficits and behavioral problems is ideally done as the boy enters school and should be repeated in preadolescence (Birnkrant et al., 2018).

LIMB-GIRDLE MUSCULAR DYSTROPHIES

The limb-girdle muscular dystrophies (LGMDs) are characterized by progressive muscle weakness of the large muscles around the shoulder and pelvic girdles (Fig. 20.9). The identification of individual causative mutations led to a more thorough picture of the phenotype, but a confusing nomenclature has developed. The initial classification of these disorders was based on the mode of inheritance, dividing them into autosomal dominant (type 1: LGMD1), autosomal recessive (type 2: LGMD2), and X-linked forms (Bushby & Beckman, 1995).

Currently, more than 30 genetic forms of LGMD are recognized, but a significant group of patients with a clinical diagnosis are not molecularly characterized. An integrated classification taking into account the type and localization of the proteins was recently proposed (Table 20.1) (Straub, Murphy, Udd, & LGMD Working Group, 2018). The diagnosis process for LGMD has changed dramatically over the last 10 years. Given the relative cost benefit and the diagnostic yield of next-generation sequencing panels and exomes, genetic testing is now recommended once clinical suspicion arises. Ancillary testing such as electromyography (EMG), imaging, muscle biopsy, and RNA sequencing can be used to clarify undiagnosed cases and variants of undetermined significance (Wicklund, 2019).

As a group, the prevalence of LGMDs has been reported to be between 2.27 per 100,000 and 10 per 100,000 (Norwood et al., 2009). In the United States, the calpainopathies are the most prevalent of the different LGMDs, followed by LGMDs with mutations in the genes for dysferlin, collagen VI, the sarcoglycans, anoctamin 5, and fukutin-related protein (FKRP) (Nallamilli et al., 2018).



Fig. 20.9 A patient with limb-girdle muscular dystrophy showing wasting of the thigh muscles and winging of the scapulae.

The following is a summary of some of the better understood and most common forms of limb-girdle dystrophies.

LIMB-GIRDLE MUSCULAR DYSTROPHY 2A (LGMD R1 CALPAIN 3–RELATED) CALPAINOPATHY

This childhood-onset LGMD has been reported as the most frequent autosomal recessive LGMD in several series (Chae et al., 2001; Dinçer et al., 1997; Richard et al., 1997; Topaloğlu et al., 1997). Although autosomal recessive is the most common pattern of inheritance in calpainopathies, when a certain single pathogenic variant in *CAPN3* is inherited, it can cause an autosomal dominant type of calpainopathy known as LGMD1I (Vissing et al., 2016).

The abnormal protein, calpain 3, is a nonlysosomal intracellular, muscle-specific, Ca^{2+}-activated neutral protease (Johnson, 1990). LGMD2A was the first form of limb-girdle dystrophy identified that is caused by deficiency of a nonstructural protein.

The calpain 3 gene (*CAPN3*) is located to chromosome 15q15.1–q21.1 and consists of 24 exons extending over a genomic region of 50 kb (Chiannilkulchai, Pasturaud, Richard, Auffray, & Beckmann, 1995; Richard et al., 1995). Homozygous null-null mutations appear to have the most severe phenotype, in terms of earlier wheelchair need, whereas a heterozygous missense mutation has the milder phenotype (Sáenz et al., 2005).

CAPN3 appears to be a cytoskeleton modulator with an important role in muscle maturation (Spencer et al., 2002). One current hypothesis is that calpain could have a protective effect and be involved in muscle detoxification, preventing a degradation of the muscle fiber (Zatz, de Paula, Starling, & Vainzof, 2003). It may also play a role in intracellular signaling pathways, and its deficiency might be associated

with myonuclear apoptosis by deregulation of the NF-κBα inhibitor/NF-κB pathway (Baghdiguian et al., 1999).

Under normal circumstances, *CAPN3* undergoes rapid autocatalytic activity after translation (Taveau et al., 2003). During the short minutes (less than 5 minutes in muscle cultures) that the protein is present, it is in a resting state, unless it becomes activated by signaling mechanisms (Rey & Davies, 2002). The autocatalytic activity resides in a Ca^{2+}-sensitive region between domains II and III of the protein.

LGMD2A has a characteristic phenotype in approximately 64% of genetically confirmed patients. Interfamilial and intrafamilial variability, though, is not uncommon (Zatz et al., 2003). Age of symptom onset is between 2 and 49 years, with a mean age of presentation of about 14 years (±8 years) (Sáenz et al., 2005). The disease causes symmetric weakness of the pelvic and shoulder girdle muscles. Cardiac muscle is not affected. Scapular winging can be seen early (Beckmann & Bushby, 1996). Most patients, regardless the age of onset, become wheelchair bound about 25 years after symptom onset. The CK level is elevated by 5-fold to 20-fold. Cognition is not impaired.

The diagnosis of calpainopathy is based on a typical phenotype and confirmatory genetic testing. If muscle biopsy is performed, the combination of a typical phenotype with an abnormal Western blot in muscle biopsy (at least two abnormal bands) brings the probability of being calpainopathy to 90% (Sáenz et al., 2005). However, if one of these tests is missing, the probability of accurate diagnosis is reduced to about 75% (Sáenz et al., 2005). A 20% to 40% false-negative rate on Western blot in these patients indicates that genetic sequencing should be pursued when there is clinical suspicion (Fanin et al., 2003; Sáenz et al., 2005).

Muscle pathologic findings are positive for necrosis, regeneration, altered myofibrillar architecture, increased centrally placed nuclei, fibrosis, fiber type I predominance, and normal immunoreactivity for dystrophin and α-sarcoglycan. Mild inflammation can also be seen.

LIMB-GIRDLE MUSCULAR DYSTROPHY 2B (LGMD R2 DYSFERLIN–RELATED): DYSFERLINOPATHY

Mutations in the dysferlin gene (*DYSF*) on chromosome 2p13 cause distinct phenotypes of muscular dystrophy: LGMD type 2B (LGMD2B), Miyoshi myopathy (MM), or juvenile-onset distal posterior compartment myopathy, as well as distal anterior compartment myopathy, which are known collectively by the term *dysferlinopathy*. These conditions represent 1% of recessive LGMD and about 33% of distal LGMD.

The *DYSF* gene encodes a 230-kDa protein with widespread expression in tissues such as skeletal muscle, cardiac muscle, kidney, placenta, lung, and brain. Immunohistochemical studies show that, in skeletal muscle, dysferlin is located at the plasma membrane, as well as in cytoplasmic vesicles (Bansal et al., 2003).

There are two common phenotypes, LGMD2B and the distal posterior compartment myopathy or MM, both presenting in the second decade of life (Takahashi et al., 2003). Two other phenotypes, distal anterior compartment and scapuloperoneal types, can also be seen earlier (Ueyama et al., 2002). The patients show normal early developmental milestones and no signs in childhood, with slowly progressive muscle weakness and wasting starting in the early to late teens (Mahjneh et al., 2001). The MM phenotype typically begins in the calves (Fig. 20.10), with later development of proximal weakness. The LGMD2B phenotype shows a predominantly proximal muscular dystrophy. Affected individuals have pelvic girdle muscle weakness, with lower limbs abducted and externally rotated and hyperlordosis as a result of hip muscle weakness. Cardiac muscle is not affected. Respiratory involvement is seen late in the disease or in those patients with very early onset of symptoms.



Fig. 20.10 A patient with Miyoshi myopathy: front (A) and back (B). Notice prominent atrophy of the posterior distal compartment muscles.

A diagnosis of dysferlinopathy is done by genetic confirmation of pathogenic mutations on the *DYSF* gene.

LIMB-GIRDLE MUSCULAR DYSTROPHIES 2C, 2D, 2E, 2F (LIMB-GIRDLE MUSCULAR DYSTROPHIES R3, R4, R5, AND R6 SARCOGLYCAN-RELATED)

SARCOGLYCANOPATHIES

The sarcoglycanopathies are a family of autosomal recessive disorders often presenting with an early and severe phenotype. The four sarcoglycans comprise a tetrameric complex of membrane proteins that contributes to the stability of the plasma membrane cytoskeleton and facilitates the association of dystrophin with the dystroglycans. The four sarcoglycan genes (alpha, beta, gamma, and delta) are related to each other structurally and functionally, but each has a discrete chromosomal location. Mutations in each gene may produce partial or complete loss of the entire complex, and as a consequence, the clinical manifestations of all four sarcoglycanopathies are very similar (Nigro et al., 1996).

The onset of symptoms varies from early childhood through adulthood, but in the majority of cases, it occurs in the first decade of life (Narayanaswami et al., 2014). Sarcoglycanopathies mimic dystrophinopathies, often with an early age of presentation and the presence of muscle hypertrophy, although cognitive deficit is rare. Muscle weakness involves first the pelvic girdle and subsequently progresses to involve the proximal upper extremities. Scapular winging,

calf hypertrophy, macroglossia, ankle contractures, and scoliosis are common features in early-onset, more severe cases. Loss of ambulation occurs in the second through fourth decades, with the majority of patients being wheelchair dependent in their teenage years. Dilated cardiomyopathy is a feature in some patients, and respiratory insufficiency necessitating nocturnal noninvasive ventilation affects many patients later in the disease course (Fayssoil et al., 2016).

LIMB-GIRDLE MUSCULAR DYSTROPHY 2I: FUKUTIN-RELATED PROTEIN DEFICIENCY

LGMD2I is one of the most common LGMD, representing from 11% to 19% of all LGMDs in different series (Krasnianski, Neudecker, Deschauer, & Zierz, 2004; Walter et al., 2004; Zatz et al., 2003).

The disease is caused by a mutation in the *FKRP* gene on chromosome 19q13.3 (Brockington, Blake, et al., 2001). The most common mutation is a single point (826C>A) missense mutation in one allele (>90%), causing a Leu276Ileu (C826A) change (Brockington, Yuva, et al., 2001). Disease severity correlated with a mutation on the second allele.

Age of onset ranges from 0.5 to 27 years, with 61% of patients presenting before age 5 years. These patients present with either a DMD phenotype, caused by heterozygous mutations, or with late-onset limb-girdle syndrome in those with homozygous mutations. The clinical course varies, usually involving weakness and wasting of the shoulder girdle muscles and proximal extremities, with significant calf hypertrophy and elevated serum CK, the increase ranging from 5-fold to 70-fold. Other clinical presentations have been described, including exercise-induced myalgias, isolated myalgias, cramps, and dilated cardiomyopathy with or without muscle weakness (Krasnianski et al., 2004). In some series, patients presented with muscle pain and myoglobinuria as the earliest presenting symptoms (Walter et al., 2004). Individuals with this form of LGMD can experience abrupt, reversible weakness in conjunction with a febrile illness. This acute illness-associated weakness sometimes occurs in children prior to onset of weakness associated with LGMD2I, lasts for a few days to a more than a month, may occur more than once, and has an associated increase in CK levels (Carlson et al., 2017).

Cardiac and respiratory involvement is relatively common in the heterozygous, earlier presentation cases, occurring in approximately 30% of patients, at times while they are still ambulatory (Mercuri et al., 2003; Poppe et al., 2003). Importantly, the severity of cardiac and skeletal muscle involvement may not correlate; thus, cardiac surveillance is recommended even in patients with mild weakness.

LIMB-GIRDLE MUSCULAR DYSTROPHIES TYPE 2L (LIMB-GIRDLE MUSCULAR DYSTROPHY R12 ANOCTAMIN 5 RELATED)

LGMD2L is an autosomal recessive disorder resulting from mutations in *ANO5*, the gene for anoctamin 5, a calcium-activated channel involved in phospholipid scrambling and important for membrane fusion and repair (Bolduc et al., 2010).

Recessive mutations in *ANO5* cause LGMD2L, Miyoshi-like distal myopathy (MMD3), and serum CK increase with variable exercise intolerance (Bolduc et al., 2010; Papadopoulos et al., 2017; Schessl, Kress, & Schoser, 2012).

Onset usually occurs in the third or fourth decades with weakness in the proximal lower extremities in LGMD2L, which very rarely leads to loss of ambulation. Dysphagia has been reported in late stages of the disease (Liewluck, Winder, & Dimberg, 2013).

Anoctamin 5 is also pressed in cardiac muscle; an increased number of patients with LGMD2L have ventricular premature complexes and some develop cardiomyopathies with reduced left ventricular ejection fractions (Wahbi et al., 2013).

LIMB-GIRDLE MUSCULAR DYSTROPHY 1A, 2G, AND 2J: SARCOMERIC PROTEINS DEFICIENCY

Limb-Girdle Muscular Dystrophy 1A (Myotilinopathy)

LGMD1A was the first autosomal dominant limb-girdle dystrophy to be linked to a specific gene locus. Initial clinical observations of the cosegregating of two rare diseases in a family with muscular dystrophy and Pelger-Huet anomaly (Schneiderman, Sampson, Schoene, & Haydon, 1969) and of a family in West Virginia with proximal weakness and nasal dysarthria (Gilchrist, Pericak-Vance, Silverman, & Roses, 1988) were followed years later by linkage studies localizing the gene to chromosome 5q31–q33 (Yamaoka et al., 1994) and the discovery of the first of several missense mutations in the gene coding for the sarcomeric protein myotilin (Hauser et al., 2002).

Myotilin has been implicated in other diseases, including having a causal role in some cases of myofibrillar myopathy (Selcen, & Engel, 2004; Selcen, Ohno, & Engel, 2004) and a secondary role in central core disease and nemaline myopathy (Schröder et al., 2003).

Limb-Girdle Muscular Dystrophy 2G (Telethonin)

Telethonin is a small 19-kD sarcomeric protein expressed in skeletal and cardiac muscle (Valle et al., 1997). Its gene maps to 17q11–12, and it is seen only in a small cohort of Brazilian families, presenting as a mainly proximal myopathy with onset from ages 9 to 15 years. Muscle biopsy revealed degenerating and regenerating muscle fibers and rimmed vacuoles (Moreira et al., 1997). Future patients can be screened with immunohistochemical techniques using anti-telethonin antibodies.

Limb-Girdle Muscular Dystrophy 2J (Titin)

Titin is a giant structural sarcomeric protein with a molecular weight of more than 3800 kD. The largest human protein, it forms the third filament system in striated muscle along with actin and myosin. Single titin molecules span half sarcomeres from Z disks to M lines in skeletal and cardiac muscle. Titin contributes to sarcomere assembly and passive tension of myofibrils as well as serving sensor and signaling functions (Granzier & Labeit, 2004; McElhinny, Perry, Witt, Labeit, & Gregorio, 2004). Titin serine kinase phosphorylates telethonin, the protein implicated in LGMD2G.

Mutations in the titin (*TTN*) gene on chromosome 2q31 most often produce autosomal dominant tibial muscular dystrophy, a distal muscular dystrophy of mid-adult life with prominent involvement of the tibialis anterior and toe extensor muscles (Hackman et al., 2002). This disorder is most commonly seen in persons of Finnish descent.

LIMB-GIRDLE MUSCULAR DYSTROPHY 1C: CAVEOLINOPATHY

Caveolins are small transmembrane proteins with intracellular domains that undergo extensive oligomerization to form membrane complexes known as *caveolae*. Skeletal muscle disorders result from mutations in the gene that encodes caveolin 3 (*CAV3*), localized to chromosome 3p25. This protein interacts with nNOS and the dystrophin-associated protein complex via the intracellular portion of β-dystroglycan (Song et al., 1996; Tang et al., 1996). The disease can present in childhood with a range of symptoms from simple exertional myalgias to slowly progressive weakness, calf hypertrophy, and CK elevation. *CAV3* mutations are also associated with autosomal dominant rippling muscle disease.

Quadriceps-Sparing Myopathy

GNE Myopathy. UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) myopathy, previously known as Nonaka myopathy or hereditary inclusion body myopathy, is a rare autosomal recessive muscle disease caused by mutations in GNE, the gene encoding the rate-limiting enzyme in sialic acid biosynthesis The pathophysiology is still not clearly understood, but hyposyalilation of the muscle glycans is thought to play an important role (Cho et al., 2017; Huizing et al., 2004).

GNE myopathy usually manifests in late teens to early adult years with distal myopathy. The typical presentation is bilateral foot drop caused by the early involvement of tibialis anterior muscles. The disease usually progresses slowly and symmetrically, first involving distal muscles of the lower extremities, followed by proximal muscles with relative sparing of the quadriceps (Argov & Yarom, 1984; Nonaka et al., 1981). Upper extremities are typically affected later in the disease. However, very rarely, hand weakness could be the initial presentation as well (De Dios et al., 2014). CK is mildly elevated and EMG shows typical myopathic features; nerve conductions are normal.

The diagnosis of GNE myopathy is made by clinical and histopathological findings. Muscle biopsies typically show rimmed vacuoles on modified Gomori trichome staining and characteristic filamentous inclusions (Argov & Yarom, 1984). The diagnosis is confirmed by the presence of pathogenic (mostly missense) mutations in both alleles of the *GNE* gene.

Treatment is only symptomatic, but there are a few therapies under investigation, including administration of precursors of the sialic acid biosynthetic pathway (sialylation-increasing therapies) (Yonekawa et al., 2014) or restoring UDP-GlcNAc 2-epimerase and ManNAc kinase enzymatic activities by gene or cell therapy approaches (Mitrani-Rosenbaum et al., 2012). A clinical trial to test the efficacy of N-acetylmannosamine (ManNAc), an orphan drug in an uncharged monosaccharide and the first committed precursor in Neu5Ac biosynthesis myopathy, is currently under way (NCT04231266).

Other Distal Muscular Dystrophies

A group of dystrophies with predominantly distal involvement that do not fall into the classification of LGMD are listed in Table 20.2 (Fig. 20.11).

EMERY-DREIFUSS MUSCULAR DYSTROPHY

Both the X-linked and autosomal dominant forms of Emery-Dreifuss muscular dystrophy result from mutations in genes coding for nuclear envelope proteins. The X-linked form of Emery-Dreifuss (XL-EDMD or EMD1) is caused by mutations of the *EMD* gene located at Xq28, which encodes a 34-kD ubiquitously expressed nuclear envelope protein, emerin (Bione et al., 1994). Approximately 95% of mutations producing XL-EDMD are null mutations associated with a complete absence of emerin in skeletal muscle, as well as smooth muscle, skin fibroblasts, leukocytes, and exfoliative buccal cells.

Autosomal dominant Emery-Dreifuss (AD-EDMD or EMD2) and autosomal recessive or sporadic Emery-Dreifuss muscular dystrophy (EMD3) result from mutations of the *LMNA* gene located on 1q21, which encodes two nuclear envelope proteins, lamins A and C (Bonne et al., 1999). Lamin A/C are alternatively spliced products of the same gene and comprise part of the nuclear lamina; they interact with chromatin and other proteins of the inner nuclear membrane, including emerin (Gruenbaum et al., 2003). Mutations of the *LMNA* gene producing the AD-EDMD phenotype are missense mutations that allow translation of full-length lamin A/C. Immunostaining of lamin A/C is therefore not reliable for confirmation of the diagnosis of AD-EDMD (Emery, 2000). The diagnosis of lamin A/C disorders requires DNA sequencing or mutation scanning (Bonne, 2003; Bonne et al., 2000; Brown et al., 2001).

New mutations have been found to explain the 40% of EMD patients who did not present with the most common emerin or lamin AC mutations, expanding the genetic heterogeneity of the EMD phenotype. EMD4 and EMD5 described in few families are caused by mutations in the synaptic nuclear envelope protein 1 (SYNE1) and 2 (SYNE2) (Zhang et al., 2007). EMD6, caused by mutation in the X-linked four-and-a-half-LIM protein 1 (FHL1) gene, is inherited as an autosomal recessive or sporadic form (Quinzii et al., 2008).

Although XL-EDMD and AD-EDMD usually share a similar phenotype, wide clinical variation, with poor genotype-phenotype correlation, has been documented in both forms (Bonne et al., 2000; Fujimoto et al., 1999; Muntoni et al., 1998). Interfamilial and intrafamilial phenotypic variability may exist in those sharing identical mutations.

The onset of contractures occurs early in the disease in the first or second decade and often precedes clinically significant weakness. Contractures are most prominent at the elbows, Achilles tendons, and posterior cervical muscles (Fig. 20.12A) (Emery, 1989). Upper extremity contractures often precede axial and lower extremity deformities. The arms are held in a semiflexed position. The feet are set in equinus, often with associated toe walking. Posterior cervical contractures preclude full neck flexion (Fig. 20.12B). Contractures usually remain disproportionate to the degree of weakness (Emery, 2000) and may be the major factor in functional impairment. Muscle weakness is relatively mild and slowly progressive. The distribution of motor deficits is humeroperoneal, with upper extremity (biceps, triceps, and spinal muscles) occurring earlier than leg weakness (tibialis anterior and peroneal muscles). Pseudohypertrophy is not seen and helps clinically differentiate XL-EDMD from dystrophinopathy (e.g., BMD).

Cardiac symptoms may include palpitations, syncope, and diminished exercise tolerance. Supraventricular arrhythmias, atrioventricular conduction block, ventricular arrhythmias, and restrictive or dilated cardiomyopathy may

Table 20.2 Distal Muscular Dystrophies

Type and Eponym	Gene Localization	Gene Product	Initial Weakness	Serum CK Level	Biopsy
Late adult-onset, predominantly in hands (Welander) (AD)	2p13	Unknown	Hands: finger/wrist extensors	Normal or slightly elevated	Myopathic: vacuoles in most cases
Late adult-onset, predominantly in legs					
IIa. Finnish (Tibial, Udd) (AD)	2q31	Titin	Legs; anterior compartment	Normal or slightly elevated	Vacuolar myopathy, sarcolemmal disruption, accumulation of myofibrillar proteins
IIb. Markesbery-Griggs[a] (AD)	10q22.3-23.2	ZASP	Legs: anterior compartment	Normal or slightly elevated	Vacuolar myopathy but fewer vacuoles
Early adult-onset, anterior compartment in legs (Nonaka type, quadriceps-sparing, HIBM2) (AR; some sporadic)	9p1q1	GNE: glucosamine (UDP-*N*-acetyl)-2-epimerase/*N*-acetylmannosamine kinase	Legs: anterior compartment	Increased, usually <5× normal	Vacuolar myopathy
HIBM with Paget disease and frontotemporal dementia (AD)	9p13-p12	Valosin-containing protein (VC)	Legs: mainly anterior compartment	Normal or slightly elevated	Vacuolar myopathy
HIBM-3 (AD)	17p13-1	MyHC-IIa: type IIa myosin heavy chain	Variable presentation	Normal in children, elevated in adults	Vacuolar myopathy
Early adult-onset posterior compartment in legs (Miyoshi) (AR)	2p13	Dysferlin (allelic to LGMD 2B)	Legs: posterior compartment	Increased, 10–150× normal	Myopathic, necrosis, no vacuoles; dysferlin deficiency
Early adult-onset (Laing) (AR)	14q11	Myosin heavy chain 7	Legs: anterior compartment; neck flexors	Slightly increased, <3× normal	Moderate myopathic changes; no vacuoles
Distal myopathy with vocal cord and pharyngeal weakness (onset in fourth to sixth decades) (AR)	5q31	Matrin 3	Legs: anterior compartment; finger extensors may first be involved	Normal to moderately increased	Vacuolar myopathy
Myofibrillar myopathy (AD, spororadic) (onset in childhood to fifth decade)	2q35 (AP.AR) 11q21-23 (AD) 5q22.3-3.13 (AR) 10q22.3-23.2 (AD) 7q32.1 (AD) 1p36 (AR)	Desmin Crystallin aB CAP myotilin ZASP Filamin C Selenoprotein N1	Hands or legs, some with scapuloperoneal	Moderately increased, <5× normal	Myopathic, usually with vacuoles; subsarcolemmal granules or cytoplasmic bodies; accumulation of desmin and other myofibrillar proteins
Others					
Some caveolinopathies	3p25 (AD)	Caveolin	Variable presentation	Elevated	Dystrophic changes, caveolin deficiency
Nebulin gene mutations	2q (AR)	Nebulin	Young adults; tibial and facial weakness	Normal	Some small nemaline rods

[a]This should be considered a myofibrillar myopathy.
AD, autosomal dominant; *AR*, autosomal recessive; CK, creatine kinase; *HIBM*, hereditary inclusion body myopathy; *MyHC*, myosin heavy chain; *ZASP*, Z-band alternatively spliced PDZ motif-containing protein

evolve. The risk of ventricular dysfunction and arrhythmias is greater in the autosomal dominant than in the X-linked form (Bécane et al., 2000; Bonne et al., 2003), but symptomatic cardiomyopathy may occur in women heterozygous for null emerin mutations. Cardiac symptoms usually evolve after the second decade.

TREATMENT AND MANAGEMENT

The management and treatment of LGMDs are in many ways similar to that for DMD, particularly when the disorders present in children. This includes the management of pulmonary complications, contractures, bracing, physical therapy and rehabilitation, and scoliosis surgery when indicated. Several LGMDs affect the heart as well, with management similar to that in DMD, sometimes requiring transplantation. Of particular importance is the management of Emery-Dreifuss muscular dystrophy, in which the severe cardiac complications and prominent contractures necessitate early, aggressive treatment.



Fig. 20.11 A patient with Welander distal myopathy. Notice the distal forearm wasting and wrist drop.

Specific treatment is not currently available for any of these disorders. As with many neuromuscular diseases, gene therapy holds great promise for some LGMD subtypes (Bengtsson et al., 2016). The small molecular weight of the coding sequences for sarcoglycans makes AAV transfer a feasible approach, and results have been favorable in the rodent model of the disease (Danièle, Richard, & Bartoli, 2007). A pilot phase 1/2 clinical trial for LGMD 2D by local injection restores alpha sarcoglycan and increases muscle fiber size (Mendell et al., 2009, 2010). A larger clinical trial is planned, and development is underway using AAV-based gene therapy approach for other LGMD subtypes as well, including LGMD2D (NCT01976091), LGMD 2E (NCT03492346), and dysferlynopathies (NCT02710500).

Many of the treatments under investigation for the treatment of DMD may also be of benefit in some of these diseases. Of great interest are drugs or other approaches that might inhibit fibrosis, promote nerve regeneration, or inhibit muscle atrophy. There is also some consideration of exon skipping approach for some forms of LGMD (Wyatt et al., 2018).

In some cases, the use of steroids has shown some benefit. These drugs have demonstrated a marked benefit in LGMD2L and LGMD2I (fukutin and FKRP associated), and some reported benefit in LGMD2D (alpha-sarcoglycan deficient) (Angelini et al., 1998; Connolly, Pestronk, Mehta, & Al-Lozi, 1998). In dysferlinopathies, despite the pronounced inflammatory response seen on muscle biopsy, steroids are not beneficial and might worsen the clinical course. Unfortunately, because of the limited number of patients with each particular disease, the performance of randomized controlled clinical trials similar to those in DMD is difficult. Therefore, decisions regarding the use of steroids in LGMDs should be considered on a case-by-case basis.

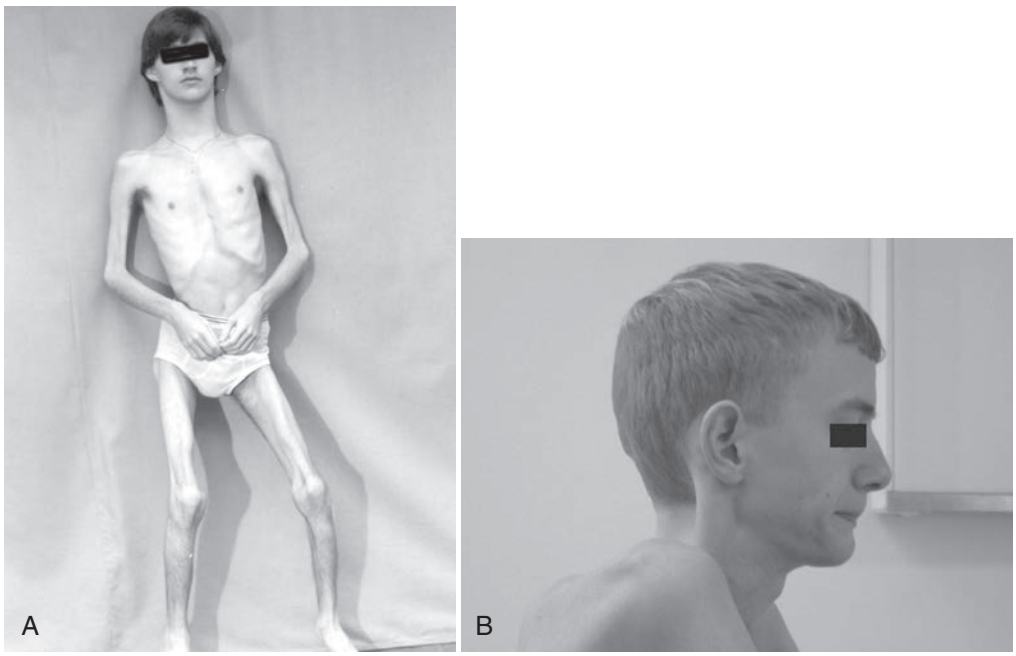


Fig. 20.12 (A) A patient with Emery-Dreifuss muscular dystrophy with diffuse muscle atrophy and prominent contractures. (Reprinted from Bertorini, T. (2001). *"Muscular dystrophies" in Pourmand's neuromuscular diseases, expert clinicians' views*. Boston: Butterworth-Heinemann.). (B) A patient with Emery-Dreifuss muscular dystrophy, with significant neck extensor contractures limiting neck flexion. (Reprinted from Escolar, D. (2006). "Muscular dystrophies" in pediatric neurology principles & practice. Philadelphia: Mosby.)

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHD) is inherited as an autosomal dominant disorder with high penetrance and variable expression. The genetics of FSHD are complex and have only recently been elucidated. From 10% to 30% of cases represent new mutations (Zatz et al., 1995). Prevalence is estimated at 1 in 20,000. FSHD1 (95% of FSHD) is associated with chromosome locus 4q35 and a sequence of repeats named D4Z4 (Wijmenga et al., 1993). Healthy individuals have 11 to 100 repeats on both alleles, whereas patients with FSHD1A have 1 to 10 repeats on one allele (Tawil, 2008). An inverse correlation exists between the D4Z4 region size and disease severity (Zatz et al., 1995), with the largest deletions resulting in severe, congenital FSHD (Brouwer, Padberg, Bakker, Wijmenga, & Frants, 1995; Brouwer, Padberg, Wijmenga, & Frants, 1994). This deletion of repetitive units is associated with hypomethylation of the region (van Overveld et al., 2003). With hypomethylation, the chromatin is relaxed, allowing transcription of the normally dormant gene *DUX4* from the terminal D4Z4 repeat (Lemmers et al., 2010). However, for the *DUX4* transcript to be polyadenylated and stabilized, the deletion must be in the correct context of one of two alleles (A and not B) (Lemmers et al., 2002).

FSHD2 (5% of FSHD) also occurs due to the hypomethylation of the D4Z4 region of chromosome 4q35. However, in this case, hypomethylation is not associated with a D4Z4 contraction. About 80% of patients with FSHD2 have a separate mutation in *SMCHD1*, a hypermethylating enzyme with a normal role in X chromosome inactivation. Mutations in *SMCHD1* (and presumably other yet-to-be-defined loci) result in hypomethylation of the D4Z4 region, which leads to *DUX4* transcript expression in the context of the A allele (Lemmers et al., 2012). The specific target genes responsible for DUX4-mediated toxicity have not been conclusively identified but are believed to make the myogenic cells more susceptible to oxidative stress (Winokur et al., 2003).

CLINICAL FEATURES

Clinical diagnostic criteria have been established by the FSHD Consortium (Tawil, Figlewicz, Griggs, & Weiffenbach, 1998). This group specifies autosomal dominant inheritance, bifacial weakness, and weakness of either the scapular stabilizers or ankle dorsiflexor muscles. Supporting criteria include asymmetry of motor deficits (a finding far more common in FSHD than any other muscular dystrophy); sparing of deltoid, neck flexor, and calf muscles; and involvement of wrist extensors and abdominal muscles. High-frequency hearing loss and retinal vasculopathy (Coats disease) are additional supportive findings. Exclusion criteria include eyelid ptosis, extraocular muscle weakness, skin rash, elbow contractures, cardiomyopathy, sensory loss, neurogenic changes on muscle biopsy, and myotonia or neurogenic motor unit potentials on needle EMG.

Weakness of the orbicularis oculi is usually asymptomatic but may be appreciated by observing incomplete burying of the eyelashes with forced eyelid closure and the ease with which the closed eyelids can be pried apart. A history of "sleeping with the eyes open' may be offered by a parent or spouse. Facial weakness may not be symmetric (Fig. 20.13).

Weakness of scapular fixation is evidenced by scapular winging accentuated by arm elevation in a forward plane (Fig. 20.14). The scapulae ride high on the back, producing the illusion of hypertrophied trapezius muscles. Arm abduction is impaired in the face of normal power and bulk of the deltoid muscles. Wasting of the biceps and triceps with preservation of deltoid and forearm muscles yields a "Popeye" configuration to the arms. Wasting of the clavicular head of the pectoral muscles produces a reversal of the axillary



Fig. 20.13 A patient with facioscapulohumeral muscular dystrophy with asymmetric facial weakness.



Fig. 20.14 A patient with facioscapulohumeral muscular dystrophy, showing wasting of the biceps and the trapezius muscle with prominence of the scapulae protruding upward.

folds with a deep upward slope. Weakness of lower abdominal muscles may result in a pot belly when standing and a positive Beevor sign (cephalad movement of the umbilicus with neck flexion) when the patient lies supine.

Lower extremity weakness is usually first noted in the ankle dorsiflexors with compromised heel walking or overt foot drop. Atrophy is most prominent in the tibialis anterior. Preservation or hypertrophy of the extensor digitorum brevis muscle clinically excludes a neurogenic etiology for the foot drop. Axial paraspinal muscle weakness may result in marked lumbar lordosis, especially in childhood-onset FSHD patients.

Congenital onset of FSHD has been associated with intellectual disability and epilepsy in children with the largest D4Z4 deletions (EcoRI fragment size of 10 kb; i.e., less than 10 repeats). The congenital-onset, or infantile, phenotype is severe and rapidly progressive, accompanied by sensorineural hearing loss and Coats disease (Fitzsimons, Gurwin, & Bird, 1987; Small, 1968; Taylor et al., 1982). Marked shoulder and pelvic girdle weakness is present before age 6 years, with loss of ambulation by age 15 years. The condition may be mistaken for Möbius syndrome. Profound weakness of facial muscles, including extraocular muscles, is typical (Fig. 20.15).



Fig. 20.15 Early onset of infantile form of facioscapulohumeral muscular dystrophy manifests with incomplete eyelid closure and lack of facial expression. (Reprinted with permission from Escolar, D. (2006). *"Muscular dystrophies" in pediatric neurology principles & practice*. Philadelphia: Mosby.)

DIAGNOSIS AND EVALUATION

Results of CK determinations are either normal or slightly elevated; CK levels more than five times laboratory norms suggest an alternative diagnosis. Genetic testing has largely replaced electrodiagnostic and muscle biopsy evaluations in suspect FSHD patients. EMG studies of moderately weak muscles reveal brief, low-amplitude motor unit action potentials consistent with myopathy; sparse fibrillations reflecting muscle fiber necrosis can also be noted. However, the needle EMG examination may be normal in clinically powerful muscles. Muscle biopsy findings are often nonspecific, with occasional small angular fibers that are more often of type 1 specificity, necrotic fibers, and "lobulated" fibers. Individual muscles may vary considerably in the extent of pathological changes. Endomysial fibrosis may occur but not to the extent seen in Duchenne dystrophy. A modest increase in the percent of hypertrophic type II muscle fibers may be seen. Foci of a predominantly T-cell CD8-positive inflammatory cells in a perivascular or endomysial distribution are commonly encountered and on occasion may lead to a pathologic misdiagnosis of an immune myopathy, particularly in younger patients (Rothstein, Carlson, & Sumi, 1971).

TREATMENT AND MANAGEMENT

Because no proven specific treatments are available for FSHD, the main therapeutic approaches are adaptive and protective. The American Academy of Neurology provided recommendations on the current treatment of FSHD based on a systematic review of the evidence (Tawil et al., 2015).

Ankle-foot orthoses for foot drop are commonly utilized. Orthopedic scapular fixation may improve upper extremity function (Bunch & Siegel, 1993; Twyman, Harper, & Edgar, 1996), but the gain may be short lived. The procedure should be reserved for those patients with preserved deltoid strength. Musculoskeletal and joint pain is common and may require nonsteroidal anti-inflammatory drugs (NSAIDs) or antidepressants if chronic. Routine auditory and ophthalmologic screening is recommended, especially in infantile-onset FSHD, in which Coats disease is most often seen. Respiratory complications should be kept in mind, and routine measurement of forced vital capacity should be performed on those patients with severe weakness or kyphoscoliosis.

Unlike muscular dystrophies associated with sarcolemmal proteins, the muscle fibers in FSHD are not prone to damage as a result of exercise. Multiple studies, in fact, demonstrate beneficial effects of both strength training and aerobic exercise in FSHD (Andersen et al., 2015; McCartney, Moroz, Garner, & McComas, 1998; Olsen, Ørngreen, & Vissing, 2005). Care should be taken, however, to avoid injury to weakened joints.

The beta-adrenergic agonist albuterol has been shown to improve muscle mass but has little effect on function (Kissel et al., 2001), a finding supported by a study examining the use of both albuterol and strength training (van der Kooi et al., 2004). Therapeutic trials of corticosteroids have been disappointing (Rose & Tawil, 2004). Data derived from a trial of creatine that included FSHD patients showed no benefit for this subgroup (Walter et al., 2000). The clinical trial of the myostatin antibody (MYO-029) discussed in the DMD section of this chapter showed no benefits in function or strength in FSHD either (Wagner et al., 2008).

Several strategies are being considered as possible treatment approaches for FSHD in the future. Because patients with FSHD demonstrate hypomethylation in the D4Z4 region, folic acid and vitamin B_{12} have been evaluated as possible treatments since they contribute to DNA methylation. Initial studies have not shown clear benefit (van der Kooi et al., 2006). Alternative methods of myostatin inhibition are also being investigated, as is the case in other dystrophic diseases (Tawil, 2008). Finally, the autologous delivery of unaffected myoblasts or mesangioblasts is under consideration as a potential approach for therapy (Tawil, 2008).

Another ongoing approach is by the use of pharmacologic screens of chemical libraries that repress DUX4 downstream targets, either through inhibiting DUX4 expression or inhibiting DUX4 activity. Losmapimod is an inhibitor of p38α/β MAPK shown in preclinical studies to reduced DUX4 expression. The medication has been previously studied in phase 1 trials (Ino et al., 2015), and phase 2 trials are currently enrolling for FSHD (Oliva et al., 2019) (NCT04003974).

MYOTONIC DYSTROPHY

MYOTONIC DYSTROPHY TYPE 1

Type 1 myotonic dystrophy (DM1) is an autosomal dominant disorder with multisystem involvement. DM1 is the second most common of the muscular dystrophies, affecting 1 in 8000 individuals. It is the most prevalent of the dystrophies in adults. Skeletal, smooth, and cardiac muscles are affected, as well as the eye, endocrine, and central nervous systems. Clinical signs and symptoms are variable, including among affected family members, with a spectrum ranging from asymptomatic to severe.

Molecular Genetics

DM1 is caused by a mutation in the length of a CTG trinucleotide repeat in the 3′ UTR of the myotonic dystrophy protein kinase (*DMPK*) gene on chromosome 19q. The normal gene has between 5 and 36 CTG trinucleotide repeats. Minimally affected individuals have as few as 50 copies; severely affected DM patients may have thousands of repeats (Redman, Fenwick, Fu, Pizzuti, & Caskey, 1993). The CTG repeat gene shows marked intergenerational and somatic instability in patients with DM1 when the repeat is expanded to more than approximately 55 repeats (De Temmerman et al., 2004). Virtually all children with the most severe congenital phenotype have inherited the *DMPK* allele from their mothers. In fact, the sex of the transmitting parent is an important factor that determines DM allele size in the offspring.

The pathophysiologic mechanism of disease in DM has been recently described as one mediated by "toxic RNA" (Cho & Tapscott, 2007). The repeat expansion of *DMPK* is actually outside of any coding region, and the protein product is therefore normal. However, the RNA transcript itself (a CUG expanded repeat) is thought to form a hairpin structure that accumulates in the nucleus (Cooper, 2006), leading to dysfunction of the RNA binding proteins MBNL1 and CUGBP1 (Philips, Timchenko, & Cooper, 1998; Savkur, Philips, & Cooper, 2001). These proteins normally regulate the alternative splicing of pre-RNA. When this process is misregulated, a "spliceopathy" of the muscle chloride channel and insulin receptor occurs, making abnormal versions of these gene products and leading to the myotonia and insulin resistance seen in DM1 (Mankodi et al., 2002; Savkur et al., 2001, 2004). Cardiac conduction disturbances in DM1 appear to be mediated by mutant RNA, increasing the expression of NKX2-5, a cardiac transcription factor (Yadava et al., 2008).

Clinical Features

The clinical presentation of DM1 is highly variable among patients and within families. Congenital DM1 is most commonly seen in infants born to mothers with *DMPK* expansion alleles of 600 or more CTG repeats. Symptoms are often noted before birth. Reduced fetal movement and polyhydramnios are warning signs. There is an increased incidence of breech presentation. At delivery, marked hypotonia, generalized weakness, and inefficient respiration are noted. Characteristic facies with a tented upper lip indicating facial diplegia is seen in nearly all infants. Arthrogryposis, most often producing talipes equinovarus deformity, is common. Life-threatening respiratory insufficiency requiring mechanical ventilator support may portend an ominous long-term prognosis.

Classic DM1 is most likely to develop in the second to fourth decade (Fig. 20.16) in patients with CTG repeat lengths of 100 or more. Teenagers and young adults may complain of "stiffness" as the first symptom of myotonia. Difficulty with fine motor skills such as handwriting and complaints referable to distal upper extremity weakness and grip-induced myotonia follow. Evolution of lower limb distal weakness progresses to foot drop and inability to skip or vertically leap. Typical myopathic facies (also described as *hatchet facies*) with temporal muscle wasting and eyelid ptosis give a "dull" appearance (Fig. 20.17).

Nonskeletal muscle signs and symptoms require close clinical attention. Cardiac conduction defects tend to evolve after age 30 years, but early cardiac screening with ECG is needed to detect those patients with progressive atrioventricular conduction block, a significant cause of early death in patients with classic DM1 (Hawley, Milner, Gottdiener, & Cohen, 1991). Smooth muscle dysfunction may produce dysphagia, constipation, or diarrhea. Hypokinesis of the small and large bowel may produce pseudo-obstruction or megacolon. Impaired sphincter of Oddi function predisposes to cholelithiasis. Endocrinopathies, including hyperinsulinism with glucose intolerance and impaired growth hormone secretion, are usually asymptomatic (Hudson et al., 1987). Gonadal atrophy and reduced fertility are common but usually evolve after the prime reproductive years. An underappreciated complication of classic DM1 is hypersomnia, often found in association with both central and obstructive sleep apnea (Rubinsztein, Rubinsztein, Goodburn, & Holland, 1998). Men may exhibit frontal balding beginning in their late teens. Christmas tree cataracts can be detected with slit-lamp examination beginning in the teens. Women with classic DM1 are at risk for obstetric complications, including spontaneous miscarriage; failure of progression of labor, necessitating cesarean section; and postpartum hemorrhage (Webb, Muir, Faulkner, & Johnson, 1978). Worsening of motor impairment rarely accompanies pregnancy. All patients

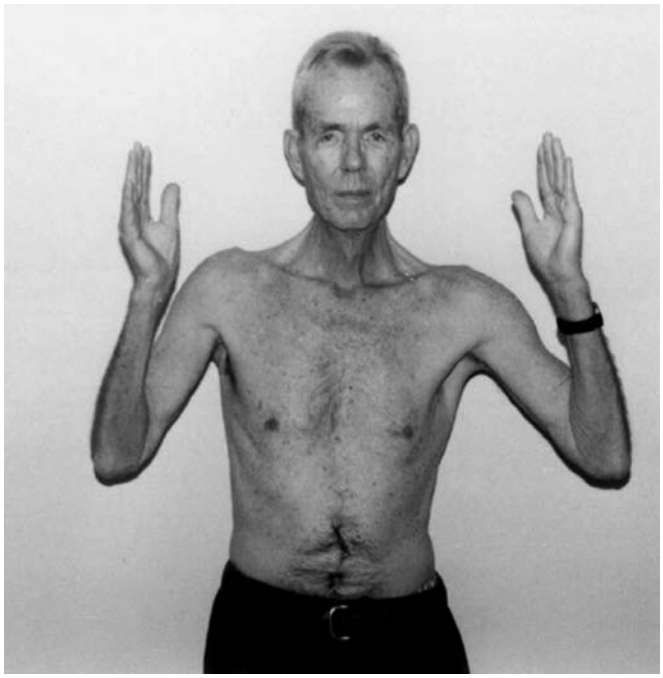


Fig. 20.16 An adult patient with myotonic dystrophy. Note wasting of the temples, anterior neck, and forearm muscles.

with classic DM1 require added precautions when undergoing surgery. Sensitivity to sedatives and inhalation anesthesia mandates close observation in the recovery room. Blunted responses to hypercarbia and hypoxemia may be partially responsible for postanesthetic complications.

Diagnosis and Evaluation

The universal availability of DNA testing for patients suspected of having DM1 has made other diagnostic investigations obsolete. Lymphocyte DNA assay for the CTG expansion repeat in the *DMPK* gene is nearly 100% accurate. PCR analysis is performed to detect up to 100 repeats; Southern blot analysis is used to quantitate CTG expansions of greater length. "False-negatives" have proven to represent other diseases, most commonly DM2.

Older diagnostic techniques for the identification of DM1 are of historical interest. They include needle EMG, which demonstrates waxing and waning high-frequency discharges typical of true myotonia. CK levels are normal or slightly elevated. Muscle biopsy in older children and adults reveals type I muscle fiber atrophy, increased numbers of internal nuclei, and ring fibers. The muscle biopsy in infants with congenital DM1 show poor fiber type differentiation and peripheral halos of many fibers void of oxidative activity. None of these morphologic findings are pathognomonic for DM1.

MYOTONIC DYSTROPHY TYPE 2

Shortly after the discovery that DM was caused by a CTG trinucleotide repeat expansion in the *DMPK* gene, reports appeared that some patients with typical clinical features of this disorder showed neither the CTG repeat expansion nor localization to 19q13.3 (Thornton, Griggs, & Moxley, 1994). Some of these patients manifest weakness in a proximal greater than distal distribution; the term *proximal myotonic myopathy* was coined to describe this newly appreciated



Fig. 20.17 A family with myotonic dystrophy. A mildly affected mother and her two sons with markedly elongated face and temporal wasting.

disorder (Ricker et al., 1994, 1995). Further phenotype-genotype investigations localized the disease to 3q21 (Ranum, Rasmussen, Benzow, Koob, & Day, 1998), and shortly thereafter, the gene was localized to the zinc finger protein 9 (*ZNF9*) gene and a CCTG repeat sequence expansion in intron 1 of this gene was discovered (Liquori et al., 2001). The toxic accumulation of RNA theory described earlier also applies to the CCTG transcript of this repeat (Liquori et al., 2001).

These manifest both proximal motor deficits as well as findings typical for classic DM. The majority of patients with DM2 present in their adult years, but patients as young as age 8 years have demonstrated symptoms. Importantly, no congenital phenotype has yet been reported (Day & Ranum, 2005; Day et al., 2003). DM1 and DM2 share common findings of myotonia, early cataracts, frontal balding, and cardiac involvement. DNA studies provide the means for definitive classification of affected patients.

Treatment and Management

Patients diagnosed with DM require education about their disease and an explanation of the phenomenon of anticipation (especially for young women of child-bearing age). Periodic pulmonary function studies and ECGs should begin in the second decade and cardiology consultation obtained liberally throughout the lives of these patients for symptoms suggestive of arrhythmias, syncope or presyncope, or progressive ECG changes. Routine ophthalmologic examination is recommended to screen for cataracts.

Myotonia is not the most serious complication of DM, although it can exacerbate disability. Trials of drugs such as phenytoin (100 mg two to three times per day), carbamazepine (600 to 800 mg/day), or mexiletine (150 to 200 mg three times per day) may be helpful for treatment of myotonia in selected patients, but their safety and efficacy have not been studied in long-term randomized controlled trials (Trip, Drost, van Engelen, & Faber, 2006). These are all sodium channel blockers, and their use could exacerbate weakness in these patients. Furthermore, mexiletine should be avoided in patients with second- and third-degree heart block, which are not uncommon in these diseases. Muscle

pain is a common complaint in patients with DM2 and may respond to NSAIDs, gabapentin, or tricyclic antidepressants.

Lethargy and fatigue may suggest central or obstructive sleep apnea. If sleep studies are negative, empiric trials of stimulant medications may be helpful for these symptoms. Patients undergoing surgery should make both surgeon and anesthesiologist aware of their neuromuscular disorder, limit the use of sedative agents, and anticipate a prolonged period of observation in the recovery room.

Ankle-foot orthoses help address distal lower limb weakness and foot drop. Lesser degrees of distal leg weakness can be helped by well-supported, high-topped athletic shoes. At later stages, the use of walkers or wheelchairs may become necessary.

The infant with congenital DM1 requires a multidisciplinary approach with occupational, physical, and speech therapy services. Nutritional consultation and trials of various food consistencies are often helpful. Parents and teachers should anticipate cognitive impairment and learning disabilities and monitor for symptoms of attention deficit disorder.

Future Targets for Specific Treatment in Myotonic Dystrophy. Because of the presumed causative nature of mutant RNA in DM, this and the mechanisms affected by it are appealing targets for therapy. The most direct approach would be elimination of the mutant RNA itself. Approaches using either ribozyme or antisense RNAs designed to degrade mutant *DMPK* alleles have shown some promise in myoblasts (Furling et al., 2003; Langlois, Lee, Rossi, & Puymirat, 2003). A study on murine models demonstrated that exon skipping with antisense oligonucleotides could achieve normal chloride channels with improvement of myotonia (Wheeler, Lueck, Swanson, Dirksen, & Thornton, 2007). Clinical trials using this approach are currently in development (NCT02312011).

Whereas the degradation of toxic RNA remains a preferential approach for the reduction of DM1 pathology, there are other approaches targeting early toxic events downstream of the mutant RNA, such as the manipulation of the expression of the RNA binding proteins MBNL1 and CUGBP1, which are affected by the accumulation of the mutant RNA (Wheeler, 2008). It has been recently found that the normalization of CUGBP1 activity with the inhibitors of GSK3 has a positive effect on the reduction of skeletal muscle and CNS pathologies in DM1 mouse models. Tideglusib, an inhibitor of GSK3, is currently being investigated on a phase 2 clinical trial (NCT02858908). There is also a phase 1, crossover study looking at the effect of ERX-963 treatment to reduce excessive daytime sleepiness/hypersomnia and improve cognitive function in patients with DM1 (NCT03959189).

OCULOPHARYNGEAL MUSCULAR DYSTROPHY

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant, adult-onset disease. The gene has been mapped to chromosome 14q11.2-q13, and the disease is caused by a trinucleotide repeat (GCG) expansion. This repeat occurs in the coding region of the polyalanine binding protein-nuclear 1 (*PABPN1*) gene. Histopathology demonstrates small angulated fibers, rimmed vacuoles in muscle fibers, and intranuclear inclusions consisting of mutated aggregates of PABPN1 (Abu-Baker & Rouleau, 2007).

OPMD typically presents after age 50 years (Brais et al., 1995). Many affected individuals of French-Canadian descent are traced to a single ancestor from France (Barbeau, 1966), although it can also occur in other ethnic groups.

OPMD is recognized in the fourth to sixth decades by onset of ptosis, partial extraocular muscle paresis, dysphagia, and tongue weakness. Proximal upper and lower extremity muscle weakness slowly develops. Serum CK level may be normal or mildly elevated.

Progressive oculopharyngeal dysfunction was described in Greek siblings, ages 11 and 14 years, who both had rimmed vacuoles; one had cytoplasmic and intranuclear tubulofilamentous inclusions 25 nm in diameter on muscle biopsy (Rose, Landon, Papadimitriou, & Morgan-Hughes, 1997). Another childhood-onset oculopharyngeal syndrome presented with intestinal pseudo-obstruction (Amato, Jackson, Ridings, & Barohn, 1995). These may be examples of recessively inherited conditions similar to dominantly inherited OPMD.

TREATMENT AND MANAGEMENT

Several specific therapies are under investigation in OPMD cells and in animal models of OPMD. Trehalose is a disaccharide chemical chaperone that has been shown to decrease PABPN1 aggregates and improve muscle weakness (Davies, Sarkar, & Rubinsztein, 2006). Antibodies to different epitopes of *PABPN1* have been identified that, when expressed intracellularly, can prevent and reduce aggregations of PABPN1 (Verheesen et al., 2006). Doxycycline has been shown to delay and lessen the severity of symptoms in a murine model as well as reduce PABPN1 aggregates (Davies et al., 2005). More recently, a group demonstrated that a two-AAV "silence" and "replace" vector-based gene therapy treatment in a mouse model of OPMD reverted already established insoluble aggregates and partially rescued the muscle from atrophy (Malerba et al., 2019).

Due to the unavailability of specific therapies, adaptive measures are of most benefit currently for OPMD patients. These include the treatment of ptosis either surgically or with eyelid crutches. For diplopia, Fresnel prisms might be helpful in some patients. Speech therapy consultation and close monitoring of swallowing function are also important.

CONGENITAL MUSCULAR DYSTROPHY

The congenital muscular dystrophies (CMDs) are a heterogeneous group of autosomal recessive disorders characterized by hypotonia, weakness, and variable degrees of muscle contractures. The summed incidence of all forms of CMD varies from approximately 1 in 21,500 (Mostacciuolo et al., 1996). However, the real incidence and prevalence are unknown and likely underestimated given the limitation of diagnostic means used in early reports. Signs and symptoms are evident in the newborn period or the first few months of

life. Serum CK is usually elevated. Historically, diagnoses of CMD have been made by clinical features and histopathology; however, recent advances in genetics and availability of new diagnostic platforms have changed dramatically the diagnostic strategy. The clinical as well as genetic complexity of the disorders included under the CMDs has resulted in different classifications (Mercuri & Muntoni, 2012; Reed, 2009).

There are three main categories of CMD. These include laminin subunit alpha 2 (LAMA2)–related (merosin deficient), collagen VI–related, and α-dystroglycan–related CMDs. Although most of the patients have their onset of symptoms in early infancy, their presentation is quite variable, with forms presenting later in life with a less severe phenotype (Bonnemann et al., 2014). Other less common CMD subtypes include *LMNA*-related CMD (overlapping with other LMNA disorders), rigid spine muscular dystrophy (overlapping with congenital myopathies due to SEPN1, RYR1, and MYH7 mutations) and Marisnesco-Sjogren syndrome.

Laminin α2–related CMD is caused by mutations in the LAMA2 gene, encoding the α2 heavy chain of the laminin 211 isoform (α 2/β1/γ1), also known as merosin. Merosin is the heavy α2 chain of laminin-2 (LAMA2). The laminins are heterotrimeric proteins that influence cell adhesion, growth, and migration. LAMA2 is expressed in the basement membrane of muscle fibers, Schwann cells of intramuscular nerves, and at neuromuscular junctions. LAMA2 promotes myotube stability and inhibits apoptosis (Vachon, Loechel, Xu, Wewer, & Engvall, 1996). Patients with complete absence of merosin present as hypotonic infants with limb weakness, normally more prominent than bulbar or respiratory impairment, and multiple joint contractures (Fig. 20.18A). On magnetic resonance imaging, white matter abnormalities, seen as increased signal on T2-weighted images, involve the centrum semiovale (Caro, Scavina, Hoffman, Pegoraro, & Marks, 1999). Epilepsy occurs frequently, even in patients with normal intellect (Pegoraro et al., 1998). Absence of immunohistochemical staining for the laminin α2 chain on snap frozen muscle biopsy is seen in patients with complete merosin deficiency (Fig. 20.18B).

Ullrich CMD is caused by autosomal recessive mutations in any of three genes encoding collagen VI, an ECM protein (Vanegas et al., 2002; Zhang et al., 2002). The protein is composed of three alpha peptide chains, which are encoded by two genes on chromosome 21q22.3 and one gene on chromosome 2q37. The disease presents with infantile weakness, hypotonia, and early severe proximal joint contractures with hyperlaxity of distal joints (Furukawa & Toyokura, 1977). The distal laxity may be replaced by progressive flexion contractures of the wrists, fingers, and ankle. Serum CK is usually normal or only slightly elevated. Muscle biopsy shows nonspecific myopathic or dystrophic changes with reduced or absent collagen VI immunostaining (Higuchi et al., 2003). Bethlem myopathy, also due to mutations in collagen VI genes, was first described as a benign myopathy with autosomal dominant inheritance

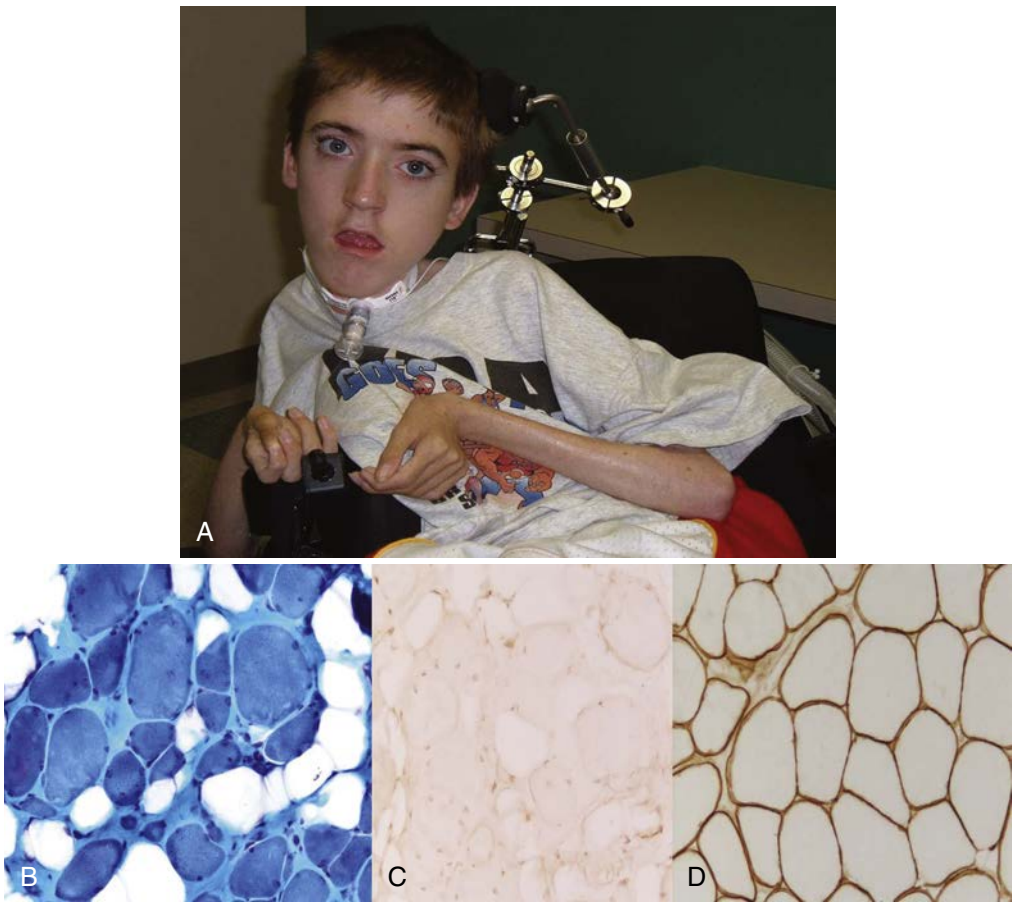


Fig. 20.18 (A) A patient with merosin-deficient congenital muscular dystrophy. The patient has a tracheotomy, prominent contractures, and scoliosis. (B) Muscle biopsy from the same patient stained modified with trichrome. Note the fiber atrophy, increased endomysial connective tissue, and fat (×400). (C) Note the lack of merosin compared with a normal control (D). (A, Reprinted with permission from Bertorini, T. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann.)

(Bethlem & Wijngaarden, 1976). Most recently, mutations on the COL12A1 gene, a member of the FACIT collagens (fibril-associated collagens with interrupted triple helices), have been described in patients with a Bethlem myopathy phenotype (Hicks et al., 2014). Clinical features are much more variable than in Ullrich CMD. Patients usually have proximal weakness in early childhood and may demonstrate the Gowers sign. More severe cases may present in neonates with hypotonia, foot deformities, torticollis, and arthogryposis. Unlike Ullrich CMD, weakness is usually nonprogressive, but contractures may develop late in the first decade in the ankles, elbow flexors, and finger flexors.

CMD due to FKRP deficiency (MDC1C) usually presents at birth or in the first few weeks of life with hypotonia and leg muscle hypertrophy. CK values are greatly increased (1000 to 10,000 IU/L). Children follow a regressive course that may include cardiomyopathy. Immunohistochemical staining reveals partial merosin deficiency and severely reduced alpha-dystroglycan.

A summary of the dystroglycoanopathies, previously described under the category of syndromic CMDs (Fukuyama CMD, muscle-eye-brain disease, and Walker-Warburg syndrome), is shown in Table 20.1. These are three clinically defined CMDs with associated brain malformations. They involve the brain because the genes and protein products of these disorders are involved in glycosylation of both extracellular muscle and brain protein.

CMD with integrin α-7 deficiency is a rare disorder that has been discovered in the analysis of large groups of patients with undefined congenital myopathies. The muscle biopsies of three patients showed deficiency of this protein with different mutations in the *ITGA7* gene on chromosome 12q13 (Hayashi et al., 1998).

CMD with early rigid spine syndrome is another rare form seen in consanguineous Moroccan, Turkish, and Iranian families that demonstrate mutations in the gene on chromosome 1p35–46 coding for selenoprotein (Moghadaszadeh et al., 2001). An American family has also been described demonstrating a phenotype of infantile hypotonia, cervical muscle weakness, and early spinal rigidity with scoliosis that maps to the same locus on 1p (Flanigan et al., 2000).

At present, there are no disease-specific therapies for CMD. The treatment of CMDs is mostly symptomatic, and these approaches are discussed in Chapter 8. Preclinical work has identified inappropriate premature apoptosis of myofiber. A phase 1 clinical trial using Omigapil, a glyceraldehyde-3-phosphate dehydrogenase inhibitor that works as an apoptotic agent, proved to be safe and well tolerated in children and adolescents with patients with Ullrich CMD or MDC1A (NCT01805024).

There are several preclinical strategies being investigated. These include treatments to improve cell-matrix adhesion, gene-based therapies, and treatments targeting fibrosis, apoptosis, autophagy and ubiquitin-proteosome system (Dowling et al., 2018).

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21 Neuromuscular Manifestations of Acquired Metabolic, Endocrine, and Nutritional Disorders

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ENDOCRINE DISORDERS

Table 21.1 summarizes the neuromuscular manifestation of these disorders.

DIABETES MELLITUS; DIABETIC NEUROPATHIES

Diabetic neuropathy (DN) is one of the most common complications of diabetes mellitus (DM), and its prevalence is increasing with the growing number of patients with DM. The reported prevalence of DN varies with the type and the criteria by which it is defined. Using criteria that include clinical symptoms, supported by examination and electrodiagnostic studies, reveals a prevalence of 6% to 15% at the time of diagnosis and more than 50% after 25 years of disease (Fig. 21.1) (Dyck et al., 1993; Pirart, 1977). Risk factors for the development of DN include the severity and duration of DM, smoking, and the presence of other complications, such as retinopathy and nephropathy (Dyck et al., 1999).

The precise etiology of DN remains unknown, and it is likely that DM affects the peripheral nerves by several mechanisms. Two main hypotheses, the microvascular and the metabolic, have been postulated for the development of DN. At one end of the spectrum, it appears that microangiopathy and arteriosclerosis affecting the vasa nervorum inflict ischemic insult to neurons and axons (Dyck et al., 1986; Malik et al., 1993). At the other end, oxidative stress with excessive accumulation of glycoproteins and polyol flux induce axonal degeneration (Greene, Lattimer, & Sima, 1987; Mizisin, Li, & Calcutt, 1977). Several investigators have provided evidence that oxidative stress damages axons, Schwann cells, and probably neurons (Low, Nickander, & Tritschler, 1997; Mizisin & Powell, 1977). Increased activation of the polyol pathway, which converts glucose to sorbitol, results in increased tissue accumulation of sorbitol and depletion of myoinositol, causing a reduction in Na^+/K^+-ATPase and subsequent slowing of nerve conduction (Stevens et al., 1994).

DM is associated with a wide spectrum of neuropathy syndromes, ranging from mild asymptomatic distal sensory polyneuropathy (PN) or sensorimotor neuropathy to a severe disabling neuropathy of variable symmetric or asymmetric presentation (Box 21.1); these disorders often coexist.

Distal Sensorimotor Polyneuropathy

Distal sensory predominant or sensorimotor PN is the most common neuropathy in patients with DM. This usually develops when DM has been present for several years, although nerve conduction study abnormalities are demonstrated in 10% to 18% of patients at the time of diagnosis of DM (Lehtinen, Uuistupa, Siitonen, & Pyörälä, 1989).

Clinically, symmetric sensory symptoms typically predominate; these may include positive symptoms (prickling, tingling, pins and needles, burning, crawling, itching, or pain) or negative symptoms (numbness, decreased sensibility, painless injuries) in the toes and feet. These symptoms progress slowly and extend up to the ankles and legs, and later to the fingers and hands. Neuropathic pain can be severe, is more prominent at night, and may compromise quality of life. Painless repetitive foot injury secondary to loss of protective sensory input contributes to the development of foot ulceration, which is a common medical cause of eventual amputation (Abbott et al., 2002). Autonomic symptoms are variably encountered. Weakness usually is absent or minimal, especially in the early years of symptom onset, but in severe cases distal weakness and atrophy of the intrinsic muscles of the feet may be present. Coexisting upper limb compression mononeuropathies (median nerve at the wrist or ulnar nerve at the elbow) are relatively common (Dyck & Dyck, 1998).

Examination demonstrates distal symmetric sensory loss or deficit in a stocking-glove pattern, diminished or absent ankle tendon reflexes, and, in more severe cases, loss of knee reflexes or upper-limb tendon reflexes. Weakness of toe and foot dorsiflexion and atrophy of the intrinsic muscles of the feet usually are noted later in the course of the disease.

Autonomic Neuropathy

Diabetic autonomic neuropathy usually coexists with sensorimotor PN from involvement of small autonomic nerve fibers, and autonomic symptoms usually become prominent with increased duration and severity of the neuropathy. Impotence is among the most common manifestations of autonomic neuropathy. Sweating abnormalities, including distal anhidrosis and truncal and gustatory sweating, are relatively common. Other manifestations include constipation alternating with diarrhea, gastroparesis and bloating, orthostatic light-headedness, postural hypotension, and bowel or urinary disturbances. Cardiac arrhythmia secondary to parasympathetic denervation contributes to increased cardiac morbidity and mortality. Diabetic patients who suffer an acute myocardial infarction are twice as likely to die as

Table 21.1 Neuromuscular Manifestation of Endocrine Disorders

Diabetes	Symptoms	Laboratory Test Results	EMG	Biopsy	Treatment
Acromegaly	Proximal weakness, CTS, neuropathy, muscle atrophy	Normal CK (may be elevated), elevated growth hormone, IGF-1, TSH	Normal or myopathic	Nonspecific; some fiber necrosis may be seen	Removal of tumor
Hypopituitarism	Weakness (may be severe); muscle fatigue	Normal CK; multiple hormone deficiencies	Not defined	Not defined	Hormone replacement
Adrenal insufficiency, Addison disease	Proximal weakness, cramps, fatigue	Elevated potassium, reduced cortisol levels, abnormally high corticotropin, normal CK	Normal	N/A	Mineralocorticoids, glucocorticoids, fluid and electrolyte replacement
Thyrotoxic periodic paralysis	Weakness with hypokalemia, usually after high-carbohydrate meals (occurs mainly in Asians, more common in men)	Elevated CK during attacks	Normal except for decreased CMAP during attacks, after exercise	Nonspecific; may show vacuolated fibers	Beta-blockers, potassium supplement, PTU, methimazole, surgery
Hypothyroidism (adult: Hoffmann syndrome; children: Kocher-Debre´ Semelaigne)	Proximal weakness, muscle spasms, pain (adults); myoedema, delayed relaxation of reflexes; peripheral neuropathy, entrapment neuropathies, CTS	Elevated CK, elevated thyrotropin or low T_4	Nonspecific	Nonspecific	Thyroid replacement
Hyperthyroidism or thyrotoxic myopathy	Proximal weakness with little atrophy, more common in women; distal weakness in 20%, some bulbar involvement; Graves ophthalmopathy can occur, myasthenia gravis and periodic paralysis may occur; fasciculations and myokymia; peripheral neuropathy	Normal CK, high T_4 and T_3, reduced thyrotropin	Myopathy, with fibrillations and fasciculations	Normal or nonspecific	Beta-blockers, surgery, radioactive iodine
Diabetes	Peripheral polyneuropathy, focal neuropathy; myopathy unusual; muscle infarcts causing unilateral weakness, swelling; proximal muscle weakness (diabetic amyotrophy)	Elevated CK	Motor unit action potentials		Diabetic control
Cushing disease (primary or drug induced)	Proximal weakness, myalgia, truncal adipose tissue accumulation, moon face	Normal CK, low potassium, elevated plasma cortisol	May show myopathic motor unit action potentials	Atrophy of type II fibers, mainly IIB	Reduction of steroids, removal of tumor
Hyperparathyroidism, primary or secondary from renal disease	Proximal weakness and atrophy, muscle cramps, possible hypotonia	Elevated calcium levels, usually low phosphate and high alkaline phosphatase, normal or mildly elevated CK, elevated PTH and vitamin D levels	Small polyphasic motor units or potentials	Type II fiber atrophy, angular atrophic fibers, increased calcium in capillaries	Removal of the adenoma, bisphosphonates, cinacalcet, vitamin D supplementation (secondary hyperparathyroidism), calcitriol
Hypoparathyroidism	Hypocalcemia-induced tetany (Chvostek, Trousseau signs), cramps	Mildly elevated CK, hypocalcemia, hypomagnesemia	Multiplex discharges	?	Calcium and vitamin D

Modified with permission from Bertorini T. E. (2008). *Neuromuscular case studies*. Philadelphia: Butterworth-Heinemann.
CK, Creatine kinase; *CMAP*, compound muscle action potential; *CTS*, carpal tunnel syndrome; *EMG*, electromyography; *IGF-1*, insulin-like growth factor-1; *PTH*, parathyroid hormone; *PTU*, propylthiouracil; *TSH*, •••.

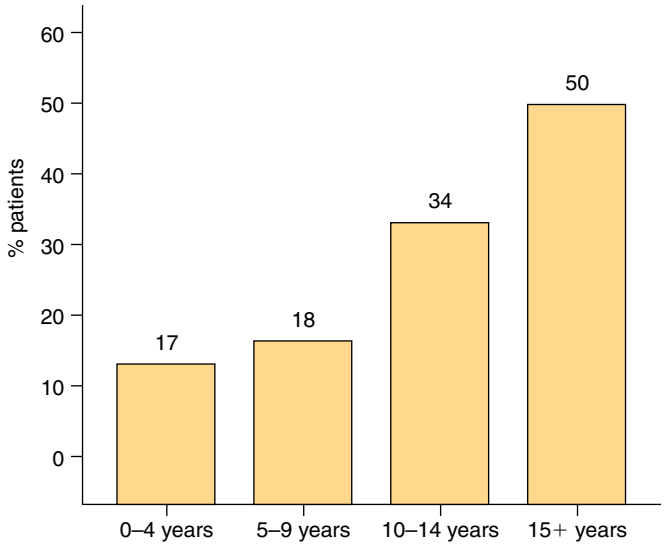


Fig. 21.1 Prevalence of distal polyneuropathy by duration of noninsulin-dependent diabetes mellitus.

Box 21.1 Clinical Classification of Diabetic Neuropathies

Symmetric

Distal sensorimotor polyneuropathy
Autonomic neuropathy
Acute painful neuropathy (insulin neuritis, neuropathic cachexia)

Asymmetric

Diabetic lumbosacral plexopathy
Compression mononeuropathies
Cranial neuropathies
Isolated thoracic radiculopathies
Mononeuritis multiplex

matched controls because of a combination of accelerated coronary artery atherosclerosis, hypertension, and autonomic neuropathy (Benvenuti, Boncinelli, & Vignoli, 1993; Hilsted & Low, 1997). These manifestations and their treatment are covered in detail in Chapter 5.

Acute Painful Neuropathy

A variant of acute or subacute severe painful neuropathy has been described in diabetic patients with rapid unwanted weight loss and poor glycemic control. It is characterized by intense diffuse neuropathic pain and has a monophasic course (Archer, Watkins, & Thomas, 1983); patients appear acutely ill. Typically, it manifests in two settings: one form, which occurs after the initiation of improved glycemic control, is called *insulin neuritis*; the other form occurs in poorly controlled non–insulin-dependent diabetes mellitus (NIDDM) and is called *diabetic neuropathic cachexia*.

Insulin neuritis was first described by Caravati in 1933 (Caravati, 1933). It is an uncommon and highly unpleasant entity that typically appears after the initiation of aggressive insulin therapy or oral agents. Patients develop intense burning pain in the feet and legs, often requiring narcotics. Objective findings on neurologic examination and electrodiagnostic studies are mild. The pain generally resolves in a few months, although the underlying PN often remains. Nutritional supplements and blood glucose level monitoring are helpful.

Diabetic neuropathic cachexia occurs in males with poorly controlled NIDDM. It is characterized by anorexia, severe weight loss, and intense pain that requires narcotic analgesics. The neurologic examination and nerve conduction studies are unrevealing or show only mild abnormalities. Weight gain after glycemic control is usually followed by slow improvement over months (Ellenberg, 1974).

Diabetic Lumbosacral Plexopathy

Diabetic lumbosacral plexopathy (DLSP) is also known as *diabetic radiculoplexus neuropathy*, *diabetic amyotrophy*, *Bruns-Garland syndrome*, or *asymmetric proximal diabetic neuropathy*. It is an uncommon debilitating neuropathy seen in 1% of patients with NIDDM (Lehtinen et al., 1989). This syndrome usually involves the lumbosacral plexus and much less commonly the thoracic and cervical roots, plexus, or nerves. The condition usually occurs in patients with NIDDM who are older than 50 years and is more common in males. It presents with sudden-onset unilateral anterior thigh pain, followed by weakness and muscle atrophy. The pain is severe, sharp, burning, or aching and often subsides in a few weeks. The weakness and muscle atrophy affect the involved segments (anterior thigh muscles) and often are so severe and debilitating that the patient may require walking aids. Sensory loss usually is minimal, and knee tendon reflex is diminished or absent. The syndrome usually is monophasic, and spontaneous slow recovery occurs over several months. The pathophysiology of DLSP is mostly microvasculopathy and inflammatory changes; secondary immune response is suspected (Dyck & Windebank, 2002; Said et al., 1997). Variations of DLSP include spreading to the contralateral side or symmetric bilateral involvement, foot drop, upper limb involvement, and thoracic radiculopathy.

Compression Neuropathies

As mentioned before, compression neuropathies are more common in diabetic patients, particularly those with associated PN. It is unclear why diabetic patients have an increased risk of developing these neuropathies, although an increased obesity rate may be a factor.

Median neuropathy at the wrist, widely known as *carpal tunnel syndrome* (CTS), is the most common, and its prevalence increases with a longer duration of DM. Nerve conduction studies demonstrate CTS in nearly 30% of diabetic patients, of whom 6% to 10% are symptomatic (Dyck et al., 1993). Thus, CTS should be suspected in any diabetic patient who complains of pain, paresthesia, and numbness in the hands, worsening at night or on awakening. Weakness of the thenar muscles is rare except in long-standing severe cases. The diagnosis is best made by nerve conduction studies; however, coexistent PN may impose a diagnostic challenge, best assessed by testing other nerves in the upper limb not subject to compression.

Other compression neuropathies include ulnar neuropathy at the elbow and possibly peroneal neuropathy at the fibular head. Radial neuropathy and lateral femoral cutaneous neuropathy (meralgia paresthetica) have been described in

diabetic patients and are indistinguishable from similar neuropathies in nondiabetic patients (Wilbourn, 1999).

Ulnar neuropathy at the elbow occurs less frequently than CTS and has been reported in 2% of diabetic patients. Clinically, ulnar neuropathy causes sensory symptoms in the ring and small fingers (Dyck et al., 1993). More severe ulnar neuropathy at the elbow is associated with progressive weakness and atrophy of the ulnar-innervated hand muscles and may have significant impact on hand function. Asymptomatic mild slowing of ulnar motor conduction across the elbow is common in diabetic patients.

Diabetic focal limb mononeuropathies not at common nerve entrapment sites are rare and coincidental, and other common causes should be considered. Lateral femorocutaneous neuropathy or meralgia paresthetica appears to be more common in obese patients with NIDDM. Likewise, mononeuritis multiplex is not among the common complications of DM, but does occur.

Cranial Mononeuropathies

Oculomotor neuropathy with pupillary sparing is characteristic of diabetic third cranial nerve palsy. The onset usually is acute and is associated with severe headache, diplopia, and ptosis. Recovery often is complete or near-complete over a few weeks to a few months.

Other cranial nerve palsies associated with diabetes include abducens, trochlear, and facial neuropathy. Facial neuropathy is more common in older diabetic patients, usually is unilateral, and has a clinical course similar to that of idiopathic facial palsy (Bell palsy).

The overall incidence of cranial neuropathies in diabetic patients is relatively low, in the range of 2% to 5%; however, a higher incidence of facial nerve palsy (6% to 10%) has been reported. This is even higher if individuals with abnormal glucose tolerance tests are included (Aminoff & Miller, 1972; Smith, 1999). Pain often is present and is associated with upper and lower facial weakness and infrequently with loss of taste and hyperacusis.

Isolated Thoracic Radiculopathy

Isolated thoracic radiculopathy, also termed *truncal radiculoneuropathy* or *diabetic thoracoabdominal neuropathy*, is a distinctive disorder that often suggests DM. It is uncommon and usually occurs in older patients, often associated with weight loss and poor glycemic control. Patients develop segmental chest or abdominal pain, cutaneous hypersensitivity or allodynia, and sensory loss. The pain usually is intense and of a burning or aching quality and may not follow a classic dermatomal distribution. Likewise, the sensory deficit may not follow a typical dermatomal pattern. The pain presentation may mimic chest or abdominal medical or surgical emergencies. The diagnosis of isolated thoracic radiculopathy is clinical, and needle electromyographic (EMG) examination may show denervation potentials in the intercostal, abdominal, or thoracic paraspinal muscles (Sun & Streib, 1981). The pathogenesis of this disorder remains uncertain but probably is similar to that of proximal DN. The site of the lesion is not firmly established, but it is likely to be at the thoracic roots, posterior rami, or both.

DIAGNOSIS AND EVALUATION

Assessment of DN is mostly noninvasive; however, rarely, invasive studies are needed (Box 21.2). Nerve conduction studies remain the gold standard in evaluation. They are widely available and are used in both clinical practice and clinical trials. The distal symmetric PN is sensory and predominantly axonal; a decline in the sensory nerve action potential (SNAP) amplitude is typically the earliest sensitive finding of PN. The most commonly used nerve conduction study is measurement of the sural SNAP amplitude behind the ankle. A decline of the sural SNAP amplitude 6 to 8 uV baseline to peak, with a surface skin temperature of 31°C, is considered abnormal (Bril, 2003). Mild conduction slowing of the sural sensory conduction velocity or peroneal motor conduction velocity and prolonged F-waves often are noted and indicate mild demyelination. Demyelinating features out of proportion to axonal loss are rare and raise suspicion of a superimposed focal neuropathy or an autoimmune demyelinating neuropathy. Superficial radial SNAP recorded at the base of the thumb is a useful index when the sural SNAP is unobtainable. Compound muscle action potential (CMAP) amplitudes usually are preserved early in the disease course; however, reduced CMAP amplitudes, especially of the foot muscles, often are seen as the disease progresses. An associated increased conduction time across the carpal tunnel or other common entrapment sites in asymptomatic patients may be encountered. Needle EMG examination of distal leg or foot muscles often shows fibrillation potentials, large motor unit potentials, and reduced recruitment, indicating chronic mild motor axonal loss and compensatory reinnervation, particularly in chronic cases. Nonetheless, in early small-fiber sensory neuropathy, nerve conduction studies can be normal, and other diagnostic tools, such as skin biopsy to assess intraepidermal nerve fiber density or autonomic testing, often are more useful.

Autonomic testing is most useful in the evaluation of suspected selective autonomic neuropathy or autonomic manifestations associated with diabetic PN; they are, however, not widely used. Sympathetic skin response is easily tested, but this usually is unrevealing except in severe autonomic neuropathy. Evaluation of heart rate variability and blood pressure changes with deep inspiration-expiration, Valsalva maneuver, and changes in posture are more informative tests and can be used to confirm autonomic neuropathy (Low, 1993). Decreased heart rate variability for matched age is a common autonomic dysfunction in diabetic patients and appears earlier than other autonomic manifestations (Ziegler, Dannehl, Mühlen, Spüler, & Gries, 1992). Tests of

Box 21.2 Assessment of Diabetic Neuropathy

Noninvasive

Nerve conduction velocity/electromyography
Quantitative sensory testing
Autonomic function tests
Routine blood tests to exclude other causes or contributory causes such as B_{12} deficiency, autoimmune neuropathies

Invasive

Punch cutaneous biopsy
Sural nerve biopsy
Lumbar puncture

sudomotor function evaluate the sympathetic efferent to sweat glands, but they are somewhat cumbersome and usually performed at specialized laboratories. These are discussed in detail in Chapter 5.

Quantitative sensory testing for vibration perception threshold, warm and cold detection thresholds, and heat pain detection threshold modalities using computers have been useful in clinical trials, but their use and reproducibility in clinical practice are limited (Shy et al., 2003).

Electrodiagnostic studies in lumbosacral plexopathy demonstrate active denervation in affected muscles and often bilaterally despite unilateral symptoms, with only mild conduction slowing, consistent with axonal loss. Magnetic resonance imaging (MRI) should be obtained to exclude structural lesions.

Focal and isolated mononeuropathies such as CTS, ulnar neuropathy, or peroneal neuropathy are best diagnosed by nerve conduction studies. Sural nerve biopsy is used on a limited scale in the diagnosis of diabetic peripheral neuropathy and is rarely needed. This shows involvement of unmyelinated and myelinated axons with axonal degeneration with some segmental demyelination. There is duplication of the basal lamina in vessels.

Differential Diagnosis

Other causes of PN must be considered and excluded in diabetic patients. In patients with distal symmetric PN, screening laboratory studies for other metabolic, toxic, drug-induced, nutritional, neoplasm-related, or infectious causes are recommended. Typically blood count, thyroid studies (thyrotropin or thyroxine [T_4]), serum protein, and serum immunoelectrophoresis are necessary. Human immunodeficiency virus (HIV) antibody and urine and blood heavy metal screens are requested if indicated. Sjögren syndrome antibodies, vitamin B_6 and vitamin E levels, and screening for malignancy and measurement of Hu antibody and MAG antibodies can be considered in patients with large-fiber sensory PN. Screening for amyloidosis, porphyria, and paraneoplastic or hereditary causes also is indicated in neuropathy with prominent autonomic symptoms. A detailed family history and, at times, nerve conduction studies of suspected family members and DNA testing are essential if a hereditary neuropathy is strongly suspected.

In those whose PN has prominent demyelinating features on nerve conduction studies, screening for hepatitis and infectious mononucleosis, serum immunoelectrophoresis, and cerebrospinal fluid studies are indicated. If there is evidence of uniform slowing, DNA testing for a hereditary cause could be considered. Recommended diagnostic considerations in diabetic mononeuropathy or multiple mononeuropathy include testing for vasculitis, connective tissue disease, and infiltrative processes such as neoplasia or sarcoidosis.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is very important in the differential diagnosis, particularly in patients who have arreflexia or hyporeflexia and large fiber sensory deficit and evidence of a predominantly demyelinating neuropathy by EMG. In some cases, an LP would help because spinal fluid protein is usually more elevated in CIDP. Contrast MRI shows enhancement of the cauda equina roots in CIDP. Nerve biopsy sometimes is necessary, but because inflammation could be patchy, the diagnosis cannot be made for certain, and a therapeutic trial should be considered.

Box 21.3 Treatment Rationale Based on Metabolic Hypothesis

- Polyol pathway activation → Aldose reductase inhibitors
- Reduction of myoinositol → Myoinositol substitution
- Reduced nerve growth factor (NGF) → Human recombinant NGF
- Alteration in fatty acid metabolism → Gamma-linolenic acid (primrose oil)
- Acetyl-L-carnitine depletion → Substitution of acetyl-L-carnitine
- Free radical–mediated oxidative stress → Antioxidants (alpha-lipoic acid)

TREATMENT AND MANAGEMENT

Several therapeutic trials for DN addressing the proposed pathophysiology have been conducted. These trials showed only modest stabilization (Box 21.3). The aldose reductase inhibitors, alpha-linolenic acid, alpha-lipoic acid, myoinositol substitution, angiotensin-converting enzyme inhibitors, and neurotrophic nerve growth factors have been studied (Pfeifer & Schumer, 1995). The aldose reductase inhibitors (sorbinil, tolrestat, ponalrestat, and epalrestat) have been used in a number of trials since 1980 and aimed to prevent excessive sorbitol flux in peripheral nerves (Pfeifer, Schumer, & Gelber, 1997). These trials, however, have been confounded by side effects, poor trial design, and lack of convincing, clinically meaningful effects. More recently, trials of the aldose reductase inhibitors ranirestat and fidarestat showed modest improvement in nerve conduction and quantitative sensory testing (Bril & Buchanan, 2006; Hotta et al., 2001). Other clinical trials of DN treatment using dietary supplementation with myoinositol, acetylcarnitine antioxidants—gamma-linoleic acid (evening primrose oil) and alpha-lipoic acid—showed no convincing effectiveness, although some benefit was observed (Jamal & Carmichael, 1990; Keen et al., 1993; Sima, Calvani, Mehra, Amato, & Acetyl-L-Carnitine Study Group, 2005; Ziegler, Nowak, Kempler, Vargha, & Low, 2004; Ziegler et al., 2011). Protein kinase C-β inhibitors showed some benefit in animal studies; in small human studies, amelioration of sensory nerve dysfunction by C-peptide in patients with insulin-dependent DM (IDDM) was reported (Ahlgren & Levine, 1994; Ekberg et al., 2003). Nerve growth factor (NGF) is a neurotrophic factor that promotes survival, differentiation, and maintenance of small sensory fibers and sympathetic neurons in the peripheral nervous system. Skin biopsy specimens from patients with PN showed reduced NGF and impaired retrograde axonal transport. A 6-month phase II controlled trial of NGF in DN showed a statistical trend toward improvement; however, a large phase III multicenter trial over 1 year was not able to confirm any beneficial effects (Apfel et al., 2000; Wellmer, Misra, Sharief, Kopelman, & Anand, 2001). Treatment using gene therapy by intramuscular administration of vascular endothelial growth factor in animal models, tested for its ability to increase blood flow in DN, showed improvement in nerve conduction and histologic changes; however, no human studies have been conducted.

Although an immune or inflammatory response may play a primary role or accelerate some forms of neuropathy initiated by a metabolic or vascular injury, there is not an established role for immunosuppression or intravenous immunoglobulin (IVIg) therapy in clinical DN. Nonetheless, Stewart, McKelvey, Durcan, Carpenter, and Karpati (1996) described diabetic patients with symmetric distal and proximal progressive neuropathy meeting the clinical and electrodiagnostic criteria for CIDP that responded to treatment for this disease. This should be considered in patients with prominent demyelinating features, which could represent CIDP in a diabetic patient.

The distal symmetric sensorimotor PN is generally slowly progressive, but early detection of neuropathy and implementation of close diabetic control are essential and seemingly prevent or delay the progression of neuropathy, retinopathy, and nephropathy. Maintaining strict blood glucose control has been demonstrated to stabilize, improve, and reduce the occurrence of DN and other diabetic complications in large clinical trials, such as the Diabetic Control and Complications Trial. This study followed a large number of patients with IDDM for 3.5 to 9 years to compare strict glycemic control by means of intensive insulin pump or multiple injections to routine diabetic control. In this trial, intensive insulin therapy reduced the occurrence of neuropathy at 5 years by 64% compared with conventional therapy (Diabetes Control and Complications Research Group, 1993; UK Prospective Diabetes Study Group, 1998). However, this degree of glycemic control is practically difficult and is associated with a higher risk of hypoglycemic reactions. Additionally, 25% of patients with intensive glycemic control develop neuropathy over 6 to 9 years. Similar protective effects are yet to be documented in patients with NIDDM. The United Kingdom Prospective Diabetes Study Research Group, in a large number of patients with NIDDM followed for an average of 10 years, showed a 25% reduction in the risk of neuropathy and microvascular complications with glycosylated hemoglobin (HbA1c, 7%) when compared with the standard treatment group (HbA1c, 7.9%) (UK Prospective Diabetes Study Group, 1998). Pancreatic transplant was shown to halt the progression and improve the symptoms of DN better than intensive glycemic control with insulin in patients followed for up to 10 years. Transplant patients showed marked improvement in nerve conduction indices and slight improvement on clinical examination, whereas the control group steadily worsened in all study outcomes (Diabetes Control and Complications Research Group, 1993; Navarro, Sutherland, & Kennedy, 1997). Nonetheless, pancreatic transplantation is effective for DN only early in the disease, before axonal loss is extensive, and the effect was not sustained in long-term follow-up (Navarro et al., 1997).

Proximal DN initially progresses rapidly, followed by slow, varying degrees of improvement. Most patients achieve good recovery and pain usually improves, but in a small number of patients, variable degrees of residual disabling weakness persist (Chokroverty, Reyes, Rubino, & Tonaki, 1977; Dyck & Windebank, 2002; Pascoe, Low, Windebank, & Litchy, 1997).

DLSP or proximal DN currently has no effective therapy, despite reported improvement with intravenous methylprednisolone in a controlled clinical trial, but the data are incomplete (Dyck et al., 2006). A Cochrane review demonstrated lack of consistent evidence of the benefit of immunotherapy (Chan, Lo, & Chan, 2017). High-dose corticosteroids may compromise diabetes control. Likewise, the role of corticosteroids or IVIg in isolated thoracic radiculopathy is uncertain.

Physical therapy is important, and protein-caloric supplements may be useful for those with associated significant weight loss.

Compression neuropathies, including CTS and ulnar neuropathy, should be treated in the same way as the idiopathic forms. Surgical decompression in symptomatic CTS is a widely used treatment, although there are no comparative outcome studies for carpal tunnel release in diabetic and nondiabetic patients. Nocturnal pain and hand paresthesia are expected to improve after surgical carpal tunnel release; however, symptoms related to the underlying PN will not change. Ulnar neuropathy at the elbow may improve with conservative treatment, including avoidance of ulnar compression and the use of soft pads at the elbow. Surgical decompression should be considered for progressive hand weakness and muscle atrophy, although the outcome is not always successful. Multiple surgical decompressions in DN are not beneficial and should be discouraged (Chaudhry, Stevens, Kincaid, & So, 2006; Mondelli, Aretini, & Rossi, 2009).

Cranial mononeuropathies, including diabetic ocular mononeuropathy, have no specific treatment; however, most patients have a spontaneous complete recovery over several weeks. The recovery of facial nerve palsy depends on the degree of axonal loss, estimated by measuring the amplitude of the facial CMAP at least 1 week after the onset of weakness (Thomander & Stälberg, 1981). Physical therapy is needed, as well as the use of eye patches for corneal protection. The treatment is otherwise the same as for the idiopathic form.

Most importantly, to decrease the progression of the neuropathies, proper DM control is needed. The pharmacologic management of DM, particularly type I DM, is with the use of insulin. Intensive insulin therapy should be done by a specialist. Barriers to intensive therapy may include the need for the patients to adhere to the recommended diet, avoidance of hypoglycemia, and the cost. Insulin usually is given using a combination of regular insulin or a rapid analog with meals and intermediate insulin twice a day or a long-acting insulin analog once a day. The recommended starting dosage of insulin is 0.3 to 0.6 units/kg of body weight/day, increasing as needed. Most patients require about 0.6 to 0.7 units/kg/day (American Diabetes Association [ADA], 2019; Davies et al., 2018; Wexler, 2020).

Insulin pumps using short-acting analogue insulin improve lifestyle and help achieve an HbA_{1c} below 7%.

In patients with type 2 DM (NIDDM), the initial treatment should be aimed at lifestyle changes, including diet, weight loss, and exercise. Bariatric surgery could be used in obese individuals, and the risks and benefits should be evaluated (Keidar, 2011). If there are no contraindications, metformin should be part of the initial therapy at diagnosis (Fig. 21.2). The initial dose is 500 mg twice daily to avoid gastrointestinal symptoms, titrated up to 2500 mg/day if necessary over a 2–3-month period. Metformin does not usually produce hypoglycemia but can be associated with lactic acidosis in patients

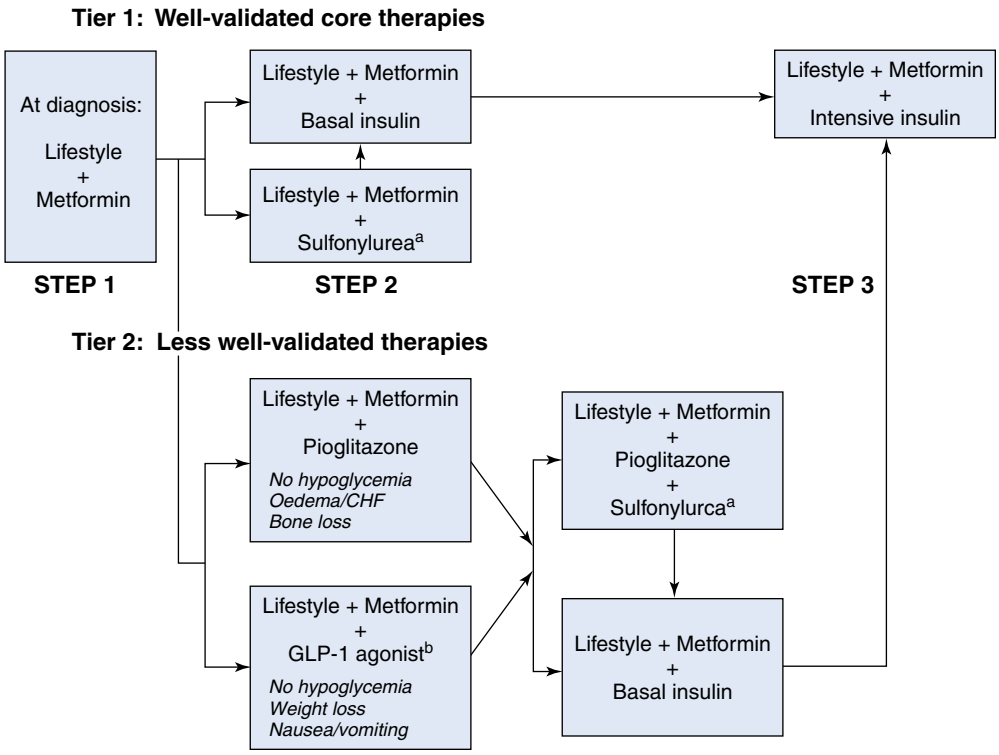


Fig. 21.2 Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit and check A_{1c} every 3 months until A_{1c} is <7% and then at least every 6 months. The interventions should be changed if A_{1c} is ≥7%. [a]Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. (Reproduced with permission from Nathan, D. M., Buse, J. B., Davidson, M. D., Ferrannini, E., Holman, R. R., Sherwin, R., et al. (2009). Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care, 32*, 193–203.)

with kidney disease or infection and in those undergoing surgery or receiving contrast radiologic agents. Metformin could cause B_{12} deficiency, and this should be monitored. If contraindications to metformin exist, sulfonylureas such as glipizide or thiazolidinediones such as pioglitazone should be used (ADA, 2019; Wexler, 2020). Meglitinides could be used if the patient has an allergy to sulfonylureas; unfortunately, these are more expensive. Insulin could be the first-line agent in patients with HbA_{1c} above 10%, fasting glucose over 250 mg/dL, or random glucose over 300 mg/dL or when it is difficult to distinguish between type 1 and type 2 DM.

If proper glycemic control is not achieved (HbA_{1c} >7%) after 3 months, a second-line agent should be started. Some consider starting dual therapy for this from the beginning. The ADA and the European Association for the Study of Diabetes (EASD) consensus guideline suggests either a basal insulin such as glargine (Lantus) or detemir (Levemir) or a sulfonylurea such as glipizide (Glucotrol) as well-validated core therapies (ADA, 2019; Davies et al., 2018; Wexler, 2020). If target HbA1c is not achieved with a second-line agent, the ADA/EASD suggest starting or intensifying insulin therapy. The use of automatic glucose monitors (i.e., FreeStyle Libre Abbott or the Dexcom G6 CGM and the Eversense implantable CGM) allows monitoring glycemia throughout the day without using finger sticks.

The pharmacologic approach should consider comorbidities; for example, those with significant atherosclerotic cardiovascular disease, particularly if there are contraindications to the use of metformin, should use sodium-glucose cotransporter inhibitors or glucagon-like type I receptor antagonist. In those with high risk of heart failure, sodium-glucose cotransporter inhibitors are preferred (Verma, 2019). In patients with chronic kidney disease (CKD), glucagon-like peptide type 1 receptor antagonists have shown to reduce kidney disease progression (ADA, 2019; Davies et al., 2018) and improve cardiovascular outcomes (semaglutide). Consultation with an endocrinologist to manage this, particularly in the choice of therapy in children, is very important.

Symptomatic Treatment of Diabetic Neuropathy

Neuropathic pain is common in patients with DN. Nearly one third of patients with DN develop neuropathic pain, which may compromise the quality of daily life and requires specific therapy. The pain can be spontaneous (lancinating, burning, paroxysmal, or cramping) or evoked (allodynia, hyperalgesia, or hyperpathia). Clinical trials of pharmacologic management of painful DN have included several drugs, such as antidepressants, anticonvulsants, topical formulations, narcotic analgesics, and others including gabapentin and pregabalin (Beydoun, Shaibani, Hopwood, & Wan, 2006; Max et al., 1992; Oskarsson, Ljunggren, & Lins, 1997; Zakin, Abrams, & Simpson, 2019). These are discussed in detail in Chapter 6.

Treatment of Autonomic Neuropathy

Autonomic symptoms are important and should be managed with proper therapy. Diabetic cardiac autonomic neuropathy is associated with increased arrhythmias, silent myocardial infarction, and a high mortality rate (Aronson, Rayfield, & Chesebro, 1997). Patients should be evaluated for cardiovascular autonomic dysfunction, and preventive measurements should be taken, including the treatment of arrhythmia and the prevention of myocardial infarcts. An exercise stress test is recommended before patients with autonomic neuropathy begin an exercise program. Orthostatic hypotension should be treated with hydration, elastic stockings, increased salt intake, or, rarely, with short-acting pressor agents.

Erectile dysfunction is among the most common complaints in patients with autonomic DN. This could be confounded by a psychogenic component, and a decreased testosterone level should be ruled out or treated. Moderately effective treatments include sildenafil and similar drugs,

penile injection of erectogenic agents, and vacuum devices (Dunsmuir & Holmes, 1996).

Gastrointestinal manifestations include anorexia, early satiety, gastroparesis, bloating, constipation, and diarrhea. These manifestations and their treatment, as well as the treatment of bladder dysfunction, are discussed in detail in Chapter 4.

HYPERTHYROIDISM

Hyperthyroidism caused by Graves disease is defined as the overproduction of thyroid hormone caused by antibodies against thyrotropin receptors in the thyroid gland, also resulting in its enlargement (Marino, Chiovato, & Pinchera, 2008). This is an autoimmune disorder most frequently seen in women and is associated with certain human leukocyte antigen titers. Hyperthyroidism can occur alone or in conjunction with other immune conditions (Kattah, 2008); it also can be caused by drugs, adenomas, and rarely by disorders of the pituitary gland (Burch & Bahn, 2008; Merchant & Ahmad, 2008).

DIAGNOSIS AND EVALUATION

Patients with hyperthyroidism generally appear thin, anxious, and irritable; they have hand tremors and insomnia. They may have autonomic symptoms from tachycardia and sometimes cardiac arrhythmia. The enlargement of the thyroid gland is sometimes accompanied by a bruit in the area. Patients also frequently have a variable degree of thyroid ophthalmopathy characterized by proptosis, with eyelid retraction and diplopia caused by ophthalmoparesis (Bahn, 2010; Burch & Bahn, 2008), with swelling of the orbits and the extraorbital tissue.

The disorder can be associated with myasthenia gravis, and 3% of patients with myasthenia gravis have hyperthyroidism (Burch & Bahn, 2008; Marinó et al., 1971; Ohno et al., 1987). Myasthenia should be suspected in patients with ophthalmopathy with extraocular muscle weakness that exceeds the proptosis. In these patients, proper measurement of acetylcholine receptor antibodies, edrophonium (Tensilon) test, and electrophysiologic studies are necessary (Marino et al., 2008). The forced duction test also helps in the diagnosis.

Hyperthyroidism also may cause a PN (Feibel & Campa, 1976; Pandit, Shankar, Gayathri, & Pandit, 1998), diffuse muscle weakness, and fatigue. Some patients also show focal pretibial myxedema and acropachy, characterized by swelling and clubbing of the distal phalanges of the fingers and toes (Pandit et al., 1998).

Hyperthyroidism rarely causes attacks of periodic paralysis, which occur particularly, but not always, in those of Asian ethnicity (Bertorini, 2008b; Pichon et al., 2005). This should be suspected in patients with an acute onset of weakness.

Measurement of thyrotropin is important in making the diagnosis, and thyroxine is always low or undetectable. Evaluation also should include measurement of T_4 and particularly free T_4 and triiodothyronine (T_3) level, which should be elevated (Bartalena et al., 1996; Kattah, 2008; Sterling, Refetoff, & Selenkow, 1970). An elevated level of thyroid globulin-binding antibodies confirms the presence of autoimmunity (Schwarz-Lauer et al., 2002).

Thyroid ultrasound helps in the diagnosis, particularly to detect not only an enlarged gland but also thyroid nodular disorders. Radioiodine uptake is not always required but can be used to rule out silent subacute thyroiditis and to diagnose factitious and drug-induced thyrotoxicosis. Serum creatine kinase (CK) and electrolytes should be measured in patients with acute paralysis.

TREATMENT AND MANAGEMENT

The treatment of hyperthyroidism consists of pharmacologic suppression of hormonal secretion, radioactive iodine, or surgery (Sugino et al., 1993). Treatment choice is based on the patient's age, response to drug therapy, and the size of the gland.

Pharmacologic management includes the use of thionamides such as methimazole and prophylthiouracyl (PTU). These agents block the synthesis of thyroid hormone. Because methimazole is 10 times more potent than PTU, its dosage is 20 to 40 mg/day compared to 200 to 400 mg/day for PTU, aiming to maintain the euthyroid state with the minimal dose (Kattah, 2008). Higher doses in addition to levothyroxine supplements are recommended by some (Rittmaster et al., 1998). This treatment should be used for 2 years; a lack of response or relapse is an indication for radiation or thyroidectomy. Inorganic iodine can be given for a short period in preparation for surgery.

In older patients, radioactive isotopes are used to destroy the gland, using dosages of 80 to 100 μCi/g; supplemental levothyroxine may be required.

Patients with severe hyperthyroidism can be treated acutely with beta-blockers, which suppress the autonomic dysfunction, or with corticosteroids, which block the conversion of T_4 to T_3 and decrease T_4 secretion.

Thyroid ophthalmopathy is treated with 30 to 40 mg of prednisone daily for a short period; in severe cases, decompression or radiation treatment is necessary. Immunosuppressant therapy also can be used (Merchant & Ahmad, 2008).

Myasthenia gravis should be treated with anticholinesterase drugs and with corticosteroids or immunosuppressants as necessary.

Attacks of thyrotoxic periodic paralysis are treated with potassium supplements; patients should receive low-sodium, low-carbohydrate diets with potassium supplementation. Propranolol can be used in acute attacks (Bertorini, 2008b; Pichon et al., 2005).

HYPOTHYROIDISM

Thyroid hormone is important in neuromuscular function because it binds to intracellular and other adrenergic receptors, regulating glycogenolysis and mitochondrial oxidation (Kaminsky et al., 1992). It regulates the activity of calcium ATPase, and in hypothyroidism there is an increase in the ratio of inorganic phosphate to ATP in resting muscle and a decrease in phosphocreatine in working muscle (Monzani et al., 1997). The hormone also participates in the mobilization of mucopolysaccharides; in hypothyroidism, thickening of the skin is caused by deposits of these substances in the subcutaneous tissue, which might be associated with nerve entrapment such as CTS (Cakir, Samanci, Balci, & Balci, 2003).

The most common cause of hypothyroidism is dysfunction of the gland from a chronic thyroiditis, but it also can occur after thyroid surgery, radiation, infiltrations, iodine deficiency, or the use of some drugs, such as lithium and amiodarone (Wiersinga, 2006). Secondary hypothyroidism is caused by decreased production of thyrotropin by the pituitary gland, for example, from tumors or rarely by decreased secretion of thyroid hormone–releasing hormone by the hypothalamus.

DIAGNOSIS AND EVALUATION

The clinical manifestations of hypothyroidism include slowness of movements; tough, thick skin; increased weight; cold intolerance; and constipation.

Neurologic complications also include encephalopathy, ataxia, and sometimes even coma. Cranial nerve dysfunction can cause hoarseness and, rarely, diaphragmatic paralysis (Crum & Bolton, 2002). Patients may exhibit bradycardia, myoedema, and delayed relaxation of the ankle reflex.

Neuromuscular complications include sensorimotor PN (Dyck & Lambert, 1970; Shirabe, Tawara, Terao, & Araki, 1975) and entrapment neuropathies, particularly CTS (Shirabe et al., 1975). Some patients also have diffuse muscle weakness and fatigue (Al-Shekhlee, Kaminiski, & Ruff, 2002; Duyff, Van den Bosch, Laman, van Loon, & Linssen, 2000; Madariaga, 2002; Tornero Estebanez, 2001), which can be accompanied by stiffness. Rare cases of rhabdomyolysis have been reported (Barahona, Mauri, Sucunza, Paredes, & Wägner, 2002; Kar, Hirani, & Allen, 2003; Kisakol, Tunc, & Kaya, 2003; Scott, Simmons, & Boyer, 2002).

Muscle enlargement accompanied by pain in adults with hypothyroidism is called *Hoffmann syndrome* (Benito-León et al., 2001; Mastropasqua, Spagna, Baldini, Tedesco, & Paggi, 2003); in children, this also manifests with dysmorphic features and muscle swelling, but without pain, and is called Kocher-Debré-Semelaigne syndrome (Tullu, Udgirkar, Muranjan, Sathe, & Kamat, 2003).

Serum cholesterol, triglycerides, and serum CK levels frequently are elevated (Bertorini, 2008a), likely because of decreased secretion of the enzyme (Karlsberg & Roberts, 1978). CK levels may be elevated in subclinical cases misdiagnosed with "idiopathic hyperCKemia." Thyroid hormone levels should be measured in these patients, particularly those with hyperlipidemia, before placing them on cholesterol-lowering drugs.

The evaluation of hypothyroidism includes measurement of serum T_4, particularly free thyroxine, T_3, and particularly thyrotropin, which is elevated in the primary form. Measurement of thyroid peroxidase antibodies is used to diagnose chronic autoimmune thyroiditis (Madariaga, 2002). Thyroid ultrasound and thyroid scans can be used in those with enlargement of the gland.

TREATMENT AND MANAGEMENT

The treatment of hypothyroidism consists of eliminating possible causes, such as medications, and treating the iodine deficiency, but the most important therapy consists of hormonal replacement with oral levothyroxine, initially at a dosage of 1.3 µg/kg/day orally and later with a maintenance dose of about 125 µg daily; this dosage varies between 50 and 200 µg daily with proper monitoring of thyrotropin levels. The dosage should be adjusted according to the effects of diet, medications, and particularly weight. The combination of levothyroxine and levothyronine at a ratio of 4:1 also is used by some (Wiersinga, 2006).

Management also includes surgery for CTS, exercise, and physical therapy.

HYPERPARATHYROIDISM

Primary hyperparathyroidism is caused by an excessive release of parathyroid hormone (PTH) by adenomas or hyperplasia of the glands and rarely by parathyroid cancer (Silverberg & Bilezikian, 2006). These tumors may be a manifestation of familial multiple endocrine neoplasms (Attie, Bock, & Auguste, 1980).

Normally, PTH acts in the kidneys by increasing calcium reabsorption and converting 25-hydroxy vitamin D_3 to the more potent metabolite 1,25-dihydroxy vitamin D (Feldman, 1999). This action is exaggerated in primary hyperparathyroidism (El-Hajj, Fuleihan, & Silva Burger, 2019).

In renal disease, failure to convert 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D decreases calcium reabsorption and causes hypocalcemia, which increases PTH production (secondary hyperparathyroidism) (Hajjar & Hagenacker, 2017). In these patients, hypocalcemia and vitamin D deficiency are accompanied by hyperphosphatemia. Tertiary hyperparathyroidism refers to an autonomous production of PTH even with normal or elevated serum calcium levels (El-Hajj et al., 2019; Michael & Kroges, 2008).

The mechanism by which hyperparathyroidism causes neuromuscular disease is unclear, but elevated levels of PTH with hypercalcemia and hypophosphatemia impair muscle function (Baczynski et al., 1985; Garber, 1983; Wrogemann & Pena, 1976). The proximal muscle weakness that occurs in vitamin D deficiency and osteomalacia suggests a link between abnormal vitamin D metabolism and neuromuscular disease.

DIAGNOSIS AND EVALUATION

Primary hyperparathyroidism is frequently diagnosed during routine laboratory studies in asymptomatic individuals by the presence of hypercalcemia (Scholz & Purnell, 1981). The disease can manifest clinically as bone disease (osteitis fibrosa cystica), kidney stones, peptic ulcers, and psychiatric symptoms (Joborn et al., 1998).

Neuromuscular manifestations include fatigability and prominent proximal muscle weakness, with atrophy mainly in the leg muscles (hyperparathyroid myopathy). Serum CK levels are normal (Patten et al., 1974). This presentation occurs in both primary and secondary hyperparathyroidism (Mallette, Patten, & Engel, 1975).

Unusual symptoms include diplopia, myotonia, and severe hypotonia. An acute necrotizing myopathy has been reported (Bertorini, 1989; Mallette et al., 1975). Rarely, symptoms resemble those of amyotrophic lateral sclerosis (Frame, Heinze, Block, & Manson, 1968), and "dropped head syndrome" can also occur (Rymanowski & Twydell, 2009).

Short-duration polyphasic motor unit action potentials can be seen on EMG, and there could be increased neuromuscular jitter on single-fiber EMG, indicating a disorder of the neuromuscular junction (Kaplan, Hines, Leestma, & Ruder, 1980). Type II muscle fiber atrophy is demonstrated on muscle biopsy, which also may show scattered esterase-positive atrophic denervated muscle fibers. Another important finding is the presence of calcium deposits in vessel walls (Bertorini, 1989); this vasculopathy in other tissues could play a role in the cardiovascular complications of hyperparathyroidism.

The laboratory diagnosis of hyperparathyroidism is based on the presence of hypercalcemia and elevated levels of PTH. However, hypercalcemia can also occur with malignancy, excessive vitamin D and A intake, and other endocrine disorders, such as thyrotoxicosis and Addison disease. In all of these, PTH levels are suppressed except for rare cases of ectopic PTH secretion in malignancy. Hypercalcemia also occurs in patients receiving lithium and thiazides

and in the hypercalcemic hypocalciuric syndrome (Michael & Kroges, 2008; Silverberg & Bilezikian, 2006).

Serum phosphate may be normal in primary hyperparathyroidism, but it is elevated in secondary hyperparathyroidism. Radiographs and densitometry occasionally provide valuable diagnostic clues.

Once the diagnosis is made, there are several methods for localization of the adenoma, including MRI, computed tomography (CT), and ultrasound. The most sensitive method is Tc-99 sestamibi uptake, especially when combined with initial single-photon emission CT scan.

TREATMENT AND MANAGEMENT

The treatment of primary hyperparathyroidism consists of surgical removal of the adenoma (Delbridge, Marshman, Reeve, Crummer, & Posen, 1988; Silverberg & Bilezikian, 2006; Wersäll-Robertson, Hamberger, Ehrén, Eriksson, & Granberg, 1986). In patients who cannot tolerate surgery, medical therapies include oral phosphate, which can cause gastrointestinal symptoms. Subcutaneous bisphosphonates are used for control of osteitis fibrosa, reducing bone turnover without affecting PTH secretion. Of the bisphosphonates, alendronate has been shown to increase bone density in hyperparathyroidism (Hassani et al., 2001). Estrogen replacement can be used in postmenopausal women, but this can be associated with deleterious effects. Inhibition of PTH synthesis can be obtained by drugs such as cinacalcet that act in the calcium-sensing receptor in parathyroid cells (Silverberg & Bilezikian, 2006).

Treatment of secondary hyperparathyroidism consists of low-phosphate diets and vitamin D replacement. Aluminum-containing phosphate-binding agents also can be used, but these can increase aluminum levels, which could cause weakness and encephalopathy and, occasionally, hypercalcemia. Currently, calcium carbonate is used in dosages not exceeding 2 g/day. Calcitriol or its analogs also can be used to inhibit PTH production. Alpha calcitriol has similar effects. Treatment also should include proper dialysis and ideally kidney transplantation.

HYPOPARATHYROIDISM

Hypoparathyroidism is defined as the decreased production of PTH; a lack of response of the target tissue to the PTH is called *pseudohypoparathyroidism* (Levine, 2006). Both disorders result in hypocalcemia and hyperphosphatemia.

Decreased production of PTH is more often the result of unintentional damage to the parathyroid glands during neck surgery for cancer or adenomas and for hyperthyroidism, and less frequently by radiation (Edis, 1979), infiltrations such as iron overload in hemochromatosis and multiple transfusions, and Wilson disease (Carpenter, Carnes, & Anast, 1983). Idiopathic hypoparathyroidism represents a heterogeneous group of rare diseases, such as autoimmune familial hypoparathyroidism associated with multiglandular syndrome (Obermayer-Straub & Manns, 1998) and congenital disorders such as DiGeorge syndrome (Baldini, 2004). Chronic hypermagnesemia may cause decreased production of PTH (Fatemi, Ryzen, Flores, Endres, & Rude, 1991), as in Kearns-Sayre syndrome, a mitochondrial disorder (Katsanos, Elisaf, Bairaktari, & Tsianos, 2001). Hypermagnesemia also can cause decreased secretion of PTH, such as occurs, for example, with high doses of intravenous magnesium used to treat toxemia.

PTH regulates calcium concentrations in the extracellular space. About 50% is protein bound, and the rest is ionized calcium. The hormone increases calcium mobilization from bone and reabsorption from the kidneys, and its deficiency results in hypocalcemia. Hyperphosphatemia is caused by diminished phosphate clearance by the kidneys.

Pseudohypoparathryoidism occurs in a group of disorders in which there is hypocalcemia with hyperphosphatemia and is associated with increased PTH production but a reduced response to the biologic action of the hormone (Breslau, 1989).

Vitamin D deficiency also can cause hypocalcemia by decreasing intestinal calcium absorption, which enhances PTH production (secondary hyperparathyroidism).

DIAGNOSIS AND EVALUATION

Hypocalcemia may be asymptomatic or may cause neuromuscular irritability in acute cases, presenting as seizures and syncope or choreoatetosis, particularly in children with rickets (Schutt-Aîné, Young, Pescovitz, Chrousos, & Marx, 1985). In adults, osteomalacia is most often caused by vitamin D deficiency. Chronic hypocalcemia in hypoparathyroidism causes muscle pains, weakness, coarse hair, dry skin, and bone disease (Bischoff-Ferrari et al., 2004; Erkal et al., 2006). Muscle weakness is accompanied by normal serum CK levels and nonspecific muscle biopsy findings (Ziambaras & Dagogo-Jack, 1997). Statin-induced myalgia in vitamin D–deficient patients has been reported to improve with vitamin D supplementation (Ahmed et al., 2009); thus, its deficiency may play a role in this complication.

Acute hypoparathyroidism presents clinically as neuromuscular irritability with carpopedal spasms, sometimes with opisthotonic posture, and positive Trousseau and Chvostek signs on examination (Hoffman, 1958).

Laboratory findings consist of a reduction of serum calcium and PTH; phosphate levels may be normal or elevated. In vitamin D deficiency, however, PTH levels are elevated and are accompanied by high levels of phosphate and alkaline phosphatase and decreased vitamin D. Also, when evaluating patients with neuromuscular irritability, it is important to measure magnesium levels, because hypomagnesemia could have a similar presentation (Abbott & Rude, 1993).

Electrophysiologic tests show normal nerve conduction velocities, and the needle EMG test demonstrates the characteristic "multiplets" motor action potentials. In acute hypoparathyroidism, electroencephalography shows no specific abnormalities, and electrocardiography may show prolongation of the QT interval.

Basal ganglia calcifications may be seen on CT scans in chronic hypoparathyroidism (Illum & Dupont, 1985; Kowdley, Coull, & Orwoll, 1999).

TREATMENT AND MANAGEMENT

Acute hypocalcemia is treated with intravenous infusions of calcium gluconate in doses of 1 to 3 g in 10 to 30 mL (10%) for 10 minutes, followed by 5% dextrose in 100 mL of calcium gluconate (10%). Oral calcium gluconate should then be given in doses of 1 to 3 g/day (Levine, 2006).

Patients with osteomalacia and rickets should receive vitamin D and calcium supplementation.

Long-term treatment of hypocalcemia in patients with hypoparathyroidism requires administration of oral calcium and vitamin D. Older patients require vitamin D analogs in addition to calcium. Calcitriol, which is the active form of vitamin D, is the treatment of choice. Patients can be effectively treated with dosages of 0.25 μg twice a day to 0.5 μg four times a day (Levine, 2006). Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) also are frequently used in long-term management, and their cost is significantly lower than that of calcitriol.

Because thiazide diuretics increase calcium reabsorption and glucocorticoids influence vitamin D metabolism, these agents should be given with caution and frequent monitoring of the serum calcium and phosphorus levels (Parfitt, 1972).

CUSHING SYNDROME

Cushing syndrome (CS) is a metabolic disorder associated with elevated levels of cortisol affecting carbohydrate, protein, and lipid metabolism. Clinical manifestations include hypertension, obesity, osteoporosis, and hyperglycemia. The most common cause of CS is the exogenous administration of corticosteroids for therapeutic purposes (Orth, 1995). Endogenous CS is caused by excessive cortisol secretion, and the syndrome may be adrenocorticotropin hormone (ACTH) dependent or independent. ACTH-dependent CS is caused by secondary adrenal hyperplasia from pituitary adenomas (Cushing disease) and more rarely by ectopic corticotropin-releasing factor secretion, which can be caused by tumors such as small cell carcinoma of the lung. Corticotropin-independent CS occurs in 15% to 20% of cases and is caused by adrenal adenomas, carcinomas, or micronodular hyperplasia (Bertorini, Perez, & Tamara, 2008; Nieman, 2007).

DIAGNOSIS AND EVALUATION

The neurologic manifestations of CS are multiple, and Chapter 7 covers the complications of corticosteroid treatment in neuromuscular diseases. These include neuropsychiatric symptoms such as mania and depression, back pain due to compression fractures, and cranial nerve palsies caused mostly by mechanical compression from the pituitary masses. Some patients also develop symmetric muscle weakness and wasting, predominantly in the legs, sometimes accompanied by myalgia. In these patients, serum CK usually is normal (Bertorini et al., 2008; Gilbert & Lim, 2008; Nieman, 2007). Those receiving corticosteroids and paralyzing agents in the intensive care unit might also develop critical illness myopathy, which is discussed in Chapter 10.

Nerve conduction tests are normal in steroid-induced weakness, and the needle EMG examination shows small motor unit action potentials without spontaneous potentials. Histologically, selective type II muscle fiber atrophy, particularly of type IIB fibers, is present.

The differential diagnoses are multiple, including inflammatory myopathies, which could be an important challenge in those treated with corticosteroids that get weaker during therapy, because this could be caused by the effects of treatment or the primary disease.

When Cushing disease is suspected, initial tests should include measurements of sugar, electrolytes, and serum CK. Bone density testing is important to assess for osteoporosis. The first steps in the diagnosis of endogenous CS are the demonstration of elevated levels of free cortisol in urine and the late evening salivary cortisol (Gilbert & Lim, 2008) and the demonstration of an inadequate suppression of cortisol secretion during the dexamethasone suppression test (Findling, Raff, & Aron, 2004). Once the diagnosis is established, the second step is to determine if CS is corticotropin dependent or independent (Nieman, 2007). Plasma cortisol levels of more than 15 pg/dL and corticotropin concentrations less than 5 pg/mL are diagnostic of cortisol secretion and corticotropin-independent CS; corticotropin concentrations of more than 15 pg/mL are diagnostic of corticotropin-dependent CS (Bertorini et al., 2008; Nieman, 2007).

TREATMENT AND MANAGEMENT

Adrenalectomy can be done in patients with adrenal hyperplasia. In those with Cushing disease caused by pituitary adenomas, treatment consists of transphenoidal microadenomectomy (Bertorini et al., 2008). The treatment of exogenous CS consists in tapering of the corticosteroid dosage and using other drugs as steroid-sparing agents if necessary (McDougall, Bhibhatbhan, & Toth, 2009).

Proper management of complications is important, such as control of hyperglycemia, hypokalemia, hypertension, and osteopenia. Physical therapy and gentle aerobic activity are recommended.

HYPERALDOSTERONISM

Hyperaldosteronism is defined as a selective increase of mineralocorticoids caused by a disorder of the zona glomerulosa of the adrenal gland, resulting in hypertension, hypokalemia, and metabolic alkalosis. This may be accompanied by muscle weakness and fatigue related to the hypokalemia (Bertorini et al., 2008). Patients also may complain of paresthesias and may develop periodic paralysis or persistent myopathy.

Hyperaldosteronism can be primary, from adenomas or inflammation of the gland, or secondary to an alteration of the renin-angiotensin system, such as in renovascular hypertension, estrogen administration, and renin-secreting tumors. Bartter syndrome is a congenital metabolic disorder manifesting as hypokalemia and alkalosis with hyperreninemia and hyperaldosteronism (Bertorini et al., 2008). Patients with Kearns-Sayre syndrome, which causes muscle weakness, deafness, cardiac arrhythmia, and short stature, can also develop hyperaldosteronism with symptoms similar to those of Bartter syndrome (Emma et al., 2006).

DIAGNOSIS AND EVALUATION

The diagnosis should be considered in patients who present with muscle weakness associated with hypokalemia, regardless of the degree of hypertension (Bautista, Gil-Neciga, & Gil-Peralta, 1979; Talib et al., 2004) and also in those with severe hypertension. Other neurologic manifestations of hyperaldosteronism include tremors, encephalopathy, and syncope, as well as tetany from metabolic alkalosis (Fujihara, Miyoshi, Yamaguchi, Araki, & Tanaka, 1990).

The laboratory diagnosis is made by measurements of electrolytes, aldosterone, and plasma renin in the early morning hours. A serum aldosterone-to-renin ratio of more

than 30 suggests a diagnosis (assuming the aldosterone level is reported in nanograms per deciliter and the renin level in nanograms per milliliter per hour). Localization of the adenoma with imaging is then necessary.

TREATMENT AND MANAGEMENT

In hyperaldosteronism, electrolyte balance and treatment of hypertension are mandatory. The specific therapy consists of correction of the cause; for example, those with renovascular hypertension may require angioplasty, and those with tumors such as adenomas may require a laparoscopic adrenalectomy (Duncan, Fuhrman, Bolton, Bowen, & Richardson, 2000).

ADRENAL INSUFFICIENCY

Adrenal insufficiency (AI) results from inadequate secretion of corticotropin caused by pituitary adenomas or a hypothalamic disease, both of which are considered secondary AI. AI usually is associated with an intact renin-angiotensin-aldosterone system and can be caused by withdrawal of glucocorticoid therapy or by surgical removal of pituitary tumors or hypopituitarism. Less common causes include infections, radiation, pituitary apoplexy, Sheehan syndrome, lymphocytic hypophysitis, and tumors (Carey, 1997; Oelkers, 1996).

Primary AI or Addison disease is caused by a disorder of the adrenal glands, which often is autoimmune or caused by infections such as tuberculosis, histoplasmosis, cysticercosis, cytomegalovirus (Carey, 1997) or HIV (Piédrola et al., 1996) amyloidosis, hemorrhage, surgical removal of the gland, or metastasis. Other causes of AI are adrenoleukodystrophy and adrenomyeloneuropathy (Bertorini et al., 2008; Moser et al., 2005; Mukherjee, Newby, & Harvey, 2006). These are X-linked inherited disorders related to a defect in chromosome Xq20a that causes a deficiency of the enzyme acyl-coenzyme A (CoA) synthetase, resulting in the inability to degrade very long chain fatty acids in peroxisomes, leading to accumulation and the formation of cytoplasmic inclusions (Moser et al., 2005). Adrenoleukodystrophy is characterized by a primary AI with a progressive demyelinating process of the cerebral hemispheres (Mukherjee et al., 2006; Oelkers, 1996). The classic form occurs in childhood and is rapidly progressive. Adrenomyeloneuropathy is a variant that affects the central and peripheral nervous systems. These disorders are discussed in detail in Chapter 14.

DIAGNOSIS AND EVALUATION

The clinical symptoms of AI include nausea, vomiting, weakness and fatigue, depression, malaise, weight loss, and orthostatic hypotension. It also may manifest as hyperkalemia and severe weakness. In primary AI, hyperpigmentation of the skin and loss of axillary hair also are present. Secondary AI may occur in association with other hormonal deficiencies.

AI can present acutely as hyperkalemia and alkalosis, and patients may develop an Addisonian crisis with severe weakness and hypotension.

The laboratory tests used in evaluation include electrolyte measurements and the demonstration of reduced plasma cortisol levels. Imaging of the adrenal or the pituitary glands also helps establish the diagnosis. Cortisol concentration should be measured between 6:30 and 8:00 AM, and levels below 3 μg/dL indicate AI, whereas levels of 19 μg/dL or higher rule out this disorder. In primary AI, corticotropin concentration usually is above 100 pg/mL, whereas aldosterone levels are low. Corticotropin levels sometimes are normal. The corticotropin stimulation test is a more specific test for the diagnosis of primary AI. Results are considered normal if plasma cortisol levels are more than 18 μg/dL after a synthetic corticotropin (Cosyntropin) 25 μg is given intravenously (Bertorini et al., 2008; Grinspoon & Biller, 1997).

TREATMENT AND MANAGEMENT

Treatment of AI consists of replacement of glucocorticoids and mineralocorticoids in conjunction with fluid and electrolyte replacement. Patients should receive hydrocortisone or cortisone. The oral dosage of hydrocortisone is 25 mg a day (15 mg in the morning and 10 mg at night). Cortisone could be given in dosages of 25 mg in the morning and 12.5 mg in the evening (Bertorini et al., 2008; Oelkers, 1996). For mineralocorticoid replacement in primary AI, oral fludrocortisone is given in doses of 0.05 to 2 mg daily.

During times of stress and when surgery is performed, the dosage of hydrocortisone should be doubled or tripled. In an Addisonian crisis, patients should receive hydrocortisone intravenously in a dosage of 100 mg every 8 hours.

Patients with AI should be advised regarding the risk of an Addisonian crisis, particularly during times of stress or during surgery. Patients and families should receive genetic counseling. Physical therapy and gait training are most important.

NEUROMUSCULAR COMPLICATIONS OF UREMIA

Patients with chronic renal failure can develop multiple neurologic complications, including central nervous system disorders such as stroke, cognitive dysfunction, and encephalopathy and/or peripheral nervous system such as PN and focal neuropathies, such as CTS or other entrapment syndromes. They may also develop shunt-related neuropathies, vascular steal syndromes, or myopathy, all of which can have multiple etiologies (Al-Hayk & Bertorini, 2007) (Table 21.2 and Box 21.4).

POLYNEUROPATHY

Uremic PN is the most common neurological complication of CKD that affects up to 70% of predialysis patients and nearly 90% of dialysis patients (Krishnan & Kiernan, 2009). Uremic PN is a progressive axonal neuropathy with secondary demyelination that causes sensory loss (Dyck, Johnson, Lambert, & O'Brien, 1971). The typical symptoms are distal tingling, paresthesia, pain, restless legs, and later distal weakness and are also a contributor to ulceration and amputation (Krishnan & Kiernan, 2007; Mendell & Sahenk, 2003; Arnold, Kwai, et al., 2014a). Uremic PN likely has multiple etiologies, including the accumulation of middle molecular weight molecules, multiple vitamin deficiencies and malnourishment, and secondary hyperparathyroidism with low vitamin D (Babb, Ahmad, Bergström, & Scribner, 1981; Di Giulio, Chkoff, Lhoste, Zingraff, & Drüeke, 1978)

Table 21.2 Uremic Neuropathies

Type	Etiology
Polyneuropathy	Middle molecule toxins Miscellaneous (vitamin deficiency, malnutrition, secondary hyperparathyroidism, abnormal carbohydrate metabolism)
Mononeuropathy	Ischemic monomelic Acute ischemia ± underlying diabetes mellitus with neuropathy, peripheral neuropathy, and atherosclerotic vascular disease
Steal syndrome	Ischemic monomelic Acute ischemia underlying diabetes mellitus with neuropathy, peripheral neuropathy, and atherosclerotic vascular disease
Carpal tunnel syndrome	Dialysis amyloid (β_2-microglobulin) accumulation
Compressive neuropathies	Nerve compression (cachectic, bedridden patients)
Traumatic	Self-retaining retractors (kidney transplant or surgical positioning)

Box 21.4 Causes of Uremia-Associated Myopathy[a]

Secondary hyperparathyroidism
Aluminum intoxication
Iron overload
β_2-microglobulin-associated amyloidosis
Vitamin D deficiency
Chronic phosphate depletion
Hypokalemia
Hyperkalemia
Hypercalcemia
Carnitine deficiency
Azotemic vasculopathy (necrotizing myopathy)
Disuse atrophy (type II muscle fiber)
Associated vasculitides
Connective tissue disease
Myopathy in dialysis-associated systemic fibrosis
Idiopathic

[a] Weakness could also occur, particularly in those receiving drugs that affect neuromuscular transmission.

(Fig. 21.3). More recent research studies have demonstrated that hyperkalemia impairs nerve function in a dose-dependent manner and induces hyperpolarizing state, which indicates that maintaining normal potassium level in CKD patients may reduce the incidence of uremic PN (Arnold, Pussell, et al., 2014b).

DIAGNOSIS AND EVALUATION

Patients with uremia usually complain of burning paresthesia and numbness and may have restless leg syndrome. They also may develop dysautonomia with significant orthostatic hypotension.

The neurologic examination demonstrates signs of a sensorimotor PN with stocking-glove sensory deficits, absent distal reflexes, and later weakness. A drop in blood pressure also may be demonstrated clinically or with a tilt-table test.

Electrophysiologic studies document the presence of an axonopathy and secondary demyelination with low-amplitude CMAPs and SNAPs, while conduction velocities are only minimally affected. The needle EMG may show signs of denervation with large motor unit action potentials.

During the evaluation, clinicians should be aware of other superimposed or associated causes of neuropathy and entrapment such as diabetic PN and connective tissue disorders, which should be ruled out.

TREATMENT AND MANAGEMENT

In addition to management of underlying renal disease, the treatment of uremic PN consists of proper vitamin supplementation, particularly vitamins D, B_6, and calcium; physical activity; pain modulators; and particularly hemodialysis (Mendell & Sahenk, 2003). The best result is obtained with kidney transplantation, which markedly improves the neuropathy (Bolton, 1976). Recent evidence suggests that maintaining normal potassium level may prevent uremic PN (Arnold, Pussell, et al., 2014b). Neuropathic pains can be managed by tricyclic antidepressants, anticonvulsants such as gabapentin or pregabalin, or serotonin-norepinephrine reuptake inhibitors such as duloxetine or venlafaxine. However, potential side effects, especially in the elderly, and dose restrictions should be considered (Pop-Busui et al., 2010) (discussed in detail in Chapter 6).

FOCAL UREMIC NEUROPATHIES

Focal uremic neuropathies include CTS and other entrapment syndromes, damage of nerves such as the lateral femoral cutaneous nerve from compression during transplantation, and peroneal and ulnar nerve palsies, especially in bedridden and cachectic CKD patients, as well as shunt-related neuropathies.

CTS is common in patients with uremic neuropathy, particularly in those receiving prolonged hemodialysis, with a prevalence rate up to 30%. This is caused by accumulation of β_2-microglobulin amyloidosis in the carpal tunnel, compressing the median nerve. Other factors that contribute to the increased incidence of CTS in CKD patients are distal ischemia and edema, uremic tumoral calcinosis, and the placement of arteriovenous fistula (Gilbert et al., 1988; Gousheh & Iranpour, 2005; Ritz & Bommer, 1988).

Ischemic monomelic neuropathy is a relatively rare acute neuropathy in which nerve damage occurs in the more distal portion of the limb secondary to severely compromised blood flow in a major limb artery proximally, usually more common in diabetic patients. Nearly all reported cases are caused by shunt occlusion after placement in the antecubital fossa or proximal arm for dialysis, or by infections, manifesting as a distal axonal neuropathy in the affected limb (Wilbourn, Furlan, Hulley, & Ruschhaupt, 1983). Although the ischemic event is severe enough to cause distal nerve fiber damage and precipitate abrupt burning pain and weakness, it is insufficient to cause skin or muscle necrosis.

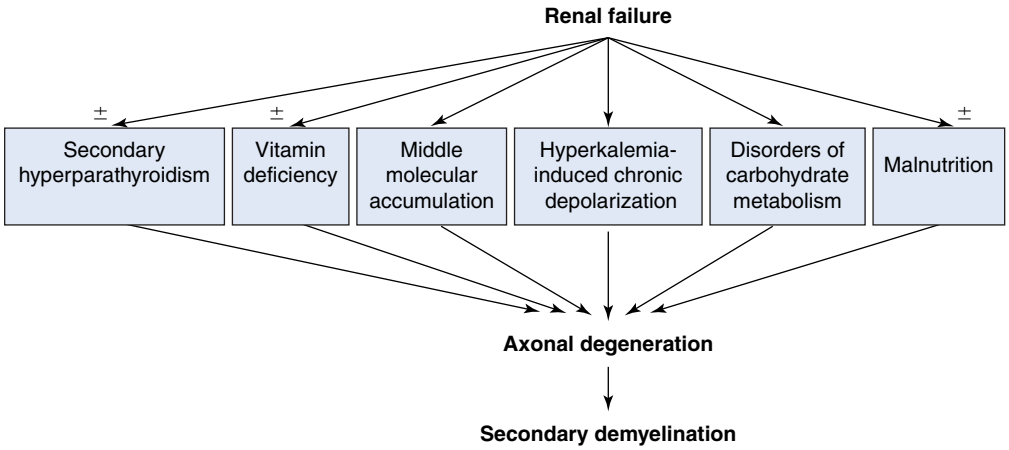


Fig. 21.3 Possible pathogenesis of uremic polyneuropathy.

Vascular steal syndrome is an insidious neuropathy that manifests days to months after shunt placement, causing neurologic deficits in the affected limbs, as well as ischemic changes in the skin. The syndrome is thought to be caused by reversal of the arterial blood flow away from the digits (Miles, 1999, 2000).

Shunt-related entrapment neuropathies occur frequently after placement of an arterial venous shunt and cause ulnar and median nerve entrapments, particularly in women with high fistular flows (Padberg, Calligaro, & Sidawy, 2008).

DIAGNOSIS AND EVALUATION

In the diagnosis of uremic PN, one should rule out other etiologies according with the clinical presentation and consider additional causes. Electrophysiological tests are important. The diagnosis of CTS should be suspected in patients with uremic PN who have more prominent symptoms in the median nerve distribution and swelling of the wrist. Electrophysiologic studies demonstrate prolongation of the median nerve CMAP and SNAP distal latencies.

Patients with ischemic monomelic neuropathy have impairment of all sensory modalities distally in the affected limbs, which is more prominent than the weakness. Usually, there are no signs of vascular insufficiency. Electrophysiologic tests show evidence of axonal loss with low-amplitude SNAPs and, to a lesser extent, CMAPs; conduction block also may be evident (Kaku, Malamut, Frey, & Parry, 1993).

Patients with vascular steal syndrome have painful paresthesias with pallor and ischemic changes in the skin that can progress to gangrene and sensory deficits in the median and ulnar nerve distributions. Nerve conduction studies document low-amplitude SNAPs and, later, CMAPs. Ultrasonography reveals reversal of the shunt flow, although some patients with retrograde flow in the shunt may be asymptomatic. Fistulography may be necessary. Digital oximetry shows decreased oxygen saturation (Al-Hayk & Bertorini, 2007; Miles, 1999).

The examination of patients with shunt-related entrapment syndromes demonstrates sensory and motor deficits in the hands and often deficits and swelling of the affected limbs (Delmez, Holtmann, Sicard, Goldberg, & Harter, 1982).

TREATMENT AND MANAGEMENT

The treatment of CTS is conservative, but decompression of the carpal tunnel is frequently necessary, although the outcome appears inferior in CKD compared to patients with idiopathic CTS. Additionally, the recurrence rate of CTS in CKD is higher, and an endoscopic approach is a treatment option in relieving persistent symptoms (Hirasawa & Ogura, 2000; Kim, Shin, & Kang, 2000). During surgery, there is evidence of an accumulation of a mucinous material, which represents β_2-microglobulin.

The treatment of ischemic monomelic neuropathy consists of immediate ligation of the arteriovenous graft, and its removal might be required to preserve neurologic function. The shunt should then be placed at another site (Gousheh & Iranpour, 2005). Antibiotic therapy and pain management are necessary. A variable outcome is seen, with persistent symptoms in some patients to substantial improvement in others occurring several months after graft ligation.

Vascular steal syndrome is treated with fistular banding, but removal of the shunt might be required (Miles, 1999, 2000).

For shunt-related entrapment syndromes, treatment depends on the severity of the symptoms. Nerve decompression can produce marked relief. Removal of the shunt also may be necessary.

AUTONOMIC NEUROPATHY

Autonomic dysfunction is highly prevalent in CKD and patients on hemodialysis, including postural hypotension, impaired sweating, impotence, gastrointestinal dysfunction, dyspepsia, cardiac arrhythmia, and intradialytic hypotension (Vita, Messina, Savica, & Bellinghieri, 1990). Although it is difficult to attribute a causal relationship, recent studies have shown that autonomic dysfunctions are detectable in the early stages of CKD (Grassi et al., 2011). The pathophysiology underlying uremic autonomic dysfunction remains unknown. However, this may include a combination of sympathetic overactivity, decrease of parasympathetic function, cardiovascular autonomic dysfunction, elevated angiotensin II, and associated hyperparathyroidism. Parasympathetic dysfunction has been shown to occur with greater frequency than sympathetic dysfunction (Chang et al., 2016; Salman, 2015; Spallone et al., 1990).

DIAGNOSIS AND MANAGEMENT

Autonomic function assessment of cardiovagal, adrenergic, and sudomotor function can be undertaken. This may

include objective measures of heart rate variability in response to deep inspiration-expiration, Valsalva maneuver, tilt-up table test of postural change, and quantitative sudomotor axon reflex test. Sympathetic skin response and sustained hand grip are less sensitive measures of sympathetic function (Wang et al., 1994). Hemodialysis and renal transplantation have shown to improve parasympathetic dysfunction, including cardiac and gastrointestinal dysfunction. Impotence can be effectively treated with sildenafil or vardenafil as tolerated. Intradialytic hypotension may be improved with midodrine administered prior to dialysis. Hypertension can be managed with angiotensin-blockers alone or in combination with other antihypertensive medications, excluding angiotensin-converting enzyme inhibitors. Cardiac arrhythmia can be treated with carvedilol, an alpha/beta-blocker that showed few side effects than beta-blockers. Optimizing glycemic control in diabetic patients with CKD is crucial to prevent progression of autonomic and PN (Arnold & Krishnan, 2014; Lasaponara et al., 2013; Matsue et al., 2013). See details in Chapter 5.

UREMIC MYOPATHY

Patients with uremia can develop insidious proximal muscle weakness related to end-stage renal disease or complications of therapy, and approximately 50% of patients on dialysis are affected by myopathy (Campistol, 2002; Lazaro & Kirshner, 1980). Symptoms including proximal muscle weakness and atrophy of skeletal muscles typically appear and progress as kidney function decline to glomerular filtrations rate below 25 mL/min (Arnold & Krishnan, 2014). The causes of uremic myopathy are multiple and include oxidative stress, secondary hyperparathyroidism, aluminum intoxication, iron overload, electrolyte imbalance, accumulation of uremic toxins, and carnitine deficiency (Bregman, Gelfand, Winchester, Manz, & Knepshield, 1980; Kaltsatou et al., 2015; Marsden, Parkinson, Ward, Ellis, & Kerr, 1979; Thompson, Irish, Kemp, Taylor, & Radda, 1997) (Box 21.4).

Some patients may develop nephrogenic fibrosing dermopathy, particularly those who receive gadolinium contrast for imaging. Symptoms include systemic fibrosis with joint contractures and weakness (Cowper, 2003; Grobner, 2006; Levine et al., 2004).

Patients with uremia also rarely develop increased muscle fatigue during daily activities secondary to a defect of neuromuscular transmission. In those receiving carnitine, the defect is believed to be related to the similarity of carnitine and acetylcholine (De Grandis et al., 1980). Impairment of neuromuscular transmission also can be secondary to neuropathy, which might be aggravated by some drugs that affect neuromuscular transmission (Niakan, Bertorini, Acchiardo, & Werner, 1981).

DIAGNOSIS AND EVALUATION

Patients with uremic myopathy have proximal weakness, more prominent in the lower limbs and out of proportion to the distal PN, and EMG studies may show evidence of "myopathic" motor unit action potentials and sometimes denervation potentials, and serum CK levels can be elevated; however, both EMG studies and muscle enzymes can be normal. The evaluation should also include measurement of vitamin D, calcium, phosphate, electrolytes, if necessary, serum carnitine, and serum aluminum levels. Muscle biopsy shows type II fiber atrophy and fiber splitting and may demonstrate the deposits of β_2-microglobulin or iron accumulation. However, muscle biopsy is rarely undertaken (Kaltsatou et al., 2015).

The diagnosis of a superimposed disorder of neuromuscular transmission depends on proper clinical assessment, and the repetitive stimulation test is necessary to document a decrement of the CMAP area. If myasthenia gravis is a clinical consideration, acetylcholine receptor and other antibodies should be measured.

TREATMENT AND MANAGEMENT

Although no specific treatment exists for uremic myopathy, treatment of contributing factors should be applied (Miller, 2019). Those with carnitine deficiency require its replacement (Bregman et al., 1980), and chelation therapy may benefit those with aluminum and iron overload (Marsden et al., 1979; Thompson et al., 1997). Systemic fibrosis is treated conservatively. The anemia in renal disease should be corrected, and patients should receive vitamin D and other vitamin replacements. Physical therapy and increased muscle activity are important. The best treatment of most of these complications is kidney transplantation, which has been shown to improve exercise tolerance and neuromuscular function (Krishnan, Pussell, & Kiernan, 2009). The treatment of those with a disorder of neuromuscular transmission is removal of the cause, particularly drugs that might impair neuromuscular transmission, or discontinuation of carnitine suppression.

MALNUTRITION AND VITAMIN DEFICIENCIES

Malnutrition is seen commonly in poor countries where people have low protein and vitamin intake, but it also occurs in patients with malabsorption syndrome from infections, celiac disease, parenteral nutrition, or gastrointestinal surgery. This also is frequently seen in alcoholics (Denny-Brown, 1947; Windebank, 1993). Only the most important neuromuscular manifestations of malnutrition and vitamin deficiencies are discussed here.

VITAMIN A

Vitamin A is a fat-soluble vitamin that includes the preformed compounds retinol and retinal, which are contained in animal foods. The provitamin A is beta-carotene. This and other carotenoids are converted in the body to retinal (Blomhoff, Green, Green, Berg, & Norum, 1991; Hammond & Wang, 2008). Retinal and carotene are converted to retinyl palmitate, which is stored in the liver (Blomhoff et al., 1991).

Most complications of vitamin A deficiency are ophthalmologic, but some patients also develop bulbar weakness, ataxia, and sometimes generalized weakness.

DIAGNOSIS AND EVALUATION

Patients with this deficiency usually present with night blindness, exophthalmia, dry eyes, keratitis, and rarely ataxia. Vitamin A deficiency should be suspected in patients with

these symptoms, and its levels should be measured in those with malabsorption and ocular manifestations.

TREATMENT AND MANAGEMENT

The recommended daily allowance of vitamin A is 1000 mcg for men and 800 mcg for women. The daily allowance for children younger than age 1 year is 375 μg and for those between 1 and 3 years of age, 400 μg; from age 4 to 10 years, this increases to 500 μg.

Patients with severe vitamin A deficiency should receive up to 500,000 units/day for 3 days and then 50,000 units/day for 14 days, followed by 10,000 to 20,000 units/day for 2 months. If oral administration is not possible, 10,000 to 50,000 units/day should be given parenterally. The maintenance dose is 400 to 500 units/day orally, increasing to 10,000 units in patients with malabsorption. Vitamin A levels should be monitored because overdoses can cause complications such as increased intracranial pressure. Normal vitamin A levels in serum are 38 to 100 μg/dL, and the normal levels of carotene are 70 to 300 μg/mL.

VITAMIN B_1 (THIAMINE)

Thiamine is a water-soluble vitamin contained in cereals and grains, particularly in those that maintain their outer layers. The recommended daily allowance of vitamin B_1 is 0.5 mg/1000 kcal or a daily intake of 1.2 mg, increasing to 1.4 mg during pregnancy and lactation. Requirements might be increased during dialysis, thyrotoxicosis, and diuretic therapy (Pingrade, 2008). B_1 deficiency also occurs in critically ill patients (Attaluri, Castillo, Edriss, & Nugent, 2018), as well as after bariatric surgery (Tang, Alsulaim, Canner, Prokopowicz, & Steele, 2018), and particularly during periods of high metabolic demands and high carbohydrate, particularly glucose, intake. The active form of vitamin B_1 is thiamine pyrophosphate (TPP), which participates in the intermediate metabolism of carbohydrates (Windebank, 1993; Zak, Burns, Lingenfelser, Steyn, & Marks, 1991).

Decreased levels of TPP cause elevated levels of pyruvate and, sometimes, lactate and reduce red blood cell (RBC) activity of transketolase, with reduction of oxygen uptake and transketolase activity in the brain stem (Brin, 1962; Jeyasingham et al., 1987).

Thiamine deficiency causes a sensorimotor PN and can cause cardiomyopathy and Wernicke-Korsakoff syndrome (Hammond & Wang, 2008).

DIAGNOSIS AND EVALUATION

The early symptoms of PN include dysesthesia and numbness, predominantly in the lower extremities. Physical examination reveals weakness and wasting in the distal muscles of the legs with areflexia. Rarely, patients have involvement of the recurrent laryngeal nerve, causing hoarseness (Zak et al., 1991). Electrophysiologic studies demonstrate an axonal, predominantly sensory neuropathy.

Normal thiamine levels in serum are 1.1 to 1.6 mg/dL, but its measurement has a limited value; measurement of serum pyruvate and lactate levels may be helpful (Brin, 1962; Hammond & Wang, 2008). More reliable tests include the measurement of RBC transketolase activity (Jeyasingham et al., 1987) and TPP stimulation of RBC transketolase levels (Jeyasingham et al., 1987). Measurement of 24-hour excretion of thiamine is also useful.

TREATMENT AND MANAGEMENT

Treatment of vitamin B_1 deficiency includes a well-balanced diet with supplements of this and other vitamins. In symptomatic deficiencies, the initial replacement is given parenterally in a dosage of 50 to 100 mg/day for 3 to 5 days and then the same dosage orally.

Alcoholics and malnourished patients should receive intravenous thiamine before receiving intravenous glucose to avoid the development of Wernicke encephalopathy. Patients receiving parenteral nutrition should receive supplementation in a dosage of 6 mg/day, increasing to 25 to 50 mg in those with a history of alcohol intake. In symptomatic children, the dosage is 10 to 25 mg/day either orally or parenterally. The dosage for infants is 0.2 mg/day, and for those age 7 to 12 years the dosage is 0.3 mg/day.

VITAMIN B_3 (NIACIN)

Niacin is a vitamin that includes both nicotinamide and nicotinic acid. Niacin is formed in the body from tryptophan. Its deficiency is prevented by exogenous intake in cereals, beef liver, and fish. Nicotinic acid and nicotinamide form nicotinamide adenine dinucleotide (NAD) and NAD phosphate; many important enzymes of energy metabolism depend on these.

Niacin is contained in legumes, peanuts, coffee, tea, meat, and fruit. Niacin deficiency is seen in people whose diet consists mainly of some cereals such as maize, which contain solid forms of the vitamin that are not nutritionally available. Niacin deficiency also occurs in alcoholics and those receiving isoniazid. The recommended daily allowance of the vitamin is 15 to 19 mg/day.

DIAGNOSIS AND EVALUATION

The clinical presentation of vitamin B_3 deficiency is called *pellagra* and is characterized by the triad of dermatitis, dementia, and diarrhea.

A selective deficiency of niacin is seldom seen except in very poor countries. The clinical presentation includes diarrhea with dermatitis and central nervous system disorders. Patients exhibit irritability, confusion, and dementia and may have ataxia, extrapyramidal symptoms, and occasionally a PN (Lewy, Spies, & Aring, 1940) or myelopathy (Pingrade, 2008).

TREATMENT AND MANAGEMENT

Pellagra should be treated with 25 mg of niacin intravenously two or three times a day in addition to other vitamins, particularly thiamine. Oral nicotinic acid is then given in a dosage of 50 to 100 mg three times a day until symptoms disappear. A maintenance dosage of 50 mg/day is recommended (Pingrade, 2008; Ruffin & Smith, 1939).

VITAMIN B_6 (PYRIDOXINE)

Pyridoxine is another water-soluble vitamin for which the recommended daily allowance is 2 mg orally in adults and 0.9 to 1.6 mg in children. This vitamin is included in most foods, particularly enriched breads, cereals, grain,

chicken, and fruits. Pyridoxine deficiency is uncommon but can occur with malnutrition or alcoholism and in infants from deficient mothers. Vitamin B_6 deficiency also occurs in patients receiving medications that are considered its antagonists, such as isoniazid, hydralazine, and D-penicillamine.

The active form of pyridoxine is pyridoxal phosphate, which is a coenzyme of amino acid metabolism, particularly methionine and tryptophan. Pyridoxal phosphate also is required in the production of niacin; thus, pyridoxine deficiency can produce a secondary deficiency of vitamin B_3. Pyridoxine also is involved in the synthesis of neurotransmitters such as GABA, dopamine, other catecholamines, and serotonin (Pingrade, 2008).

DIAGNOSIS AND EVALUATION

Vitamin B_6 deficiency produces a mixed symmetric sensorimotor PN characterized by numbness and pain and later atrophy and weakness. Distal reflexes are absent, and there is sensory loss to all modalities. Electrophysiologic studies demonstrate a predominantly axonal PN.

Pyridoxine levels can be measured in the plasma (normal levels are 5 to 30 ng/mL).

TREATMENT AND MANAGEMENT

The recommended daily dosage of vitamin B_6 is 100 to 450 mg/day, and this dosage should be used to prevent the development of neuropathy in patients receiving medications such as isoniazid. For prophylaxis in those at risk, the recommended dosage is 25 mg to 100 mg/day of the oral supplement.

An important consideration is that the usage of megadoses of pyridoxine as large as 2 g/day could produce a predominantly sensory ataxic PN (Albin & Albers, 1990), but this has also been reported in patients receiving lower dosages (Parry & Bredesen, 1985) or those who take high-energy drinks (Blackburn & Warren, 2017).

VITAMIN B_{12} (COBALAMIN)

Cobalamin is a compound that participates in the conversion of methylmalonic CoA from methylmalonic acid to form succinyl CoA, an important enzyme of the intermediate metabolism. It also participates in the synthesis of methionine from homocysteine and tetrahydrofolate from folic acid. Methionine and tetrahydrofolate are used in DNA synthesis and methylation reactions in the nervous system (Figs. 21.4 and 21.5).

Cobalamin is an essential vitamin that is not synthesized in the body and requires proper supplementation from meats and dairy products. Cobalamin is liberated in the stomach by the action of gastric acid, where it binds to haptocorrins (R-binders). It is liberated by tripsin in the duodenum, where it binds to an intrinsic factor produced by the parietal cells of the stomach; ultimately the vitamin is absorbed in the ileum (Table 21.3).

Vitamin B_{12} deficiency is caused by a lack of the intrinsic factor, as in pernicious anemia, gastric surgery, and excessive use of proton pump inhibitors. It also occurs in patients with pancreatic insufficiency and malabsorption or bacterial overgrowth and from deficiencies of transcobalamin II, a protein that binds cobalamin after absorption. Vitamin B_{12} deficiency also can be caused by chronic exposure to nitrous oxide because this inhibits the formation of methionine (Snow, 1999; Toh, 2017; Wang, Aamodt, & Barohn, 2008) (Box 21.5), treatment with metformin in diabetics (Ahmed, Muntingh, & Rheeder, 2016; Alvarez, Sierra, Saavedra, & Moreno, 2019), and from a congenital deficiency of transcobalamine II. Patients that undergo bariatric surgery could develop B_{12} deficiency (Murali, 2019).

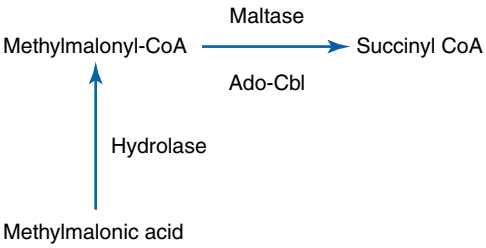


Fig. 21.4 Conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA. *Ado-Cbl,* Adenosyl cobalamin; *Cbl*, cobalamin. (Reprinted with permission from Snow, C. F. (1999). Laboratory diagnosis of vitamin B_{12} and folate deficiency. *Archives of Internal Medicine, 159*, 1289–1298.)

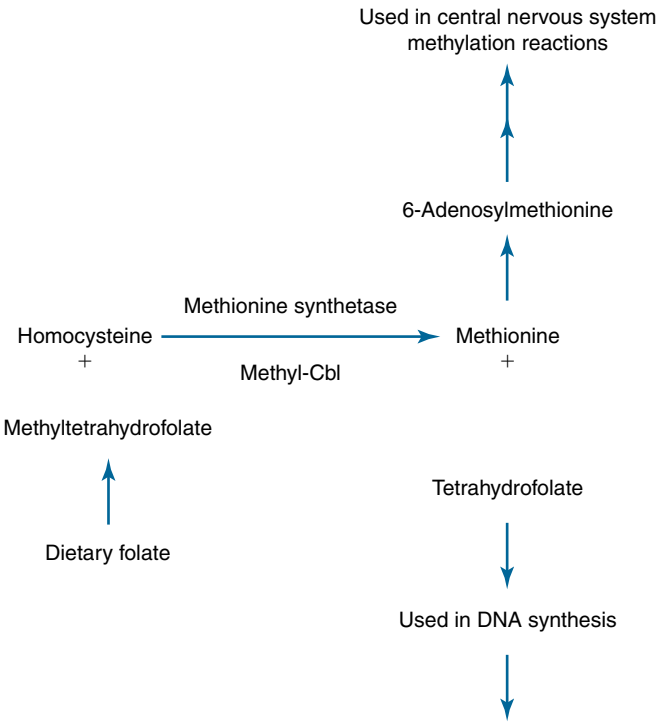


Fig. 21.5 Synthesis of methionine from homocysteine and methyl-cobalamin (Cbl). (Reprinted with permission from Snow, C. F. (1999). Laboratory diagnosis of vitamin B_{12} and folate deficiency. *Archives of Internal Medicine, 159*, 1289–1298.)

DIAGNOSIS AND EVALUATION

Patients with vitamin B_{12} deficiency present with numbness in the feet and hands, and there could be evidence of a distal predominantly sensory neuropathy (Cox-Klazinga & Endtz, 1980; Healton, Savage, Brust, Garrett, & Lindenbaum, 1991). Patients also may develop confusion, dementia, and combined degeneration of the spinal cord with

Table 21.3 Cobalamin Absorption and Transport

Step	Clinical Significance
In many foods, Cbl is bound to proteins. When food enters the stomach, acid facilitates the even release of Cbl. The presence of food also stimulates the secretion of IF, a glycoprotein produced by gastric parietal cells. However, in conditions of low pH, unbound Cbl preferentially attaches to salivary haptocorrin (formerly referred to as R-binder) rather than to IF.	If gastric production of acid is reduced, Cbl absorption from food may be impaired, even when IF is present. However, unbound Cbl supplemental vitamin preparations will still be absorbed normally. A decrease in serum Cbl levels has been demonstrated after 3 to 4 years of omeprazole therapy, and it has been suggested that serum Cbl levels be measured in patients undergoing prolonged treatment with proton pump inhibitors.
In the neutral pH of the duodenum, IF displaces the salivary haptocorrin with the aid of pancreatic enzymes.	Patients with pancreatic insufficiency may have reduced Cbl absorption, although they rarely become Cbl deficient.
The IF-Cbl complex passes through the small intestine and is taken up by receptor-mediated endocytosis in the terminal ileum.	Bacterial overgrown of fish tapeworm infestation may cause Cbl deficiency because of competition for Cbl in the intestine before the IF-Cbl complex reaches the terminal ileum.
Cbl is released from the complex and binds either to the TC II protein or to serum haptocorrins despite normal serum Cbl levels. In some patients with myeloproliferative disorders or liver disease, levels of serum haptocorrins may increase, leading to increases in the measured serum Cbl level.	Congenital TC II deficiency may cause megaloblastic anemia (formerly referred to as TC I and TC III). TC II, which accounts for only 10% to 30% of the measurable serum Cbl level, is the physiologically important transport protein.
An active enterohepatic circulation conserves the vitamin. Once Cbl reenters the gut in the bile, IF is again necessary for reabsorption.	Compared with patients with pernicious anemia, strict vegetarians (who produce IF normally) retain more Cbl from the enterohepatic circulation and therefore take much longer (10 to 20 years) to become Cbl deficient.

Reprinted with permission from Snow, C. D. (1999). Laboratory diagnosis of vitamin B12 and folate deficiency. *Archives of Internal Medicine, 159*, 1294.
Cbl, Cobalamin; *IF*, intrinsic factor; *TC*, transcobalamin.

Box 21.5 Causes of Cobalamin Deficiency

Malabsorption: pernicious anemia, gastrectomy or gastric bypass, protein-bound cobalamin malabsorption, ileal disease or resection, pancreatic insufficiency, abuse of nitrous oxide, drug induced (colchicine, neomycin, aspirin, or omeprazole), congenital absence, or dysfunction of intrinsic factor
Biologic competition for dietary cobalamin, bacterial overgrowth syndromes, fish tapeworm infestation
Dietary lack: strict vegetarians
Impaired utilization: congenital transcobalamin II deficiency

Modified with permission from Snow, C. F. (1999). Laboratory diagnosis of vitamin B_{12} and folate deficiency. *Archives of Internal Medicine*, 159, 1291.

Box 21.6 Causes of Misleading Serum Cobalamin Levels

Falsely Normal

Myeloproliferative disorders: polycythemia vera, chronic myelogenous leukemia, others
Liver disease
Antecedent administration of cobalamin

Falsely Low

Folate deficiency
Pregnancy
Use of oral contraceptives
Congenital deficiency of serum haptocorrins
Multiple myeloma

Modified with permission from Snow, C. F. (1999). Laboratory diagnosis of vitamin B_{12} and folate deficiency. *Archives of Internal Medicine*, 159, 1289–1298.

spasticity, hyperreflexia, and a positive Babinski sign. Some patients, however, are hyporeflexic (Victor & Lear, 1956).

MRI studies show lesions with an increased signal on T2-weighted images of the cervical cord. Somatosensory-evoked responses show abnormalities of conduction in the central sensory pathways (Fine, Soria, Paroski, Petryk, & Thomasula, 1990). EMG studies document the presence of a predominantly sensory neuropathy.

Blood tests show a macrocytic anemia with hypersegmented white cells; vitamin B_{12} levels should always be measured in patients with these findings. Because neurologic disorders can be seen in patients with "normal" vitamin B_{12} levels, homocysteine and methylmalonic acid should be measured; both are elevated in vitamin B_{12} deficiency. Misleading abnormal levels can be seen in several conditions (Box 21.6).

Although still useful, the Schilling test is not routinely done. When malabsorption is suspected, stage 3 of the test is useful. This stage of the test is repeated after antibiotic therapy (Table 21.4). Evaluation of the gastrointestinal tract and measurement of parietal cell antibodies can be valuable (Windebank, 1993). Those suspected of having a malabsorption syndrome should be evaluated for its causes, such as parasites in the stools.

TREATMENT AND MANAGEMENT

The treatment of vitamin B_{12} deficiency consists initially of replacement therapy with intramuscular injections of 1000 μg/week for 4 weeks and then 1000 μg monthly. Periodic monitoring every 3 to 6 months is recommended. Some

Table 21.4 Interpretation of Schilling Test Results in Cobalamin-Deficient Patients

Stage, Result	Possible Interpretations
1, Normal	Dietary deficiency, protein-bound Cbl malabsorption, hypochlorhydria, partial gastrectomy, congenital transcobalamin II deficiency
1, Abnormal 2, Normal	Pernicious anemia, previous gastrectomy or gastric bypass, congenital absence or dysfunction of intrinsic factor, inadequate urine collection in stage 1
1 and 2, Both abnormal	Ileal disease or resection, pernicious anemia with ileal dysfunction secondary to prolonged Cbl deficiency, pernicious anemia with inadequate urine collection in stage 2; renal insufficiency, inadequate urine collection in both stages 1 and 2; bacterial overgrowth syndromes, fish, tapeworm infestation, pancreatic insufficiency

Reprinted with permission from Snow, C. D. (1999). Laboratory diagnosis of vitamin B12 and folate deficiency. *Archives of Internal Medicine*, 159, 1294.
Cbl, Cobalamin.

nasal preparations are available and can be used to avoid intramuscular injections. Vitamin B_{12} supplementation should be given orally in vegetarians.

Patients should undergo physical therapy, rehabilitation, and management of the symptomatic neuropathy.

FOLIC ACID

Folic acid is an important vitamin used in nervous system metabolism in all age groups, and its deficiency has been associated with several congenital malformations, particularly in newborns from mothers who do not receive adequate amounts during pregnancy (Aurora & Suri, 2008).

There are various hereditary disorders of cobalamin and folic acid metabolism that can manifest with hematologic and nervous system disorders, such as hereditary folate absorption deficiency and dihydrofolate reductase deficiency, which is caused by homogenous mutation of the DHFR gene and presents with severe neurologic and hematologic deficits (Cario et al., 2011; Scaglia & Blair, 2013). In these cases, serum folate could be normal, but there is a reduction of methylenetetrahydrofolate in the spinal fluid. The condition is treated with folinic acid. This enzyme is a target of methotrexate, which inhibits pyrimidine and purine synthesis. Methylenetetrahydrofolate deficiency is another hereditary disorder of folate metabolism that can cause seizures, developmental delay, and cerebral abnormalities, and in adults could present with spastic paraparesis, neuropathy, and leukoencephalopathy; it is treated with betaine. These patients have high homocysteine levels.

Other folate metabolic disorders include methylenetetrahydrofolate formyltransferase and folate receptor deficiency. These are not discussed in detail.

Folic acid is present in foods such as leafy vegetables and fruits. The deficiency occurs in alcoholics, those with malabsorption syndromes, and those with vitamin B_{12} deficiency (Blomhoff et al., 1991; Hammond & Wang, 2008; Zak et al., 1991).

Deficiency of folic acid causes hyperhomocysteinemia, which could increase the risk of stroke and PN. Folic acid deficiency also may cause a combined degeneration of the spinal cord similar to that seen in pernicious anemia.

DIAGNOSIS AND EVALUATION

Folic acid deficiency should be suspected in patients with macrocytic anemia, depression, or dementia, particularly when vitamin B_{12} deficiency has been ruled out as a cause. Electrophysiologic tests, imaging, and somatosensory-evoked responses may be useful.

Normal serum folate levels are 2.5 to 20 μg/mL. Normal RBC folate levels are 40 mg or above. During evaluation, vitamin B_{12}, homocysteine, and methylmalonic acid should be measured because methylmalonic acid levels are elevated in vitamin B_{12} deficiency but usually are normal in folate deficiency.

TREATMENT AND MANAGEMENT

There are no clear guidelines on treatment, but patients should receive about 1 to 5 mg of folate a day to reverse the clinical manifestations and allow metabolic recovery.

VITAMIN D

The name "vitamin D" is applied to fat-soluble substances, called cholecalciferol or D_3 and calciferol or D_2 (what is called vitamin D_1 is in reality a mixture of substances with antirachitic activity). The principal provitamin is 7-dehydrocholesterol, which is converted to cholecalciferol by ultraviolet light and by a thermal reaction. This is then hydrolyzed in the liver to 25-hydroxy vitamin D; in the kidney, this forms 1,25-dihydroxy vitamin D, the biologically active form of the vitamin (Hammond & Wang, 2008), which is important in the metabolism of calcium and phosphorus. The clinical manifestations of vitamin D deficiency are related to its effects on bone and muscle. There is also a suggestion of a vitamin D role in autoimmunity (Guan et al., 2019; Murdaca et al., 2019), although the evidence is not conclusive (Yamamoto & Jørgensen, 2019).

DIAGNOSIS AND EVALUATION

Infants and children with vitamin D deficiency exhibit rickets, which may be associated with bone disease and hypotonia. Adults have characteristic osteomalatic bone disease accompanied by generalized weakness and muscle pain.

EMG studies may demonstrate the presence of a sensorimotor PN, but myopathic motor unit action potentials may be seen on needle EMG. Muscle biopsy shows type II muscle fiber atrophy.

TREATMENT AND MANAGEMENT

Vitamin D supplementation is necessary in patients at risk, such as those with fat malabsorption, decreased fat

absorption, or kidney disease; those receiving certain medications; and those with decreased exposure to sunlight. Levels should be maintained between 30 and 50 mg/mL, and oral supplements of vitamin D_2 should be given in the form of 50,000 units weekly with close monitoring of levels. Patients should be reevaluated after 8 weeks and periodically thereafter.

VITAMIN E

Vitamin E is a fat-soluble vitamin present in vegetable oils and wheat. It is absorbed in the intestine in the form of alpha-tocopherol, which is converted in the liver to the active form of the vitamin. The daily allowance is 15 mg, increasing to 19 mg during lactation (Evans & Burr, 1928).

Vitamin E is an antioxidant and free-radical scavenger, and its deficiency is seen particularly in patients with malabsorption, those receiving parenteral nutrition, and in children with cystic fibrosis, causing a neuropathy and encephalopathy (Wysota, Michael, Hiew, Dawson, & Rajabally, 2017), but it also can occur in some genetic disorders, particularly in the autosomal recessive disease caused by mutation of the *aTTP* gene on chromosome 8q13 (Jackson, Amato, & Barohn, 1996).

The neurologic manifestations of vitamin E deficiency are related to its antioxidant and free-radical scavenger functions.

DIAGNOSIS AND EVALUATION

Patients with vitamin E deficiency usually have weakness, ataxia, dysarthria, and areflexia and may exhibit a myelopathy similar to Friedreich ataxia, with retinitis pigmentosa and cardiomyopathy (Hammond & Wang, 2008; Sokol, 1990; Wysota et al., 2017).

Alpha-tocopherol can be measured in serum, and normal levels are 5 μg/mL or greater in adults. In children older than age 12 years, normal levels are 3 to 4 μg/mL. Because vitamin E may appear normal in hyperlipemic states, the ratio of vitamin E to total lipids should be measured in those patients. The normal ratio in children is 0.6 mg/g and in adults is 0.8 mg/g or less (Hammond & Wang, 2008).

Electrophysiologic studies document a predominantly sensory neuropathy. The assessment also may require somatosensory-evoked responses and MRI of the cervical spine and brain to rule out other causes.

TREATMENT AND MANAGEMENT

Vitamin E replacement may halt the progression of neurologic symptoms when used in dosages of 1 to 4 g/day of oral supplementation. In children with cystic fibrosis, it should be given orally in a dosage of 5 to 10 mg/kg. This is adjusted according to alpha-tocopherol levels.

COPPER

Copper is a trace mineral that is incorporated in many enzymes in the body, such as ceruloplasmin and superoxide dismutase. Its deficiency can be associated with abnormalities of mitochondrial function and oxidative metabolism.

The dietary requirements for copper are low because this metal is commonly found in nature; a deficiency, however, can occur in patients who undergo gastric surgery or have malabsorption syndromes (Cavallieri et al., 2017; Kumar et al., 2016). Copper is absorbed in the stomach and the proximal bowel, and this absorption is impaired by excessive intake of zinc, iron, phosphate, and calcium. Vitamin C can also reduce copper from its cupric state to its less bioavailable cuprous state. In some cases, the exact cause of copper deficiency is unknown (Kumar, 2006).

Those with copper deficiency may develop ataxic syndrome and have manifestations of combined degeneration of the spinal cord similar to those in patients with vitamin B_{12} deficiency (Kumar, Crum, Petersen, Vernino, & Ahlskog, 2004; Kumar, Gross, & Ahlskog, 2003). They also may develop neuropathy or PN. Swayback is a neurologic dysfunction seen in copper-deficient animals, particularly rodents, in which pathologic studies demonstrate prominent demyelination and axonal degeneration (Kumar, 2006).

DIAGNOSIS AND EVALUATION

Patients present with gait difficulty and have paresthesia with clinical evidence of sensory ataxia, spasticity, and hyperreflexia with Babinski signs or hyporeflexia (Kumar et al., 2003).

Copper levels and particularly zinc levels should be measured; zinc levels have been found to be elevated in copper deficiency, sometimes even in patients not receiving zinc supplements (Summerfield, Steinberg, & Gonzalez, 1991; Willis et al., 2005).

Somatosensory-evoked responses document conduction abnormalities of the spinal cord, and MRI shows lesions of the posterior columns in T2-weighted images.

EMG studies demonstrate the presence of a predominantly sensory neuropathy (Chai & Bertorini, 2010; Crum & Kumar, 2005).

TREATMENT AND MANAGEMENT

The initial treatment consists of 6 mg/day in three divided doses for a week, tapered to 4 mg/day for another week, and then maintained at 2 mg/day with proper frequent monitoring (Kumar, 2006). Removal of the cause, such as excessive intake of zinc, is important. Patients should receive physical therapy and gait training when necessary.

STRACHAN SYNDROME

This syndrome, which is likely caused by multiple vitamin deficiencies, was described initially in Jamaican sugar cane workers who presented with a sensorimotor PN that was called *peripheral neuritis of Jamaica*. The neuropathy is accompanied by other neurologic dysfunctions and optic neuropathy (Strachan, 1888, 1897). The same disorder apparently occurred in Canadian prisoners of war during World War II (Fisher, 1955; Scott, 1918) and more recently in Cuba when patients developed myeloneuropathy and optic neuropathy (Borrajero et al., 1994).

DIAGNOSIS AND EVALUATION

The most common manifestation is a peripheral and sensory motor PN with visual loss from central or cecocentral scotomas, gingival lesions, and sensory nerve hearing loss.

The diagnosis is made by the neurologic manifestations, which are usually accompanied by other signs of malnutrition, although they might not be present. Measurements of

vitamins, particularly the B vitamins, folate, and vitamin B_{12}, are important.

Nerve conduction tests and visual evoked responses are useful.

TREATMENT AND MANAGEMENT

Treatment consists of supplementation of all deficient vitamins, particularly the B group, and proper nutrition with adequate caloric and protein intake, which could reverse the neurologic symptoms.

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22 Treatment and Management of Autoimmune Myopathies

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The autoimmune inflammatory myopathies comprise five major and distinct subsets: *polymyositis* (PM), *dermatomyositis* (DM), *necrotizing autoimmune myositis (NAM), overlap myositis and antisynthetase syndromes* (OM-AS), and *inclusion body myositis* (IBM) (Dalakas, 2015). Although moderate to severe muscle weakness, endomysial inflammation, and variable creatine kinase (CK) elevation are common features in all these conditions, unique clinical, immunopathologic, and histologic criteria characterize each subset (Callen, 2000; Dalakas, 1991, 1995, 2004a, 2015; Dalakas & Hohlfeld, 2003a, 2003b; Dalakas & Karpati, 2010; Engel & Hohlfeld, 2004; Mastaglia, 2005; Mastaglia & Phillips, 2002; Stenzel et al., 2015). Fasciitis, another autoimmune condition in which the pathologic picture consists of inflammation of the fascia and perimysium, is also briefly described as it may coexist or overlap with some of these myositis subsets, especially the antisynthetase syndromes (Stenzel et al., 2015).

DERMATOMYOSITIS

DM occurs in both children and adults. It is a distinct clinical entity because of a characteristic rash that accompanies or, more often, precedes muscle weakness. The skin manifestations include a heliotrope rash (blue-purple discoloration) with edema on the upper eyelids, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron rash) (Fig. 22.1) (Callen, 2000; Dalakas, 1991, 2015; Dalakas & Hohlfeld, 2003b). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a V sign), and back and shoulders (shawl sign), and may be exacerbated after exposure to the sun. The initial erythematous lesions may result in scaling of the skin, accompanied by pigmentation and depigmentation, giving a shiny appearance at times. Dilated capillary loops at the base of the fingernails are also characteristic of DM. 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." DM in children resembles the adult disease. An early abnormality in children is "misery," defined as an irritable child who feels uncomfortable, has a red flush on the face, is fatigued, does not feel like socializing, and has varying degrees of muscle weakness (Dalakas & Hohlfeld, 2003b). A tiptoe gait due to flexion contracture of the ankles is not unusual. In DM, the affected muscles are predominantly proximal, but the degree of weakness varies. It can be mild, moderate, or severe, leading to quadriparesis. In advanced cases, atrophy of the affected muscles takes place. Ocular and facial muscles remain normal even in advanced cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be in doubt. The pharyngeal and neck extensor muscles can be involved, causing dysphagia and difficulty holding up the head. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles. The respiratory muscles are rarely affected, but respiratory symptoms may not be uncommon due to interstitial lung disease. Myalgia and muscle tenderness may occur early in the disease, especially when DM occurs in the setting of a connective tissue disorder. In patients with DM who have severe muscle pain, involvement of the fascia should be suspected.

Some patients with the classic skin lesions may have clinically normal strength, even 3 to 5 years after onset. This form of DM, referred to as *dermatomyositis sine myositis* or *amyopathic dermatomyositis* (Callen, 2000), has a better overall prognosis. Although in these cases the disease appears limited to the skin, the muscle biopsy shows significant perivascular and perimysial inflammation with immunopathologic features identical to those seen in classic DM, suggesting that the amyopathic and myopathic forms are part of the range of DM affecting skin and muscle to varying degrees (Dalakas, 2015; Dalakas & Hohlfeld, 2003b).

DM usually occurs alone, but it may overlap with scleroderma and mixed connective tissue disease. Fasciitis and skin changes similar to those found in DM have occurred in patients with eosinophilia-myalgia syndrome caused by the ingestion of contaminated L-tryptophan and in patients with eosinophilic fasciitis or macrophagic myofasciitis. In up to 15% of adult patients, the DM has a paraneoplastic association. Ovarian cancer is most frequent, followed by intestinal, breast, lung, and liver cancer. In Asian populations, nasopharyngeal cancer is more common (Callen, 2000). Because tumors are often uncovered at autopsy or on the basis of abnormal findings on medical history and physical examination, blind radiologic searches are rarely fruitful. A complete annual physical examination with breast, pelvic, and rectal examinations (including colonoscopy in high-risk patients); urinalysis; complete blood cell count; blood chemistry tests; and chest radiograph is usually sufficient and is highly recommended, especially for the first 3 years.

Extramuscular manifestations may also be prominent in some patients with DM and include (1) dysphagia; (2) subcutaneous calcifications (Fig. 22.2), sometimes opening onto the skin and causing ulcerations and infections, especially in children (Dalakas & Hohlfeld, 2003b); (3) contractures of the joints, especially in the childhood form; (4) pulmonary involvement due to interstitial lung disease, especially in patients who have anti-Jo-1 antibodies, as discussed later; (5) gastrointestinal ulcerations, due to vasculitis or infections; (6) general systemic disturbances, such as



Fig. 22.1 The characteristic Gottron rash seen in a patient with dermatomyositis.



Fig. 22.2 Subcutaneous calcifications in the elbow of a patient with dermatomyositis.

fever, malaise, weight loss, and arthralgia; and (7) Raynaud phenomenon, especially when DM is associated with a connective tissue disorder.

POLYMYOSITIS

PM has no unique clinical features, and it is often a diagnosis of exclusion (Dalakas, 1991, 2015; Dalakas & Hohlfeld, 2003b; Dalakas & Karpati, 2010; Mastaglia, 2005). PM is a rare disorder that, by all accounts, is the most overdiagnosed acquired myopathy. The study of PM requires a scholarly review of the neurologic examination, muscle histopathology, immunopathology, and biochemistry to ensure that toxic, metabolic, or mitochondrial muscle diseases are not missed and that two more common entities, the IBM and the NAM, are not overlooked (Dalakas, 2015). If all other myopathies are carefully excluded, PM may not even exist today as a distinct entity (Dalakas,2020). For historical reasons, PM is best defined as an inflammatory myopathy of subacute onset (weeks to months) and steady progression that occurs in adults who do not have rash on the face, trunk, or fingers, as seen in DM; involvement of eye and facial muscles; family history of a neuromuscular disease; endocrinopathy; history of exposure to myotoxic drugs or toxins; and another myopathy such as dystrophy, metabolic myopathy, or IBM. Unlike DM, in which the rash secures early recognition, the actual onset of PM cannot be easily determined and the disease may exist for several months before the patient seeks medical advice.

Patients with PM commonly present with proximal and often symmetrical muscle weakness that develops over weeks to months, and rarely acutely. An acute onset should raise the suspicion of a necrotizing myopathy. Fine-motor movements that depend on the strength of distal muscles are affected only late in the disease. If these muscles are affected from the outset or early in the course of the disease, the diagnosis of IBM should be suspected. In advanced cases, atrophy of the affected muscles takes place. Ocular muscles remain normal even in advanced cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be in doubt. In contrast with IBM, in which the facial muscles are affected in the majority of patients, in PM, the strength of the facial muscles remains normal except in rare advanced cases. The pharyngeal and neck extensor muscles can be involved, causing dysphagia and difficulty holding up the head. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles. The respiratory muscles are rarely affected, but respiratory symptoms are not uncommon owing to interstitial lung disease, especially in patients with anti-Jo-1 antibodies or antibodies to various ribonucleoproteins (Dalakas, 1991, 2009; Dalakas & Hohlfeld, 2003b; Dalakas & Karpati, 2010; Mastaglia, 2005). Although myalgia may occur early in the disease, most often, in the setting of a coexisting connective tissue disorder, severe muscle pain should raise the suspicion of fasciitis even if there are no overt signs of skin induration and thickness.

PM is extremely rare in childhood, and if a diagnosis is made in patients younger than 16 years, a careful review is needed to exclude another disease, especially one of the inflammatory dystrophies.

PM appears to be a syndrome of diverse causes. As a standalone clinical entity, it may not probably exist based on recent evidence (Dalakas, 2020). It is more frequently seen in association with connective tissue disorders, systemic autoimmune diseases, or viral infections, such as Sjögren syndrome, rheumatoid arthritis, Crohn disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet disease, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto disease, granulomatous diseases, agammaglobulinemia, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, immunoglobulin A deficiency, and acquired immunodeficiency syndrome (AIDS). Among viruses, human immunodeficiency virus (HIV) and human T-lymphotrophic virus type I (HTLV-I) are the only viruses convincingly associated with PM. Claims that other viruses, such as enteroviruses, can be causally connected with PM are unproved. In contrast to DM, PM is not more frequently associated with cancer compared to other chronic autoimmune disorders treated with immunosuppressants.

Several animal parasites, such as protozoa (*Toxoplasma, Trypanosoma*), cestodes (*cysticerci*), and nematodes (*trichinae*), may produce a focal or diffuse inflammatory myopathy known as "parasitic polymyositis" (Dalakas, 1991). In the tropics, a suppurative myositis known as "tropical polymyositis" or "pyomyositis" may be produced by *Staphylococcus*

aureus, *Yersinia*, *Streptococcus*, or other anaerobes. Pyomyositis, previously rare in the West, can now be seen in patients with AIDS. Certain bacteria, such as *Borrelia burgdorferi* of Lyme disease and *Legionella pneumophila* of legionnaires' disease may infrequently be the cause of PM.

Drugs do not cause PM. The only drug that could change immunoregulation and trigger PM is D-penicillamine (Dalakas, 1992, 2009). Zidovudine and the cholesterol-lowering drugs can be myototoxic, but they cause a mitochondrial or a necrotizing myopathy that lacks the features of primary T-cell-mediated endomysial inflammation as seen in PM. In these cases, the muscle fibers demonstrate prominent mitochondrial or necrotic features with macrophages.

NECROTIZING AUTOIMMUNE MYOSITIS (ALSO REFERRED TO AS IMMUNE-MEDIATED NECROTIZING MYOPATHY)

NAM is turning out to be the most common subset among all the inflammatory muscle diseases, if IBM is excluded, based on the number of cases identified each year in busy referred clinics and reported in large series; accordingly, it should not be missed because it is potentially treatable if identified early (Dalakas, 2015, 2018a; Watanabe et al., 2016). However, NAM still remains an overlooked entity, often misdiagnosed as PM. The patients present with high CK, in the thousands; moderate to severe muscle weakness of acute or subacute onset; and histological features of muscle fiber necrosis mediated by macrophages as the main effector cell (Dalakas, 2015, 2018a; Watanabe et al., 2016). There are no T-cell infiltrates or ubiquitous major histocompatibility complex class I (MHC-I) expression as seen in PM and IBM, but the MHC-I expression is spotty. Up to 65% of these patients have antibodies against signal recognition particles (SRPs) or against a 100-kd autoantigen identified as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) (Dalakas, 2015, 2018a; Watanabe et al., 2016).

ANTISYNTHETASE SYNDROME" OR "OVERLAP MYOSITIS" OR "ANTI-JO-1 SYNDROME"

Anti-Jo-1 antibodies, directed against the histidyl-transfer RNA synthetase, the most common among the antisynthetases, define the "antisynthetase" or "overlap myositis" syndrome, which has now evolved into a distinct entity. It is characterized by (a) myositis with prominent pathologic changes at the periphery of the fascicles and the perimysial connective tissue in the form of necrotizing perimysial and perifascicular myositis with actin myonuclear inclusions (Dalakas, 2015, 2018a, 2020; Mescam-Mancini et al., 2015; Stenzel et al., 2015; Watanabe et al., 2016); (b) interstitial lung disease; (c) arthritis; (d) Raynaud phenomenon; (e) fever; and (f) mechanic's hands. The association of this clinicopathological phenotype with anti-Jo-1 antibodies appears strong in defining this distinct myositis subset, even if the Jo-1 antibodies are not pathogenic (Dalakas, 2015, 2018a; Mescam-Mancini et al., 2015; Stenzel et al., 2015; Watanabe et al., 2016).

INCLUSION BODY MYOSITIS

IBM is the most common of the inflammatory myopathies. It affects men more often than women and is the most commonly acquired myopathy in men older than 50 years. Although IBM may be suspected when a patient with presumed PM does not respond to therapy, involvement of distal muscles, especially foot extensors and deep finger flexors in almost all cases (Fig. 22.3), should be a clue to an early clinical diagnosis (Carpenter, 1996; Dalakas, 1991, 2006a, 2015; Engel & Arahata, 1984; Griggs et al., 1995; Hohlfeld, Goebels, & Engel, 1993; Karpati, 1997; Karpati & Carpenter, 1993; Needham & Mastaglia, 2007; Sekul & Dalakas, 1993). Some patients present with falls because their knees collapse owing to early weakness of the quadriceps muscles. Others present with weakness in the small muscles of the hands, especially the long finger flexors, and complain of inability to hold certain objects such as golf clubs, play the guitar, turn a key, or tie a knot. The weakness and the accompanying atrophy can be asymmetrical, with preferential involvement of the quadriceps (Fig. 22.3A–C), iliopsoas, triceps, biceps, and finger flexors in the forearm. This involvement is in contrast to the hereditary or familial quadriceps-sparing IBM (Argov & Yarom, 1984; Sivakumar & Dalakas, 1996, 1997), in which the quadriceps remains strong in spite of the weakness in the other muscles. The selective involvement of the flexor digitorum profundus has been confirmed with magnetic resonance imaging (Sekul, Chow, & Dalakas, 1997). Dysphagia is quite common, occurring in up to 60% of the patients, especially late in the disease. Because of the distal and at times asymmetrical weakness and atrophy and the early loss of the patellar reflex, a lower motor neuron disease is occasionally suspected, especially since serum CK activity is either not elevated or only moderately increased (Dalakas, 1991). Sensory examination is generally normal except for a mildly diminished vibratory sensation at the ankles, presumably related to the patient's age. Contrary to early suggestions, the distal weakness does not represent neurogenic involvement but is part of the distal myopathic process, as confirmed with macro-electromyography (EMG) (Luciano & Dalakas, 1997). In contrast to PM and DM, in which facial muscles are spared, mild facial muscle weakness is very common and is noted in more than 60% of IBM patients (Sekul & Dalakas, 1993).

Sporadic IBM (s-IBM) can be associated with systemic autoimmune or connective tissue diseases in up to 33% of affected patients (Badrising et al., 2004; Koffman, Rugiero, & Dalakas, 1998). An increased frequency of DRb10301 and DQb10201 alleles associated with DR and DQ phenotypes has been documented in up to 75% of patients (Koffman, Sivakumar, Simonis, Stroncek, & Dalakas, 1998). A frequent association with HLA-B8-DR3 haplotype has been also observed (Badrising et al., 2004). Familial aggregation of IBM with the typical clinical phenotype of s-IBM, and with histologic and immunopathologic features identical to the sporadic form, can also occur, as seen in other autoimmune disorders (Sivakumar, Semino-Mora, & Dalakas, 1997). Our group has designated this as *familial inflammatory IBM* and emphasized that it should be distinguished from hereditary inclusion body myopathy (h-IBM), a noninflammatory vacuolar myopathy that spares the quadriceps (Argov et al.,

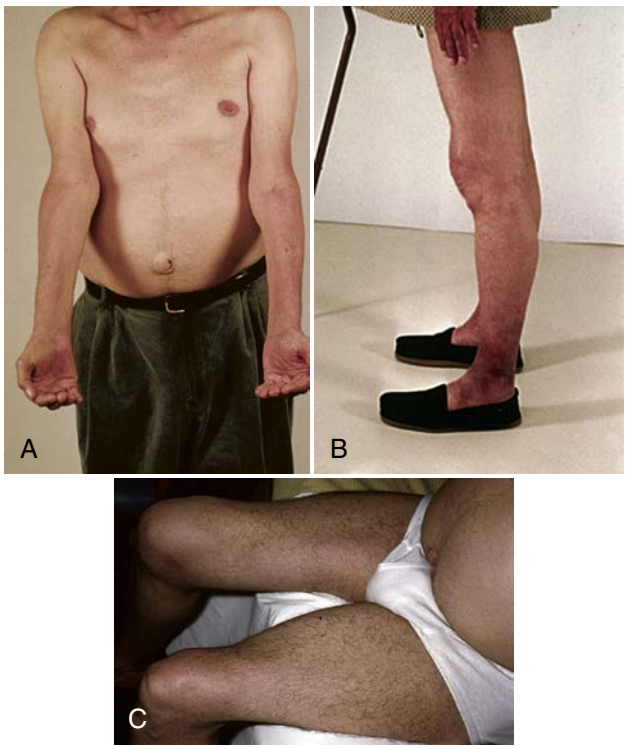


Fig. 22.3 Notice the following in a patient with inclusion body myositis: wasting of the forearm muscles with difficulty making a grip (A), quadriceps atrophy (B, C), and "locking up" of the knee to avoid falls (B).

1997; Sivakumar & Dalakas, 1996) and occurs mostly in Iranian Jews but also in other ethnic groups (Argov et al., 1997; Sivakumar & Dalakas, 1996). This disorder results from mutations in the uridine diphosphate-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (*GNE*) gene (Rosenbaum & Silverberg, 2004).

Progression of s-IBM is slow but steady. Data from 86 patients studied consecutively by the author's group revealed that progression is faster when the disease begins later in life. Patients whose disease began in their 60s required an assistive device many years later compared with those whose disease began in their 70s, presumably because of lesser reserves (Peng, Koffman, Malley, & Dalakas, 2000).

EOSINOPHILIC SYNDROMES AND FASCIITIS

Prominent presence of eosinophilic polymorphonuclear leukocytes in muscle (or fascia) can occur in isolation or with systemic eosinophilia and is due to parasitic infection, vasculitis, hypereosinophilic syndrome, or toxic factors. In eosinophilic PM (Lakhanpal, Duffy, & Engel, 1988; Layzer, Shearn, & Satya-Murti, 1977), muscle involvement is part of a systemic hypereosinophilic syndrome. A marked systemic eosinophilia is present. Proximal limb muscles show stiffness, pain, and variable weakness. An important feature is thickening of the skin, mimicking scleroderma (Dalakas, 2015). Serum CK activity is moderately elevated. The pathologic picture is similar to that of idiopathic PM, except that there is a conspicuous presence of eosinophilic polymorphonuclear leukocytes in the inflammatory infiltrates. Certain patients with genetically defined calpain-gene mutations were reported to have eosinophilic infiltrates in their muscle (Krahn et al., 2006). The frequency of this phenomenon and the role of eosinophils in myopathy remain unclear.

In eosinophilic fasciitis, the inflammatory reaction is restricted to the fascia and is best shown by a biopsy of the fascia lata. Eosinophilia-myalgia syndrome was also described in patients after prolonged oral intake of large doses of a contaminated L-tryptophan preparation taken as a therapeutic over-the-counter agent (Hertzman et al., 1990). There was marked systemic eosinophilia with generalized myalgia and moderate muscle weakness (Hertzman et al., 1990). The lymphocytic inflammatory infiltrates (CD8+ cytotoxic cells) also included either abundant or few eosinophilic polymorphonuclear leukocytes, mainly in the perimysial region and less often in the interstitial space of muscle (Illa, Dinsmore, & Dalakas, 1993; Seidman et al., 1991). Coexisting peripheral neuropathy was also noted. The pathogenic factor was a contamination of L-tryptophan with an acetaldehyde ditryptophan derivative, which seems to induce autosensitization. A distinctive inflammatory myofasciitis was also identified in up to 80 French patients who presented with myalgias, fatigue, and mild muscle weakness (Gherardi et al., 1998). Muscle biopsy revealed pronounced infiltration of the connective tissue around the muscle (epimysium, perimysium, and perifascicular endomysium) by sheets of periodic acid–Schiff base-positive macrophages and occasional CD8+ T cells. The serum CK or erythrocyte sedimentation rate may at times be elevated. Most patients respond to glucocorticoid therapy, and the overall prognosis is favorable. The pathologic change is almost always seen at the sites of previous vaccinations, even several months later, and has been linked to a type of aluminum component used as a substrate for preparation of the vaccines. Macrophagic myofasciitis has been reported exclusively from France.

DIAGNOSIS AND EVALUATION

The diagnosis of these disorders is based on the combination of clinical history, serum muscle enzymes, EMG, and muscle biopsy. The CK is elevated in all three subsets, but it can be normal or only slightly elevated in DM and IBM. The EMG is myopathic in all three and, although useful to exclude neurogenic disorders, it is insensitive to differentiate an inflammatory myopathy from other toxic or dystrophic myopathic processes. The muscle biopsy shows inflammatory features distinct for each subset and remains the most sensitive diagnostic tool. In DM, the inflammation is perivascular or at the periphery of the fascicle and is often associated with perifascicular atrophy (Fig. 22.4); in PM and IBM, the inflammation is in multiple foci within the endomysial parenchyma (Fig. 22.5) and consists predominantly of CD8+ T cells that invade healthy muscle fibers expressing the MHC-I antigen (Karpati, Pouliot, & Carpenter, 1988). The MHC/CD8 complex is characteristic and useful for the diagnosis of PM and IBM (Dalakas, 1991; Dalakas & Hohlfeld, 2003a, 2003b). Plasma cells and dendritic cells are frequent among the infiltrates in all three disorders (Greenberg,

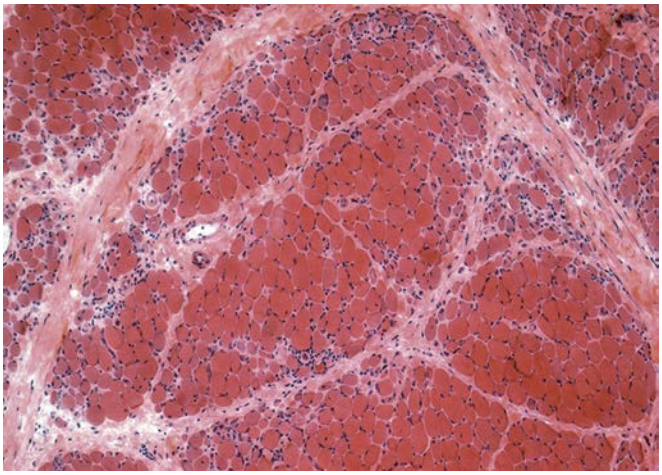


Fig. 22.4 Muscle biopsy in a patient with dermatomyositis shows the characteristic perifascicular muscle atrophy and necrosis (hematoxylin and eosin stain ×100).

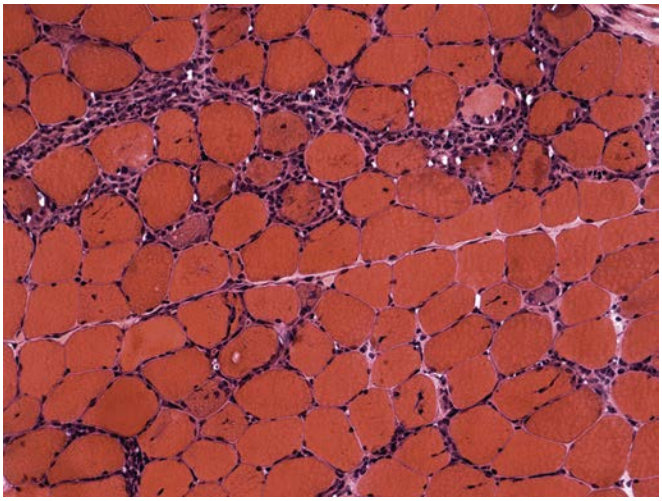


Fig. 22.5 Interstitial inflammation in polymyositis and some regenerating muscle fibers (hematoxylin and eosin stain ×200.)

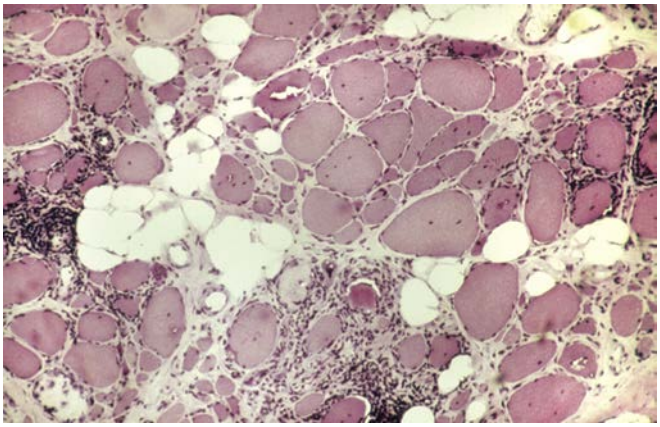


Fig. 22.6 Muscle biopsy of a patient with inclusion body myositis. Notice fiber atrophy, internalized nuclei, interstitial inflammatory infiltrates, and rimmed vacuoles. There is also increased endomysial connective tissue and fat (hematoxylin and eosin stain ×200).

2007). An additional feature in IBM is the presence of vacuoles containing 12- to 16-nm tubulofilaments with tiny deposits of amyloid and amyloid-related proteins (Fig. 22.6) (Askanas & Engel, 1998; Mendell, Sahenk, Gales, & Paul, 1991). In IBM, the presence of 15- to 18-nm tubular filamentous masses in nuclei or cytoplasm of muscle fibers can be demonstrated with extensive ultrastructural scrutiny (Lotz, Engel, Nishino, Stevens, & Litchy, 1989). These filamentous masses are not disease specific but have been reported to be identical to the paired helical filaments found in neurons in Alzheimer disease (Askanas, Engel, Bilak, Alvarez, & Selkoe, 1994). The blue granules, located in or along the wall of the vacuoles, correspond to whorls of cytomembranes or myelin figures, detectable by electron microscopy (Dalakas & Karpati, 2010). Most important, congophilic material, best visualized by Texas-red fluorescent optics, can be found in a variable number of fibers usually in or near rimmed vacuoles (Askanas, Engel, & Alvarez, 1993; Askanas, Engel, Alvarez, & Glenner, 1992; Askanas, Serdaroglu, Engel, & Alvarez, 1992). Other degeneration-associated molecules such as beta-amyloid and its precursor protein, alpha-chymotrypsin, tau proteins, ubiquitin, apolipoprotein E, prion protein, and others are also found in a small percentage of fibers (Askanas & Engel, 2006; Mendell et al., 1991). Although they help toward confirming the histologic diagnosis of IBM, they are not specific because they have been found in other myopathies (De Bleecker, Ertl, & Engel, 1996) or even in chronic neurogenic conditions such as the postpolio syndrome (Semino-Mora & Dalakas, 1998). In IBM, the beta-amyloid appears targeted for lysosomal degradation via macroautophagy, as specific studies indicate (Lünemann et al., 2007). Ragged red, cytochrome oxidase–negative muscle fibers with mitochondrial excess and multiple mitochondrial DNA deletions have been demonstrated in most examined cases (Horvath et al., 1998). Uniform expression of class I MHC products at the surface of most muscle fibers is characteristic of PM, IBM, and, in most cases, NAM, whereas in DM, this phenomenon may be evident only in the perifascicular or other random regions (Emslie-Smith, Arahata, & Engel, 1989; Karpati et al., 1988). Ubiquitous expression of MHC-I does not occur in limb girdle dystrophy, denervating diseases, or metabolic myopathies (except in regenerating fibers or in fiber invaded by macrophages and lymphoid cells), which makes MHC immunostaining a very helpful diagnostic tool for PM, NAM, and IBM (Dalakas, 2006b).

CAUSES OF MISDIAGNOSIS

A relatively common erroneous practice that has an impact on investigative and therapeutic decisions is the failure to distinguish IBM and NAM from PM and from "inflammatory dystrophies" (muscular dystrophies with prominent inflammation seen on histologic examination) (Kissel, Burrow, & Rammohan, 1991). The most common cause of a clinical misdiagnosis is an erroneous pathologic interpretation of the biopsy based on the following errors (Dalakas, 2010a; Dalakas & Karpati, 2010):

1. Failure to distinguish the muscle fiber necrosis due to invasion of muscle fibers by cytotoxic lymphocytes, as seen in PM and IBM, from the invasion of muscle fibers by macrophages, as seen in inflammatory dystrophies. In some of these dystrophies (i.e., Duchenne muscular dystrophy, dysferlinopathy, calpainopathy, merosin-deficient

sarcoglycanopathy), endomysial infiltration by lymphocytes may also occur, but these cells lack the MHC/CD8 complex typical of PM and IBM, as discussed later (Dalakas, 2010a).

2. Failure to recognize that NAM is a common myositis and differs from inflammatory dystrophies because of acute or subacute onset and the presence of autoantibodies seen in up to 65% of the patients (Dalakas, 2015, 2020; Watanabe et al., 2016).
3. Failure to recognize that the pathologic involvement may be spotty and a given biopsy may not contain convincing pathologic changes ("skip areas") requiring repeat biopsy.
4. Being unaware that in DM, changes typical of perifascicular atrophy are diagnostic, even if there is the lack of inflammatory cell infiltrates.
5. Failure to recognize that up to 15% of biopsies from patients with typical clinical features of IBM demonstrate inflammation like that seen in PM but without the classic vacuoles. These patients have been labeled as having PM/IBM (Chahin & Engel, 2008). A careful view of these biopsies, however, shows a large number of COX-negative fibers and signs of chronicity (large fibers, splitting, increased connective tissue) that denote probable IBM (Dalakas, 2006b).

These errors can be avoided by a combined evaluation of the clinical picture with the histologic and immunopathologic findings (Chahin & Engel, 2008).

IMMUNOPATHOLOGY

The cause of PM, DM, and IBM is unknown, but an autoimmune pathogenesis is strongly implicated.

IMMUNOPATHOLOGY OF DERMATOMYOSITIS

In DM, there is evidence of a complement-mediated process based on immunopathologic studies performed on muscle biopsy specimens. The primary antigenic targets appear to be components of the endothelium of the blood vessels in the endomysium and probably the skin. Alterations in the endothelial cells consisting of pale and swollen cytoplasm with microvacuoles and tubuloreticular aggregates appear early in the disease. These changes are caused by immune complexes immunolocalized in the endomysial blood vessels along with the C5b-9 membranolytic attack complex, the lytic component of the complement pathway. The membranolytic attack complex and the early complement components C3b and C4b are deposited on the capillaries early in the disease and precede the signs of inflammation or structural changes in the muscle fibers (Dalakas, 1991, 2015; Dalakas & Hohlfeld, 2003b; Engel & Hohlfeld, 2004; Kissel et al., 1991). These complement fragments are also detected in the serum and correlate with disease activity. The disease probably begins when putative antibodies or other factors activate complement C3, C3b, and C4b fragments that lead to the formation of membranolytic attack complex, which is deposited in the endomysial microvasculature and leads to osmotic lysis of the endothelial cells and capillary necrosis (Dalakas, 1991, 2015; Dalakas & Hohlfeld, 2003b; Dalakas & Karpati, 2010; Engel & Hohlfeld, 2004). As a result, there is reduction in the number of capillaries per muscle fiber, impaired perfusion, and dilatation of the loop of the remaining capillaries in an effort to compensate for the ischemic process. Larger intramuscular blood vessels are also affected in the same pattern, leading to muscle fiber destruction (often resembling microinfarcts) and inflammation. The perifascicular atrophy often seen in more chronic stages is probably a reflection of the endofascicular hypoperfusion that is prominent distally.

The activation of complement induces the release of cytokines and chemokines such as interleukins (IL-1, IL-6) and tumor necrosis factor (TNF), which, in turn, upregulate the expression of VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) on the endothelial cells and facilitate the transmigration of activated T cells to the perimysial and endomysial spaces. Immunophenotypic analysis of the lymphocytic infiltrates demonstrates B cells, CD4+ cells, and plasmacytoid dendritic cells in the perimysial and perivascular regions, supporting the view that a humoral-mediated mechanism plays the major role in the disease. In the perifascicular regions, there is also upregulation of various molecules such as cathepsins and signal transduction and activation of transducer molecules, probably triggered by interferon-γ, TGF-β (transforming growth factor-beta), and myxovirus resistance protein MxA induced by α/β interferon, which is probably secreted by the large number of plasmacytoid dendritic cells (Greenberg, 2007). Based on gene arrays, a number of adhesion molecules, cytokines, and chemokine genes are also upregulated in the muscles of DM patients. Most notable among those genes are the X-linked Kallmann syndrome-1 protein (KAL-1) adhesion molecule (Raju & Dalakas, 2005) and genes induced by α/β interferon (Greenberg, 2007). KAL-1 is upregulated by TGF-β and may have a deleterious role in DM by inducing fibrosis. Of interest, KAL-1, along with TGF-β, is downregulated in the muscles of DM patients who improved after therapy, and it is most clinically relevant (Dalakas, 2010b). A summary of the immunopathology of DM is shown in Fig. 22.7.

IMMUNOPATHOLOGY OF POLYMYOSITIS AND INCLUSION BODY MYOSITIS

PM and IBM may be some of the best studied or prototypic T cell–mediated disorders in which cytotoxic T cells directed against heretofore unidentified muscle antigens form an immunologic synapse with the MHC-I antigen expressed on the surface of muscle fibers. The cytotoxicity of the autoinvasive T cells has been supported by the presence of perforin granules that are directed toward the surface of the muscle fiber and lead to muscle fiber necrosis on release. The specificity of the T cells has been further examined by studying the gene rearrangement of the T-cell receptors (TCRs) of the autoinvasive T cells (Hohlfeld & Engel, 1994; Wiendl, Hohlfeld, & Kieseier, 2005). In patients with PM, as well as IBM, only certain T cells of specific TCR-alpha and TCR-beta families are recruited to the muscle from the circulation. Cloning and sequencing of the amplified endomysial TCR gene families have demonstrated a restricted use of the *J-beta* gene with conserved amino acid sequence in the CDR3 region, the antigen-binding region of the TCR, indicating that CD8+ cells are specifically selected and clonally expanded in situ by muscle-specific autoantigens. Studies combining laser microdissection, immunocytochemistry, polymerase chain reaction (PCR), and sequencing of the

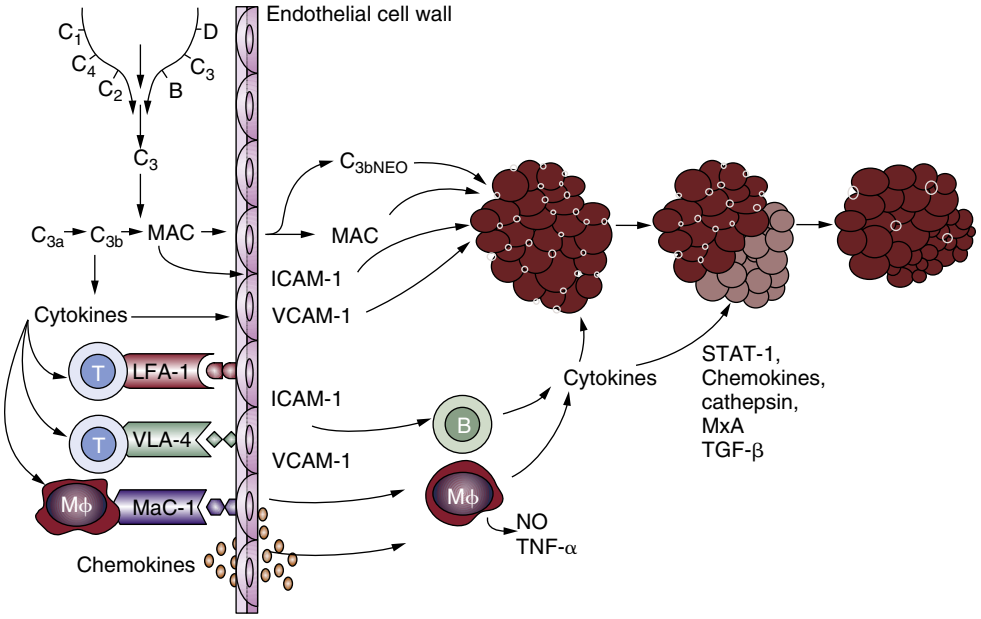


Fig. 22.7 Proposed mechanisms in the immunopathogenesis of dermatomyosis. C_{3bNEO}, Complement component 3b neoantigen; *ICAM-1*, intercellular adhesion molecule-1; *LFA-1*, lymphocyte function–associated antigen 1; *MAC*, membrane attack complex; *MaC-1*, macrophage 1 antigen; *MxA*, myxovirus (influenzavirus) resistance protein 1; *NO*, nitrous oxide; *STAT-1*, signal transducer and activator of transcription protein 1; *TGF-β*, transforming growth factor-beta; *TNF-α*, tumor necrosis factor-alpha; *VCAM-1*, vascular cell adhesion molecule-1; *VLA-1*, very late antigen-1.

most prominent TCR families have shown that only the autoinvasive, not the perivascular, endomysial CD8+ cells are clonally expanded. Comparison of the TCR repertoire between PM and DM with spectratyping has confirmed that perturbations of the TCR families occur only in PM but not DM. Further, among the circulating T cells, clonal expansion occurs only in the cytotoxic CD8+ cells that express genes for perforin and infiltrate the MHC-I-expressing muscle fibers (Fig. 22.8).

The clonally expanded CD8+ T cells form immunologic synapses with the muscle fibers they invade, as supported by the coexpression of costimulatory molecules B7-1, B7-2, BB1, CD40, or inducible costimulator (ICOS) ligand (ICOS-L) on the muscle fibers and the respective counterreceptors CD28, cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD40 ligand (CD40L), or ICOS on autoinvasive T cells (Dalakas, 2006d; Hohlfeld & Engel, 1994; Wiendl et al., 2005). Cytokines, chemokines, and metalloproteinases (fundamental molecules for T-cell activation, trafficking, antigen recognition, and T-cell attachment) are also upregulated in the muscle tissue. Some of these cytokines, such as interferon-γ, IL-1β, and TNF, may exert a direct cytotoxic effect on the muscle tissue. Unique to the muscle is the observation that the various cytokines and chemokines can also stimulate the muscle fibers to endogenously produce certain proinflammatory cytokines, such as interferon-γ, which enhances and perpetuates the immune response.

In PM, MHC-I is expressed in all fibers, even in those not invaded by T cells, often throughout the course of the disease. Such a chronic MHC-I upregulation may be exerting a deleterious stress effect to the endoplasmic reticulum (ER) of the myofiber, independent of T cell–mediated cytotoxicity, as discussed next.

The factors triggering the T cell–mediated process in PM and IBM remain unclear. Viruses may be responsible for breaking tolerance, and several of the common viruses, including coxsackievirus, influenza virus, paramyxoviruses, cytomegalovirus, and Epstein-Barr virus, have been directly associated with chronic and acute myositis (Dalakas, 2006e). Very sensitive PCR studies, however, have repeatedly failed to confirm the presence of such viruses in these patients' muscle biopsies (Leff et al., 1992; Nishino, Engel, & Rima, 1989).

The best evidence of possible viral connection in PM and IBM is with the retroviruses. Monkeys infected with the simian immunodeficiency virus and humans infected with HIV and HTLV-I develop PM or IBM. In humans infected with HIV or HTLV-I, an isolated inflammatory myopathy may occur as the initial manifestation of the retroviral infection or myositis may develop later in the disease course (Cupler et al., 1996; Dalakas, London, Gravell, & Sever, 1986; Dalakas & Pezeshkpour, 1988; Dalakas, Pezeshkpour, Gravell, & Sever, 1986; Dalakas et al., 2007; Illa, Nath, & Dalakas, 1991; Leon-Monzon, Illa, & Dalakas, 1994; Leon-Monzon, Lamperth, & Dalakas, 1993; Morgan, Rodgers-Johnson, Mora, & Char, 1989; Ozden, Gessain, Gout, & Mikol, 2001; Ozden et al., 2004; Saito et al., 2002). The association of retroviruses with s-IBM is more than a coincidence because large numbers of HIV/HTLV-I positive patients with IBM have been now reported from many centers worldwide (Cupler et al., 1996; Dalakas et al., 2007; Ozden et al., 2001, 2004; Saito et al., 2002). In these seropositive patients, the disease appears before the age of 50 but several years after the first manifestations of the retroviral infection, suggesting that in HIV-positive patients who live longer and harbor the virus for several years, the disease is more frequently recognized. The clinical phenotype and muscle histologic findings in HIV-IBM patients are identical to the retroviral-negative IBM (Cupler et al., 1996; Dalakas et al., 2007). Using in situ hybridization, PCR, immunocytochemistry, and electron microscopy, viral antigens could not be detected within the muscle fibers but only in occasional endomysial macrophages (Cupler et al., 1996; Dalakas et al., 2007; Illa et al., 1991; Leon-Monzon et al., 1993, 1994; Ozden et al., 2001, 2004; Saito et al., 2002). Molecular immunologic studies using tetramers have shown that retrovirus-specific cytotoxic T cells, whose TCR contains amino acid residues for specific HLA/viral peptides, are recruited within the clonally expanded T cells and invade muscle fibers (Dalakas et al., 2007; Ozden et al., 2004). We have interpreted these observations to suggest that in HIV and HTLV-I IBM, there is no evidence of persistent infection of the muscle fibers with the

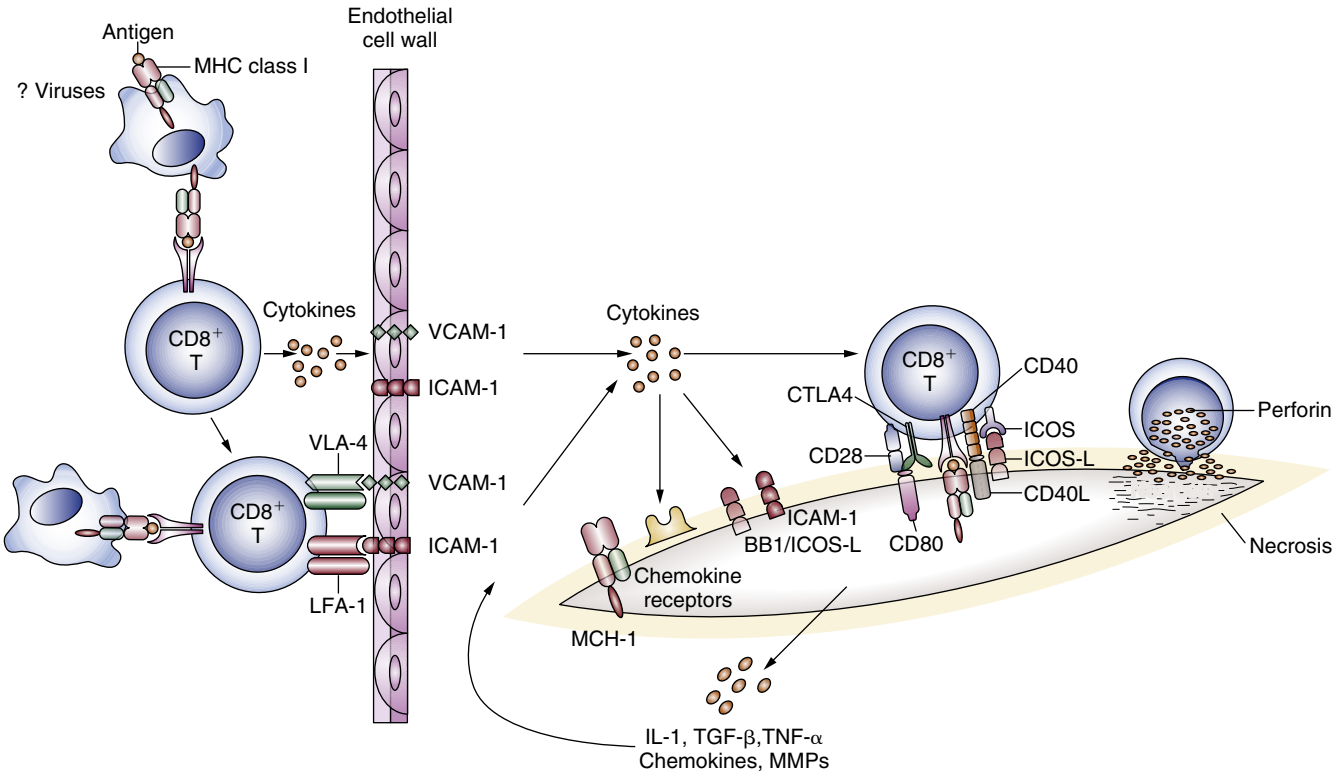


Fig. 22.8 Immunopathogenesis of dermatomyositis. *BB1/ICOS-L*, BB1-costimulatory molecule ligand; *CD40L*, CD40 ligand; *CTLA-4*, cytotoxic T-lymphocyte antigen-4; *ICAM-1*, intercellular adhesion molecule-1; *ICOS*, inducible costimulator; *IL-1*, interleukin 1; *LFA-1*, lymphocyte function–associated antigen 1; *MHC*, major histocompatibility complex; *MCH-1*, major histocompatibility complex 1; *MMPs*, matrix metalloproteinases; *TGF-ß*, transforming growth factor-beta; *TNF-α*, tumor necrosis factor-alpha; *VCAM-1*, vascular cell adhesion molecule-1; *VLA-4*, very late antigen-4.

virus or viral replication within the muscle but rather that the chronic retroviral infection, in genetically susceptible individuals, triggers a persistent inflammatory process that leads to s-IBM (Dalakas, 2003; Gold, Dalakas, & Toyka, 2003).

Humoral factors also seem to play a role in IBM as exemplified by observations of isolated single plasma cells from muscle sections. A series of recombinant immunoglobulins reconstructed from these cells recognized self-antigens expressed by cell lines and in muscle tissue homogenates. One of the putative antigens is identified as the 5'-nucleotidase 1A (anti-cN1A), an enzyme involved in nucleotide metabolism that is highly expressed in skeletal muscle. Anti-cN1A antibodies were detected in 33% to 50% of patients with IBM (Larman et al., 2013; Pluk et al., 2013). Although these antibodies do not have distinct specificity for IBM as they are also observed with lower frequency in other autoimmune diseases (Dalakas, 2015), their presence strengthens the view of a humoral immune response in IBM.

IMMUNOPATHOLOGY OF NECROTIZING AUTOIMMUNE MYOSITIS

The cause of NAM is multifactorial. A higher incidence of cancer has been observed in several cases (Dalakas, 2015), while others developed NAM during therapy with checkpoint inhibitors for advanced malignancies (Dalakas, 2018b); some patients have an active viral infection (i.e., HIV); others may have a smoldering underlying autoimmune process; and still others have no other disease or apparent exposure to exogenous agents (Dalakas, 2015). Recently, in the setting of COVID19 viral infection, a number of patients with clinical features on NAM and very high CK levels have been observed (Dalakas 2020). Some cases have been thought to have a statin exposure (Mammen et al., 2011; Watanabe et al., 2016) based on the assumption that statins, in addition to rarely causing an acute self-limited toxic myopathy, can also induce an autoimmune necrotizing myositis that persists after statin withdrawal, although a connection with statin-triggered autoimmunity has never been established (Dalakas, 2018b). It is likely that NAM could be an antibody-mediated disease, as implied by the presence of specific antibodies and complement deposits, even though the pathogenic role of these antibodies has not been established (Allenbach et al., 2018; Dalakas, 2015, 2018a, 2018b). It is still unclear if the recruitment of macrophages represents an antibody-dependent cell-mediated cytotoxicity process (Allenbach et al., 2018; Dalakas, 2018a).

The connection of NAM with statins has been strongly promoted by one group based on retrospective—over many years—historical chart review, which revealed anti-HMGCR autoantibodies in 45 of 750 patients (6%) with all myopathies, and among those patients aged 50 years and older, 92.3% had at some point taken statins (Mammen et al., 2011). Because statins upregulate the expression of HMGCR in cultured cells and HMGCR is the target of action of statins, a possible triggering cause was formulated and the term "statin myopathy" was coined. Such cause-and-effect relationship was never, however, substantiated, nor did it take into account that 25% of Americans above 40 years take statins. Further, studies from many centers throughout the world have now shown that anti-HMGCR autoantibodies are

more often seen in statin-naïve patients with autoimmune necrotizing myositis, challenging the statin connection (Allenbach et al., 2018; Watanabe et al., 2016). Considering that NAM is now one of the most common inflammatory myopathies and millions of people above 40 years take statins, the association between statins and NAM is likely a chance phenomenon, especially since their role in inducing NAM has not been proven (Dalakas, 2018a, 2020). Some authors correctly proposed that the term "statin myopathy" should not be used because only a minority of NAM patients had statin exposure and, most importantly, they developed NAM many years after statin initiation, which makes their causative role dubious.

PRESENCE OF AUTOANTIBODIES

Various autoantibodies against nuclear (antinuclear antibodies) or cytoplasmic antigens are found in as many as 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens are directed against ribonucleoproteins that are involved in translation and protein synthesis and include various synthases and translation factors, including Jo-1, PL-7, PL-12, OJ, EJ, PMS1, and PMS2 (Dalakas, 2015, 2020). Of these, the anti-Jo-1, directed against the histidyl-transfer RNA synthetase, accounts for 75% of all the antisynthetases and is clinically useful in defining the distinct subset mentioned previously (Allenbach et al., 2018). Overall, however, these antibodies may not be muscle specific or pathogenic because (1) they are directed against ubiquitous intracellular targets; (2) their function has not been defined; (3) they are almost always associated with interstitial lung disease or seen in patients with interstitial lung disease who do not have active myositis; and (4) they also occur in IBM and DM, despite the clinical and immunopathologic differences of these disorders, suggesting that their presence may be part of the normal immune repertoire (Dalakas, 2015, 2018a; Watanabe et al., 2016). Other autoantibodies are seen when PM is associated with connective tissue disease and are the hallmarks of the other disease, such as Ro/SSA, La/SSB, or Ki/SL in Sjögren or tRNA, ANA, LE, or a 56 kDanRNP in lupus (Dalakas, 2015, 2020). As mentioned, two autoantibodies, anti-SRP and anti-HMGCR, appear to be markers of necrotizing myositis and are of diagnostic value because they are detected in up to 65% of patients with NAM (Allenbach et al., 2018; Dalakas, 2015, 2018a; Mescam-Mancini et al., 2015; Stenzel et al., 2015; Watanabe et al., 2016), regardless of statin exposure. Claims that these antibodies may be pathogenic because they can cause muscle fiber atrophy and affect regeneration in vitro are irrelevant to the mechanism of the disease because the main cause of NAM is a macrophage-mediated muscle fiber necrosis with devastating muscle destruction and not muscle fiber atrophy (Dalakas, 2015, 2018a, 2020).

IMMUNE CHECK-POINT INHIBITORS AS TRIGGERING FACTORS OF POLYMYOSITIS AND NECROTIZING AUTOIMMUNE MYOSITIS

These agents are directed against (1) CTLA-4 (ipilimumab); (2) PD-1 (pembrolizumab and nivolumab); and (3) PD-L1 (atezollizumab, avelumab, and durvalumab). The drugs are used for advanced malignancy and prevent CTLA-4 or PD-1 from binding to their respective receptors CD80/86 and PDL-1 and, by doing so, inhibit the "inhibitory" costimulatory interactions between T cells and tumor cells, resulting in positive costimulation and strong cell activation, like taking the "brakes off" the immune system (Dalakas, 2018b). This blockade allows T cells to kill tumor cells, but the resulting enhanced costimulation causes an uncontrolled T-cell activation that disrupts immune tolerance, resulting in immune-related events against muscle, mainly expressed as PM and NAM, which at times occurs concurrently with myasthenia gravis (Dalakas, 2015, 2018b; Kao et al., 2017). Eosinophilic fasciitis and orbital myositis have also been seen.

NONIMMUNE FEATURES IN THE MUSCLES OF INCLUSION BODY MYOSITIS: RECONCILING THE ROLES OF INFLAMMATION AND "DEGENERATION"

IBM is a more complex disease because, in addition to the primary autoimmune and inflammatory features discussed previously, there are concomitant features of cell stress and degeneration molecules, highlighted by the presence of rimmed vacuoles (almost always in fibers not invaded by T cells), intracellular deposition of Congo red–positive amyloid, and accumulation of amyloid-related molecules, including β-APP, phosphorylated tau, presenilin-1, apolipoprotein E, γ-tubulin, clusterin, α-synuclein, and gelsolin. These accumulations are not, however, unique to s-IBM, because they are also observed to a similar extent in other vacuolar myopathies and most of the myofibrillar ones. What appears unique to IBM, however, compared to other chronic vacuolar myopathies is the strong presence of primary inflammation and the overexpression of MHC-I molecule on most, if not all, of the fibers. It has been proposed that in muscle fibers overloaded by MHC molecules, the presented antigenic peptides cannot undergo proper conformational change to bind to MHC-I complex, leading to ER stress and protein misfolding (Dalakas, 2006b; Nagaraju et al., 2005; Nishino et al., 1989). This model is supported by the noted enhanced immunoproteasome activity, enhanced MHC-I protein assembly, misfolding of accumulated glycoproteins, and signs of a cell stress response, with upstream upregulation of αB-crystallin in intact and MHC-I–positive muscle fibers (Askanas & Engel, 2003; Banwell & Engel, 2000; Ferrer et al., 2004; Schmidt et al., 2008; Vattemi, Engel, & McFerrin, & Askanas, 2004). Such stressor effects are also seen in transgenic mice that overexpress MHC-I, indicating that chronic overexpression of MHC-I alone might be sufficient to induce ER stress to myofiber (Nagaraju et al., 2005).

The overexpression of beta-amyloid precursor protein in the muscles of IBM patients has led some investigators to propose that the pathogenesis of IBM may be similar to that of Alzheimer disease. Overexpressing beta-amyloid precursor protein in cultured human muscle and transgenic mice models has produced pathologic findings resembling those seen in IBM (Askanas & Engel, 1998). The precise role of beta-amyloid precursor protein in the pathogenesis of IBM, however, remains unclear. It has been proposed that the accumulation of beta-amyloid and the related proteins appears to result from protein misfolding (Askanas, Engel, & Nogalska, 2015; Ferrer et al., 2004). The elevated levels of

mutant ubiquitin noted in the muscles of these patients may result in the aggregation of beta-amyloid and phosphorylated tau by inhibiting cellular housekeeping enzymes (the proteosome), as proposed in Alzheimer disease. Deposits of TDP43, a DNA-binding protein aberrantly translocated from the nuclei to the cytoplasm, and p62, a shuttle protein that transports polyubiquitinated proteins, detected within the muscle fibers with the use of immunostaining, have been advocated as diagnostic markers (Askanas et al., 2015; Dalakas, 2015). Although in vitro evidence suggests that amyloid-β42 and its oligomers may be involved in the pathway of intracellular toxicity, it remains unclear how these proteinaceous aggregates, which are also seen in other vacuolar myopathies, induce an inflammatory and degenerative myopathy and what triggers disease, inflammation, or protein aggregation (Dalakas, 2015). Compelling evidence suggests that aging, abnormal proteostasis (the network controlling proteins), impaired autophagy, cell stress induced by MHC-I or nitric oxide, long-standing inflammation, and proinflammatory cytokines such as interferon-γ and interleukin-1β may cumulatively trigger or enhance degeneration, leading to further accumulation of stressor molecules and misfolded proteins (Dalakas, 2015).

Although the factors triggering immune and protein dysregulation or vacuolar formation remain unknown, our group favors a primary inflammatory process that leads to degeneration (Dalakas, 2006b, 2008, 2010b; Schmidt et al., 2008) because (1) IBM is frequently seen with autoimmune disorders and increasingly with HIV and HTLV-I infection, (2) T-cell invasion of nonnecrotic fibers is found early and in higher frequency than the Congo red–positive fibers (Pruitt, Showalter, & Engel, 1996), (3) the cytotoxic T cells at the immunologic synapses do not recognize amyloid-related proteins as antigens, and (4) the cytokine-induced upregulation of MHC-I occurs early and is capable of triggering cell stress and degeneration (Dalakas, 2008). Most important, endomysial inflammation alone can cause muscle destruction and clinical weakness, as seen in PM; whether the tiny amyloid deposits are sufficient alone to trigger muscle degeneration in humans remains unclear, especially because the same molecules accumulate in various vacuolar myopathies and muscular dystrophies caused by genetic mutations, but in other conditions these deposits appear innocuous.

The possibility that "degenerative" changes are the primary events while the inflammatory features are secondary is another view. In this scenario, accumulation of altered elements of muscle fibers may not only be toxic but also represent neoantigens as a result of transcriptional dysregulation of certain molecules, triggering cytotoxic lymphocytic attack on muscle fiber (Gold et al., 2003; Greenberg, 2007, 2019).

Regardless of whether the primary event is a dysimmune or protein dysregulation process, there is now strong evidence that in IBM, not only do proinflammatory cytokines correlate with the intramuscular accumulation of amyloid, phosphorylated tau, ubiquitin, and αB-crystallin but also that inflammatory mediators such as IL-1 can enhance the production and intracellular accumulation of amyloid and stressor proteins such as αB-crystallin (Dalakas, 2008; Schmidt et al., 2008). Cytokines also stimulate myofibers to produce inflammatory mediators in an autoamplificatory mechanism, further enhancing the chronicity of inflammation, amyloid formation, and cell stress (Dalakas, 2008; Schmidt et al., 2008). A scheme illustrating the interaction between the long-standing chronic inflammatory process and degeneration, leading to cell stress and deposits of amyloid and misfolded proteins, is presented in Fig. 22.9 (from Dalakas, 2015). Theoretically, successful inhibition of inflammatory molecules can halt the degenerative process and stop the disease progression (Dalakas, 2008).

TREATMENT AND MANAGEMENT OF INFLAMMATORY MYOPATHIES

GOAL OF THERAPY

The goal of therapy in inflammatory myopathies is to improve muscle strength and activities of daily living. Although when strength improves the serum CK falls concurrently, the reverse is not always true because most of the immunosuppressive therapies can result in a decrease in serum muscle enzymes without necessarily improving muscle strength (Dalakas, 2003, 2010a). Unfortunately, this is commonly interpreted as a positive sign and, when associated with a patient's subjective sense of feeling better (but not stronger), gives the erroneous impression of improvement and forms the basis for the common habit of "chasing" or "treating" the CK level instead of the muscle weakness. It is essential, therefore, to discontinue the applied therapies if an adequate trial has led only to a reduction in CK and not to an objective improvement in muscle strength. The level of CK is helpful only as an auxiliary measure and not as a guide to start or monitor therapy.

On assessing strength, in addition to using routine Medical Record Council scales, it is essential to ask the patients specific questions about changes in performing routine physical tasks at home or work and activities of daily living. The patients also need to be informed from the onset that these are chronic disorders and long-term therapy is anticipated. The potential long-term side effects of the drugs need to be explained and the patient's cooperation should be sought from the outset. This is especially useful when steroids are used and the patients need to adhere to a strict dietetic regimen.

TREATMENT OF DERMATOMYOSITIS AND POLYMYOSITIS

In spite of the progress in elucidating the specificity of the immune response, a number of fundamental issues remain unanswered, hindering the prospects of specific immunotherapy. Accordingly, none of the available therapies are selective or antigen specific but rather attack indiscriminately the various T-cell or B-cell functions (Gold et al., 2003; Hohlfeld & Dalakas, 2003; Mastaglia, 2000; Mastaglia, Phillips, & Zilko, 1997).

STARTING THERAPY: THE ROLE OF CORTICOSTEROIDS

Prednisone is the first drug of choice, based on experience but not on controlled trials. Because the effectiveness and relative safety of prednisone therapy (Dalakas, 2001, 2003, 2005, 2010a; Hohlfeld & Dalakas, 2003; Mastaglia,

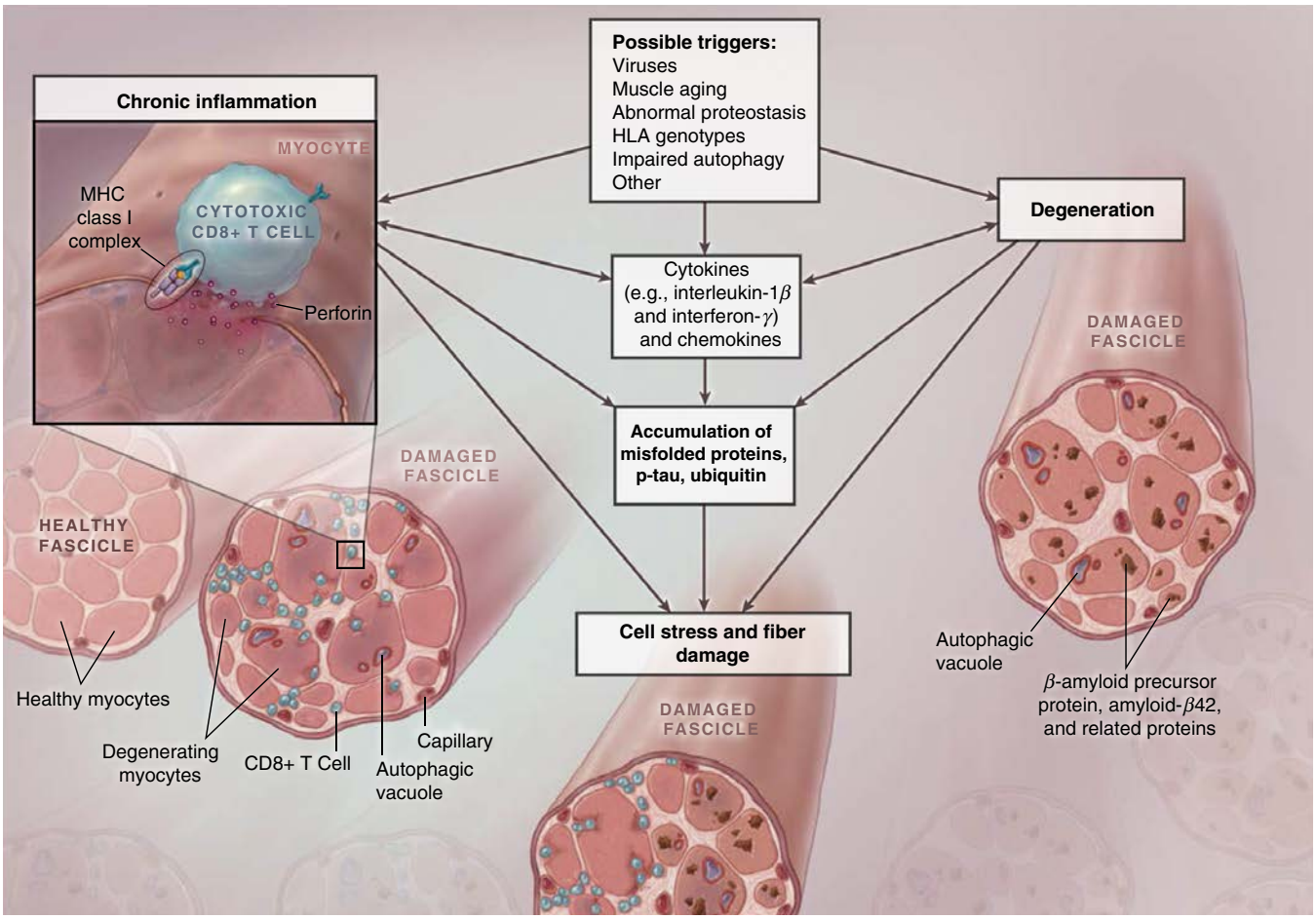


Fig. 22.9 Proposed mechanisms in inclusion body myositis linking inflammation with degeneration. A hypothetical scheme of the inclusion body myositis pathogenesis highlights the interaction between the long-standing chronic inflammatory process and degeneration, leading to cell stress and deposits of amyloid and misfolded proteins, similar to the ones seen in neuroinflammatory disorders like Alzheimer disease, making inclusion body myositis a peripheral model of "neuroinflammation." What triggers the disease is unclear, but viruses, autoimmune attack, endoplasmic reticulum (ER) stress and muscle aging, impairment of autophagy, abnormal proteostasis with protein misregulation and accumulation of toxic proteins, and HLA genotypes may play a role, either alone or in combination. Whether the primary event is inflammatory or degenerative is highly debated and presently unsettled (Dalakas, 2015).

2000; Mastaglia et al., 1997) determines the future need for stronger immunosuppressive drugs, our preference has been to start with a high-dose prednisone beginning early in the disease. A high dose, at least 1 mg/kg or 60 to 80 mg/day, as a single daily morning dose (after breakfast) for an initial period of 3 to 4 weeks is preferable. In patients with severe PM or DM and systemic manifestations, I prefer to start treatment with IV methylprednisolone 1 g/day for 3 to 5 days and then continue with the oral prednisone regimen, as mentioned earlier. After 1 month of high-dose, oral, daily prednisone, I switch to an alternate-day dose. This is accomplished by gradually reducing the alternate, "off-day" dose by 5 to 10 mg per 1 or 2 weeks, or faster if necessitated by side effects. When reaching the every-other-day regimen without serious adverse effects, the dosage is reduced gradually by 5 to 10 mg every 3 to 4 weeks until the lowest possible dose that controls the disease is reached. The single-dose, alternate-day program minimizes adverse effects while adequately maintaining control of the underlying disease. It has been my preference to give the prednisone as a single dose in the morning because it is less likely to suppress the evening secretion of adrenocorticotropic hormone (ACTH) and more likely to secure a normal endogenous cortisol secretion the next morning (corticosteroids and other immunosuppressant drugs are discussed in detail in Chapter 7).

The ultimate goal in a patient who responds to steroid therapy is to find the lowest dose that controls the disease with the fewest adverse effects. This is often accomplished by adding a steroid-sparing drug, while lowering the amount of steroid, without a breakthrough of disease. We do not advocate a concurrent use of steroids with another immunosuppressant from the outset of treatment except if the disease has a very aggressive course and the patient is rapidly worsening. Conversely, if by the time the steroid dosage has been reduced to 60 to 80 mg every other day (approximately 14 weeks after initiating therapy), there is no objective benefit (defined as increased muscle strength and not as lowering of the CK or a subjective feeling of increased energy), the patient may be considered unresponsive to prednisone, and tapering is accelerated while the next mode of therapy is started.

To minimize side effects, every patient should be requested from the beginning of steroid therapy to start a strict

low-carbohydrate, low-salt, high-protein diet. Antacids or one of the histamine H_2-receptor antagonists may be used if patients experience stomach upset. Coadministration of calcium supplement (1 g/day) and vitamin D (50,000 units per week) may be useful for long-term steroid administration. In postmenopausal women, when long-term therapy is required, I consider adding Fosamax once weekly based on its proven efficacy in the prophylaxis of steroid-related osteoporosis. Monitoring for osteoporosis with dual-energy x-ray absorptiometry scan may be helpful.

STEROID MYOPATHY VERSUS DISEASE ACTIVITY

The long-term use of prednisone may theoretically cause worsening of muscle strength associated with a normal or unchanged CK level, referred to as *steroid myopathy*. The term "steroid myopathy" is a misnomer because steroids do not cause histologic signs of myopathy but, rather, selective atrophy of type II muscle fibers. Contrary to what is believed, the condition is not common. Rarely, it may be difficult to distinguish a developing steroid-induced myopathic weakness from the increased weakness related to disease activity or to other factors such as decreased mobility, infections, or a concomitant systemic illness. The decision to adjust the prednisone dosage in a patient with myositis who has previously responded to treatment may be influenced by reviewing the past 1 to 2 months' history of strength, mobility, serum CK, medication changes, and associated medical conditions (Dalakas, 1995, 2006c). For example, in a patient who, for the past 1 to 2 months, has had increased CK levels, no new overt signs of steroid toxicity with reduced or unchanged dosage of steroids, and no evidence of a systemic illness or infection, increasing muscle weakness is most likely due to worsening of the disease that either may require more prednisone or has become steroid-resistant, requiring another drug. When these signs are not clear, one may arbitrarily raise the prednisone dosage and wait for the answer, which can be evident in about 2 to 8 weeks, according to the change in the patient's strength. A clinical sign that I have found to be of some help in a few patients is the strength of neck extensor muscles, which usually worsens with exacerbation of the disease but remains unchanged with steroid-induced muscle intoxication. EMG, when it shows increased spontaneous activity, is also useful to explore evidence of active disease.

RELAPSES WHILE ON MAINTENANCE STEROID THERAPY

Relapses may occur while the steroid dose is decreased below a critical level for a given patient or in patients who are seemingly stable but decompensate after a viral illness, during a concurrent infection, or because of disease worsening. Many such patients can be controlled if the dose of prednisone is increased to a high single daily dose (as high as the initial), or to a high alternate-day dose (if the relapse is mild), for a month followed by a slow taper. More often, however, relapses require more aggressive strategies, such as intravenous immunoglobulin (IVIg) or addition of an immunosuppressant, as described later.

USE OF STEROID-SPARING REGIMENS IN STEROID-RESPONSIVE PATIENTS

The decision to start an immunosuppressive drug is based on its "steroid-sparing" effect when, in spite of steroid responsiveness, the patient has developed significant complications or when attempts to lower a high steroid dosage have resulted in worsening of muscle strength. The preference for selecting an immunosuppressive drug for these circumstances is empirical because control studies have not been conducted. The choice is usually based on our prejudices or personal experience with each drug and our own assessment of the relative efficacy/safety ratio. My preference depends on disease severity, clinical setting, and other conditions. The following immunosuppressive drugs are used (Dalakas, 2007; Gold et al., 2003; Hohlfeld & Dalakas, 2003).

Azathioprine

Although lower doses (1.5–2.0 mg/kg) are commonly used, I prefer higher doses up to 3 mg/kg for effective immunosuppression. Because azathioprine is usually effective after 6 months of treatment, patience is required before it is concluded that the drug is ineffective. The major toxicity of azathioprine includes thrombocytopenia, anemia, leukopenia, pancytopenia, drug fever, nausea, and liver toxicity. An elevation of liver enzymes, if slight, needs only observation. Azathioprine, which is metabolized by xanthine oxidase, if given concurrently with allopurinol, can be severely toxic to the liver or bone marrow, and combined use of these two drugs is not recommended. The susceptibility to toxicity is genetically dependent on interindividual variations in thiopurine *S*-methyl transferase enzyme activity based on the genetic polymorphism of high- versus low-metabolizing alleles. Patients with low enzyme activity concentrations have an increased risk of bone marrow suppression. Because of these side effects, I prefer to use mycophenolate mofetil (Cellcept), which also acts faster.

Mycophenolate Mofetil

This drug is a morpholinoethylester of mycophenolic acid that blocks de novo purine synthesis and acts on both B and T cells. It is an antipurine antimetabolite, like azathioprine, but it does not cause significant bone marrow suppression or hepatotoxicity. It is a well-tolerated drug when used at doses up to 3 g/day, but most commonly 2 g/day. It does not work as fast as initially thought, and it may take up to 2 or 3 months to see any clinical benefit. In organ rejection, Cellcept works fast because it inhibits the production of new B and T cells; in autoimmune diseases, however, the initial goal is to affect the autoreactive, existing lymphocytes, which is accomplished with other drugs, such as prednisone, while waiting for Cellcept to act later by inhibiting the new B or T cells.

Methotrexate

An antagonist of folate metabolism, methotrexate is a useful drug. I prefer the oral route starting at 7.5 mg weekly for the first 3 weeks (given in a total of three doses, 2.5 mg every 12 hours), increasing it gradually by 2.5 mg per week up to a total of 25 mg weekly, but most commonly 15 mg weekly. A rarely reported side effect (but admittedly never seen by this author) is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease seen in some patients with inflammatory myopathies. Other adverse effects include stomatitis, gastrointestinal symptoms, leukopenia, thrombocytopenia, renal toxicity, hepatotoxicity, and malignancies. Because it acts faster than azathioprine, it might be preferable to use as a steroid-sparing agent.

Cyclosporine

Cyclosporine affects T cell–mediated immunity by inhibiting transcription of certain genes, mostly the IL-2 gene, resulting in reduced IL-2 and other cytokines. At doses of 150 mg twice a day (not more than 5 mg/kg/day) and frequent monitoring of the optimal trough serum level (100–200 ng/mL), this drug can be given without major complications. The kidney function should be closely monitored and nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) are avoided. When creatinine increases more than 30%, the drug should be discontinued. The concomitant use of ketoconazole (which inhibits the P480 cytochromal enzyme in the liver) allows for a lower (up to 80%) dose with less toxicity. The advantage of cyclosporine compared to azathioprine is that it acts faster.

WHEN STEROIDS ARE INADEQUATE: THE USE OF HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN

In my experience, when corticosteroids have failed to induce remission, or in rapidly progressive cases with evolving severe weakness, the aforementioned immunosuppressive agents, used only for "steroid-sparing" toxicity, are inadequate to substantially increase strength. In these circumstances, the choice is IVIg.

IVIg has multiple mechanisms of actions, most of which include inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor binding on macrophages or the immunoglobulins on B cells, blocking the Fc receptors on target antigens, interaction with sialic acid–specific receptors on regulatory macrophages exerting an anti-inflammatory effect, or interference with antigen recognition by sensitized T cells. More than one of these actions is probably responsible for the observed benefit (Dalakas, 2006c). The dose is 2 g/kg, given in two to five divided daily doses, initially every 4–5 weeks for 2–3 months, followed by 1g/kg if it is still required to achieve remission. In a double-blind study conducted in patients with refractory DM, IVIg significantly improved the patients' strength compared to placebo (Dalakas, 2004b; Dalakas et al., 1993). The improvement becomes noticeable about 15 days after the first IVIg infusion, and it is clear and definitive after the second infusion. Marked improvement is also noticed in the active violaceous rash or the chronic scaly eruptions on the knuckles. Repeated infusions may be required every 6 to 12 weeks to maintain improvement. In several patients, we have been able to lower the prednisone dose and keep only a low maintenance dose. Some patients with DM who had become unresponsive to steroids may respond again to prednisone after a few IVIg infusions.

Because DM responds to steroids, IVIg therapy is best reserved for steroid-resistant patients, either as a second-line therapy or as a third-line add-on therapy in patients who are not adequately controlled with combination of steroids and methotrexate or azathioprine and for patients who are immunodeficient or in whom immunosuppressants are contraindicated. In children and in older patients, it can be used as a first-line therapy after a short course of steroids.

The beneficial effect of IVIg in PM has been documented only in open-label trials. A controlled study started by our group 15 years ago was never completed because of the rarity of PM, as discussed earlier. It is common experience, however, that IVIg is effective in the majority of patients with PM.

IF STEROIDS AND INTRAVENOUS IMMUNOGLOBULIN ARE INEFFECTIVE OR INADEQUATE TO INDUCE REMISSION

In most of these cases, it is prudent to evaluate the patient's diagnosis. If the diagnosis is secured (based on the unique clinical features, as in DM, or with new muscle biopsy, as in PM) or the patient had clearly responded to steroid and IVIg early in the disease course, the following can be used.

Rituximab

This drug is a monoclonal antibody against CD20+ B cells resulting in B-cell depletion that lasts for at least 6 months. There is evidence based on number of reports that rituximab at 2 g (divided in two biweekly infusions) can be beneficial to patients with DM, NAM, OM-AS, and PM resistant to therapies (Chung, Genovese, & Fiorentino, 2007; Levine, 2005; Valiyil, Casciola-Rosen, Hong, Mammen, & Christopher-Stine, 2010).

A placebo-controlled study conducted in 200 patients (76 with adult DM, 48 with juvenile DM, and 76 with PM) did not meet the primary end-point largely because of a study design. Patients were randomized to a rituximab-early group receiving the drug or placebo at weeks 0 and 1 and to a rituximab-late group receiving placebo or rituximab in weeks 8 and 9. There was no difference between placebo and rituximab at week 8, but at week 44, when all patients had received the drug, 83% of them had met the definition of improvement (Oddis et al., 2013). Rituximab is now the preferred treatment in patients poorly responding to immunosuppressants and IVIg.

Cyclophosphamide

In patients who have interstitial lung disease and severe clinical myopathy unresponsive to other agents, this drug can be used at doses of 0.5 to 1 g/m^2 intravenously per month. Adequate hydration the day before and antiemetics are helpful. Adverse reactions include nausea, vomiting, alopecia, hemorrhagic cystitis, bone marrow suppression. It is critical to monitor the neutrophil and the lymphocyte count and perform frequent urinalysis even after the drug was stopped.

Tacrolimus

Formerly known as FK 506, tacrolimus is structurally different from cyclosporine, although they share the ability to selectively inhibit the transcription of cytokines, specifically IL-2. There is evidence that tacrolimus is effective in some difficult cases of PM, especially when there is interstitial lung disease (Oddis, Sciurba, Elmagd, & Starzl, 1999; Shimojima et al., 2004; Yamada, Ohshima, Omata, Yasutomi, & Mayumi, 2004).

Other, Newer Agents

In difficult cases, other agents have been used with limited success. These include anti-TNF-α agents such as etanercep (Embrel) and infliximab, anakinra, canakinumab, sirolimus, and Campath (Hengstman et al., 2003; Kosmidis, Alexopoulos, Tzioufas, & Dalakas, 2013; Kosmidis, Pikazis, Vlachoyiannopoulos, Tzioufas, & Dalakas, 2019; Labioche et al., 2004; Nadiminti & Arbiser, 2005). A large controlled study with Bigramumab was also negative (Greenberg, 2019).

A promising agent for DM may be eculizumab, a complement C5 inhibitor.

STEP-BY-STEP APPROACH

In the absence of evidence-based studies, an algorithm in the management of these diseases remains empirical and somewhat biased. In my experience, the excellent effect of IVIg in many DM and PM patients and the limited beneficial effect achieved by the other immunosuppressants have changed the order in which I use these agents. If steroids are inadequate, I go directly to IVIg, followed by the addition of one of the aforementioned immunosuppressants. A personal step-by-step approach to the treatment of DM and PM is as follows (Dalakas, 2015):

Step 1. Prednisone (in aggressive cases, combination with another agent listed in steps 2 and 3 is preferred by some practitioners).

Step 2. IVIg (the use of IVIg as a second-line therapy is justified based on the observation that the immunosuppressants listed in step 4 have a mild effect alone and mostly a steroid-sparing effect).

Step 3. Rituximab

Step 4. Immunosuppressants, such as azathioprine, methotrexate, mycophenolate, or cyclosporine, only as steroid-sparing agents. These drugs are usually ineffective in steroid-resistant cases.

TREATMENT OF INCLUSION BODY MYOSITIS

In spite of the immunopathologic features identical with PM, IBM patients are difficult to treat. Although a number of patients may transiently respond to steroids, the majority do not. Methotrexate in a controlled study was not better than placebo. Cyclosporine, azathioprine, and Cellcept are mostly ineffective, although some patients may initially respond to some degree. IVIg may provide some benefit to a small number of patients for a period of time, especially in dysphagia, as demonstrated with controlled studies (Cherin et al., 2002; Dalakas et al., 1997; Walter et al., 2000). Although no statistically significant differences were noted overall, regional difference in certain muscle groups, especially the muscles of swallowing, were observed (Dalakas et al., 1997). Dysphagia appears to be the main symptom that improves consistently, as documented on subsequent open-label trials (Cherin et al., 2002). Because dysphagia is life-threatening, IVIg can be considered in patients with significant swallowing difficulties and choking episodes (Dalakas, 1995, 2006c; Labioche et al., 2004). Cricopharyngeal myotomy may be another option (Verma, Bradley, Adesina, Sofferman, & Pendlebury, 1991), although in our experience it does not always work. Collectively, my approach to the treatment of patients with IBM is sequentially as follows:

1. Inform the patient that there is no proven effective therapy. I prescribe coenzyme $Q_{10,}$ even though there is no demonstrable benefit, as a means to enhance endurance, given the mitochondrial changes in the biopsy. I also advocate a systematic nonfatiguing exercise program that has shown to be of benefit (Spector et al., 1997).
2. Administer low-dose, every-other-day prednisone combined with mycophenolate in some patients hoping for disease stability with a clear explanation that the benefit from this regimen is anecdotal and short-lived and is not based on controlled studies.
3. Begin a trial with IVIg if there is significant worsening of muscle strength or life-threatening dysphagia.
4. Encourage patients to participate in one of the experimental trials. Our trial with Campath has been encouraging in inducing some short-term stability (Dalakas et al., 2009), but a controlled study is needed. A trial with agents to inhibit degenerative molecules failed (Hanna et al., 2019).

SUPPORTIVE THERAPY

We recommend physical therapy early in the disease to preserve existing muscle function, avoid disuse atrophy of the weak muscles, and prevent joint contractures. Evaluation of swallowing function is also recommended because dysphagia is common, especially in IBM. Speech pathologists provide practical tips on how to prevent choking episodes and diminish the anxiety of an impending aspiration not only for the patient but also for the immediate family.

Occupational and rehabilitation therapists help the patients with their ambulation by providing canes, braces, or wheelchairs according to the stage of their disease or by teaching them how to walk without falling (by "locking" on the knees or by using light braces) and how to perform easier fine motor tasks. Proper emotional support to accept these aids is essential; the patients and their families should be convinced that these means are not demoralizing but realistic approaches to improve transportation and socialization. Emotional support is also fundamental, especially for young patients with DM who are discouraged by a disfiguring rash, calcifications, and steroid side effects. Reassurance that these symptoms improve with aggressive therapies and many steroid side effects are short-lived is important.

PRACTICAL THERAPEUTIC CONSIDERATIONS

In light of the information presented earlier regarding the efficacy of these therapies, the following observations and practical tips may be useful:

Patients with bona fide PM and DM should almost always respond to prednisone to a certain degree and for some period of time.

A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or an "inflammatory dystrophy." In these cases, a repeat muscle biopsy and a more vigorous search for the other disease are recommended.

Calcinosis, a manifestation of DM rarely seen today with the use of better immunotherapeutic agents, does not resolve with immunotherapies. New calcium deposits may be prevented if the primary disease responds to the available therapies. Diphosphonates, aluminum hydroxide, probenecid, colchicines, low doses of warfarin, and surgical excision have all been tried without success. Diltiazem may also be of benefit (Bertorini, Sebes, Palmieri, Igarashi, & Horner, 2001).

If prednisone or the other immunosuppressive therapies have not helped or have become ineffective in improving the patient's strength, they should be discontinued to avoid severe, irreversible adverse effects because, contrary to common belief, there is no evidence that their continuation maintains stability or prevents further disease progression.

In patients with cancer-associated myositis, the treatment should be aggressive to treat the cancer. Searches for possible cancer in DM patients should be a consideration during the first 3 years.

Patients with interstitial lung disease may have a high mortality rate and require aggressive treatment with cyclophosphamide, cyclosporine, or tacrolimus.

Physical therapy to preserve existing muscle function, avoid disuse atrophy of the weak muscles, and prevent joint contractures should start early in the disease.

When treatment of PM is unsuccessful, the patient should be reevaluated, and the muscle biopsy reexamined. A new biopsy might be considered to make sure that the diagnosis is correct and that IBM or one of the inflammatory dystrophies has not been overlooked. The disorders most commonly mistaken for PM are IBM, an inflammatory sporadic limb-girdle dystrophy with endomysial inflammation resembling PM (such as dysferlinopathies, calpainopathy, caveolinopathy, and sarcoglyconopathy), metabolic myopathy (such as phosphorylase or acid maltase deficiency), endocrinopathy, drug-induced myopathies with some secondary inflammatory features (such as the one due to statins), and neurogenic muscular atrophies.

The major pitfalls leading to failure of steroid or immunosuppressive treatment include the following:

- Inadequate initial dose of prednisone or cytotoxic drugs
- Short duration of therapy or quick tapering
- Early discontinuation of prednisone without keeping a "maintenance" low-dose therapy
- Early development of preventable side effects necessitating early discontinuation of prednisone
- Wrong diagnosis

OUTCOME

DM and NAM respond more favorably to therapy than PM does. Overall, most patients improve, and many of them make a full functional recovery, which is sustained with maintenance therapy if treatment is promptly initiated (Dalakas, 2001). However, up to 30% of the patients may be left with residual muscle weakness or calcifications. The 5-year survival rate for treated patients with PM and DM is now approaching 80%. On the other hand, IBM is predictably disabling. Most of these patients will require use of an assistive device such as a cane, walker, or wheelchair. The older the age at onset, the more rapidly progressive the course of IBM appears to be.

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23 Treatment and Management of Hereditary Metabolic Myopathies

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Hereditary metabolic myopathies are a group of muscle disorders that result from a shortage of energy production (i.e., deficiency of adenosine triphosphate [ATP]). In muscle, ATP is produced by aerobic glycogenesis or glycogenolysis and glycolysis, using the respiratory chain, or by anaerobic glycolysis, resulting in lactate production. For sustained work, muscle switches its energy source to fatty acid oxidation. Important pathways in muscle metabolism are shown in Fig. 23.1. Therefore, metabolic myopathies typically present with exercise-induced symptoms, including myalgia, cramps, muscle weakness, and rhabdomyolysis resulting in myoglobinuria. In glycogenoses, symptoms typically emerge after short exercise, whereas myopathies of lipid metabolism manifest after prolonged exercise. However, these typical signs are not present in all metabolic myopathies. In some disorders, there is permanent, predominantly proximal muscle weakness that resembles limb-girdle muscular dystrophies. Many different enzyme defects are known to cause metabolic myopathies. They are classified as glycogenoses, myopathies of lipid metabolism, and mitochondrial myopathies. Some of them are very rare, but a few disorders are rather common. Myophosphorylase deficiency (McArdle disease) and acid α-glucosidase deficiency (Pompe disease) are common glycogenoses. Carnitine palmitoyltransferase II (CPT II) deficiency is a common disorder of lipid metabolism and a frequent cause of hereditary myoglobinuria. Chronic progressive external ophthalmoplegia (CPEO) is a common mitochondrial disorder. These conditions are discussed in some detail in this chapter. Additionally, this chapter also covers the management of rhabdomyolysis.

MUSCLE DISORDERS OF GLYCOGEN METABOLISM

Disorders of glycogen metabolism, termed *glycogenoses* or *glycogen storage diseases* (GSDs), are caused by genetic deficiencies of various enzymes or transporters, involved either directly in the synthesis or breakdown of glycogen or in the utilization of its catabolite, glucose-1-phosphate (Fig. 23.2). Glycogenoses can be multisystemic disorders or can preferentially affect only certain tissues, often but not always reflecting the tissue specificity of expression of the mutant gene. Liver and muscle are the tissues in which glycogen is most abundant and in which it plays its most prominent physiologic roles: as a reservoir for systemic glucose homeostasis in liver and for local glycolytic energy production in exercising muscle. Therefore, most glycogenoses manifest primarily in liver, in muscle, or in both, although in some forms the kidney, heart, nervous system, or erythrocytes can also be affected.

Muscle glycogenoses comprise different subtypes (types 0, II, III, IV, V, VII, IX, X, XI, XII, XIII, XIV, XV) depending on the causative enzyme defect (Table 23.1). Here, we present the most frequent forms (GSD II or Pompe disease, GSD III, IV, V, and VII) that predominantly affect skeletal muscle metabolism. The two main syndromes of muscle glycogenoses can be defined as exercise intolerance with myalgia, early fatigue, and painful cramps; or permanent muscle atrophy and weakness. In some GSD patients, these syndromes may overlap from the beginning or muscle weakness may appear years after symptoms of exercise intolerance begin.

CLINICAL PRESENTATION OF MYOPATHIES CAUSED BY ENZYME DEFECTS OF GLYCOGEN METABOLISM

GLYCOGEN STORAGE DISEASE II (POMPE DISEASE)

GSD type II (Pompe disease) is an autosomal recessive disorder caused by a lack of the lysosomal enzyme acid α-glucosidase, also called *acid maltase*. Acid α-glucosidase catalyzes the hydrolysis of glycogen to glucose within the acidic milieu of lysosomes. In acid α-glucosidase deficiency, the pool of glycogen that enters the lysosomes via autophagy is poorly degraded and overloads the lysosomal system. This leads to a progressive and irreversible cellular damage, mostly of the skeletal and cardiac muscle fibers.

The number of individuals born with GSD II is estimated to be 1 in 40,000. GSD II patients present with a continuous spectrum of phenotypes, with variable age at onset, variable severity, and variable rate of progression. A registry for confirmed GSD II patients has been established (https://clinicaltrials.gov/ct2/show/NCT00231400) to understand the clinical course of the disease and to evaluate long-term treatment effectiveness in Pompe disease. Although there is a wide continuum, three forms have been described in more detail in the literature: (1) infantile GSD II ("classic" Pompe disease) presents in the first few months of life, and most infants die within 12 months from cardiorespiratory insufficiency; (2) "nonclassic" GSD II begins between ages 1 and 2 years; and (3) late-onset GSD has the onset of symptoms at any time after age 2 years, including GSD II presenting in childhood, adolescence, and adulthood (Fig. 23.3). The natural course of late-onset GSD II was studied in detail

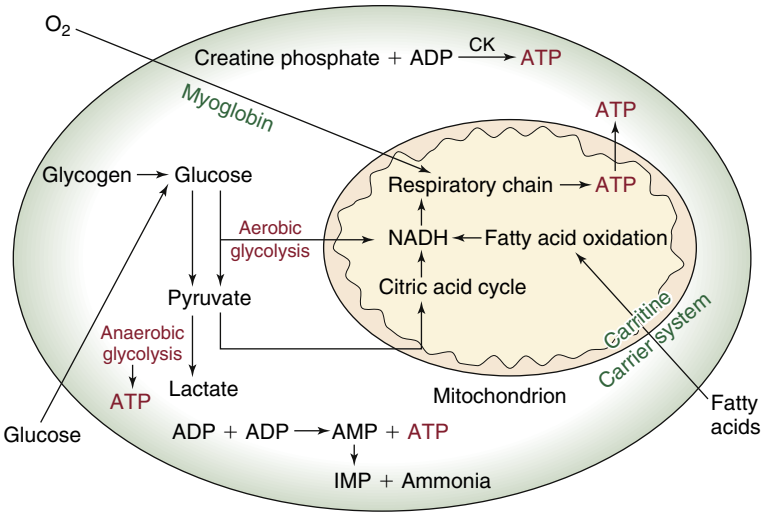


Fig. 23.1 Schematic presentation of important energy pathways in muscle metabolism. *ADP*, Adenosine diphosphate; *AMP*, adenosine monophosphate; *ATP*, adenosine triphosphate; *CK*, creatine kinase; *IMP*, inosine 5'-phosphate; *NADH*, reduced nicotinamide adenine dinucleotide.

in 54 Dutch patients from 45 families. In this large group of patients, the first complaints started at a mean age of 28 ± 14.3 years and were mostly related to mobility problems and limb-girdle weakness. Problems in running and playing sports were reported in approximately 70%, climbing stairs in about 30%, rising from an armchair in 20%, walking in 17%, and rising from a lying position in about 10% of the patients. Fatigue and muscle cramps were frequent first complaints. Approximately 60% of the adult patients had mild muscular symptoms during childhood, such as running more slowly than other children, being unable to keep up with other children during physical exercise or when playing games, as well as frequent falls or gait disturbance. In 28% of the patients, the final diagnosis was made more than 5 years after the first visit to a physician for disease-related symptoms. Some patients were initially diagnosed as having spinal muscular atrophy, Duchenne muscular dystrophy, or Becker muscular dystrophy. Nearly all patients experienced problems walking, varying from imbalance or a waddling gait to a complete inability to walk. About 50% of the group used a wheelchair, and the mean age at which patients started using a wheelchair was 46.1 ± 12.4 years. Approximately 40% required artificial ventilation at the time of investigation, either noninvasively by nose hood or facemask or invasively by tracheal cannula. The mean age at the start of artificial ventilation was 48.6 ± 16.3 years. The course of the late-onset GSD II form was shown to be quite variable between patients with respect to age at onset and rate of disease progression. There was also variability regarding the time at which patients first needed wheelchairs or artificial ventilation.

More than 500 different mutations within the *GAA* gene have been identified so far (www.pompecenter.nl). Approximately 63% of these lead to total loss of acid α-glucosidase, 12% to partial deficiency, and 25% are nonpathogenic. In general, there is good correlation among the nature of the mutation, the degree of residual enzyme activity, and the severity of the clinical presentation. Many patients with the late-onset form carry the c.-32-13T>G mutation on one allele with another *GAA* mutation on the second allele. Some of the mutations are found more frequently in different ethnic groups (Joshi et al., 2008). In the Netherlands, where extended molecular studies have been undertaken, a deletion at nucleotide 525 in exon 2 (del525T) leading to a frameshift (p.Glu176fsX45) and a large deletion of exon 18 (c.2481+102_2646+31del) are frequent. The p.R854X (c.2560C>T) mutation was frequently found among Blacks, and the p.D645E (c.1935C>A) mutation, among Asians.

GLYCOGEN STORAGE DISEASE III

Glycogen-debranching enzyme plays an important role in the degradation of glycogen and has two independent catalytic activities, oligo-1,4→1,4-glucanotransferase and amylo-1,6-glucosidase, on a single 160-kDa protein. Both activities and glycogen binding are required for complete function. In GSD III, debrancher activities are virtually absent in affected organs; the deficiency causes excessive accumulation of abnormal glycogen with truncated outer chains. Most patients (GSD IIIa) have liver and muscle involvement of variable severity and clinical onset. Typical symptoms include fasting hypoglycemia, hepatomegaly, growth retardation, progressive myopathy, and cardiomyopathy. Some patients have only liver involvement without evidence of a myopathy (GSD IIIb).

GLYCOGEN STORAGE DISEASE IV (ANDERSEN DISEASE)

Andersen disease (GSD IV, or amylopectinosis) is an autosomal recessive disease caused by mutations in the glycogen branching enzyme 1 (*GBE1*) gene, resulting in deficiency of the glycogen branching enzyme (GBE). GBE participates with glycogen synthase in the synthesis of glycogen by transferring a minimum of six α-1,4-linked glycosyl units into an α-1,6 position. The human *GBE1* gene is located on chromosome 3p12.3 and has a coding sequence of 2.106 bp with 16 exons encoding a 702–amino acid GBE protein, which is ubiquitously expressed.

Deficiency of GBE results in the accumulation of abnormal, amylopectin-like polysaccharide with fewer branching points, more 1,4-linked units, and longer outer branches

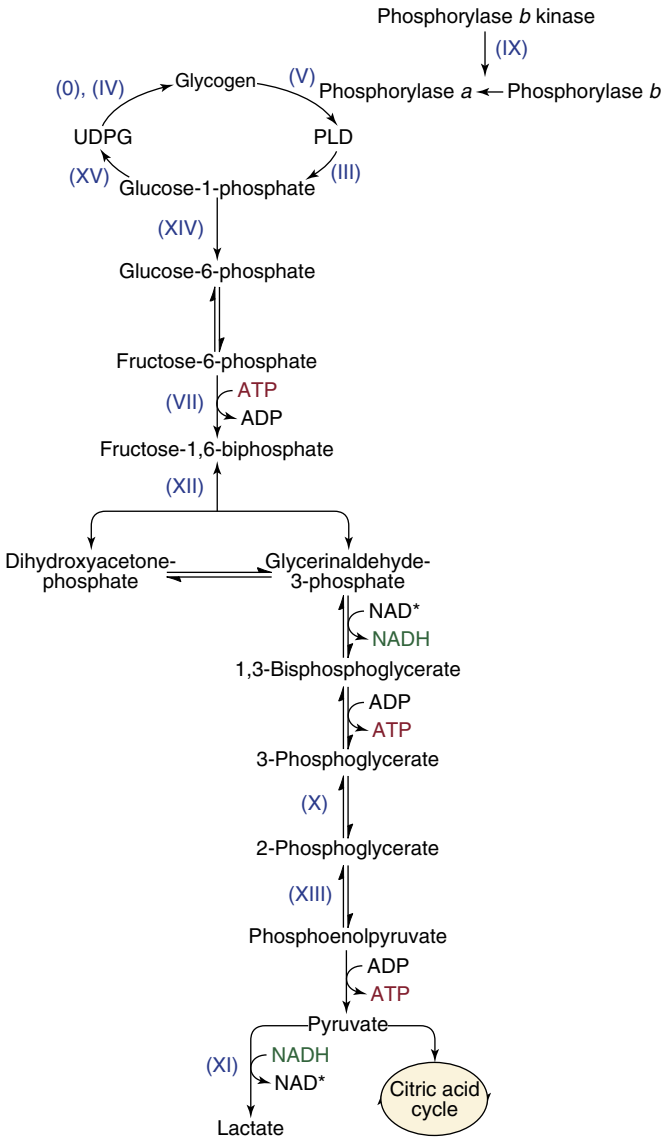


Fig. 23.2 Schematic diagram of the cytosolic glycogen metabolism and glycolysis. Roman numerals indicate the enzymes that are deficient in muscle glycogenoses: 0, glycogen-synthase III, debranching enzyme; IV, branching enzyme; V, myophosphorylase; VII, phosphofructokinase; IX, phosphorylase kinase; X, phosphoglycerate mutase; XI, lactate dehydrogenase; XII, aldolase A; XIII, β-enolase; XIV, phosphoglucomutase 1; XV, glycogenin; PLD, phosphorylase limit dextrin; UDPG, uridine diphosphate glucose. Glycogen storage disease II is caused by a defect of acid maltase, which is located within the lysosomes (not shown in the figure). *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *NAD*, nicotinamide adenine dinucleotide; *NADH*, reduced nicotinamide adenine dinucleotide. (Modified from DiMauro, S., & Lamperti, C. (2001). Muscle glycogenoses. *Muscle & Nerve, 24*, 984–999.)

than normal glycogen. These are called *polyglucosans*, and they accumulate in all tissues to various degrees. The typical clinical phenotype of GSD IV as originally described is characterized by failure to thrive, hepatosplenomegaly, and progressive liver cirrhosis leading to death in early childhood. The neuromuscular presentation of GSD IV is remarkably heterogeneous, with four main variants. The perinatal form presents as fetal akinesia deformation sequence and is characterized by multiple congenital contractures (arthrogryposis multiplex congenita), hydrops fetalis, and perinatal death. The congenital form includes hypotonia, muscle wasting, neuronal involvement, inconsistent cardiomyopathy, and death in early infancy. The childhood form is dominated by myopathy, a neuromuscular form, or cardiomyopathy. The adult form can present as an isolated myopathy or as a multisystem disorder with central and peripheral nervous system involvement (adult polyglucosan body disease).

GLYCOGEN STORAGE DISEASE V (MCARDLE DISEASE)

Glycogenosis type V (GSD V), also known as *myophosphorylase deficiency* or *McArdle disease*, is the most common disorder of muscle carbohydrate metabolism with an estimated prevalence of 1 in 140,000 people (Santalla et al., 2017). GSD V is inherited in an autosomal recessive manner; patients have mutations in both alleles of the *PYGM* gene, which encodes myophosphorylase, the skeletal muscle isoform of glycogen phosphorylase. Myophosphorylase initiates the breakdown of muscle glycogen by removing α-1,4-linked glycosyl units from the outer branches of glycogen, which leads to the liberation of glucose-1-phosphate. Glucose-1-phosphate is normally converted to glucose-6-phosphate, which subsequently undergoes glycolysis, resulting in pyruvate production. Muscle pyruvate can be converted to lactate in anaerobic conditions, which is then released to the blood. Most of the pyruvate crosses the mitochondrial membrane, where it is converted to acetyl coenzyme A (acetyl-CoA) and further metabolized in the citric acid cycle. GSD V patients have absent myophosphorylase activity and are unable to mobilize muscle glycogen stores during exercise. However, they can take up glucose from the blood, which is converted to glucose-6-phosphate and metabolized via the intact glycolytic pathway.

GSD V typically presents with symptoms of exercise intolerance, such as myalgia, painful cramps, muscle contractures, premature fatigue, and episodic myoglobinuria during static or dynamic exercise. In most patients, a few minutes of rest relieves these symptoms. The onset of exercise intolerance usually occurs in childhood; fixed weakness and severe limitations of daily life activities may occur with increasing age.

We examined the muscle pain characteristics in 24 German GSD V patients using detailed pain questionnaires (Rommel et al., 2006); 23 patients complained of intermittent pain, and it was exercise induced in 15. Eight patients reported a more permanent muscle pain, and seven of those had superimposed exercise-induced myalgia. The patients with permanent pain were more often female, and they experienced more problems during higher-impact general activities, resulting in decreased sleep and more fatigue. This study showed that a substantial number of McArdle patients have permanent pain as a major complaint. Because this permanent pain is not related to age or disease duration, it might represent a clinically relevant subgroup of GSD V, differing from those with "pure" exercise-induced symptoms.

A specific feature of GSD V is the "second-wind" phenomenon, which denotes a sudden improvement in exercise capacity after a few minutes of sustained exercise or when resuming exercise after a brief rest. This second wind is produced by an exercise-related increase in the capacity for muscle oxidative phosphorylation, which correlates with

Table 23.1 Clinical Symptoms and Classification of Muscle Glycogen Storage Diseases

GSD	Enzymatic Defect	Chromosome	Clinical Syndrome(s)	Characteristic Features on Muscle Biopsy
Defects in glycogen metabolism				
0	Muscle glycogen synthase	19q13	Cardiomyopathy, exercise intolerance	Lack of glycogen
II (Pompe)	Lysosomal α-1,4-1,6-glucosidase (acid maltase)	17q25	Infantile "classic" form: multiorgan involvement (heart, muscle, liver) Late-onset form: myopathy with atrophy and weakness, respiratory insufficiency	PAS-positive vacuoles; secondary changes: increased acid phosphatase reaction, mitochondrial alterations, autophagic vacuoles, neurogenic-like changes
III (Cori-Forbes)	Debranching enzyme (oligo-1,4-1,4-glucanotransferase, amylo-1,6-glucosidase)	1p21	IIIa: liver (hepatomegaly, growth retardation, fasting hypoglycemia), myopathy with atrophy and weakness or exercise intolerance IIIb: only liver involvement	PAS-positive vacuoles
IV (Andersen)	Branching enzyme (amylo-1,4-1,6-transglucosidase)	3p12	Congenital form: myopathy, cardiomyopathy, neuronal involvement Childhood form: myopathy, cardiomyopathy Adult form: myopathy or APBD	Diastase-resistant PAS-positive deposits; polyglucosan bodies
V (McArdle)	Myophosphorylase	11q13	Exercise intolerance, myopathy with atrophy and weakness (during late disease course), infantile form	PAS-positive deposits; negative phosphorylase staining
IX	Phosphorylase kinase α (muscle) subunit or β-subunit	Xq13 16q13	Exercise intolerance, muscle weakness Liver and muscle involvement	PAS-positive deposits
XIV	Phosphoglucomutase 1	1p31	Exercise intolerance	PAS-positive vacuoles
XV	Glyogenin	3q24	Muscle weakness; cardiac arrhythmia	PAS-positive deposits, polyglucosan bodies
Defects of glycolytic metabolism				
VII (Tarui)	Phosphofructokinase (muscle isoform)	12q13.3	Exercise intolerance, chronic hemolysis, infantile form (rare)	PAS-positive deposits; negative PFK staining; polyglucosan bodies
	Phosphoglycerate kinase	Xq13	Exercise intolerance, chronic hemolysis; rare form with CNS involvement (oligophrenia, delayed motor development, epilepsy)	PAS-positive deposits
X	Phosphoglycerate mutase (muscle isoform)	7p12	Exercise intolerance	PAS-positive deposits
XI	Lactate dehydrogenase (muscle isoform)	11p15	Exercise intolerance, dermatologic symptoms	Normal
XII	Aldolase A	16q22-q24	Exercise intolerance, chronic hemolysis	Normal
XIII	β-Enolase	17pter-p12	Exercise intolerance	PAS-positive deposits
	Triosephosphate isomerase		Myopathy with atrophy and weakness, chronic hemolysis	PAS-positive deposits; secondary changes; mitochondrial alterations

APBD, Adult polyglucosan body disease (motor neuron involvement, polyneuropathy, dementia, urinary incontinence); *CNS*, central nervous system; *GSD*, glycogen storage disease; *PAS*, periodic acid–Schiff; *PFK*, phosphofructokinase.



Fig. 23.3 (A) Patient with late-onset glycogen storage disease II on intravenous enzyme replacement therapy. (B and C) He presents with scapula alata and proximal muscle weakness.

increased availability of blood-borne fuels such as glucose and free fatty acids. It was recently shown that fat oxidation is augmented with the onset of second wind in GSD V patients during a prolonged, low-intensity exercise of 50% to 60% of maximal oxygen uptake capacity (Ørngreen et al., 2009). These results support the theory that the energy deficit in GSD V may be compensated by trials of moderate aerobic exercise to enhance fat oxidation.

In rare cases, GSD V may present with a severe generalized weakness at birth and death in childhood or with late-onset permanent muscle atrophy and weakness not preceded by symptoms of exercise intolerance.

Heterozygous individuals carrying one mutation in the *PYGM* gene may develop muscle symptoms that are considered to be caused by a critically low residual level (30%–40%) of myophosphorylase activity in muscle. A few GSD V families with an apparent autosomal dominant transmission have been reported. Molecular genetic analysis in such "pseudo-dominant" families identified either symptomatic heterozygous carriers in one parent or "true" recessive GSD V in one parent and heterozygosity in the other.

The most common mutation in European and North American GSD V patients is the nonsense mutation at p.R50X (previously referred to as p.R49X). More than 60 different mutations located throughout the entire *PYGM* gene on chromosome 11q13 have been reported. We performed molecular genetic analysis in a large cohort of 56 GSD V patients from Germany, the United Kingdom, and several other European countries. Allele frequency of the p.R50X mutation was 58%, and 71% of the McArdle disease patients carried this mutation on at least one allele. This study also detected 26 other less common mutations, with no clear genotype-phenotype correlation with respect to age of onset or severity (Deschauer et al., 2007). A European Registry for GSD V patients and other rare muscle GSD forms was recently established to collect clinical and epidemiological data for future clinical trials (http://www.euromacregistry.eu).

GLYCOGEN STORAGE DISEASE VII (TARUI DISEASE)

Tarui disease (GSD VII) is caused by an inherited deficiency of muscle phosphofructokinase (PFK) and manifests with the combination of myopathy and hemolysis. Typically, GSD VII begins in early childhood and causes painful cramps or contractures on exercise, limitation of vigorous activity, hyperuricemia, a compensated hemolytic anemia, and, less frequently, myoglobinuria. The disease seems to be prevalent among people of Jewish-Russian ancestry, and the transmission is autosomal recessive. The clinical phenotype of GSD VII is similar to that of McArdle disease, so definitive diagnosis requires biochemical demonstration of the enzyme defect.

GLYCOGEN STORAGE DISEASE

Phosphorylase kinase (Phk) is a regulatory protein kinase that stimulates glycogen breakdown. It receives input from hormonal and neuronal signals transmitted through the second messengers Ca^{2+} and adenosine 3',5'-cyclic monophosphate and responds by phosphorylating and thus activating glycogen phosphorylase. Phk deficiency alone accounts for approximately 25% of all cases of GSDs. Phk consists of four subunits in a hexadecameric complex $(\alpha\beta\gamma\delta)_4$, and each of these subunits has isoforms or splice variants differentially

expressed in different tissues. Consequently, Phk deficiency occurs in several subtypes that differ in mode of inheritance and tissue involvement.

Muscle-specific glycogenosis due to Phk deficiency can manifest in three different clinical forms. Frequently, the disorder becomes clinically apparent at a juvenile or early adult age, presenting with exercise intolerance, which includes pain, cramps, early fatigue, and sometimes myoglobinuria, resembling GSD V. A late-adult-onset form, manifesting with slowly progressive atrophy and weakness, and a neonatal form with generalized muscle hypotonia and respiratory insufficiency have also been described. Most patients with muscle-specific Phk deficiency are male, and mutations in the X-chromosomal gene of the muscle isoform of the Phkα subunit (*PHKA1*) have been identified in a mouse mutant and in two male human patients (Burwinkel et al., 2003).

OTHER MUSCLE GLYCOGENOSES

A family with cardiomyopathy and exercise intolerance caused by mutations in the muscle glycogen synthase gene (*GYS1*) was reported by Kollberg et al. (2007). Glycogen synthase catalyzes the addition of glucose monomers to the growing glycogen molecule through the formation of α-1,4-glycoside linkages (see Fig. 23.2). Although this autosomal recessive metabolic myopathy showed a lack of glycogen deposition in muscle biopsy specimens, it has been classified as muscle GSD type 0 (GSD 0) because of its enzyme defect within the first step of muscle glycogen synthesis.

Phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency (GSD X), lactate dehydrogenase (LDH) deficiency (GSD XI), and β-enolase deficiency (GSD XIII) are rare disorders that present mainly with symptoms of exercise intolerance. In addition to muscle symptoms, most of the glycolytic defects may produce signs of chronic hemolytic anemia. Phosphoglycerate kinase deficency and a subform of GSD IX are inherited in an X-chromosomal recessive manner and only males are reported to be affected, whereas the other muscle GSDs are autosomal recessive disorders. In aldolase A deficiency (GSD XII), muscle atrophy and weakness were associated with symptoms of exercise intolerance. Triosephosphate isomerase deficiency was described in a young girl with chronic hemolytic anemia and myopathy, and her muscle biopsy revealed elevated glycogen and mitochondrial alterations (Eber et al., 1991). GSD XV is caused by digenic mutations in the glycogenin-1 gene (GYG1), the crucial primer enzyme of glycogen synthesis in muscle. GSD XV presents with predominant skeletal muscle symptoms (mainly adult onset limb-girdle muscle weakness) or cardiomyopathy (Hedberg-Oldfors et al., 2017). Abnormally structured PAS-positive glycogen, partially resistant to α-amylase, accumulates as polyglucosan bodies in striated muscle or cardiac tissue.

An additional group of patients present with neuromuscular symptoms and periodic acid–Schiff (PAS)–positive vacuolar changes on muscle biopsy with increased glycogen concentration and without a definite enzymatic defect. These patients should be classified as having a *muscle GSD with an unclear primary defect* and should be further studied on a molecular level when we have more knowledge of the complex regulation and fine-tuning of glycogen metabolism in muscle.

DIAGNOSIS AND EVALUATION

Increased levels of serum creatine kinase (CK) at rest are typical in muscle GSD and may reach the highest levels in rhabdomyolysis as a severe complication of the disease. The degree of CK elevation, however, is not specific for any of the GSD forms and may vary significantly during the disease course. Serum CK can even be normal in some GSD patients, so that normal values do not exclude the diagnosis of GSD.

The ischemic ("anaerobic") forearm test is a simple, widely used test to screen for disorders of muscle glycogen metabolism. It involves measuring plasma ammonia and lactate levels after a short period of isometric contraction of the forearm muscles under ischemic conditions. This test is useful to screen patients before more invasive or expensive investigations, such as muscle biopsy, genetic analysis, or enzymatic analyses, are performed. It shows a characteristic flat lactate response and enhanced ammonia production in most muscle glycogenoses but may produce false-negative results in weak or less motivated patients. In GSD II and IV patients, the forearm test is normal because the cytoplasmic glycogen degradation and glycolytic production of pyruvate are not primarily affected. Compartment syndrome has been described as a severe complication of the ischemic forearm test, so a modified, less unpleasant, and less traumatic aerobic version of the noninvasive test has been developed. This does not require restriction of blood circulation; thus, it is better tolerated and is as sensitive as the classic ischemic test (Kazemi-Esfarjani, Skomorowska, Jensen, Haller, & Vissing, 2002).

If, during the exercise test, there is a lasting lack of raised lactate, the procedure should be repeated, including measurement of pyruvate to detect a possible LDH defect. In LDH deficiency an excessive increase of pyruvate is seen, in contrast to other defects of glycolysis, in which no rise of pyruvate occurs because the metabolic block is located "above" the level of LDH (see Fig. 23.2).

Myoadenylate deaminase (MAD) catalyzes the deamination of AMP to inosine monophosphate in skeletal muscle and plays an important role in the purine nucleotide cycle. In primary MAD deficiency, a flat response of ammonia and a normal increase of lactate can be documented with the forearm test. Thus, this simple test is a useful screening test not only for muscle GSD but also for the more common MAD defect. MAD deficiency presents in approximately 3% of the normal population, and the pathogenic relevance of this enzyme defect is doubtful (Hanisch, Joshi, & Zierz, 2008).

The diagnostic gold standard in muscle glycogenoses is the skeletal muscle biopsy and demonstration of the primary enzyme defect. Histochemical examination of muscle biopsies typically shows vacuoles filled with PAS-positive glycogen in most patients (Fig. 23.4). Diastase can degrade glycogen in skeletal muscle; thus, PAS-positive staining disappears with diastase preincubation, but not in atypical glycogen storage, as in polyglucosan storage disease (GSD IV). PAS-positive deposits of glycogen may be very subtle and only present under the sarcolemma in some muscle fibers. Some GSDs with glycolytic defects may not show increased glycogen with PAS staining. In GSD 0, there is a lack of glycogen in skeletal muscle. Acid phosphatase staining of muscle biopsy in GSD II patients often shows an increased lysosomal activity within cytoplasmic vacuoles (see Fig. 23.4). In GSD V and GSD VII, absent histochemical staining for myophosphorylase or PFK leads to the diagnosis (Fig. 23.5).

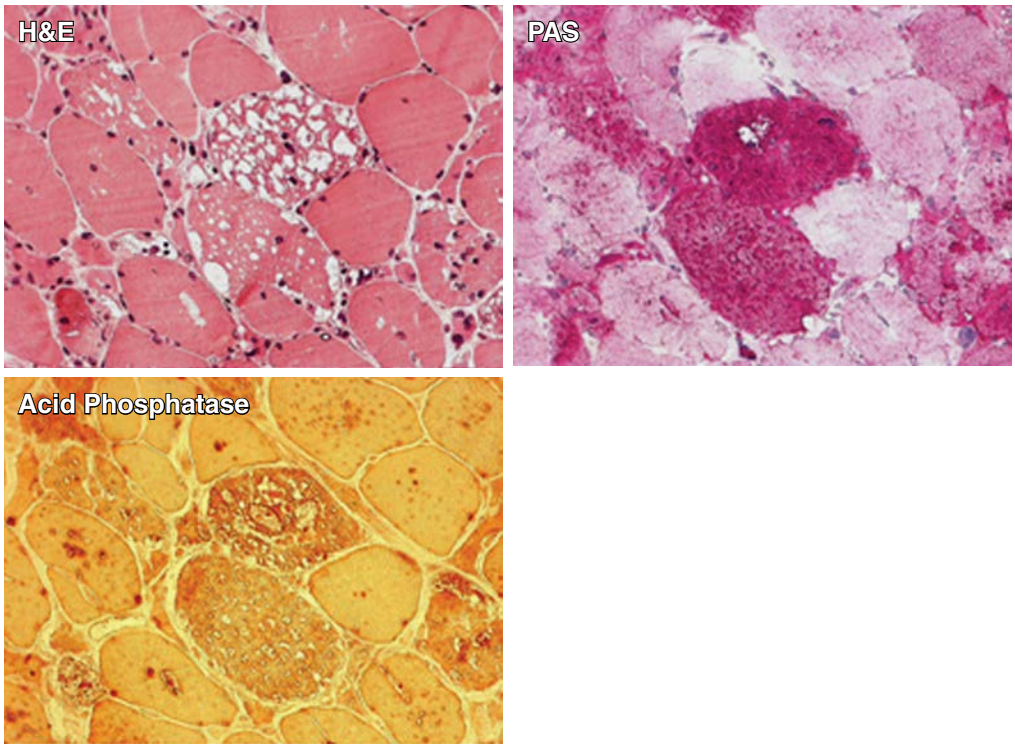


Fig. 23.4 Vacuolar myopathy in late-onset glycogen storage disease II (Pompe disease). Muscle fibers harbor vacuoles in frozen sections stained with hematoxylin and eosin (H&E). Many fibers are reactive for acid phosphatase, and most vacuoles are filled with periodic acid–Schiff (PAS)–positive material.

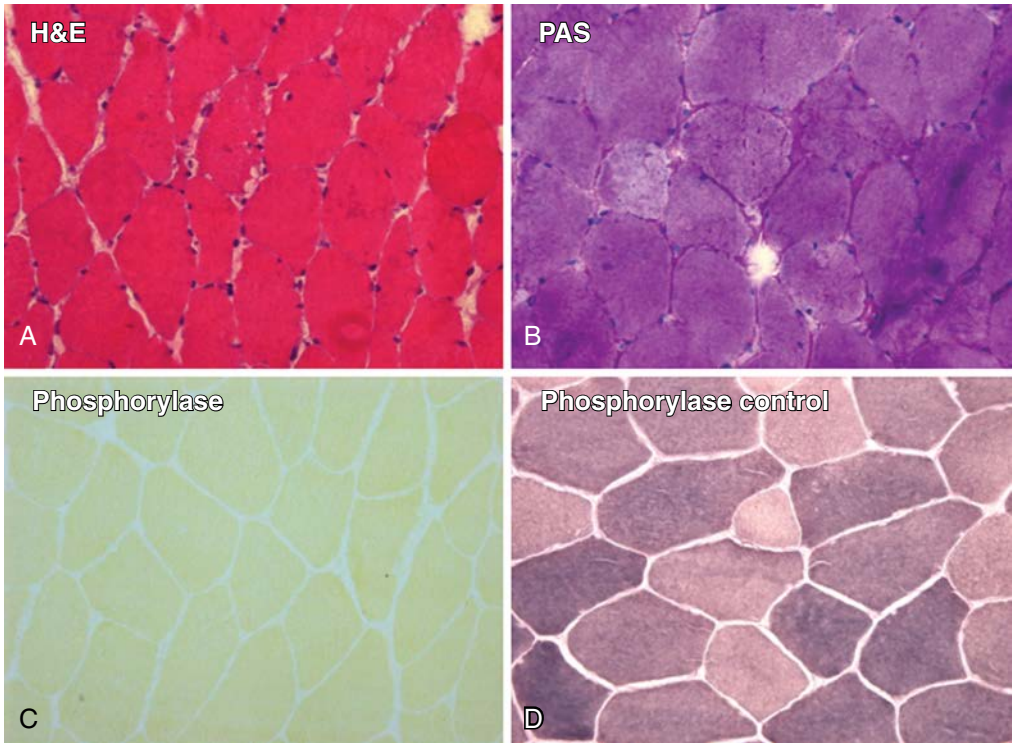


Fig. 23.5 (A) Muscle biopsy specimen from a patient with glycogen storage disease V (myophosphorylase deficiency). Hematoxylin and eosin (H&E) stain shows subsarcolemmal vacuoles. Some fibers harbor periodic acid–Schiff (PAS)–positive deposits of glycogen (*stained pink*) under the sarcolemma (B). All fibers show absent histochemical reaction for phosphorylase (C), whereas phosphorylase reaction is normal in a control patient (D).

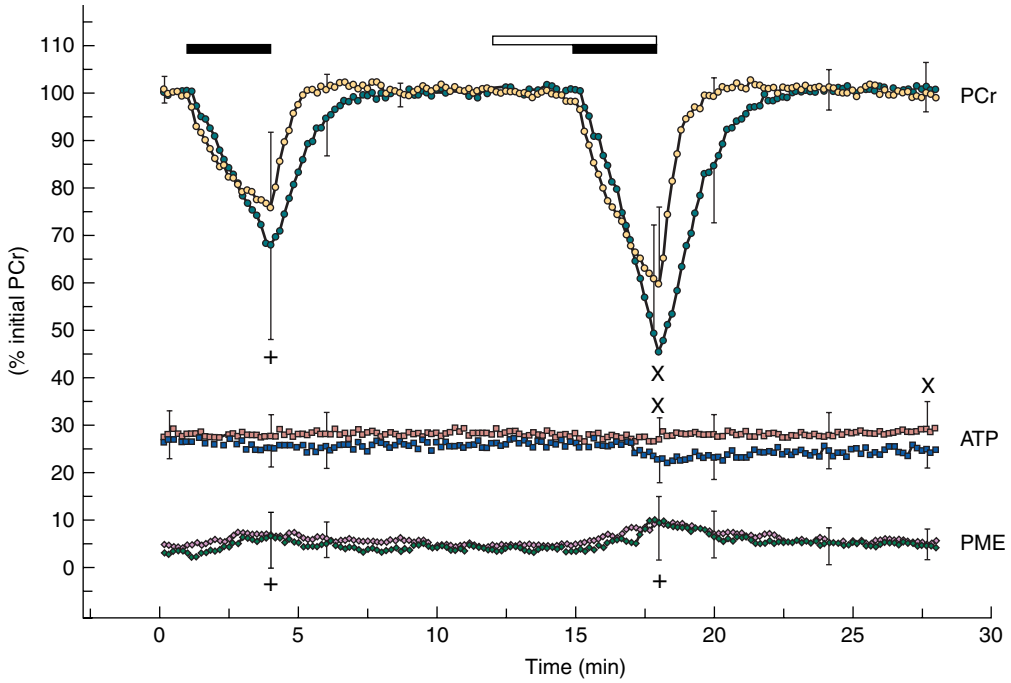


Fig. 23.6 Phosphorus-31 magnetic resonance spectroscopy in the calf muscle of patients with glycogen storage disease V (GSD V; McArdle disease) (*dark circles*) and healthy controls (*circles*). During aerobic (*filled bar*) and muscle contraction with arterial occlusion (*open bar*), moderate acidosis and moderate phosphocreatine (PCr) consumption are found in healthy controls, while adenosine triphosphate (ATP) is kept on constant levels. In patients with GSD V, however, the test contractions always result in a large alkalinization. Alkalinization is caused by the significantly larger PCr consumption than in controls and the absent increase of H^+ by lactic acid formation. In most GSD V patients, a distinct drop in ATP levels is found, which, on average, resulted in significantly lower ATP concentrations at the end of contraction compared to the previous state at rest and to corresponding values of healthy controls. The decrease in ATP is mirrored by an increase in the phosphomonoester (PME) signal, most likely indicating an increase in inosine monophosphate by the degradation of the total adenosine phosphate pool. (From Zange, J., Grehl, T., & Disselhorst-Klug, C. (2003). Breakdown of adenine nucleotide pool in fatiguing skeletal muscle in McArdle disease: A noninvasive 31P-MRS and EMG study. *Muscle & Nerve, 27*, 728–736.)

In GSD X, tubular aggregates in addition to glycogen storage are characteristic.

Enzymatic testing can provide a definitive diagnosis of GSD. In GSD III, GSD IV, and GSD VII, the enzymatic tests can be performed not only on skeletal muscle tissue but also on leukocytes, because the enzymes primarily involved in these disorders are also expressed in blood cells. In most types of GSD, the enzymatic assays show either absent activity or some residual activity of the defective enzyme, usually with variable and unspecific increase in glycogen concentration. The fluorometric technique for the assessment of GAA activity in dried blood specimens instead from lymphocytes provides a reliable diagnosis for all variants of Pompe disease. The assay protocol was simplified for neonatal screening, which allows a facilitated diagnosis (Lukacs et al., 2010).

Molecular genetic analysis is performed mostly to confirm the diagnosis. In GSD families with a known mutation, it is the method of choice in symptomatic members suspected to have the disease. In such cases, muscle biopsy and enzymatic testing can be avoided. Mutation analysis should also be considered in patients in whom a definite diagnosis cannot be achieved on the basis of clinical, laboratory, and enzymatic studies alone.

We have used phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) to measure muscle energy metabolism noninvasively in various muscle GSDs. In GSD V patients, 3 minutes of isometric exercise at 30% to 40% of maximal voluntary contraction results in a strong H^+ consumption and an increase in pH by about 0.3 units. In contrast, H^+ consumption assessed by phosphocreatine (PCr) breakdown is typically overwhelmed by lactic acidosis in healthy subjects, resulting in moderate acidosis. GSD V patients typically consume more PCr for a given workload, and, in most patients, ATP levels decrease because CK reaction and oxidative phosphorylation cannot compensate for the ATP consumption (Fig. 23.6). In GSD VII, muscle exercise additionally results in an impressive increase in the phosphomonoester peak, representing a massive sugar phosphate accumulation "above" the enzymatic block of PFK (Fig. 23.7). Taking these findings to the bedside, we use ^{31}P-MRS to screen patients with symptoms of exercise intolerance suspected to have GSD V or GSD VII. If they show such typical MRS findings, we go forward with mutational studies to reach a definite diagnosis and avoid a muscle biopsy. This method is available in only a few centers and is not done routinely.

TREATMENT

GLYCOGEN STORAGE DISEASE II

Enzyme replacement therapy (ERT) with recombinant alglucosidase alfa (Myozyme, Genzyme Corp., Framingham, MA) became available in 2006 for all forms of GSD II; this represents the first effective, disease-specific treatment for Pompe disease patients. It has been demonstrated that ERT improves cardiorespiratory and motor functions and

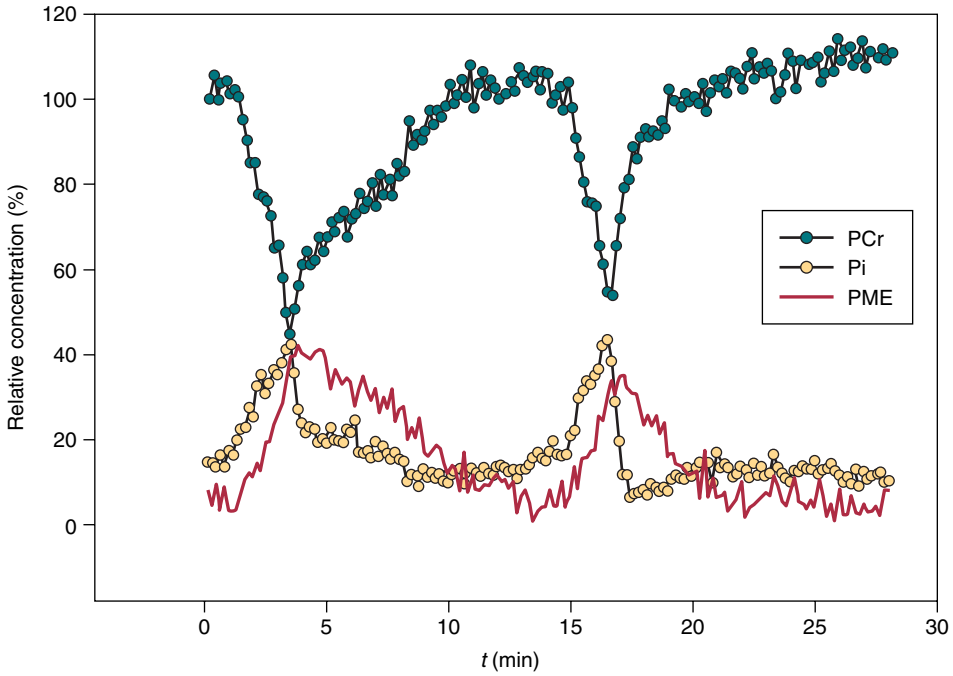


Fig. 23.7 Phosphorus-31 magnetic resonance spectroscopy in a patient with glycogen storage disease VII (GSD VII: phosphofructokinase deficiency). The absence of glycolytic adenosine triphosphate production results in a linear time course of phosphocreatine (PCr) breakdown during aerobic (first 3 minutes) and ischemic submaximal contraction of calf muscle. The level of phosphomonoesters (PMEs) shows a drastic increase during aerobic and ischemic muscle contraction, indicating an excessive accumulation of hexose phosphates (e.g., glucose-6- and fructose-6-phosphate) during submaximal exercise. *Pi*, Inorganic phosphate. (From Grehl, T., Müller, K., & Vorgerd, M., et al. (1998). Impaired aerobic glycolysis in muscle phosphofructokinase deficiency results in biphasic post-exercise phosphocreatine recovery in 31P magnetic resonance spectroscopy. *Neuromuscular Disorders, 8*, 408–488.)

prolongs survival in infantile GSD II patients (Amalfitano et al., 2001; Kishnani et al., 2006, 2007; Klinge et al., 2005; Klinge, Straub, Neudorf, & Voit, 2005; Van den Hout et al., 2000, 2004). In older children and adults, ERT improves or stabilizes skeletal muscle strength, muscle function, respiratory function, and also life expectancy (Van der Ploeg et al., 2010). However, the magnitude of the therapeutic responses varies considerably among individual patients. In a prospective multicenter study in GSD II adults, the majority benefit from long-term ERT, but many patients experience some secondary deterioration in muscle strength, walking ability, and/or pulmonary function after 3–5 years (Harlaar et al., 2019).

Recommendations on starting and stopping the expensive ERT in adult patients were developed, based on experience of experts and evidence reported in the literature (Van der Ploeg et al., 2017). Patients receiving this treatment must have a confirmed diagnosis and presence of symptoms to start ERT. The commonly used treatment protocol consists of alglucosidase alfa 20 mg/kg body weight infusion every other week, although doses as high as 40 mg/kg per infusion have been used in individual patients. Regular 6-minute walking tests and forced vital capacity should be performed to follow the individual disease course and evaluate the treatment effects in late-onset GSD II patients receiving ERT. Stopping ERT should be considered in patients suffering from severe infusion-associated reactions or in patients with high antibody titers that significantly counteract the ERT effect. ERT continuation can be considered during pregnancy and lactation (Van der Ploeg et al., 2017).

GLYCOGEN STORAGE DISEASE V

In contrast to GSD II, no ERT or effective gene therapy is available for the other muscle GSDs. In these disorders, treatment is mainly symptom oriented (Quinlivan, Beynon, & Martinuzzi, 2008). Creatine is an amino acid formed from arginine, glycine, and methionine in a two-step reaction that takes place in the kidneys and liver. After this, creatine incorporates in skeletal muscle, where it is transported across the cell membrane via a sodium-dependent creatine membrane transporter (Willott et al., 1999). Due to the equilibrium reaction of CK, it is expected that an uptake of creatine by muscle fibers results in an elevation of intracellular PCr levels. Transphosphorylation of ATP on creatine and subsequent rephosphorylation of ADP by oxidative phosphorylation should result in the detection of elevated PCr/ATP ratios in ^{31}P-MRS of muscle. However, in patients with McArdle disease, oral creatine supplementation at both high (150 mg/kg/day) and low (60 mg/kg/day) doses did not result in elevated PCr/ATP ratios. With low-dose creatine, working capacity during ischemic exercise improved; a higher consumption of PCr during aerobic and low-level ischemic low-level exercise was seen in McArdle disease patients (Vorgerd et al., 2000). However, high-dose creatine cannot be recommended because it worsened the clinical symptoms of exercise intolerance; patients reported an increase in the number of pain episodes and an increase in the myalgia pain score (Vorgerd et al., 2002).

In a crossover open design, we compared the effects of a carbohydrate-rich (20% fat, 15% protein, 65% carbohydrate) versus a protein-rich (15% fat, 55% proteins, 30%

carbohydrate) diet in GSD V patients. Exercise tolerance and maximal work capacity were tested on a cycle ergometer, using a constant workload for 15 minutes, followed by an incremental workload to exhaustion. The carbohydrate-rich diet improved the maximal work capacity and the exercise tolerance of submaximal workloads (Andersen & Vissing, 2008).

Moderate aerobic exercise was tested in GSD V patients who pedaled a cycle ergometer for 30 to 40 minutes a day, 4 days a week, for 14 weeks, at an intensity corresponding to 60% to 70% of maximal heart rate. This exercise program increased average work capacity, oxygen uptake, cardiac output, and mitochondrial enzyme levels without causing pain or cramping or increasing serum CK. This study suggests that regular, submaximal aerobic exercise increases oxidative capacity and should be a consistent component of therapy in GSD V patients (Haller, Wyrick, Taivassalo, & Vissing, 2006).

In GSD V patients, a genotype (D/D) associated with higher angiotensin-converting enzyme (ACE) activity showed a more severe phenotype of exercise intolerance (Martinuzzi et al., 2003; Rubio et al., 2007). It was suggested that modulation of ACE activity through the use of inhibitors such as ramipril could positively affect disease expression and increase exercise capacity. A controlled trial of 12 weeks of low-dose ramipril treatment (2.5 mg/day) in GSD V patients did not show changes in the primary outcome measures of exercise physiology, although it showed a possible benefit in patients with the D/D ACE genotype (Martinuzzi et al., 2008).

Aminoglycosides may allow the potential to read through stop codons and thus may induce synthesis of a full-length protein. In most GSD V patients, the primary genetic abnormality is a missense mutation R50X in the phosphorylase gene, leading to a premature stop codon. Daily intravenous (IV) gentamicin sulfate 8 mg/kg/day was given for 10 days in four R50X homozygous GSD V patients in an open study. This short-term aminoglyoside treatment appeared to have no effect on muscle energy metabolism as assessed by ^{31}P-MRS (Schroers et al., 2006). It is possible that the lack of benefit was due to the short treatment time or that the type of nonsense mutation was not amenable to the effects of the drug. This potential therapeutic strategy may be exploited in the future with new pharmacologic compounds with similar effects.

Sucrose, a disaccharide of glucose and fructose, is the most important sugar in plants. Six GSD V patients were tested after ingestion of either 75 g of sucrose 40 minutes before exercise or 37 g of sucrose 5 minutes before exercise (Andersen, Haller, & Vissing, 2008). Treatment effects were assessed by monitoring heart rate and perceived exertion during exercise. Both sucrose treatments improved exercise tolerance; the low-dose, 5-minute sucrose trial had a more sustained effect on exercise capacity than the 40-minute trial. The authors recommend low-dose sucrose ingestion immediately before episodes of more strenuous exercise. This provides a sustained elevation in plasma glucose during exercise, which partially rescues muscle oxidative metabolism early in exercise (Box 23.1).

A ketogenic diet may bypass the enzyme defect of glycogen utilization and may be a feasible tool to improve GSD V symptoms; this has been demonstrated in one patient (Busch et al., 2005). Another dietary approach is the ingestion of vitamin B_6, which has shown beneficial effects in one GSD V patient (Phoenix et al., 1998). Both approaches, however, require more systematic evaluation in a larger group of patients.

Box 23.1 Treatment Options in McArdle Disease (GSD V)

High-carbohydrate and low-fat diet
Low-intensity aerobic exercise
Supplementation with oral creatine (60 mg/kg/day)
Sucrose before exercise

In summary, in the most severe infantile GSD II patients without ERT, death results from cardiac and respiratory failure within the first 1 or 2 years of life. In the milder late-onset forms, cardiac muscle is usually spared and a progressive skeletal muscle weakness is the main symptom. Weakness of respiratory muscle is the major cause of death in late-onset GSD II. Long-term ERT positively affects or slows deterioration of skeletal and/or pulmonary function in GSD II adults. In most cases, the natural course of GSD V and GSD VII appears nonprogressive, without significant limitations of life expectancy and without severe cardiorespiratory complications. Currently, no systematic data are available on the natural disease course of the other muscle glycogenoses due to the extreme rarity of these conditions.

When subjected to surgery and anesthesia, GSD patients have the potential to develop perioperative complications, such as hypoglycemia, rhabdomyolysis, myoglobinuria, acute renal failure, postoperative fatigue, and possibly malignant hyperthermia. Because a small subset of GSD V patients were shown to have a positive in vitro contracture test, in all GSD patients simple prophylactic measures as with malignant hyperthermia must be recommended (also see Chapter 10). A retrospective study using questionnaires in German and UK women with GSD II showed no increased risk of pregnancy or delivery complications. However, muscle weakness and respiratory complications might manifest or worsen during pregnancy in some women (Karabul et al., 2014).

CONCLUSION

Thus far, an effective causative therapy in glycogen storage myopathies is available only for the lysosomal GSD II (Pompe disease), underscoring the need for a definite and early diagnosis in this disease. All GSD patients reporting exercise intolerance must be advised to avoid trigger factors of rhabdomyolysis (e.g., static and dynamic muscle contractions at a high-intensity level) and should follow a high-carbohydrate diet. Nutritional supplementation with low-dose creatine or sucrose may help to reduce symptoms of exercise intolerance in GSD V and possibly the other GSDs with similar symptoms. There is an urgent need to further develop molecular-oriented therapeutic strategies in the future.

MUSCLE DISORDERS OF LIPID METABOLISM

Enzyme deficiencies that affect lipid metabolism, impairing the transport of fatty acids into the mitochondria (carnitine transporter system), beta-oxidation, and utilization of

Table 23.2 Defects of Lipid Metabolism Resulting in Myopathy

Biochemical Defect	Affected Gene(s)	Typical Muscle Phenotype	Characteristic Changes of Acyl-Carnitine Spectrum in Blood	Muscle Histology
Carnitine palmitoyl-transferase II deficiency	*CPT II*	Attacks with myoglobinuria	C16:0 and C18:1 carnitine elevated	Often normal interictally
Multiple acyl-coenzyme A (CoA) dehydrogenase deficiency (glutaric aciduria type 2)	*ETFDH*, *ETFA*, or *ETFB*	Permanent muscle weakness	Multiple acyl-carnitines (C4–C18:1) elevated	Lipid storage
Medium-chain acyl-CoA dehydrogenase deficiency	*MCAD*	Attacks with myoglobinuria; permanent muscle weakness	C8 carnitine elevated	Lipid storage
Very long chain acyl-CoA dehydrogenase deficiency	*ACADVL*	Attacks with myoglobinuria	C14:1 carnitine elevated	Often normal interictally
Primary muscle carnitine deficiency	Unknown	Permanent muscle weakness	Carnitine rarely reduced	Lipid storage
Primary systemic carnitine deficiency (carnitine transporter defect)	*SLC22A5 (OCTN2)*	Hypotonia, cardiomyopathy	Carnitine reduced	Lipid storage
Trifunctional protein deficiency (deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase, long-chain 2-enoyl-CoA hydratase, and long-chain 3-ketoacyl-CoA thiolase)	*HADHA* and *HADHB*	Attacks with myoglobinuria	3-hydroxy C16 and C18 acylcarnitine elevated (can be normal interictally)	Often normal interictally
Short-chain acyl-CoA dehydrogenase deficiency	*ACADS*	Hypotonia	C4 carnitine elevated	Sometimes lipid storage
Neutral lipid storage disease with ichthyosis	*ABHD5 (GCI58)*	Permanent muscle weakness	Normal	Abundant lipid storage
Neutral lipid storage disease without ichthyosis Carnitine-acylcarnitine-translocase deficiency (CACT deficiency) Lipin deficiency Long chain acyl-CoA deficiency (LCAD deficiency) Short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (SCHAD deficiency) Median-chain 3-ketoacyl-CoA thiolase (MCKAT deficiency)	*SLC25A20* *LPIN1* *ACLDL* *HADH* *MCKAT*	Permanent muscle weakness Hypotonia Attacks of myoglobinuria, permanent muscle weakness Attacks of myoglobinuria, permanent muscle weakness Attacks of myoglobinuria, permanent muscle weakness Attacks of myoglobinuria	Normal C16:0, C18:0, C18:1, C18:2 carnitine elevated C14:1 carnitine elevated C4 carnitine elevated C4 carnitine elevated C12–C16 carnitine elevated	Abundant lipid storage Not reported Normal interictally Normal interictally Often normal interictally Not reported

triglycerides, can cause muscle disease. The frequently used term *lipid storage myopathies* for these disorders is accurate only for some forms, because several of these disorders do not show lipid accumulation on muscle biopsy. Thus, the term *myopathies of lipid metabolism* is more appropriate for this group of metabolic myopathies. All known enzyme defects of lipid metabolism follow an autosomal recessive mode of inheritance. Muscle is not the only tissue affected in these disorders; the brain, heart, liver, and skin can also be involved. In children, myopathy is often overshadowed by encephalopathy or cardiomyopathy, but in adults, muscle problems are usually the primary manifestation. At present, nine different enzyme defects are known to affect lipid metabolism of muscle (Table 23.2). Some of these have been described in only a few patients, whereas others are more common. However, data about the frequency of myopathies due to disorders of lipid metabolism are not available. CPT II deficiency seems to be the most frequent form.

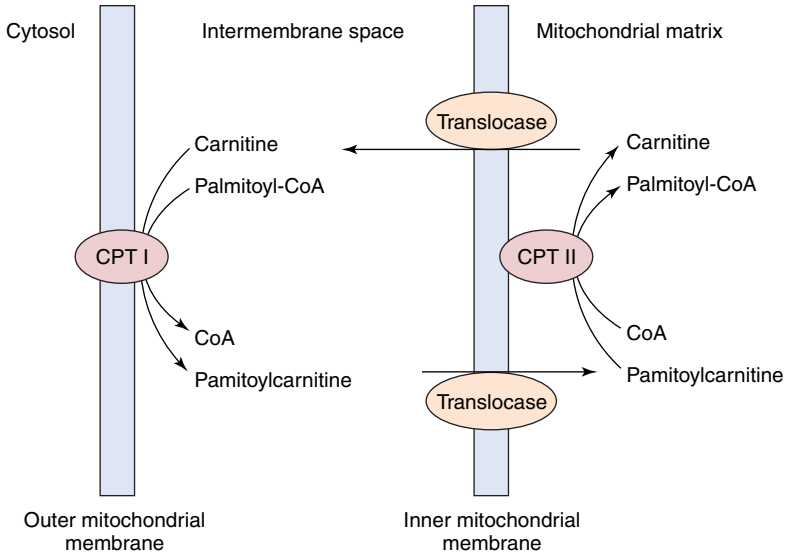


Fig. 23.8 Carnitine shuttle system for import of long-chain fatty acids through the inner mitochondrial membrane. *CoA*, Coenzyme A; *CPT*, carnitine palmitoyltransferase.

CLINICAL PRESENTATION

Disorders of lipid metabolism can present with a profound enzyme deficiency, resulting in severe early onset multisystemic disease. Typically, episodes of hypoketotic hypoglycemia and liver failure (Reye-like disease) occur. These children present with encephalopathy leading to lethargy and coma, muscle weakness, and cardiac arrhythmias. Milder phenotypes are restricted to muscle with onset not only in childhood but also in adulthood. These show higher residual enzyme activities in regard to muscle involvement. Two clinical presentations can be distinguished. Some manifest with recurrent attacks of rhabdomyolysis triggered by long-lasting exercise, fasting, infections, or cold. Other disorders present with permanent muscle weakness.

Recurrent attacks of rhabdomyolysis occur in CPT II deficiency. The enzymes CPT I and II are part of the carnitine transporter system located in the outer (CPT I) and inner (CPT II) mitochondrial membranes to incorporate long-chain fatty acids from the cytosol into the mitochondrial matrix (Fig. 23.8). In the most common form of CPT II deficiency, symptoms are restricted to muscle. This form is a common cause of hereditary rhabdomyolysis and is also called the "adult" form of CPT II deficiency. Despite the common adult onset, first attacks can occur in early childhood. In contrast to McArdle disease (GSD V)—another rather frequent metabolic myopathy that causes rhabdomyolysis—patients with CPT II deficiency do not suffer from muscle cramps. In addition to the muscle form of CPT II deficiency, a multisystemic form is seen in infants, affecting the liver and heart and sometimes associated with muscle weakness. This type manifests mainly with lethargy and encephalopathy as consequences of hypoketotic hypoglycemia. Finally, there is a neonatal lethal form with congenital anomalies. However, these forms are much less common than the muscle form.

Another disorder of the carnitine carrier system that involves muscle is primary carnitine deficiency, which results from a defect of the carnitine transporter. These patients excrete the filtered carnitine in the urine. There are two clinical manifestations of primary carnitine deficiency: systemic primary carnitine deficiency, which presents as a multisystemic infantile disease with metabolic crises, and primary muscle carnitine deficiency, with late-onset and permanent muscle weakness (Longo, Di San Filippo, & Pasquali, 2006). Secondary forms of carnitine deficiency are observed in several other muscle disorders, including acyl-CoA dehydrogenase deficiencies. Moreover, drugs such as valproate and zidovudine can also cause a secondary carnitine deficiency.

Different enzymes are necessary for beta-oxidation of fatty acids within the mitochondria depending on the length of the fatty acids that are metabolized (short, medium, long, and very long chain acyl-CoA). The different defects can result in late-onset metabolic myopathies or in infantile multisystemic diseases, including muscular hypotonia.

Clinical presentation of the late-onset myopathic form of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is similar to that of muscle CPT II deficiency. Patients present with attacks of rhabdomyolysis after long-lasting exercise or fasting (Voermans, van Engelen, Kluijtmans, Stikkelbroeck, & Hermus, 2006). In patients with infantile hepatic manifestations of VLCAD deficiency, the myopathic phenotype can present in later life (Shchelochkov, Wong, Shaibani, & Shinawi, 2009). Attacks of rhabdomyolysis are also observed in the late-onset form of trifunctional protein deficiency, frequently associated with peripheral neuropathy. However, in contrast to VLCAD and CPT II deficiencies, these were observed only in childhood (Spiekerkoetter, Bennett, Ben-Zeev, Strauss, & Tein, 2004).

Multiple acyl-CoA dehydrogenase deficiency (MADD) is caused by defects in flavoproteins that are responsible for transfer of electrons from flavin adenine dinucleotide to the respiratory chain: electron transfer flavoprotein (ETF), encoded by two genes—*ETFA* (subunit A) and *ETFB* (subunit B)—and ETF ubiquinone oxidoreductase (ETF:QO), encoded by the *ETFDH* gene. MADD affects not only multiple acyl-CoA dehydrogenases but also the metabolism of amino acids and choline. The defect of amino acid metabolism

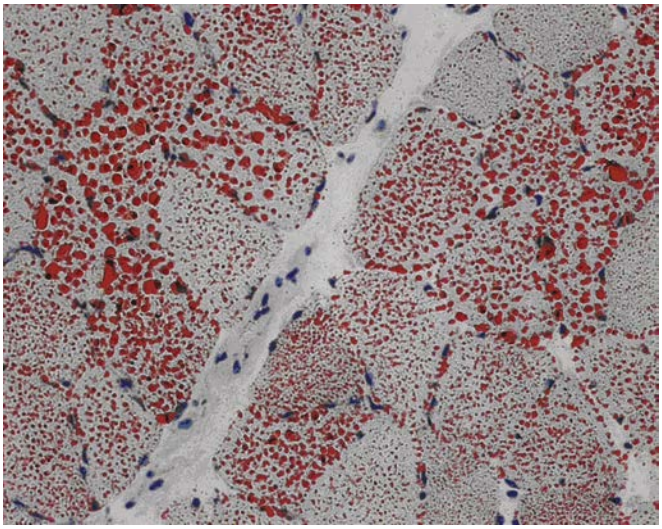


Fig. 23.9 Oil Red O staining showing lipid droplets.

results in glutaric aciduria; MADD is also called *glutaric aciduria type II*. MADD can manifest as a severe neonatal disorder, but later-onset cases are seen in children and adults, affecting muscle only and resulting in permanent weakness. Some patients with later onset can also have episodes of encephalopathy generally precipitated by an infection. Children typically suffer from recurrent episodes of vomiting (Gempel et al., 2007; Olsen et al., 2007).

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a common disorder of fatty acid metabolism resulting in infantile metabolic decompensation, including hypotonia or rhabdomyolysis (Hsu et al., 2008). Late-onset disease with predominant muscle involvement is rare. Short-chain dehydrogenase deficiency typically manifests in childhood. Muscle weakness is seen in some patients as a manifestation of a mild multisystemic presentation in which developmental delay is the leading feature. A juvenile late-onset form with muscle weakness is observed rarely (van Maldegem et al., 2006).

Finally, there are disorders affecting the utilization of stored triglycerides due to a defect of the triglyceride lipase. These are called *neutral lipid storage diseases*. Two different forms of neutral lipid storage disease are associated with different gene defects: neutral lipid storage disease with ichthyosis, also known as *Chanarin-Dorfman syndrome* (*ABHD5* gene), which manifests an ichthyosiform nonbullous erythroderma (Bruno et al., 2008), and *neutral lipid storage disease without ichthyosis* (*PNPLA2* gene) (Fischer et al., 2007). The latter form can present not only with proximal but also with distal muscle weakness.

DIAGNOSIS AND EVALUATION

Analysis of the acyl-carnitine profile and carnitine level in blood by tandem mass spectrometry can provide insights about the underlying enzyme deficiency of lipid metabolism. This is a useful screening test in patients with unknown myopathy and can be performed before a muscle biopsy. It is also done in newborn screening using dried blood spots (Guthrie card), but analysis of serum samples should be preferred. In enzyme defects of lipid metabolism, there is accumulation of certain fatty acids in blood. For example, in CPT II deficiency, the long-chain fatty acids C16 and C18:1 are increased (Gempel et al., 2002). Typical profiles of different disorders of muscle lipid metabolism are listed in Table 23.2. The diagnostic yield is maximized if the specimens are obtained during a metabolic crisis or after fasting overnight. However, a normal acyl-carnitine spectrum does not exclude a myopathy of lipid metabolism because the acyl-carnitine profile can be normal between attacks.

Serum CK is often normal between attacks in muscle disorders of lipid metabolism that are characterized by episodes of rhabdomyolysis. A mild or moderate elevation of CK is typically observed in patients with permanent weakness. Creatinine levels should always be obtained to detect renal failure in patients with rhabdomyolysis. Myoglobin and ketones should be measured in blood and urine. In children with Reye-like symptoms, mild hyperammonemia and elevated liver enzymes can be present. Analysis of organic acid profile in urine is important, especially to detect glutaric aciduria in MADD.

Histologic studies typically reveal clear lipid accumulation only in those with permanent weakness. In patients with attacks of myoglobinuria, muscle biopsies done during the acute phase can show only necrotic fibers, but these are frequently normal interictally, and these forms may demonstrate little or no lipid accumulation. Muscle biopsies should not be taken during the phase of rhabdomyolysis, but several weeks later, because necrosis can mask the characteristic features of metabolic myopathies. Lipid accumulation is frequently more pronounced in the oxidative type I fibers than in type II fibers, because normal muscle also contains more lipid in type I fibers. The most pronounced lipid accumulation is seen in neutral lipid storage disease. Lipid droplets can be stained by Oil Red O (Fig. 23.9) or by Sudan Black. VLCAD deficiency can be detected by immunohistochemistry (Ohashi et al., 2004). In neutral lipid storage diseases, peripheral blood smears typically show neutral lipid vacuoles in leukocytes (Jordan anomaly) (Bruno et al., 2008; Fischer et al., 2007).

Further investigations of the enzyme molecular genetic defect are necessary to confirm the diagnosis of lipid myopathies. In late-onset cases, there is often considerable residual enzyme activity that makes diagnosis difficult. For example, in patients with muscle CPT II deficiency, there is normal activity of CPT under optimal assay conditions. However, abnormal regulation of the enzyme can be seen by abnormal inhibition by malonyl CoA. Biochemical analysis of enzyme deficiencies in lipid metabolism of muscle is difficult, and these studies are performed only in specialized laboratories. Fibroblasts and lymphocytes are also tissues in which the enzymes can be measured. Fatty acid oxidation rates can be measured in fibroblasts by incubating cells with radiolabeled fatty acids of different chain length. This method can differentiate short-, medium-, or long-chain defects. Carnitine levels can be measured not only in blood but also in muscle, bearing in mind that secondary carnitine deficiency is quite common. Secondary coenzyme Q (CoQ) deficiency in muscle can be measured in MADD due to a defect of ETF:QO (Gempel et al., 2002).

Molecular genetic testing is relatively simple for CPT II and MCAD deficiencies. Although more than 40 mutations are known in the *CPT2* gene, a missense mutation p.S113L in patients with muscle CPT II deficiency is found in approximately 60% of mutant alleles. More than 90% of the patients carry

this mutation on at least one allele (Joshi, Deschauer, & Zierz, 2014). In patients with MCAD deficiency, there is a common point mutation p.K329E with similar frequency compared to the CPT II mutation p.S113L (Hsu et al., 2008). Such common mutations are not present in other genes affected in myopathies of lipid metabolism, and molecular genetic testing requires primary sequencing of the gene.

TREATMENT

Treatment strategies for myopathies caused by defects of lipid metabolism include avoidance of exacerbating factors, dietary regimens containing high amounts of carbohydrate, supplementation with fatty acids that bypass the enzyme defect, riboflavin or carnitine, and IV glucose.

Avoidance of exacerbating factors still plays a large role in the management of patients with attacks of rhabdomyolysis or metabolic crises. In children, fasting and infections are the major causes of metabolic decompensation and rhabdomyolysis. Thus, regular feedings are essential in children. In adults, exercise and cold temperatures are the major precipitants of rhabdomyolysis. Thus, avoidance of intense or prolonged exercise and protection from cold are necessary. Certain drugs, such as valproate, diazepam, and ibuprofen, can trigger attacks in patients with CPT II deficiency.

In general, the recommended dietary regimen for patients with disorders of lipid metabolism is a high-carbohydrate, low-fat diet with frequent and regularly scheduled meals. Slow-release carbohydrate intake should be increased during intercurrent illness or sustained exercise.

In patients with muscle CPT II deficiency, it has been shown that ingestion of polysaccharides can improve exercise intolerance, whereas oral glucose ingestion does not (Ørngreen, Ejstrup, & Vissing, 2003). This study also demonstrated that IV glucose infusions improve exercise intolerance in patients with CPT II deficiency (Box 23.2). IV glucose can be recommended in crises of infantile CPT II deficiency (including insulin that reduces mobilization of the stored lipids) (Bonnefont et al., 2004) but is not generally given in patients with other disorders of lipid metabolism. A study in patients with VLCAD deficiency did not show a benefit of IV glucose (Ørngreen et al., 2009) (Box 23.2).

Supplementation with medium-chain triglycerides (MCT) could be beneficial in disorders with long-chain fatty acid oxidation defects because medium-chain acyl-CoA esters can bypass the long-chain oxidation enzymes. Anecdotal evidence suggests that MCT is effective in cases of trifunctional protein deficiency, VLCAD, and CPT II deficiency. However, no effect of oral MCTs was observed in a study on patients with VLCAD deficiency (Ørngreen et al., 2009). MCT supplements are contraindicated in patients with medium- or short-chain beta-oxidation defects or MADD.

Oral intake of the triglyceride triheptanoin, which contains the odd-chain (C7) fatty acid hepanoate, can provide an alternative source to fill the citric cycle. This so-called *anaplerotic diet* was investigated for patients with VLCAD deficiency (Roe, Sweetman, Roe, David, & Brunengraber, 2002) and muscle CPT II deficiency (Roe et al., 2008). In children with VLCAD deficiency, cardiomyopathy, hepatomegaly, and muscle weakness were improved. In patients with CPT II deficiency, triheptanoin intake reduced muscle pain after exercise and might prevent attacks of rhabdomyolysis.

Box 23.2 Treatment Options in Carnitine Palmitoyltransferase II Deficiency

- High-carbohydrate and low-fat diet with frequent and regularly scheduled meals
- Increased intake of polysaccharides during sustained exercise
- Intravenous glucose in crisis
- Supplementation with medium-chain triglycerides
- Oral intake of the triglyceride triheptanoin
- Bezafibrate

L-Carnitine substitution (100–400 mg/kg/day in children and 2–4 g/day in adults) is unequivocally beneficial in cases of primary carnitine deficiency (Longo et al., 2006). The role of carnitine supplementation in other fatty acid oxidation disorders remains controversial. Secondary carnitine deficiency is common, caused by either acylcarnitine wastage or inhibition of the plasma membrane carnitine transporter by accumulating acylcarnitines.

Riboflavin (vitamin B_2) is the cofactor shared by ETF, ETFDH, and all acyl-CoA dehydrogenases. Many of the patients with MADD presenting with myopathy improve with riboflavin supplementation (100–400 mg/day). It has been shown that riboflavin-responsive myopathy with MADD is frequently caused by *ETFDH* mutations (Gempel et al., 2007; Olsen et al., 2007). A secondary CoQ deficiency was observed in one study (Gempel et al., 2007), arguing that additional CoQ supplementation (150–500 mg/day) should be considered.

Bezafibrate, which can induce upregulation of different genes involved in lipid metabolism by activating the peroxisome proliferator-activated receptor α, as a therapeutic option is controversial.

It was shown that administration of bezafibrate (600 mg/day for 6 months) in six patients with muscle CPT II deficiency resulted in an increased rate of palmitoylcarnitine oxidation in muscle mitochondria (Bonnefont, Bastin, Behin, & Gobin, 2009). No adverse effects were reported, an important finding because rhabdomyolysis is a potential side effect of bezafibrate. Clinical benefits persisted in a follow-up study of 3 years (Bonnefont et al., 2010). However, a 3-month, randomized, double-blind, crossover study of bezafibrate in patients with muscle CPT II deficiency did not improve fatty acid oxidation or heart rate during exercise, indicating that bezafibrate has no meaningful effects in vivo (Ørngreen et al., 2014). Thus, a general recommendation for treatment cannot be given.

In conclusion, treatment of myopathies of lipid metabolism remains inadequate. However, dietary advice is the only therapeutic option as long as there are no therapeutic effects of specific drugs. Because many disorders of lipid metabolism are rare, clinical studies are difficult to perform. In the future, gene therapy might correct the metabolic defect.

OUTCOME

The outcome is usually much better in patients with myopathies of lipid metabolism that manifest late in life only with muscular symptoms than in those with infantile

multisystemic manifestations. The most favorable disease course is seen in patients presenting with attacks of rhabdomyolysis, such as the muscle form of CPT II deficiency. At rest and except for episodes of myoglobinuria, muscle strength is normal. Patients usually have an excellent long-term prognosis. In many cases, attacks can be effectively prevented after the diagnosis is made by avoiding situations that can provoke rhabdomyolysis and by increasing carbohydrate intake during prolonged exercise or other situations that provoke attacks. Acute tubular necrosis as a result of massive myoglobinuria is the only life-threatening complication. Although renal failure has been documented in approximately 25% of patients, if it is promptly recognized and appropriately treated, a complete recovery should be expected in virtually all cases. Cardiac arrest can occur very rarely during an attack in the muscle form of CPT II deficiency. Only one case with a fatal outcome has been reported (Kelly, Garland, Tang, Shug, & Chusid, 1989), and respiratory failure from muscle weakness was reported in another patient (Smolle, Kaufmann, & Gasser, 2001).

In patients with muscle disorders of lipid metabolism with persistent weakness, the disease is usually slowly progressive but can lead to significant disability over years. Typically, proximal weakness is present, but involvement of facial, bulbar, or respiratory muscles is rare. Cardiomyopathy can result in heart failure or in cerebral cardiac embolism (Fischer et al., 2007). Children with metabolic crises can progress into coma if they are not treated promptly with IV glucose. These children have a high risk of sudden death due to cardiac arrhythmia.

MITOCHONDRIAL MYOPATHIES

The term *mitochondrial myopathy* is generally used only for defects of the respiratory chain. Myopathies with defects located elsewhere in the metabolic pathways within the mitochondria are generally not classified as mitochondrial myopathies (e.g., myopathies due to defects in the beta-oxidation of fatty acids are classified as myopathies of lipid metabolism). Mitochondrial disorders are frequently multisystemic diseases; the term *mitochondrial myopathy* is used for those with predominant muscle involvement.

From the genetic point of view, mitochondrial disorders are unique because mitochondria have their own genome, enabling intramitochondrial protein synthesis. However, only a very small proportion of mitochondrial proteins are encoded by the mitochondrial DNA. The majority are encoded by nuclear DNA, and these proteins are imported into the mitochondria. Therefore, mitochondrial disorders can follow both Mendelian and maternal traits of inheritance.

Mitochondrial genetics differ from Mendelian genetics in several aspects. Due to the polyploid nature of the mitochondrial genome, with several thousand copies per cell, a mixture of mutant and normal mtDNA is frequently observed. Called *heteroplasmy*, this has implications for molecular diagnostics because the mutant mtDNA may be absent or present only in very low levels in certain tissues. Moreover, the level of heteroplasmy influences the phenotype: a threshold of mutant mtDNA has to be reached before biochemical effects and phenotypical abnormalities occur.

CLINICAL PRESENTATION

CPEO is the most common form of mitochondrial myopathy; it can present as an isolated disorder or as the leading manifestation of a multisystemic syndrome. Ptosis is frequently the first symptom, and old photographs are helpful for establishing the age of onset. The disease typically manifests in the teenage years or early adulthood, but childhood or late adult onset also occurs. Ptosis may occur unilaterally at first but will eventually become bilateral (Fig. 23.10).

Ophthalmoparesis develops over many years and may lead to complete ocular paralysis. Additionally, many patients have some weakness of the orbicularis muscle. Some patients seek medical attention only when ptosis covers the optic axis and leads to visual disturbance. Patients with CPEO use their frontalis muscles to lift their eyelids and show compensatory chin elevation. Together with the ptosis, this is called *Hutchinson triad*. Ophthalmoplegia is often symmetric and may not lead to complaints because patients simply turn their heads to compensate. Only a minority of patients suffer from diplopia. Muscle weakness is often not restricted to the extraocular muscles, and severe weakness of the facial muscles can present with the facies myopathica. Many patients also suffer from exercise intolerance. In most cases, neurologic examination shows limb weakness, most prominent in the proximal muscles of the lower extremities.

Important differential diagnoses of CPEO are oculopharyngeal muscular dystrophy (OPMD) and ocular myasthenia. OPMD typically manifests after age 40 years, whereas CPEO typically starts before that age. Ocular myasthenia

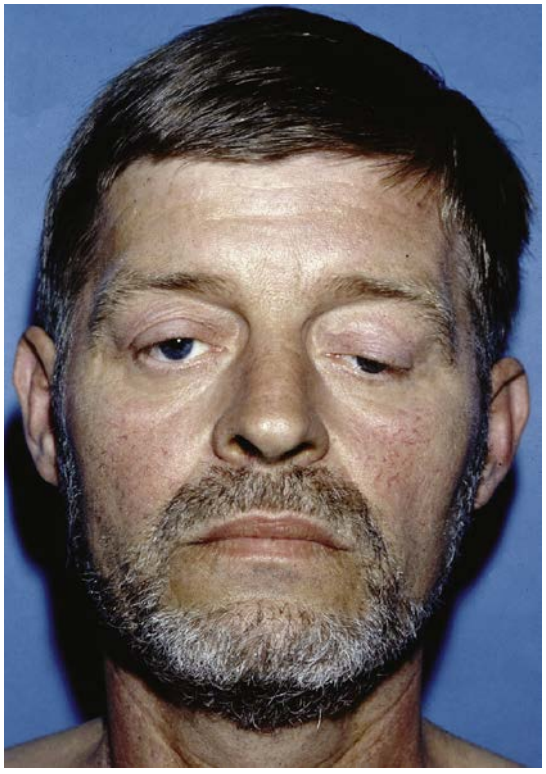


Fig. 23.10 Patient with chronic progressive external ophthalmoplegia showing ptosis (left > right) and strabismus.

symptoms fluctuate, and in both OPMD and ocular myasthenia, ptosis is more prominent than ophthalmoplegia throughout the disease course.

Additionally, involvement of systems other than muscle is possible in CPEO. The term *CPEO-plus* was established for these patients. Ocular manifestations include retinopathy (typically with a salt-and-pepper–like appearance), optic atrophy, and, rarely, cataracts. Cardiac manifestations include cardiac conduction block and cardiomyopathy. Cerebral manifestations include epilepsy, cerebellar ataxia, and dementia. The peripheral nervous system can also be affected, typically with axonal sensory neuropathy. Endocrine involvement includes diabetes mellitus, hypothyroidism, hypoparathyroidism, and hypogonadism. Sensorineural hearing loss and gastrointestinal involvement are also possible. Typical multisystemic signs and symptoms of CPEO-plus are shown in Fig. 23.11.

Some specific CPEO-plus syndromes have been defined; of these, Kearns-Sayre syndrome is a severe multisystemic phenotype with onset before age 20. This syndrome is characterized by CPEO with retinopathy, heart block, and cerebellar ataxia as well as elevated protein in cerebrospinal fluid (CSF) (DiMauro, Bonilla, Zeviani, Nakagawa, & DeVivo, 1985). Two other multisystemic mitochondrial syndromes associated with CPEO are SANDO (sensory ataxia, neuropathy, dysarthria and ophthalmoplegia) (Hanisch et al., 2015) and MNGIE (mitochondrial neurogastrointestinal encephalomyopathy). MNGIE is a rare disorder with prominent gastrointestinal symptoms leading to cachexia (Nishino et al., 2000).

Myopathy is also observed in other classical mitochondrial syndromes that predominantly affect the brain, such as MERRF (myoclonic epilepsy with ragged-red fibers) and MELAS (mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes) (Deschauer et al., 2001). In children with Leigh syndrome or Leigh-like syndrome, hypotonia can be observed.

Although CPEO is the prominent feature of mitochondrial myopathies, patients with mitochondrial myopathies without CPEO or multisystemic involvement have been increasingly recognized. These patients can present with mild disease (exercise intolerance, muscle stiffness, and attacks of myoglobinuria) or with progressive severe proximal limb weakness resembling limb-girdle muscular dystrophy (Andreu et al., 1999; Deschauer, Swalwell, Strauss, Zierz, & Taylor, 2006; Müller, Deschauer, Neudecker, & Zierz, 2005; Swalwell et al., 2006).

Another autosomally inherited mitochondrial myopathy is caused by CoQ deficiency. This is important because this disorder is treatable by oral supplementation. Patients genetically proven to have primary CoQ deficiency typically have multisystemic involvement, frequently presenting with cerebellar ataxia. CPEO has not been described in patients with genetically proven CoQ deficiency, although a secondary CoQ deficiency is documented occasionally in CPEO (Zierz, Jahns, & Jerusalem, 1989).

DIAGNOSIS AND EVALUATION

CLINICAL EXAMINATIONS

The diagnosis of mitochondrial myopathies requires a close collaboration between clinicians and laboratory investigators. Because of multisystemic involvement, patients should be examined by an ophthalmologist, cardiologist, and otorhinolaryngologist, in addition to a neurologist.

Knowledge of the patient's family history is extremely important. It is also helpful to perform a clinical examination of family members because oligosymptomatic patients are possible (e.g., with mild sensorineural hearing loss or ptosis).

Laboratory testing should include resting lactate which, when elevated, indicates impaired oxidative phosphorylation. A more sensitive test is to measure lactate after low-level cycling exercise (30 W for 15 minutes), showing an abnormal lactate increase (Fig. 23.12), with a sensitivity of 70%. One must keep in mind that moderate lactate elevations (not exceeding 4 mmol/L with the previously mentioned protocol) can be observed in patients with other myopathies. Specificity of the bicycle exercise test has been estimated at 90% (Hanisch, Müller, Muser, Deschauer, & Zierz, 2006). In patients with mitochondrial disorders affecting the brain, lactate should also be measured in CSF. In addition to an increased lactate level, pyruvate can also be elevated, resulting in a decreased ratio of lactate/pyruvate in blood and CSF, especially in patients with pyruvate dehydrogenase complex deficiency. In this childhood disorder, alanine can be increased in blood or urine because pyruvate is metabolized to alanine instead of acetyl-CoA. Fibroblast growth factor 21 and growth differentiation factor 15 are more recent biomarkers showing high sensitivity in blood

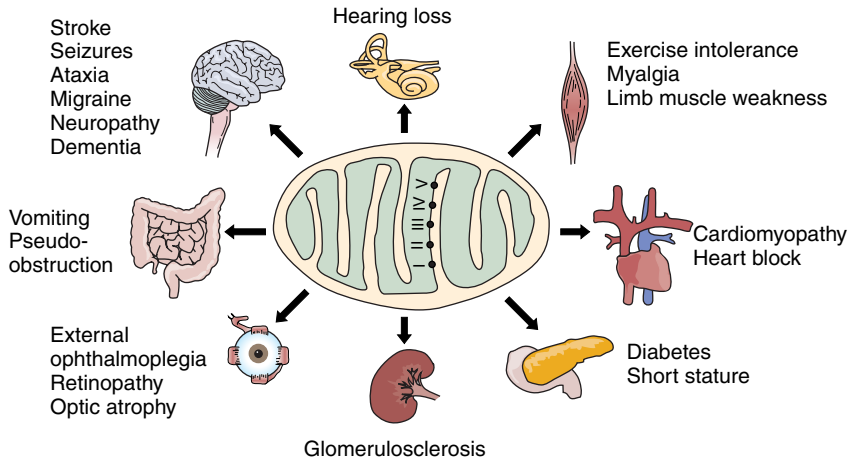


Fig. 23.11 Possibilities of multisystemic involvement in mitochondrial disorders.

of patients with mitochondrial myopathies (Suomalainen et al., 2011; Yatsuga et al., 2015).

Mild elevation of CK is frequently seen in patients with mitochondrial myopathies. Measurement of glucose metabolism can disclose diabetes mellitus. Measurements of thyroid hormones, thyrotropin, corticotropin, cortisol, parathyroid hormone, growth hormone, estradiol, progesterone, and testosterone are also useful in some patients.

Audiograms may detect subclinical hearing impairment, and electrophysiologic examination of the peripheral nerves may reveal a subclinical neuropathy. Cardiac examination should include electrocardiography and echocardiography. Brain magnetic resonance imaging is necessary to detect cerebral involvement. Magnetic resonance imaging may detect a leukoencephalopathy, strokelike lesions typically with occipital localization, or lesions within the basal ganglia, indicating Leigh syndrome. Analysis of CSF may show elevated protein.

ANALYSIS OF MUSCLE BIOPSY

Clinical examination can suggest mitochondrial myopathy, but the diagnosis must be confirmed by histologic and biochemical analysis of muscle biopsy. Moreover, muscle is the best tissue to test for mutations in mtDNA.

Myohistologic analysis shows abnormal mitochondrial proliferation in modified Gomori trichrome staining or in succinate dehydrogenase (SDH) staining. These fibers are called *ragged-red fibers* (Fig. 23.13A). Sometimes, the classical ragged-red fibers are missing; some fibers show only subsarcolemmal accumulation of mitochondria without a ragged appearance. These fibers are called *ragged red–like fibers*. A more sensitive technique is sequential histochemical staining for cytochrome *c* oxidase (COX = complex IV) and SDH to detect COX-negative fibers (Fig. 23.13B). However, in patients with gene defects that do not affect COX, this staining is normal. Some patients with mitochondrial myopathy show only minor changes in histology (less than 5% abnormal fibers) (Deschauer et al., 2003). In such cases, only molecular genetic testing can confirm the diagnosis.

It is important to recognize that mitochondrial abnormalities in muscle biopsies are also seen in normal aging and in other muscle diseases (e.g., myositis). Electronmicroscopy typically shows enlarged and irregularly shaped mitochondria with paracrystalline inclusions. In general, however, electronmicroscopy is not mandatory for diagnosis. Abnormal mitochondria can be seen with electronmicroscopy in many other myopathies, indicating only secondary alterations.

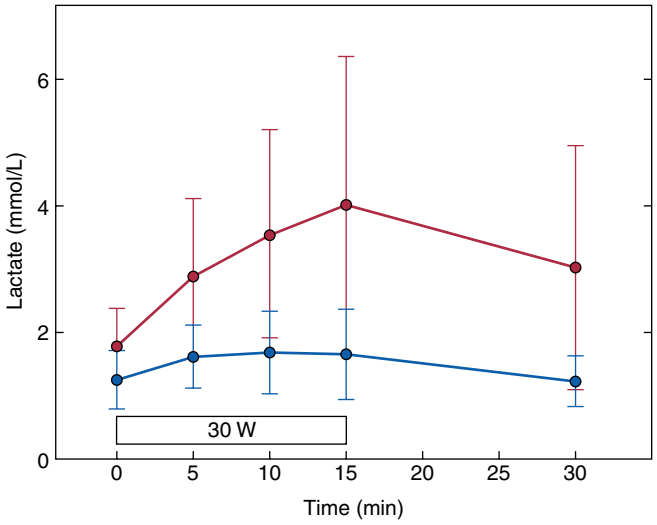


Fig. 23.12 Changes in serum lactate levels in 22 patients with chronic progressive external ophthalmoplegia after bicycle exercise shown in *red* compared to normal controls shown in *blue*. Error *bars* show one standard deviation, *circles* show mean values.

BIOCHEMISTRY

Biochemistry of muscle biopsy samples can show decreased activity of respiratory chain complexes. Frequently, there is a combined defect in the complexes because the underlying genetic defect of the mtDNA (large-scale deletions or tRNA mutations) affects several subunits of different complexes (Gellerich et al., 2002). If there is an isolated deficiency of one complex, a genetic defect in one subunit can be assumed. This is more frequent in children with mitochondrial disorders. Additionally, mitochondrial enzymes that are not encoded by mtDNA, such as citrate synthase or SDH, can be increased, indicating mitochondrial proliferation. Generally, biochemistry is not as important as histology for the diagnosis. The enzyme testing is complex and is available only in specialized laboratories. However, it is important to measure CoQ levels in muscle if histology shows lipid accumulation in addition to mitochondrial proliferation, because these findings can be present in potentially treatable CoQ deficiency.

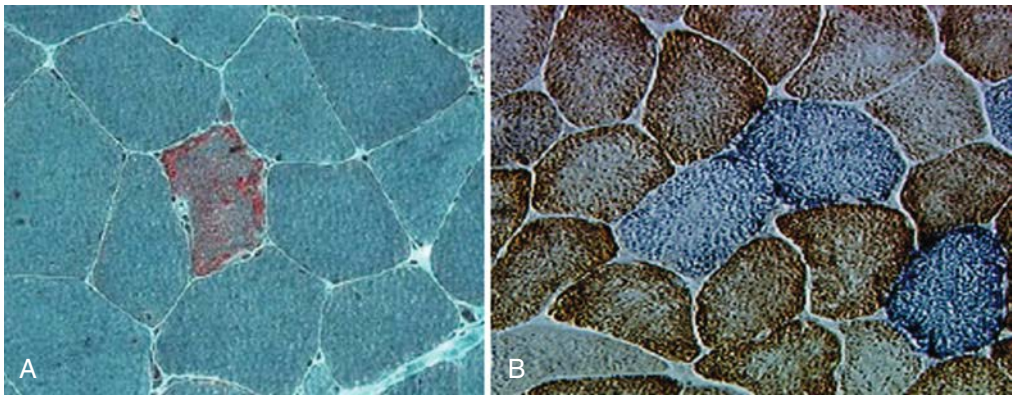


Fig. 23.13 (A) Modified Gomori-trichrome staining showing a ragged-red fiber. (B) Sequential cytochrome *c* oxidase/succinate dehydrogenase staining showing cytochrome *c* oxidase–negative fibers in *blue*.

MOLECULAR GENETIC INVESTIGATIONS

Genetic analysis is important not only to confirm the diagnosis but also to allow for genetic counseling. Patients with CPEO have different underlying genetic defects. Approximately 50% of those with CPEO carry large-scale single deletions of mtDNA. These single deletions are heteroplasmic, with a length between 1 and 9 kb, and are commonly located within the major arc of mtDNA between both origins of replication (origin of heavy-strand replication O_H and light-strand replication O_L) (Fig. 23.14). There is one common deletion with a length of 5 kb. The deletion break points are typically characterized by direct repeats. Most cases of CPEO with single deletions are sporadic. It is postulated that deletions occur in the oocyte, and mitotic segregation during embryogenesis results in high levels of deleted mtDNA in certain tissues like muscle, with low levels in other tissues, including the germline cells. This can explain why mother-to-offspring transmission of single deletions is rarely observed. The risk for an affected mother to have an affected child is only 4% (Chinnery et al., 2004).

In contrast to single deletions of mtDNA, patients with autosomal inheritance of CPEO demonstrated multiple deletions, indicating that these deletions are not the primary gene defect but secondary changes due to a nuclear gene mutation. Consequently, several nuclear gene defects have been identified during the past years. They are located in nuclear genes important in the replication of mtDNA. Those forms of CPEO are therefore classified as defects of mtDNA maintenance disorders (Fig. 23.15). In some of them, not only multiple deletions but also depletion of mtDNA can occur. Several nuclear genes can be mutated: Most frequently, mutations in polymerase gamma (*POLG*), progressive external ophthalmoplegia 1 (*PEO1*; also called *C10orf1* or *TWINKLE*), and ribonucleotide reductase small subunit of p53 (*RRM2B*) are described. Patients with mutations in the *OPA1* gene always show optic atrophy in addition to CPEO. Mutations in the thymidine phosphorylase (*TP*) gene have been identified in patients with MNGIE. Currently, 16 genes are known that can be mutated; they are listed in Table 23.3 with the modes of inheritance.

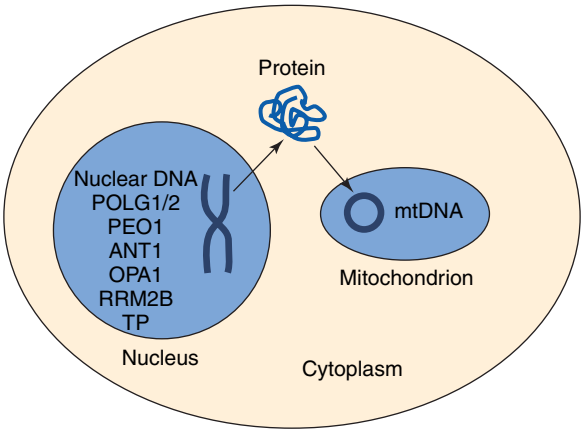


Fig. 23.15 Defects of intergenomic communication. Mutations of different nuclear genes result in defective proteins that in turn cause multiple deletions or depletion of mitochondrial genome (mtDNA). *ANT1*, Adenine nucleotide translocator gene; *DNA*, deoxyribonucleic acid; *OPA1*, optic atrophy 1 gene; *PEO1*, progressive external ophthalmoplegia 1 gene; *POLG1/2*, polymerase gamma 1/2 genes; *TP*, thymidine phosphorylase gene.

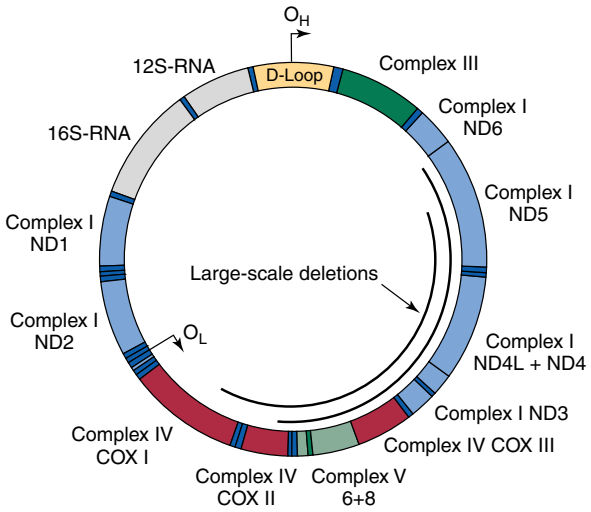


Fig. 23.14 Schematic presentation of the mitochondrial genome (mtDNA) and two exemplary large-scale deletions of mtDNA. The genes that encode the subunits of complex I (*ND1–ND6* and *ND4L*) are shown in *light blue*; cytochrome *c* oxidase (*COX I–COX III*) is shown in *red*; cytochrome *b* of complex III is shown in *dark green*; and the subunits 6 and 8 of the ATP synthase (complex V) are shown in *light green*. The two ribosomal ribonucleic acids (rRNAs; 12S and 16S) are shown in *gray* and the 22 tRNAs are shown in *dark blue* (not labeled). The displacement loop (D-loop), or noncoding control region, is shown in *yellow*. It contains sequences that are vital for the initiation of both mtDNA replication and transcription, including the origin of heavy strand replication (shown as O_H). The origin of light strand replication is shown as O_L.

Table 23.3 Gene Defects with Possible Modes of Inheritance That Are Associated with CPEO

Gene	Modes of Inheritance	
	Recessive Mutations	**Dominant Mutations**
POLG	X	X
PEO1	X	X
RRM2B	X	X
OPA1		X
ANT1		X
POLG2		X
TK2	X	
TP	X	
DGUOK	X	
MPV17	X	
SPG7	X	X
MGME1	X	
AFG3L2	X	

CPEO, Chronic progressive external ophthalmoplegia.

Deletions of mtDNA in muscle can be easily detected by long-range polymerase chain reaction (PCR) technique (Deschauer et al., 2003). However, it is important to know that low levels of mtDNA deletions are also observed in normal aging. In general, deletions of mtDNA are detectable only in muscle and not in blood. However, with sensitive PCR techniques, it is sometimes possible to detect single deletions in blood. If multiple deletions of mtDNA are detected, analysis of nuclear genes causing mtDNA maintenance disorders should be performed. Analysis should start with *POLG* because this gene is most often mutated with two common recessive mutations (p.A467T and p.W748S) (Horvath et al., 2006). The *OPA1* gene should be sequenced first in patients with CPEO and optic atrophy. Gene panel analysis can detect rarer mutations in those 16 genes listed in Table 23.3.

Rarely, point mutations of mtDNA, which are inherited maternally, can be associated with CPEO. A common point mutation of mtDNA is the 3243A>G mutation, which is located in one of the two mitochondrial tRNA genes for leucine. This mutation is typically associated with MELAS, but CPEO was also observed in patients carrying this mutation (Deschauer et al., 2001). Moreover, several very rare point mutations can be associated with CPEO (www.mitomap.org).

Patients with mitochondrial myopathy without CPEO can show different point mutations within mtDNA. Many of them are located in tRNA genes (Deschauer et al., 2006; Müller et al., 2005; Swalwell et al., 2006), but mutations in protein coding genes have also been described that are present in muscle only (Andreu et al., 1999).

Increasingly, nuclear gene defects were recognized as the cause of mitochondrial myopathies due to next-generation sequencing techniques. Childhood onset is frequent in these disorders. For example, primary CoQ deficiency is associated with myopathy typically as part of a multisystemic disease. Defects in at least nine different genes of CoQ biosynthesis have been identified (Alcázar-Fabra, Trevisson, & Brea-Calvo, 2018). Secondary CoQ deficiency was observed, e.g., in MADD due to a defect of ETF:QO (see the "Muscle Disorders of Lipid Metabolism" section in this chapter) (Gempel et al., 2007).

Table 23.4 Treatment Options for Multisystemic Symptoms in Mitochondrial Myopathies

Symptom/Sign	Treatment
Exercise intolerance	Aerobic endurance training
Ptosis	Surgery using frontalis muscle suspension
Cardiac conduction block	Pacemaker
Diabetes mellitus	Avoid metformin
Strokelike episodes	Steroids, L-arginine
Seizures	Avoid valproic acid; ketogenic diet
Hearing loss	Amplification aids
Cardiomyopathy	Pharmacologically (e.g. beta-blockers), heart transplantation
Hypogonadism	Testosterone
Hypothyroidism	Thyroid hormone
Myalgia	Physical therapy
Neuropathic pain	Pregabalin
Cachexia	High caloric nutrition, tube feeding
Dysphagia due to cricopharyngeal achalasia	Myotomy
Myopathy due to coenzyme Q deficiency	Coenzyme Q substitution

TREATMENT AND MANAGEMENT

Causative therapy is available in certain diseases only, but symptomatic treatment is important in patients with mitochondrial myopathies because of the various multisystemic symptoms (Table 23.4). Patients should be cared for by an interdisciplinary team.

SUPPLEMENTATION OF VITAMINS AND COFACTORS

In general, supplementation with vitamins and cofactors has not been shown to be effective. However, in patients with proven CoQ deficiency, supplementation with CoQ (300 to 2000 mg/day) can result in remarkable improvement. In patients with CPEO, improvement after CoQ substitution has been reported only anecdotally; for example, in a patient with Kearns-Sayre syndrome, cachexia, ataxia, and tremor disappeared but ophthalmoplegia and retinopathy remained unchanged (Zierz et al., 1989). Due to its antioxidant effect, CoQ supplementation might also be helpful in patients with normal CoQ level, because defects of the respiratory chain can result in an increased production of reactive oxygen species. Idebenone, an analogue of CoQ with better penetration of the blood-brain barrier, is effective in patients with Leber hereditary optic neuropathy to improve recovery of vision (Klopstock et al., 2011). It was approved in Europe in 2015.

Reduced levels of folinic acid have been measured in CSF in patients with Kearns-Sayre syndrome; improvement after high-dose supplementation with folinic acid was observed in a child with Kearns-Sayre syndrome (Pineda et al., 2006). Substitution of vitamins and cofactors has virtually no serious side effects, at least in low doses. A therapeutic trial of several months is therefore reasonable (Chinnery & Bindoff, 2003).

SYMPTOMATIC TREATMENT

Ptosis not only impairs vision but can also be a cosmetic problem and a source of embarrassment for younger patients. However, surgery for ptosis should be recommended only if the visual axis is obscured. This is due to the risk of complications of corneal exposure in cases of postoperative lagophthalmus. The preferred surgical technique is frontalis muscle suspension, avoiding levator palpebrae muscle resection, because this ensures better protection of the cornea. Lid height can be adjusted if necessary.

Generally, corneal exposure symptoms are treated with lubricants. Some patients with ptosis do well with "eyelid crutches" mounted on their glasses. Fresnel prisms can be helpful if there is diplopia, especially in patients with poor convergence. However, it is often difficult or impossible to suppress diplopia with prisms in the presence of

noncomitant strabismus. When spectacles are prescribed, the motility deficits should be taken into account (e.g., no bifocals in impaired downgaze) (Bau & Zierz, 2005).

Cardiac conduction blocks should be monitored at frequent intervals (at least once per year) because timely placement of a pacemaker can be lifesaving. Cardiomyopathy can be treated pharmacologically (e.g., beta-blockers) or by heart transplantation in carefully selected cases, with no other serious multisystemic symptoms. Physical therapy is important to relieve myalgia and to maintain mobility of joints.

Diabetes mellitus should be treated by standard methods. However, metformin should be avoided because this drug can cause lactic acidosis. Hormone replacement with estrogen or testosterone should be considered in patients with hypogonadism. Thyroid hormone can be given to patients with hypothyroidism, and calcium and vitamin D to patients with hypoparathyroidism. However, growth hormone treatment for children with short stature might be harmful because an increased metabolic demand could be a problem in metabolically impaired patients with mitochondrial disease.

Cachexia should be treated with high-caloric nutrition and tube feeding if dysphagia is present. Myotomy can help in patients with dysphagia due to incomplete opening of the upper esophageal sphincter (cricopharyngeal achalasia) (Kornblum et al., 2000). Endurance training to reduce exercise intolerance is safe and efficient. It has been shown that endurance training can increase oxygen uptake, peak work capacity, and activity of citrate synthase in muscle (Jeppesen et al., 2006; Taivassalo et al., 2006).

Whether L-arginine is effective in stroke-like episodes is controversial (Koga et al., 2005; Ng et al., 2019). Dichloracetate is effective in reducing lactic acidosis, but its use is limited by severe neuropathy, a frequent side effect. Bicarbonate can be used in the acute phases of lactic acidosis.

Valproic acid should be avoided in the treatment of seizures because it can trigger hepatic failure in patients with *POLG* defects (Horvath et al., 2006). Lamotrigine and levetiracetam are frequently used in patients with mitochondrial disorders to control seizures. A ketogenic diet is effective in treating seizures. Because of the taste, it is difficult to administer in patients who are not receiving tube feedings. Antiepileptic drugs such as pregabalin can be used in patients with neuropathic pain.

Amplification aids can help overcome hearing loss. If necessary, cochlear implants can be safely and successfully installed.

Allogeneic stem cell transplantation was used in several patients with MNGIE syndrome to restore TP activity and to reduce the thymidine level. However, treatment was associated with a high mortality. Analysis of all known MNGIE patients treated with allogeneic hematopoietic stem cell transplantation between 2005 and 2011 showed that only 9 of 24 patients were alive during the last follow-up, with a median follow-up of surviving patients after 4 years (Halter et al., 2015). Other possibilities to reduce the thymidine level are liver transplantation, dialysis, infusions of platelets that have high TP activity, or carrier erythrocyte entrapped TP ERT. For these techniques, proof of principle was provided in single patients, but no clinical trials were performed.

During surgery and anesthesia, patients with mitochondrial disorders need special care because some drugs (e.g., propofol and midazolam) can inhibit the respiratory chain in vitro. In addition, malignant hyperthermia-like reactions have been reported in single cases, so trigger agents (e.g., succinylcholine) should be avoided if possible.

GENE THERAPY AND PREVENTION OF TRANSMISSION

Due to the complex genetics of mitochondrial disorders, different strategies to provide gene therapy are under current development, albeit at an early stage. One promising strategy is to reduce the ratio of mutant to wild-type mitochondrial genomes (*gene shifting*) by inhibiting the replication of mutant genomes. Maternal transmission of mtDNA point mutations could be prevented by nuclear transplantation. After in vitro fertilization of an oocyte carrying an mtDNA mutation, the pronucleus is transferred into an enucleated normal donor oocyte. The resulting embryo has the nuclear genomes of the parents but mainly the mitochondrial genome of the donor female, thus showing only very low levels of heteroplasmy, well below the threshold. This approach was performed in humans for the first time in 2017 in a woman with the m.8993T>G mutation (Zhang et al., 2017).

OUTCOME

Muscle weakness generally develops slowly and progressively in mitochondrial myopathies. Sometimes, myopathy results in severe muscle wasting and weakness with severe disability (Müller et al., 2005). Exercise intolerance and myalgia can also lead to disability in some patients. Ophthalmoplegia and ptosis usually do not result in major visual impairment; severe ptosis that totally covers the optic axis can be improved by surgery. Optic atrophy frequently results in severe visual impairment, whereas retinopathy typically leads to moderate impairment only. CNS involvement can result in dementia.

Life-threatening symptoms can occur due to some multisystemic manifestations of the disease. Cardiac disease can be especially problematic. Heart block can result in cardiac arrest, or severe cardiomyopathy can develop. Cachexia can be serious in patients with MNGIE and MELAS. Intractable status epilepticus can occur, especially in patients with *POLG* mutations.

Patients with mitochondrial disorders do have a reduced life expectancy. However, the variety and the severity of multisystemic involvement seen among these disorders results in very different outcomes. The main causes of death in patients with mitochondrial disorders are cardiopulmonary failure and status epilepticus (Klopstock, Jaksch, & Gasser, 1999).

RHABDOMYOLYSIS

Rhabdomyolysis may occur as an acute complication of metabolic myopathies but may also be caused by other conditions affecting muscle membranes, membrane ion channels, and muscle energy supply (e.g., exertion, crush injury and trauma, alcoholism, drugs, and toxins) (Box 23.3). It is characterized by acute damage of the sarcolemma of the skeletal muscle, leading to release of potentially toxic muscle cell components into the circulation, most notably potassium and myoglobin. Typical symptoms include muscle pain, weakness, and dark urine. This disorder may result in potentially life-threatening complications, such as acute myoglobinuric renal failure (occurring in 4% to 33% of patients), cardiac arrhythmias via elevated potassium level, disseminated intravascular coagulation, and compartment syndrome. The mainstay of treatment is hospitalization with early aggressive IV fluid replacement to minimize

the occurrence of renal failure and correction or prevention of electrolyte abnormalities (Huerta-Alardín, Varon, & Marik, 2005). Additional adjunctive therapies, such as alkalinization of the urine with sodium bicarbonate, diuretic therapy, and renal protection with mannitol, although commonly recommended, are of unproven benefit. In severe cases, appropriate management may also include continuous venovenous hemofiltration, mechanical ventilatory support, and administration of antibiotics. The overall prognosis for rhabdomyolysis is favorable when treated early and aggressively with proper fluid replacement, and full recovery of renal function is common.

CONCLUSION

Metabolic disorders are important causes of myopathy. Diagnosis can be difficult because many different enzyme defects are possible. It is important to detect the underlying enzyme defect because this may present relevant therapeutic options, although no cure is possible in most disorders. Identification of the molecular genetic defect is important for genetic counseling. Fig. 23.16 suggests a diagnostic algorithm in patients with suspected metabolic myopathies.

Box 23.3 Causes and Treatment Options in Rhabdomyolysis

Causes

Metabolic myopathies
Exertion
Drugs (e.g., statins)
Toxins (e.g., alcohol)
Crush injury, trauma

Treatment Options

Hospitalization
Intravenous fluid replacement
Alkalinization of the urine
Pain control

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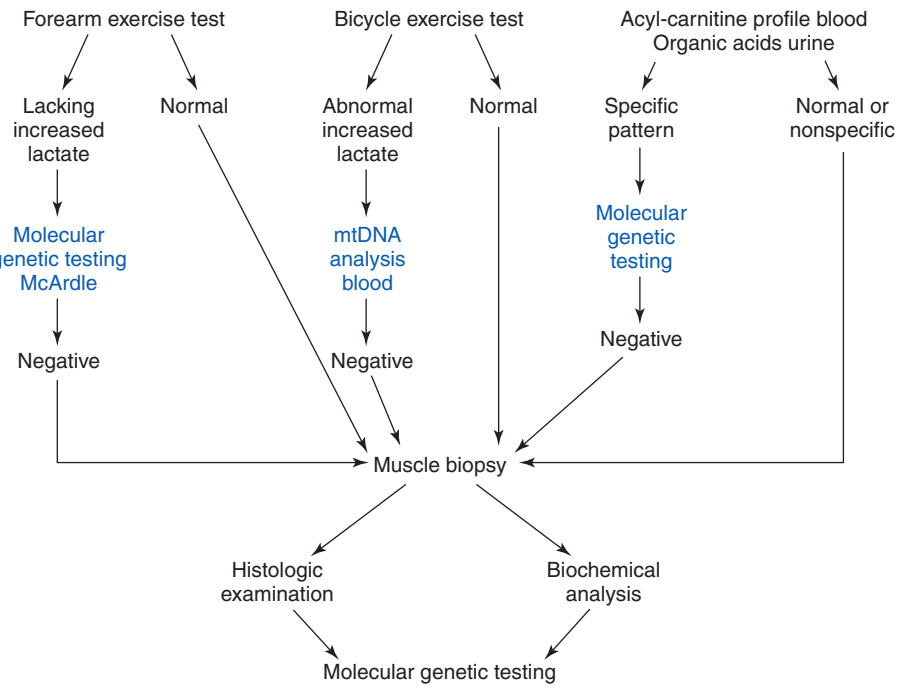


Fig. 23.16 Diagnostic algorithm in patients with suspected metabolic myopathies. *mtDNA*, Mitochondrial genome.

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