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460 Muscular Dystrophies and Other Muscle Diseases

Narayanaswami P et al: International consensus guidance for man

agement of myasthenia gravis: 2020 update. Neurology 96:114, 2021. Ohno K et al: Clinical and pathologic features of congenital myas thenic syndromes caused by 35 genes: A comprehensive review. Int J Mol Sci 24:3730, 2023. Piehl F et al: Efficacy and safety of rituximab for new-onset general ized myasthenia gravis: The RINOMAX randomized clinical trial. JAMA Neurol 79:1105, 2022. Sacca F et al: Efficacy of innovative therapies in myasthenia gravis: A systematic review, meta-analysis and network meta-analysis. Eur J Neurol 30:3854, 2023. Salari N et al: Global prevalence of myasthenia gravis and the effec tiveness of common drugs in its treatment: A systematic review and meta-analysis. J Transl Med 19:516, 2021. Wolfe GI et al: Long-term effect of thymectomy plus prednisone ver sus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. Lancet Neu rol 18:259, 2019. PART 13 Neurologic Disorders VIDEO 459-1 Myasthenia gravis and other diseases of the neuromuscular junction. Anthony A. Amato, Robert H. Brown, Jr.

Muscular Dystrophies and

Other Muscle Diseases Myopathies are disorders with structural changes or functional impair ment of muscle and can be differentiated from other diseases of the motor unit (e.g., lower motor neuron or neuromuscular junction pathologies) by characteristic clinical and laboratory findings. Myas thenia gravis and related disorders are discussed in Chap. 459; inflammatory myopathies are discussed in Chap. 377. ■ ■CLINICAL FEATURES The most important aspect of assessing individuals with neuromus cular disorders is taking a thorough history of the patient’s symp toms, disease progression, and past medical and family history, as well as performing a detailed neurologic examination. Based on this and additional laboratory workup (e.g., serum creatine kinase [CK], electromyography [EMG]), one can usually localize the site of the lesion to muscle (as opposed to motor neurons, peripheral nerves, or neuromuscular junction) and the pattern of

muscle involvement. It is this pattern of muscle involvement that is most useful in narrow ing the differential diagnosis (Table 460-1). Most myopathies present with proximal, symmetric limb weakness with preserved reflexes and sensation. However, asymmetric and predominantly distal weakness can be seen in some myopathies. An associated sensory loss suggests a peripheral neuropathy or a central nervous system (CNS) abnormal ity (e.g., myelopathy) rather than a myopathy. On occasion, disorders affecting the motor nerve cell bodies in the spinal cord (anterior horn cell disease), the neuromuscular junction, or peripheral nerves can mimic findings of myopathy. Muscle Weakness Symptoms of muscle weakness can be either intermittent or persistent. Disorders causing intermittent weakness (Table 460-1 and Fig. 460-1) include myasthenia gravis, periodic paralyses (hypokalemic or hyperkalemic), and metabolic energy defi ciencies of glycolysis (especially myophosphorylase deficiency), fatty acid utilization (carnitine palmitoyltransferase [CPT] deficiency), and some mitochondrial myopathies. The states of energy deficiency cause activity-related muscle breakdown accompanied by myoglobinuria.

Most muscle disorders cause persistent weakness (Table 460-1 and Fig. 460-2). In the majority of these, including most types of muscular dystrophy and inflammatory myopathies, the proximal muscles are weaker than the distal and are symmetrically affected, and the facial muscles are spared, a pattern referred to as limb-girdle weakness. The differential diagnosis is more restricted for other patterns of weak ness. Facial weakness (difficulty with eye closure and impaired smile) and scapular winging (Fig. 460-3) are characteristic of facioscapulo humeral dystrophy (FSHD). Facial and distal limb weakness associated with hand grip myotonia is virtually diagnostic of myotonic dystrophy type 1. When other cranial nerve muscles are weak, causing ptosis or extraocular muscle weakness, the most important disorders to consider include neuromuscular junction disorders, oculopharyngeal muscu lar dystrophy, mitochondrial myopathies, or some of the congenital myopathies (Table 460-1). A pathognomonic pattern characteristic of inclusion body myositis is atrophy and weakness of the flexor forearm (e.g., wrist and finger flexors) and quadriceps muscles that is often asymmetric. Less frequently seen, but important diagnostically, are the axial myopathies that predominantly affect the paraspinal muscles and include dropped head syndrome indicative of selective neck exten sor muscle weakness. The most important neuromuscular diseases associated with this axial muscle weakness include myasthenia gravis, amyotrophic lateral sclerosis, sporadic late-onset nemaline rod myopa thy (SLONM), late-onset ryanodine receptor 1 (RyR1) myopathies, hyperparathyroidism, focal myositis, and some forms of inclusion body myopathy. A final pattern, recognized because of preferential distal extremity weakness, is seen in the distal myopathies. It is important to examine functional capabilities to help disclose certain patterns of weakness (Table 460-1 and Table 460-2). The Gower sign (Fig. 460-4) is particularly useful. Observing the gait of an individual may disclose a hyperlordotic posture caused by combined trunk and hip weakness, frequently exaggerated by toe walking (Fig. 460-5). A waddling gait is caused by the inability of weak hip muscles to prevent hip drop or hip dip. Hyperextension of the knee (genu recurvatum or back-kneeing) is characteristic of quadriceps muscle weakness, and a steppage gait, due to foot drop, accompanies distal weakness. Any disorder causing muscle weakness may be accompanied by fatigue, referring to an inability to maintain or sustain a force (patho logic fatigability). This condition must be differentiated from asthenia, a type of fatigue caused by excess tiredness or lack of energy. Associated symptoms may help differentiate asthenia and pathologic fatigability. Asthenia is often accompanied by a tendency to avoid physical activi ties, complaints of daytime sleepiness, necessity for frequent naps, and difficulty concentrating on activities such as reading. There may be feelings of

overwhelming stress and depression. In contrast, pathologic fatigability occurs in disorders of neuromuscular transmission and in disorders altering energy production, including defects in glycolysis, lipid metabolism, or mitochondrial energy production. Pathologic fati gability also occurs in chronic myopathies because of difficulty accom plishing a task with less muscle. Pathologic fatigability is accompanied by abnormal clinical or laboratory findings. Fatigue without those supportive features almost never indicates a primary muscle disease. Muscle Pain (Myalgias), Cramps, and Stiffness Some myopa thies can be associated with muscle pain, cramps, contractures, stiff or rigid muscles, or inability to relax the muscles (e.g., myotonia) (Table 460-1). Muscle cramps are abrupt in onset, short in duration, triggered by voluntary muscle contraction, and may cause abnormal postur ing of the joint. Muscle cramps often occur in neurogenic disorders, especially motor neuron disease (Chap. 448), radiculopathies, and polyneuropathies (Chap. 457), but are not a feature of most primary muscle diseases. A muscle contracture is different from a muscle cramp. In both con ditions, the muscle becomes hard, but a contracture is associated with energy failure in glycolytic disorders. The muscle is unable to relax after an active muscle contraction. The EMG shows electrical silence. Confusion is created because contracture also refers to a muscle that cannot be passively stretched to its proper length (fixed contracture)

TABLE 460-1 Myopathies by Pattern of Weakness/Muscle Involvement Proximal (Limb-Girdle) Weakness Late-onset central core (RYR1 mutations) SLONM Metabolic (late-onset Pompe, McArdle disease, lipid storage, mitochondrial) Hyperparathyroidism/osteomalacia/vitamin D deficiency Myasthenia gravis Most dystrophies (e.g., dystrophinophies, limb-girdle, myofibrillar myopathy, myotonic dystrophy type 2, rare FSHD) Congenital myopathies (e.g., central core, multiminicore, centronuclear, nemaline rod) Metabolic myopathies (e.g., glycogen and lipid storage diseases) Mitochondrial myopathies Inflammatory myopathies (DM, PM, IMNM, anti-synthetase syndrome) Toxic myopathies (see Table 460-6) Endocrine myopathies Neuromuscular junction disorders (myasthenia gravis, LEMS, congenital myasthenia, botulism, see Chap. 459) SLONM Distal Weakness Distal muscular dystrophies/myofibrillar myopathy (see Table 460-5) Congenital myopathies (e.g., late-onset centronuclear and nemaline rod myopathies) Oculopharyngeal distal myopathy Metabolic Glycogen storage disease (e.g., brancher and debrancher deficiency, rarely McArdle disease) Lipid storage disease (e.g., neutral lipid storage myopathy, multiacyldehydrogenase deficiency) NMJ disorders (e.g., rare myasthenia gravis and congenital myasthenia) Proximal Arm/Distal Leg Weakness (Scapuloperoneal or Humeroperonal) Weakness Facioscapulohumeral muscular dystrophy (FSHD) Scapuloperoneal myopathy and neuropathy Myofibrillar myopathies Emery-Dreifuss muscular dystrophy (EDMD) Bethlem myopathy Distal Arm/Proximal Leg Weakness Inclusion body myositis (usually wrist and finger flexors in arms, hip flexors and knee extensors in legs, and asymmetric) Myotonic dystrophy (uncommon presentation) Axial Muscle Weakness Inflammatory (cervicobrachial myositis) sIBM and hIBM Myotonic dystrophy 2 Isolated neck extensor myopathy/bent spine syndrome FSHD Abbreviations: DM, dermatomyositis; hIBM, hereditary inclusion body myopathy; IMNM, immune-mediated necrotizing myopathy; LEMS, Lambert-Eaton myasthenic syndrome; NMJ, neuromuscular junction; PM, polymyositis; sIBM, sporadic inclusion body myositis; SLONM, sporadic late-onset nemaline myopathy. because of fibrosis. In some muscle disorders, especially in Emery-Dreifuss muscular dystrophy (EDMD) and Bethlem myopathy, fixed contrac tures occur early and represent distinctive features of the disease. Myotonia is a condition of prolonged muscle contraction followed by slow muscle relaxation. It always follows muscle activation (action myotonia), usually voluntary, but may be elicited by mechanical stimu lation (percussion myotonia) of the muscle. Myotonia typically

causes difficulty in releasing objects after a firm grasp. In myotonic muscular dystrophy type 1 (DM1), distal weakness usually accompanies myoto nia, whereas in DM2, proximal muscles are more affected. Myotonia also occurs with myotonia congenita (a chloride channel disorder), but in this condition, muscle weakness is usually not prominent. Myotonia may also be seen in individuals with sodium channel mutations (hyper kalemic periodic paralysis or potassium-sensitive myotonia). Another sodium channelopathy, paramyotonia congenita (PC), also is associated with muscle stiffness. In contrast to other disorders associated with myotonia in which the myotonia is eased by repetitive activity, PC is named for a paradoxical phenomenon whereby the myotonia worsens

Eye Muscle Weakness (Ptosis/Ophthalmoparesis) Ptosis without ophthalmoparesis Myotonic dystrophy Congenital myopathies Neuromuscular junction disorders Ptosis with ophthalmoparesis Oculopharyngeal dystrophy Oculopharygeal distal myopathy Mitochondrial myopathy hIBM type 3 Neuromuscular junction disorders CHAPTER 460 Episodic Weakness or Myoglobinuria Related to exercise Glycogenoses (e.g., McArdle disease, etc.) Lipid disorders (e.g., CPT2 deficiency) Mitochondrial myopathies (e.g., cytochrome B deficiency) Not related to exercise RYR1 mutations can cause malignant hyperthermia, episodic rhabdomyolysis/ Muscular Dystrophies and Other Muscle Diseases myoglobinuria, and atypical periodic paralysis Other causes of malignant hyperthermia Drugs/toxins (e.g., statins) Prolonged/intensive eccentric exercise Inflammatory (e.g., PM/DM—rare, viral/bacterial infections) Delayed or unrelated to exercise Periodic paralysis (e.g., hereditary hyper- or hypokalemic, thyrotoxic, associated renal tubular acidosis, acquired electrolyte imbalance) NMJ disorders Muscle Stiffness/Decreased Ability to Relax Myotonic dystrophy 1 and 2 Myotonia congenita Paramyotonia congenita Hyperkalemic periodic paralysis with myotonia Potassium aggravated myotonia Schwartz-Jampel syndrome Other: rippling muscle disease (acquired and hereditary), acquired neuromyotonia (Isaacs' syndrome), stiff-person syndrome, Brody's disease with repetitive activity. Potassium-aggravated myotonia is an allelic disorder in which myotonia is brought on by consumption of too much potassium-containing foods. Muscle stiffness can refer to different phenomena. Some patients with inflammation of joints and periarticular surfaces feel stiff. This condition is different from the disorders of hyperexcitable motor nerves causing stiff or rigid muscles. In stiff-person syndrome, spon taneous discharges of the motor neurons of the spinal cord cause involuntary muscle contractions mainly involving the axial (trunk) and proximal lower extremity muscles. The gait becomes stiff and labored, with hyperlordosis of the lumbar spine. Superimposed episodic muscle spasms are precipitated by sudden movements, unexpected noises, and emotional upset. The muscles relax during sleep. Serum antibodies against glutamic acid decarboxylase are present in approximately twothirds of cases. In acquired neuromyotonia (Isaacs' syndrome), there is hyperexcitability of the peripheral nerves manifesting as continuous muscle fiber activity in the form of widespread fasciculations and myokymia with impaired muscle relaxation. Muscles of the leg are stiff,

Yes No Exam normal between attacks Proximal > distal weakness during attacks Variable weakness includes EOMs, ptosis, bulbar and limb muscles AChR or Musk AB positive Abnormal Yes No Check for dysmorphic features Genetic testing for Anderson-Tawil syndrome Decrement on 2–3 Hz repetitive nerve stimulation (RNS) or increased jitter on single fiber EMG (SFEMG) Acquired seropositive MG Check chest CT for thymoma Yes No PART 13 Neurologic Disorders Consider: Seronegative MG Congenital myasthenia* Psychosomatic weakness** Lambert-Eaton myasthenic syndrome Check: Voltage gated Ca channel Abs Chest CT for lung Ca *Genetic testing (Chap. 459) **If Abs, RNS, SFEMG are all normal or negative FIGURE 460-1 Diagnostic evaluation of intermittent

weakness. AChR AB, acetylcholine receptor antibody; CPT, carnitine palmitoyltransferase; EKG, electrocardiogram; EMG, electromyogram; EOMs, extraocular muscles; MG, myasthenia gravis; PP, periodic paralysis. and the constant contractions of the muscle cause increased sweating of the extremities. This peripheral nerve hyperexcitability is mediated by antibodies that target voltage-gated potassium channels. There are two painful muscle conditions of particular importance, neither of which is associated with muscle weakness. Fibromyalgia is a common, yet poorly understood myofascial pain syndrome in which patients complain of severe muscle pain and tenderness, severe fatigue, and often poor sleep. Serum CK, erythrocyte sedimentation rate (ESR), EMG, and muscle biopsy are normal (Chap. 385). Polymyalgia rheu matica occurs mainly in patients aged >50 years and is characterized by stiffness and pain in the shoulders, lower back, hips, and thighs Persistent Weakness Patterns of Weakness on Neurologic Exam Proximal > distal IMNM; PM; DM;

anti-synthetase

syndrome;

muscular dystrophies;

mitochondrial

and metabolic

myopathies;

toxic, endocrine

myopathies Facial, distal, quadriceps; handgrip myotonia Myotonic muscular dystrophy Ptosis, EOMs OPMD; mitochondrial myopathy; myotubular myopathy Facial weakness and scapular winging (FSHD) Myopathic EMG confirms muscle disease and excludes ALS Repetitive nerve stimulation abnormalities suggest a neuromuscular junction disorder (e.g., MG, LEMS, botulism) CK elevation supports myopathy May need DNA testing for further distinction of inherited myopathies Muscle biopsy will help distinguish many disorders FIGURE 460-2 Diagnostic evaluation of persistent weakness. Examination reveals one of seven patterns of weakness. The pattern of weakness in combination with the laboratory evaluation leads to a diagnosis. ALS, amyotrophic lateral sclerosis; CK, creatine kinase; DM, dermatomyositis; EMG, electromyography; EOMs, extraocular muscles; FSHD, facioscapulohumeral dystrophy; IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; MG, myasthenia gravis; OPMD, oculopharyngeal muscular dystrophy; PM, polymyositis.

Intermittent weakness Myoglobinuria Exam usually normal between attacks Proximal > distal weakness during attacks EKG Forearm exercise Normal Normal lactic acid rise Consider CPT deficiency or other fatty acid metabolism disorders No Yes Myotonia on exam Reduced lactic acid rise Consider glycolytic defect Low potassium level Normal or elevated potassium level Genetic testing Hypokalemic PP Hyperkalemic PP Paramyotonia congenita No diagnosis Muscle biopsy DNA test confirms diagnosis (Chap. 375). The ESR and CRP are elevated, while serum CK, EMG, and muscle biopsy are normal. Muscle Enlargement and Atrophy In most myopathies, muscle tissue is

replaced by fat and connective tissue, but the size of the muscle is usually not affected. However, in many limb-girdle mus cular dystrophies, enlarged calf muscles are typical. The enlargement represents true muscle hypertrophy; thus, the term pseudohypertrophy should be avoided when referring to these patients. The calf muscles remain very strong even late in the course of these disorders. Muscle enlargement can also result from infiltration by sarcoid granulomas, amyloid deposits, bacterial and parasitic infections, and focal myositis. Dropped head/ Axial MG; PM; ALS; hyperpara- thyroid; Axial myopathy Proximal & distal (hand grip), and quadriceps IBM Distal Distal myopathy (see Table 460-1)

FIGURE 460-3 Facioscapulohumeral dystrophy with prominent scapular winging. In contrast, muscle atrophy is characteristic of other myopathies. In Miyoshi myopathy, which can be caused by mutations in the genes that encode for dysferlin and anoctamin 5, there is a predilection for early atrophy of the gastrocnemius muscles, particularly the medial aspect. Atrophy of the humeral muscles is characteristic of FSHD and EDMD. ■ ■LABORATORY EVALUATION Various tests can be used to evaluate a suspected myopathy, including CK levels, endocrine studies (e.g., thyroid function tests, parathyroid hormone and vitamin D levels), autoantibodies (associated with myo sitis and systemic disorders), forearm exercise test, muscle biopsy, and genetic testing. Electrodiagnostic studies can be useful to differenti ate myopathies from other neuromuscular disorders (motor neuron disease, peripheral neuropathies, neuromuscular junction disorders) but, in most instances, do not help distinguish the specific type of myopathy. Serum Enzymes CK is the most sensitive measure of muscle dam age. The MM isoenzyme predominates in skeletal muscle, whereas CK-myocardial bound (CK-MB) is the marker for cardiac muscle. Serum CK can be elevated in normal individuals without provocation, presumably on a genetic basis or after strenuous activity, trauma, a pro longed muscle cramp, or a generalized seizure. Aspartate aminotrans ferase (AST), alanine aminotransferase (ALT), aldolase, and lactate dehydrogenase (LDH) are enzymes sharing an origin in both muscle and liver. Problems arise when the levels of these enzymes are found to be elevated in a routine screening battery, leading to the erroneous TABLE 460-2 Observations on Examination That Disclose Muscle Weakness FUNCTIONAL IMPAIRMENT MUSCLE WEAKNESS Inability to forcibly close eyes Upper facial muscles Impaired pucker Lower facial muscles Inability to raise head from prone position Neck extensor muscles Inability to raise head from supine position Neck flexor muscles Inability to raise arms above head Proximal arm muscles (may be only scapular stabilizing muscles) Inability to walk without hyperextending knee (back-kneeing or genu recurvatum) Knee extensor muscles Inability to walk with heels touching the floor (toe walking) Shortening of the Achilles tendon Inability to lift foot while walking (steppage gait or foot drop) Anterior compartment of leg Inability to walk without a waddling gait Hip muscles Inability to get up from the floor without climbing up the extremities (Gowers’ sign) Hip, thigh, and trunk muscles Inability to get up from a chair without using arms Hip muscles

CHAPTER 460 Muscular Dystrophies and Other Muscle Diseases FIGURE 460-4 Gower sign showing a patient using his arms to climb up the legs in attempting to get up from the floor. assumption that liver disease is present when in fact muscle could be the cause. An elevated γ-glutamyl transferase (GGT) helps to establish a liver origin because this enzyme is not found in muscle. Rarely, aldose can be elevated in an inflammatory myopathy when CK, AST, and ALT are normal, signifying that the inflammation predominantly affects the perimysium (dermatomyositis, graft-versus-host disease) or the sur rounding fascia (fasciitis). Electrodiagnostic Studies EMG, repetitive nerve stimulation, and nerve conduction studies (NCS) (Chap. 457) are helpful in dif ferentiating

myopathies from motor neuron disease, neuropathies, and neuromuscular junction diseases. Routine NCS are typically normal in myopathies, but reduced amplitudes of compound muscle action potentials may be seen in atrophied muscles. The needle EMG may reveal irritability on needle insertion and spontaneously that is suggestive of a myopathy with active necrosis or muscle membrane instability (inflammatory myopathies, dystrophies, toxic myopathies, myotonic myopathies), whereas a lack of irritability is characteristic of long-standing myopathic disorders (muscular dystrophies with severe fibrofatty replacement, endocrine myopathies, disuse atrophy, and many of the metabolic myopathies between bouts of rhabdomyolysis). In addition, the EMG may demonstrate myotonic discharges that will narrow the differential diagnosis (Table 460-1). Another important

PART 13 Neurologic Disorders FIGURE 460-5 Hyperlordotic posture, exaggerated by standing on toes, associated with trunk and hip weakness. EMG finding is the presence of short-duration, small-amplitude, polyphasic motor unit action potentials (MUAPs). In myopathies, the MUAPs fire early but at a normal rate to compensate for the loss of individual muscle fibers, whereas in neurogenic disorders, the MUAPs fire faster. An EMG is usually normal in steroid or disuse myopathy, both of which are associated with type 2 fiber atrophy; this is because the EMG preferentially assesses the physiologic function of type 1 fibers. The EMG can supplement the clinical examination in choosing an appropriately affected muscle to biopsy. Imaging Studies Skeletal magnetic resonance imaging (MRI) and ultrasound are increasingly utilized to assess the pattern of muscle involvement, which can help in narrowing the diagnosis, and are often more sensitive than the clinical examination and EMG, particularly early in a disease course. For example, there is early predilection of the vastus lateralis and medialis muscles with relative sparing of the rectus femoris muscles on imaging of thigh muscles in patients with inclusion body myositis, and this can be appreciated on imaging prior to weakness being detected on manual muscle testing. MRI can also demonstrate fasciitis when the clinical examination and EMG are normal. Imaging can also be used to help guide what muscle to biopsy in patients with weakness on manual muscle testing and EMG abnormalities only in muscles that are not typically biopsied (e.g., paraspinal or hip girdle). We have found imaging helpful in patients with presumed muscular dystrophy when the muscle biopsy is not diagnostic and genetic test ing shows only a variation of unclear significance. In this situation, the pattern of muscle involvement on imaging can support the known pattern of muscle involvement of a specific hereditary myopathy. The cost and availability of MRI preclude routine use in some settings, but ultrasound is more readily available and less expensive. Genetic Testing This is increasingly available and is the gold stan dard for diagnosing patients with hereditary myopathies. Next-generation

sequencing panels are increasing utilized, but clinicians need to know their limitations; large deletions and duplications can be missed, as can mutations in noncoding (intronic) regions. Furthermore, testing often reveals sequence alterations of unclear significance. Forearm Exercise Test With exercise-induced muscle pain and myoglobinuria, there may be a defect in glycolysis. For safety, the test should not be performed under ischemic conditions to avoid an unnec essary insult to the muscle, causing rhabdomyolysis. The test is per formed by placing a small indwelling catheter into an antecubital vein. A baseline blood sample is obtained for lactic acid and ammonia. The forearm muscles are exercised by asking the patient to vigorously open and close the hand for 1 min. Blood is then obtained at intervals of 1, 2, 4, 6, and 10 min for comparison with the baseline sample. A three- to fourfold rise of lactic acid is typical. The simultaneous measurement of

ammonia serves as a control because it should also rise with exercise. In patients with myophosphorylase deficiency and certain other glyco lytic defects, the lactic acid rise will be absent or below normal, while the rise in ammonia will reach control values. If there is lack of effort, neither lactic acid nor ammonia will rise. Patients with selective failure to increase ammonia may have myoadenylate deaminase deficiency. This condition has been reported to be a cause of myoglobinuria, but deficiency of this enzyme in asymptomatic individuals makes interpre tation controversial. Muscle Biopsy Muscle biopsy is extremely helpful in evaluation of acquired myopathies but is performed less frequently in suspected hereditary myopathies as genetic testing has become more widely available. However, muscle biopsy can be helpful in cases of suspected hereditary myopathy in which genetic testing was nondiagnostic. Almost any superficial muscle can be biopsied, but it is important to biopsy one that is affected clinically but not too severely (for example, grade 4 out of 5 strength or movement against moderate resistance by manual muscle testing) (Chap. 433). A specific diagnosis can be estab lished in many disorders. HEREDITARY MYOPATHIES Muscular dystrophy refers to a group of hereditary progressive dis eases, each with unique phenotypic and genetic features (Tables 460-3 through 460-6 and Fig. 460-6). The prognosis of dystrophies is slow progressive weakness, though the severity and course are variable between and even within subtypes. Some are associated with cardiac and ventilatory muscle involvement, which are the leading causes of mor tality. Unfortunately, there are no specific medical therapies for most of the muscular dystrophies, and treatment is aimed at maintaining function with physical and occupational therapy. Noninvasive ventila tion and tracheostomy may be warranted. Those with cardiomyopathy may require afterload reduction, antiarrhythmic agents, pacemakers or intracardiac defibrillators, and occasionally cardiac transplantation. We will focus primarily on those that manifest in adulthood. ■ ■DUCHENNE AND BECKER MUSCULAR DYSTROPHY (DMD AND BMD) DMD and BMD are X-linked recessive muscular dystrophies caused by mutations in the dystrophin gene. Affecting 1 in 3000 male births, DMD is the most common mutational disease affecting boys. The inci dence of BMD is ~5 per 100,000. Clinical Features Proximal muscles, especially of the lower extremities, are prominently involved in both disorders. This becomes evident in DMD very early; boys with DMD have difficulty climbing stairs and never run well. As the disease progresses, weakness becomes more generalized. Hypertrophy of muscles, particularly in the calves, is an early and prominent finding. Most patients with BMD first experience difficulties between ages 5 and 15 years, although onset in the third or fourth decade or even later can occur. Life expectancy for DMD and BMD is reduced, but most BMD cases survive into the fourth or fifth decade. Intellectual disability may occur in both dis orders but is less common in BMD. Cardiac involvement is common in both DMD and BMD and may result in heart failure; some BMD

TABLE 460-3 Autosomal Dominant (AD) Limb-Girdle Muscular Dystrophies (LGMDs) OLD / NEW NOMENCLATURE INHERITANCE GENE AFFECTED PROTEIN LGMD1A / MFM3 AD MYOT Myotilin LGMD1B / EDMD AD LMNA Lamin A and C LGMD1C / Rippling muscle disease AD CAV3 Caveolin-3 LGMD1D / LMGDD1 AD DNAJB6 DNAJ heat shock protein family (Hsp40) member B6 LGMD1E / MFM1 AD DES Desmin LGMD1F / LGMDD2 AD TNPO3 Transportin 3 LGMD1G / LGMDD3 AD HNRNPDL Heterogeneous nuclear ribonucleoprotein D like protein LGMD1H / Discarded due to false linkage LGMD1I / LGMDD4 AD CAPN3 Calpain 3 Bethlem myopathy / LGMDD5 AD COL6A1/2/3 Collagen type VI alpha patients manifest with only heart failure. Other less common presenta tions of dystrophinopathy are asymptomatic hyper-CK-emia, myalgias without weakness, and myoglobinuria. Laboratory Features Serum CK levels are usually elevated. Mus cle biopsies

demonstrate dystrophic features. Western blot analysis of muscle biopsy samples demonstrates absent dystrophin in DMD or reduction in levels or size of dystrophin in BMD. In both disor ders, mutations can be established using DNA from peripheral blood TABLE 460-4 Autosomal Recessive (AR) Limb-Girdle Muscular Dystrophies (LGMDs) OLD / NEW NOMENCLATURE INHERITANCE GENE AFFECTED PROTEIN LGMD2A / LGMDR1 AR CAPN3 Calpain 3 LGMD2B / LGMDR2 AR DYSF Dysferlin LGMD2C / LGMDR5 AR SGCG γ-Sarcoglycan LGMD2D / LGMDR3 AR SGCA α-Sarcoglycan LGMD2E / LGMDR4 AR SCGB β-Sarcoglycan LGMD2F / LGMDR6 AR SCGD δ-Sarcoglycan LGMD2G / LGMDR7 AR TCAP Telethonin LGMD2H / LGMDR8 AR TRIM32 Tripartite motif-containing 32 LGMD2I / LGMDR9 AR FKRP Fukutin-related protein LGMD2J / LGMDR10 AR TTN Titin LGMD2K / LGMDR11 AR POMT1 Protein O-mannosyltransferase 1 LGMD2L / LGMDR12 AR ANO5 Anoctamin 5 LGMD2M / LGMDR13 AR FKTN Fukutin LGMD2N / LGMDR14 AR POMT2 Protein O-mannosyltransferase 2 LGMD2O / LGMDR15 AR POMGnT1 Protein O-linked mannose Beta-1,2-N-acetyl glucosaminyltranferase-1 LGMD2P / LGMDR16 AR DAG1 α-Dystroglycan LGMD2Q / LGMDR17 AR PLEC1 Plectin 1 LGMD2R / MFM1 AR DES Desmin LGMD2S / LGMDR18 AR TRAPPC11 Trafficking protein particle complex 11 LMGD2T / LGMDDR19 AR GMPPB DP-mannose pyrophosphorylase B LGMD2U / LGMDR20 AR CRPPA CDP-L-ribitol pyrophosphorylase A (also known as ISPD) LGMD2V / Pompe disease AR GAA A Alpha-glucosidase LGMD2W / PINCH-2-related myopathy AR LIMS2 PINCH-2 LGMD2X / LGMDR25 AR BVES Blood vessel endothelial substance LGMD2Y / TOR1AIP1-related myopathy AR TOR1AIP1 Torsin A interacting protein 1 LGMD2Z / LGMDR21 AR POGLUT1 Protein O-glucosyltransferase 1 Bethlem myopathy /LGMDR22 AR COL6A1/2/3 Collagen VI subunits A1, A2, or A3 Laminin α2-related dystrophy / LGMDR23 AR LAMA2 Laminin subunit alpha 2 POMGNT2-related dystrophy/ LGMDR24 AR POMGNT2 Protein O-linked mannose beta 1,4-N-acetylglucosaminyltransferase 2 NA / LGMDR26 AR POPDC3 Popeye domain-containing protein 3 NA / LGMDR27 AR JAG2 Jagged2 Abbreviation: NA, not applicable.

CHAPTER 460 leukocytes. In most cases, muscle biopsies are no longer performed when DMD or BMD is suspected, as genetic testing is less invasive, less costly, and routinely available. Deletions within or duplications of the dystrophin gene are common in both DMD and BMD; in ~95% of cases, the mutation does not alter the translational reading frame of messenger RNA. These “in-frame” mutations allow for production of some dys trophin, which accounts for the presence of altered rather than absent dystrophin on Western blot analysis and a milder clinical phenotype. Muscular Dystrophies and Other Muscle Diseases

TABLE 460-5 Hereditary Distal Myopathies/Dystrophies DISORDER INHERITANCE GENE AFFECTED PROTEIN Welander AD TIA1 T-cell restricted intracellular antigen Udd AD TTN Titin Markesbery-Griggs AD LDB3 ZASP GNE myopathy (Nonaka; hIBM2) AR GNE UDP-N-acetylglucosamine 2-epimerase/

n-acetylmannosamine kinase Miyoshi 1 AR DYSF Dysferlin Miyoshi 3 AR ANO5 Anoctamin 5 Laing AD MYH7 Myosin heavy chain 7 Williams AD FLNC Filamin C Distal myopathy with vocal cord and pharyngeal weakness (VCPDM) AD MTR3 Matrin 3 KLHL9 myopathy AD KLH9 KELCH-like homologue 9 ADSSL myopathy AR ADSSL Adenylosuccinate synthase PART 13 Neurologic Disorders PLIN4 myopathy AD PLIN4 Perilipin-4 Abbreviations: AD, autosomal dominant; AR, autosomal recessive. TREATMENT Duchenne and Becker Muscular Dystrophy Glucocorticoids slow progression in DMD, but their use has not been adequately studied in BMD. Physical and occupational ther apy are important in helping maintain function. As death is often from the associated cardiomyopathy, it is

important to follow patients with a cardiologist and treat appropriately. Small studies suggest that there may be a clinical benefit in selected cases of DMD from short oligonucleotides that permit skipping of mutant exons, leading to expression of a short but nonetheless functional dystro phin protein. In parallel, other studies suggest that small molecules may permit read-through of protein-truncating mutations in some DMD cases. Gene therapy studies have not as yet been conducted in BMD. ■ ■LIMB-GIRDLE MUSCULAR DYSTROPHY The limb-girdle muscular dystrophies (LGMDs) are a genetically heterogenous group of dystrophies in which males and females are affected equally, with typical onset ranging from late in the first decade to the fourth decade. The LGMDs usually manifest with progressive weakness of pelvic and shoulder girdle musculature and are often clini cally indistinguishable from DMD and BMD. Respiratory insufficiency from weakness of the diaphragm may occur, as may cardiomyopathy. Serum CKs are elevated, and the EMG is myopathic. Muscle biopsies reveal dystrophic features, but the findings are not specific to differ entiate subtypes from one another unless immunohistochemistry is employed (e.g., immunostaining for various sarcoglycans, dysferlin, TABLE 460-6 Myofibrillary Myopathies (MFM) MYOFIBRILLAR MYOPATHY INHERITANCE GENE AFFECTED PROTEIN MFM1 AD/AR DES Desmin MFM2 AD CRYAB Alpha-B crystallin MFM3 AD MYOT Myotolin MFM4 AD LDP3 ZASP MFM5 AD FLNC Filamin C MFM6 AD BAG3 Bcl-2-binding protein MFM7 AD KY Kyphoscoliosis peptidase MFM8 AD PYROXD1 Pyridine nucleotide-disulfide oxidoreductase

domain-containing protein 1 MFM9 AD TTN Titin MFM10 AD SVIL Supervillin MFM11 AD UNC45B UNC45 myosin chaperone B MFM12 AD MYL2 Myosin light chain 2 Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

alpha-dystroglycan) or there are features to suggest one of the myofi brillar myopathies. Nonetheless, definitive diagnosis requires genetic testing. The traditional classification of LGMD is based on autosomal domi nant (LGMD1) and autosomal recessive (LGMD2) inheritance. Super imposed on the backbone of LGMD1 and LGMD2, the classification uses a sequential alphabetical lettering system (LGMD1A, LGMD2A, etc.) based on genotype. However, ever-expanding discoveries of new genes have outgrown the alphabet. The European Neuromuscular Centre (ENMC) proposed a new nomenclature in which autosomal dominant cases are termed LGMD “D” and autosomal recessive as LGMD “R,” followed by a numerical number based on genotype. Fur thermore, this new classification only includes cases in which at least two unrelated families have been reported, the predominant weakness at onset was proximal, independent ambulation was achieved at some time, CK is elevated, and muscle biopsies or imaging revealed dystro phic features. Thus, mutations in the CPN3 gene leading to a deficiency in calpain-3, which traditionally were classified as LGMD2A, are classified as LGMDR1 by this new system. In contrast, mutations in myotilin (LGMD1A) and desmin (LGMD1E and LGMD2R) and that often have more distal weakness and have biopsy features of a myofi brillar myopathy are not classified as a LGMD in this new scheme but rather as subtypes of myofibrillar myopathy. Likewise, laminopathies (LGMD1B) are considered a subtype of EDMD rather than an LGMD. The myofibrillar myopathies are now considered as being separate from LGMD. This new classification of LGMD and distal muscular dystrophies is summarized in Tables 460-3 and 460-4. A recent metanalysis reported the prevalence of LGMD to be 1.63 per 100,000 (range, 0.56–5.75 per 100,000), while estimated prevalences

MDC1A, LGMDR23 (α 2 lamin or merosin) ISPD, LARGE, TMEM5, GMPPB, B3GNT1, GTDC2, B3GALNT2, POMK, cause MDDGA, MDDGB, MDDC and LGMD (FKRP) LGMDR9 LGMDD5, LGMDR22 Bethlem and Ullrich myopathy (Collagen VI) LGMDR6 Sarcospan LGMDR4 LGMDR3 α-SG β-SG LGMDR5 α-SG γ-SG Rippling muscle disease LGMD1C (Caveolin-3) LGMDR2 (Dysferlin) (Duchenne and Becker dystrophy) LGMDR12 (Anoctamin 5) MFM3/LGMD1A (myotilin) LGMDR7 (Telethonin) Other Z-disk proteins; ZASP, BAG3, α B-crystallin, Nebulin, α Actinin, FHL1, Filamin C, Kyphoscoliosis peptidase, Supervillin, PYROXD1, UNC45B Titin Myosin Actin

LGMDR10 Udd distal myopathy HMERR MFM10 Myofibrillar myopathy Nemaline myopathy FIGURE 460-6 Proteins involved in the muscular dystrophies. This schematic shows the location of various sarcolemmal, sarcomeric, nuclear, and enzymatic proteins associated with muscular dystrophies. The diseases associated with mutations in the genes responsible for encoding these proteins are shown in boxes. Dystrophin, via its interaction with the dystroglycan complex, connects the actin cytoskeleton to the extracellular matrix. Extracellularly, the sarcoglycan complex interacts with biglycan, which connects this complex to the dystroglycan complex and the extracellular matrix collagen. Various enzymes are important in the glycosylation of the α-dystroglycan and mediate its binding to the extracellular matrix and usually cause a congenital muscular dystrophy with severe brain and eye abnormalities but may cause milder limbgirdle muscular dystrophy (LGMD) phenotype. Mutations in genes that encode for sarcomeric and Z-disk proteins cause forms of LGMD and distal myopathies (including myofibrillar myopathy, forms of hereditary inclusion body myopathy) as well as nemaline rod myopathy and other “congenital” myopathies. Mutations affecting nuclear membrane proteins are responsible for most forms of Emery-Dreifuss muscular dystrophy (EDMD). Mutations in other nuclear genes cause other forms of dystrophy. (Reproduced with permission from AA Amato et al (eds): Amato and Russell’s Neuromuscular disorders, 3rd ed. New York: McGraw Hill; 2025.) of individual specific subtypes of LGMDs vary. The most common types of adult-onset LGMD are calpainopathy (LGMD2A/LGMDR1), fukutin-related protein (FKRP) deficiency (LGMD2I/LGMDR9), and anoctaminopathy (LGMD2L/LGMDR12). Calpainopathy (LGMD2A/LGMDR1), the most common cause of LGMD in those with ancestry from Spain, France, Italy, and Great Britain, is associated with marked scapular winging, lack of calf muscle hypertrophy, and lack of cardiac and lung involvement. Of note, autosomal dominant mutations in an intron of the calpain-3 gene is responsible for LGMD1I/LGMDD4. LGMD2I/LGMDR9 is more common in individuals with northern European ancestry, is associated with calf muscle hypertrophy, and can have cardiac and lung involvement out of proportion to extremity weakness. LGMD2L/LGMDR12 accounts for ~7% of LGMD in the United States, and the prevalence is higher in northern Europe; as seen in dysferlinopathies (LGMD2B/LGMDR2 and Miyoshi myopathy type 1), anoctaminopathy has an early predilection for medial calf atrophy and weakness. Importantly, immune-mediated necrotizing myopathies can mimic LGMD clinically and histopathologically (Chap. 377). Any one suspected of having an LGMD but without definite pathogenic mutation(s) identified on genetic testing should be screened for the

Extra cellular matrix (POMT1) LGMDR11 also cause forms of MDDG (Fukutin) LGMDR13

(POMT2) LGMDR14 (POMGnT1) LGMDR15 LGMDR16 α-DG (POMGnT2) LGMDR24 also cause forms of MDDG β-DG LGMDR8 LGMDR18 TRIM32 TRAPPC11 Myofibrillar myopathy MFM1 (Desmin) CHAPTER 460 EDMD7 (TMEM43) Dystrophin EDMD4, EDMD5 (Nesprin 1, Nesprin 2)

LGMDR1 (Calpain-3) EDMD1 (Emerin) Muscular Dystrophies and Other Muscle Diseases LGMD1B EDMD2, 3 (Lamin A/C) Nucleus PABN2 Transportin3 LGMDD3 OPMD LRP12 GIPC1 NOTCH2NLC RILPL1 VCP HNRPA2BI HNRNPAI Sequestome Matrin3 OPDM1 OPDM2 OPDM3 OPDM4 MSP1 MSP2 MSP3 MSP4 MSP5 Laing myopathy Hyaline myopathy H-IBM3 MFM12 Torsin A-Interacting Protein 1 presence of serum antibodies against HMGCR and SRP to assess for a treatable autoimmune cause. ■ ■EMERY-DREIFUSS MUSCULAR DYSTROPHY There are at least seven subtypes of EDMD that have been associated with mutations in EMD (EDMD1), LMNA (EDMD2 and EDMD3), SYNE1 (EDMD4), SYNE2 (EDMD5), FHL1 (EDMD6), and TMEM43 (EDMD7), encoding emerin, lamin A/C, nesprin-1, nesprin-2, FHL1, and LUMA, respectively. Mutations in EMD and FHL produce X-linked inheritance, whereas the others can be autosomal dominant (LMNA, SYNE1, SYNE2, LUMA) or autosomal recessive (LMNA1). The clinical phenotypes are quite similar. Clinical Features Prominent contractures can be recognized in early childhood and teenage years, often preceding muscle weak ness. The contractures persist throughout the course of the disease and are present at the elbows, ankles, and neck. Muscle weakness affects humeral and peroneal muscles at first and later spreads to a limb-girdle distribution (Table 460-1). The cardiomyopathy is poten tially life threatening and may result in sudden death. A spectrum of atrial rhythm and conduction defects includes atrial fibrillation,

atrial standstill, and atrioventricular heart block. Some patients have a dilated cardiomyopathy. Female carriers of the X-linked variant may manifest with a cardiomyopathy.

Laboratory Features Serum CK is usually slightly elevated, and the EMG is myopathic. Muscle biopsy usually shows nonspecific dystrophic features, although cases associated with FHL1 mutations have features of myofibrillar myopathy. Immunohistochemistry reveals absent emerin staining of myonuclei in X-linked EDMD due to emerin mutations. Electrocardiograms (ECGs) demonstrate atrial and atrio ventricular rhythm disturbances. X-linked EDMD usually arises from defects in the emerin gene encoding a nuclear envelope protein. FHL1 mutations are also a cause of X-linked scapuloperoneal dystrophy but can also present with an X-linked form of EDMD. The autosomal dominant disease can be caused by mutations in the LMNA gene encoding Lamin A/C; in the synaptic nuclear envelope protein 1 (SYNE1) or 2 (SYNE2) encod ing nesprin-1 and nesprin-2, respectively; and in TMEM43 encoding LUMA. These proteins are essential components of the filamentous network underlying the inner nuclear membrane. Loss of structural integrity of the nuclear envelope from defects in emerin, Lamin A/C, nesprin-1, nesprin-2, and LUMA accounts for overlapping phenotypes. PART 13 Neurologic Disorders TREATMENT Emery-Dreifuss Muscular Dystrophy Supportive care should be offered for neuromuscular disability, including ambulatory aids, if necessary. Stretching of contractures is difficult. Management of cardiomyopathy and arrhythmias (e.g., early use of a defibrillator or cardiac pacemaker) may be lifesaving. ■ ■MYOTONIC DYSTROPHY There are two distinct forms of myotonic dystrophy (dystrophia myo tonica [DM]), namely myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2), also called proximal myotonic myopathy (PROMM). Clinical Features The clinical expression of DM1 varies widely and involves many systems other than muscle. Affected patients may have a “hatchet-faced” appearance due to temporalis, masseter, and facial muscle atrophy and weakness. Frontal baldness is frequent. Weakness of wrist and fingers occurs early, as does foot drop. Proximal muscles are less affected. Palatal, pharyngeal, and tongue involvement can lead to dysarthria and dysphagia. Some patients have diaphragm and intercostal muscle weakness, resulting in ventilatory insufficiency. Myotonia is usually apparent by the age of 5 years and is best

demon strable by percussion of the thenar eminence or asking patients to close their fingers very tightly and then relax. ECG abnormalities include first-degree heart block and more exten sive conduction system involvement. Complete heart block and sudden death can occur. Congestive heart failure occurs infrequently but may result from cor pulmonale secondary to respiratory failure. Other associated features include intellectual impairment, hypersomnia, pos terior subcapsular cataracts, gonadal atrophy, insulin resistance, and decreased esophageal and colonic motility. Congenital myotonic dystrophy is a more severe form of DM1 and occurs in ~25% of infants of affected mothers. It is characterized by severe facial and bulbar weakness, transient neonatal respiratory insuf ficiency, and intellectual disability. DM2 or PROMM involves mainly proximal muscles. Other features of the disease overlap with DM1, including cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia, and cognitive defects. Cardiac conduction defects occur but are less common. The hatchet face and frontal baldness are also less consistent features. A very strik ing difference is the failure to clearly identify a congenital form of DM2. Laboratory Features The diagnosis of myotonic dystrophy can usually be made on the basis of clinical findings. Serum CK levels may be normal or mildly elevated. EMG evidence of myotonia is present

in most cases of DM1 but is more patchy in DM2. Muscle biopsy is not typically performed for diagnosis but is sometimes done when the clinical features and electrophysiologic features are not recognized. The major histopathologic features in both DM1 and DM2 are numerous internalized nuclei in individual muscle fibers combined with many atrophic fibers with pyknotic nuclear clumps. DM1 and DM2 are autosomal dominant disorders. DM1 is transmit ted by an intronic mutation consisting of an unstable expansion of a CTG trinucleotide repeat in a serine-threonine protein kinase gene (named DMPK). An increase in the severity of the disease phenotype in succes sive generations (genetic anticipation) is accompanied by an increase in the number of trinucleotide repeats. The unstable triplet repeat in myo tonic dystrophy can be used for prenatal diagnosis. Congenital disease occurs almost exclusively in infants born to affected mothers. DM2 is caused by a DNA expansion mutation consisting of a CCTG repeat in intron 1 of the CNBP gene encoding the CCHC-type zinc finger nucleic acid binding protein. The DNA expansions in DM1 and DM2 impair muscle function by a toxic gain of function of the mutant mRNA. In both DM1 and DM2, the mutant RNA appears to form intranuclear inclusions composed of aberrant RNA. These RNA inclusions sequester RNA-binding proteins essential for proper splicing of a variety of other mRNAs. This leads to abnormal transcription of multiple proteins in a variety of tissues/organ systems, in turn causing the systemic manifestations of DM1 and DM2. TREATMENT Myotonic Dystrophy The myotonia in DM1 and DM2 is usually not so bothersome to warrant treatment, but when it is, mexiletine may be helpful. A cardiac pacemaker or implantable cardioverter defibrillator should be considered for patients with significant arrhythmia. Molded ankle-foot orthoses help stabilize gait in patients with foot drop. Excessive daytime somnolence with or without sleep apnea is not uncommon. Sleep studies, noninvasive respiratory support (bipha sic positive airway pressure [BiPAP]), and treatment with modafinil may be beneficial. ■ ■FACIOSCAPULOHUMERAL (FSHD) MUSCULAR DYSTROPHY There are two forms of FSHD that have similar pathogenesis. Most patients have FSHD type 1 (95%), whereas ~5% have FSHD2. Both forms are clinically and histopathologically identical. The prevalence FSHD is ~5 per 100,000 individuals. Clinical Features FSHD typically presents in childhood or young adulthood. In most cases, facial weakness is the initial manifestation, appearing as an inability to smile, whistle, or fully close the eyes. Loss of scapular stabilizer muscles makes arm elevation difficult. Scapular winging (Fig. 460-3) becomes apparent with attempts at abduction

and forward movement of the arms. Biceps and triceps muscles may be severely affected, with relative sparing of the deltoid muscles. Weak ness is invariably worse for wrist extension than for wrist flexion, and weakness of the anterior compartment muscles of the legs may lead to foot drop. In 20% of patients, weakness progresses to involve the pelvic muscles, and severe functional impairment and possible wheel chair dependency result. The heart is not involved, but there can be ventilatory muscle weakness in 5% of affected individuals. There is an increased incidence of nerve deafness. Coats' disease, a disorder consist ing of telangiectasia, exudation, and retinal detachment, also occurs. Laboratory Features The serum CK level may be normal or mildly elevated. EMG and muscle biopsy show nonspecific abnormali ties but on occasion can reveal a prominent inflammatory infiltrate leading to an incorrect diagnosis of myositis (Chap. 377). FSHD1 is associated with deletions of tandem 3.3-kb repeats at 4q35. The deletion reduces the number of repeats to a fragment of <35 kb in most patients. Within these repeats lies the DUX4 gene, which usually is not expressed after early muscle development. In

patients with FSHD1, these deletions in the setting of a specific poly morphism lead to hypomethylation of the region and toxic expression of the DUX4 gene. In cases of FSHD2, there is no deletion, but rather mutations in three different genes have been identified, each of which interestingly leads to hypomethylation of the DUX4 region and the permissive expression of the DUX4 gene. Dominant mutations in the structural maintenance of chromosomes hinge domain 1 (SMCHD1) gene are the most common cause of FSHD2, but heterozygous muta tions in the DNA methyltransferase 3B (DNMT3B) gene and homozy gous mutations in the ligand-dependent nuclear receptor-interacting factor 1 (LRIF1) gene also cause autosomal recessive FSHD2. These proteins normally interact with SMCHD1, and mutations lead to hypo methylation of DUX4. As in FSHD1, this leads to an overexpression of the DUX4 transcript that encodes for double homeobox 4, which itself is a transcription factor controlling the expression of other genes. In turn, this likely results in the altered expression of additional genes. TREATMENT Facioscapulohumeral Muscular Dystrophy No specific treatment is available, though clinical trials assessing the safety and efficacy of reducing DUX4 expression are ongoing. Physical and occupational therapy are the current mainstays of treatment. Ankle-foot orthoses are helpful for foot drop. Scapular stabilization procedures improve scapular winging and function. ■ ■OCULOPHARYNGEAL DYSTROPHY (OPMD) OPMD represents one of several disorders characterized by progressive external ophthalmoplegia, which consists of slowly progressive ptosis and limitation of eye movements with sparing of pupillary reactions for light and accommodation. Patients usually do not complain of diplo pia, in contrast to patients having conditions with a more acute onset of ocular muscle weakness (e.g., myasthenia gravis). Clinical Features OPMD has a late onset; it usually presents in the fourth to sixth decade with ptosis or dysphagia. The extraocular muscle impairment is less prominent in the early phase but may become severe over time. The swallowing problem may lead to aspiration. Weakness of the neck and proximal extremities can develop but is usually mild in degree. Laboratory Features The serum CK level may be two to three times normal. EMG can identify myopathic changes in weak muscles. Muscle biopsies are no longer necessary for diagnosis in most cases but, when performed, demonstrate muscle fibers with rimmed vacuoles. On electron microscopy, a distinctive feature of OPMD is the presence of 8.5-nm tubular filaments in some muscle cell nuclei. OPMD is an autosomal dominant disorder that has a high inci dence in certain populations (e.g., French-Canadians, individuals of Spanish ancestry, and Ashkenazi Jews). The molecular defect in OPMD is an expansion of a polyalanine repeat tract in a poly-RNAbinding protein (PABP2) gene. PABP2 is involved in polyadenylation of mRNAs and their transport through the nuclei pores into the cyto

plasm. The expansion of the GCG repeats results in abnormal folding of the polyalanine domains of PABP2 and its resistance to nuclear proteasomal degradation. This in turn may result in (1) direct toxicity of the intranuclear aggregates; (2) intranuclear sequestration of essential transcription factors, molecular chaperones, RNA binding proteins, and RNAs by these intranuclear aggregates; or (3) suppression of the normal function of the wild-type protein. TREATMENT Oculopharyngeal Dystrophy Dysphagia can lead to significant undernourishment and aspira tion. Cricopharyngeal myotomy may improve swallowing. Eyelid crutches can improve vision when obstructed by ptosis; candidates for ptosis surgery must be carefully selected—those with severe facial weakness are not suitable.

■ ■OCULOPHARYNGEAL DISTAL MYOPATHY (OPDM)

Clinical Features OPDM is characterized by adult-onset ptosis, external ophthalmoplegia, facial muscle weakness, distal limb muscle weakness and atrophy, and pharyngeal involvement, resulting in dys phagia and dysarthria. Some patients manifest with only ptosis without pharyngeal or distal weakness. Laboratory Features Serum CK levels are normal or only mildly elevated. EMG is myopathic. Muscle biopsies reveal dystrophic fea tures including muscle fibers with rimmed vacuoles. Intramyonuclear inclusions immunostaining with anti-phospho-p62/SQSTM1 anti bodies are evident. Similar intranuclear inclusions are found on skin biopsies. OPDM is a genetically heterogeneous autosomal disorder caused by trinucleotide repeat expansions (CTG) in the 5′ untranslated region (UTR) regions of LRP12 (OPDM1), G1PC1 (OPDM2), NOTCH2NLC (OPDM3), and RILPL1 (OPMD4). Notably, the CGG repeat expan sion in NOTCH2NLC is also the cause of neuronal intranuclear hya line inclusion disease and other neurodegenerative diseases affecting the brain. These repeat expansion disorders lead to RNA-mediated sequestration of RNA-binding proteins and altered translation of proteins. CHAPTER 460 Muscular Dystrophies and Other Muscle Diseases TREATMENT Oculopharyngeal Distal Myopathy Treatment of dysphagia and ptosis is similar to that noted with OPMD. ■ ■DISTAL MYOPATHIES/DYSTROPHIES The distal myopathies are notable for their preferential distal distri bution of muscle weakness in contrast to most muscle conditions associated with proximal weakness. The major distal myopathies are summarized in Tables 460-1, 460-5, and 460-6. Clinical Features Welander, Udd, and Markesbery-Griggs type distal myopathies are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years. Welander distal myopathy preferentially involves the wrist and finger exten sors, whereas the others are associated with anterior tibial weakness leading to progressive foot drop. Laing distal myopathy is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life. GNE myopathy (previously known as Nonaka distal myopathy and auto somal recessive hereditary inclusion body myopathy) and Miyoshi myopathy are distinguished by autosomal recessive inheritance and onset in the late teens or twenties. GNE and Williams myopathy pro duce prominent anterior tibial weakness, whereas Miyoshi myopathy is unique in that gastrocnemius muscles are preferentially affected at onset. Finally, the myofibrillar myopathies (MFMs) are a clini cally and genetically heterogeneous group of muscular dystrophies that can be associated with prominent distal or proximal weakness; they can be inherited in an autosomal dominant or recessive pattern (Table 460-6). Laboratory Features Serum CK levels are markedly elevated in Miyoshi myopathy, but in the other conditions, serum CK is only slightly increased. EMGs are myopathic and can be irritable with myotonic discharges in MFM. Muscle biopsy shows nonspecific dystrophic features and, with the exception of Laing and Miyoshi myopathies, often shows rimmed vacuoles. MFM is associated with the accumulation of

dense inclusions and amorphous material best seen on Gomori trichrome staining along with myofibrillar disruption on electron microscopy. Immune staining sometimes demonstrates accumulation of desmin and other proteins in MFM, large depos its of myosin heavy chain in the subsarcolemmal region of type 1 muscle fibers in Laing myopathy, and reduced or absent dysferlin in Miyoshi myopathy type 1.

TREATMENT Distal Myopathies Occupational therapy is offered for loss of hand function; anklefoot orthoses can support distal lower limb muscles. The MFMs can be associated with cardiomyopathy (congestive heart failure or arrhythmias) and respiratory failure that may require medical management. Laing-type distal myopathy can also be associated with a cardiomyopathy. ■ ■MULTISYSTEM PROTEINOPATHIES (MSP) The multisystem proteinopathies (MSPs) are genetically heterogenous disorders featured by hereditary inclusion body myopathy (IBM), amyotrophic lateral sclerosis, parkinsonism, frontotemporal dementia, and Paget disease of bone. Some forms have also been referred to as IBMPFD for some of the above major clinical features. Patients present in adulthood with progressive proximal or distal weakness. Serum CK is usually mildly elevated. EMG shows features of an irritable myopathy but also neurogenic features as well. Muscle biopsies in patients with myopathy show rimmed vacuoles, inclusions that immunostain with ubiquitin, and TDP-43 extrusion from myonuclei. Most are caused by mutations in genes that encode for RNA-binding proteins or proteins involved in the elimination of other aged proteins. There are at least five types of MSP (Table 460-7). PART 13 Neurologic Disorders ■ ■SPORADIC LATE-ONSET NEMALINE MYOPATHY Clinical Features Sporadic late onset nemaline myopathy (SLONM) should not be confused with congenital forms of nemaline myopathy, which usually are congenital and/or hereditary in nature. SLONM is not a genetic disorder and usually presents after the age of 40 years with proximal extremity weakness. Some patients may present with an axial myopathy, isolated head drop, or bent spine syndrome from paraspinal muscle weakness. Ventilatory muscle involvement and cardiomyopathy may develop. Additionally, SLONM can complicate HIV infection. Laboratory Features Serum CK is usually normal or mildly ele vated and can be lower than normal. EMG reveals signs of an irritable myopathy. About 50% of cases are associated with a monoclonal gam mopathy of undetermined significance (IgG or IgA). Muscle biopsies can reveal inflammatory cell infiltrates, trabeculated or lobulated fibers, many atrophic muscle fibers, and fibers with nemaline rods. The rods are often smaller than ones seen in the hereditary nemaline myopathies and may be missed on routine light microscopy if thick ness of the sections is >3 μm. However, the rods are almost always appreciated on electron microscopy, and on immunohistochemistry, the rods are usually immunoreactive to anti-α-actinin antibody. TREATMENT SLONM Some patients with SLONM respond to intravenous immunoglobu lin or other immunosuppressive therapies. Autologous stem cell transplantation has been beneficial in some patients with SLONM and a monoclonal gammopathy. TABLE 460-7 Multisystem Proteinopathies MULTISYSTEM PROTEINOPATHY INHERITANCE GENE AFFECTED PROTEIN MSP1 / IBMPFD1 AD VCP Valosin-containing protein MSP2 / IBMPFD2 AD HNRPA2B1 HNRPA2B1 MSP3 / IBMPFD3 AD HNRNPA1 HNRNPA1 MSP4 AD SQTM1 Sequestome MSP5 AD MTR3 Matrin 3 Abbreviations: AD, autosomal dominant; HNRNPA1, heterogeneous nuclear ribonucleoprotein A1; HNRPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; IBMPFD, inclusion body myopathy, Paget disease, frontotemporal dementia; MSP, multisystem proteinopathy.

DISORDERS OF MUSCLE ENERGY METABOLISM There are two principal sources of energy for skeletal muscle—fatty acids and glucose. Abnormalities in either glucose or lipid utilization can be

associated with distinct clinical presentations that can range from an acute, painful syndrome with rhabdomyolysis and myoglo binuria to a chronic, progressive muscle weakness simulating muscular dystrophy (Table 460-1). As with the muscular dystrophies, there are no specific medical treatments available. ■ ■GLYCOGEN STORAGE AND GLYCOLYTIC DEFECTS Disorders of Glycolysis Causing Exercise Intolerance Sev eral glycolytic defects are associated with recurrent myoglobinuria. The most common is McArdle disease caused by mutations in the PYGM gene leading to myophosphorylase deficiency. Symptoms of muscle pain and stiffness usually begin in adolescence. With severe episodes, myoglobinuria can occur. Certain features help distinguish some enzyme defects. In McArdle disease, exercise tolerance can be enhanced by a slow induction phase (warm-up) or brief periods of rest, allowing for the start of the “second-wind” phenomenon (switching to utilization of fatty acids). Varying degrees of hemolytic anemia accompany deficiencies of both phosphofructokinase (mild) and phosphoglycerate kinase (severe). In phosphoglycerate kinase deficiency, the usual clinical presentation is a seizure disorder associated with intellectual disability; exercise intoler ance is an infrequent manifestation. In all of these conditions, the serum CK levels fluctuate widely and may be elevated even during symptom-free periods. CK levels >100 times normal are expected accompanying myoglobinuria. A forearm exercise test reveals a blunted rise in venous lactate with a normal rise in ammonia. A definitive diagnosis of glycolytic disease can be made by muscle biopsy with appropriate staining and enzyme assays, but genetic testing is now done in lieu of biopsy in most cases. Training may enhance exercise tolerance, perhaps by increasing perfusion to muscle. Dietary intake of free glucose or fructose prior to activity may improve function, but care must be taken to avoid obesity from ingesting too many calories. Disorders of Glycogen Storage Causing Progressive

Weakness • `-GLUCOSIDASE, OR ACID MALTASE, DEFICIENCY (POMPE DISEASE) Three clinical forms of α-glucosidase, or acid maltase, deficiency (type II glycogenosis) can be distinguished. The infantile form is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, car diomegaly, hepatomegaly, and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem con tributes to muscle weakness. Death usually occurs by 1.5 years of age. In the childhood form, the picture resembles DMD with delayed motor milestones resulting from proximal limb muscle weakness and involve ment of respiratory muscles. The heart may be involved, but the liver and brain are unaffected. The adult form usually begins in the third or fourth decade but can present as late as the seventh decade. Ventila tory weakness can be the initial and only manifestation in 20–30% of late-onset cases. The serum CK level is 2–10 times normal in infantile or childhoodonset Pompe disease but can be normal in adult-onset cases. EMG can demonstrate muscle membrane irritability, particularly in the paraspinal muscles. The muscle biopsy in infants typically reveals vacuoles containing glycogen and the lysosomal enzyme acid phos phatase. Electron microscopy reveals membrane-bound and free tissue glycogen. However, muscle biopsies in late-onset Pompe disease may demonstrate only nonspecific abnormalities. Enzyme analysis of dried blood spots is a sensitive technique to screen for Pompe disease. A definitive diagnosis is established by genetic testing. Pompe disease is inherited as an autosomal recessive disorder caused by mutations of the α-glucosidase gene. Enzyme replacement therapy (ERT) with IV recombinant human α-glucosidase is beneficial in infantile-onset Pompe disease. In late-onset cases, ERT has a more modest benefit.

OTHER GLYCOGEN STORAGE DISEASES WITH PROGRESSIVE WEAK NESS In debranching enzyme deficiency (type III glycogenosis), a slowly progressive form of muscle weakness can develop after

puberty. Rarely, myoglobinuria may be seen. Patients are usually diagnosed in infancy, however, because of hypotonia and delayed motor milestones; hepa tomegaly, growth retardation, and hypoglycemia are other manifesta tions. Branching enzyme deficiency (type IV glycogenosis) is a rare and fatal glycogen storage disease characterized by failure to thrive and hepatomegaly. Hypotonia and muscle wasting may be present, but the skeletal muscle manifestations are minor compared to liver failure. An autosomal dominant glycogen storage disease was reported in a single family that was due to a mutation in the PYGM gene that typically causes autosomal recessive McArdle disease. Affected individuals pre sented with progressive proximal weakness, no exercise intolerance, normal CK, and a normal lactic acid increase with exercise. ■ ■LIPID AS AN ENERGY SOURCE AND ASSOCIATED DEFECTS Lipid is an important muscle energy source during rest and during prolonged, submaximal exercise. Oxidation of fatty acids occurs in the mitochondria. To enter the mitochondria, a fatty acid must first be converted to an “activated fatty acid,” acyl-CoA. The acyl-CoA must be linked with carnitine by the enzyme CPT for transport into the mitochondria. Carnitine Palmitoyltransferase 2 (CPT2) Deficiency CPT2 deficiency is the most common recognizable cause of recurrent myoglobinuria. Onset is usually in the teenage years or early twen ties. Muscle pain and myoglobinuria typically occur after prolonged exercise but can also be precipitated by fasting or infections; up to 20% of patients do not exhibit myoglobinuria, however. Strength is normal between attacks. In contrast to disorders caused by defects in glycolysis, in which muscle cramps follow short, intense bursts of exercise, the muscle pain in CPT2 deficiency does not occur until the limits of utilization have been exceeded and muscle breakdown has already begun. Serum CK levels and EMG findings are both usually normal between episodes. A normal rise of venous lactate during forearm exercise dis tinguishes this condition from glycolytic defects. Muscle biopsy does not show lipid accumulation and is usually normal between attacks. The diagnosis requires direct measurement of muscle CPT or genetic testing. Attempts to improve exercise tolerance with frequent meals and a low-fat, high-carbohydrate diet, or by substituting medium-chain triglycerides in the diet, have not proven to be beneficial. MITOCHONDRIAL MYOPATHIES Mitochondria play a key role in energy production. Oxidation of the major nutrients derived from carbohydrate, fat, and protein leads to the generation of reducing equivalents. The latter are transported through the respiratory chain in the process known as oxidative phosphoryla tion. The energy generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical gradient coupled to ATP synthesis. A novel feature of mitochondria is their genetic composition. Each mitochondrion possesses a DNA genome that is distinct from that of the nuclear DNA. Human mitochondrial DNA (mtDNA) consists of a double-strand, circular molecule comprising 16,569 base pairs (bp). It codes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 polypeptides of the respiratory chain enzymes. The genetics of mitochondrial dis eases differ from the genetics of chromosomal disorders. The DNA of mitochondria is directly inherited from the cytoplasm of the gametes, mainly from the oocyte. The sperm contributes very little of its mito chondria to the offspring at the time of fertilization. Thus, mitochon drial genes are derived almost exclusively from the mother, accounting for maternal inheritance of some mitochondrial disorders. Patients with mitochondrial myopathies have clinical manifesta tions that usually fall into three groups: chronic progressive external ophthalmoplegia (CPEO), skeletal muscle–CNS syndromes, and pure myopathy simulating muscular dystrophy or metabolic myopathy.

Unfortunately, no specific medical therapies are clearly beneficial, although coenzyme Q10 supplements are often prescribed.

Kearns-Sayre Syndrome (KSS) This is a widespread multiorgan system disorder with a defined triad of clinical findings: onset before age 20, CPEO, and pigmentary retinopathy, plus one or more of the following features: complete heart block, cerebrospinal fluid (CSF) protein >1 g/L (100 mg/dL), or cerebellar ataxia. The cardiac disease includes syncopal attacks and cardiac arrest related to the abnor malities in the cardiac conduction system: prolonged intraventricular conduction time, bundle branch block, and complete atrioventricular block. Death attributed to heart block occurs in ~20% of the patients. Varying degrees of progressive limb muscle weakness and easy fatiga bility affect activities of daily living. Many affected individuals have intellectual disabilities. Endocrine abnormalities are also common, including gonadal dysfunction in both sexes with delayed puberty, short stature, and infertility. Diabetes mellitus occurs in ~13% of KSS patients. Other less common endocrine disorders include thyroid dis ease, hyperaldosteronism, Addison's disease, and hypoparathyroidism. CHAPTER 460 Serum CK and lactate levels are normal or slightly elevated. Serum levels of fibroblast growth factor 21 (FGF-21) and growth and dif ferentiation factor 15 (GDF-15) are often elevated in mitochondrial disorders with muscle weakness. EMG is often myopathic. NCS may be abnormal related to an associated neuropathy. Muscle biopsies reveal ragged red fibers and cytochrome oxidase (COX)–negative fibers. By electron microscopy, there are increased numbers of mitochondria that often appear enlarged and contain paracrystalline inclusions. Muscular Dystrophies and Other Muscle Diseases KSS is a sporadic disorder caused by single mtDNA deletions that are presumed to arise spontaneously in the ovum or zygote. The most common deletion, occurring in about one-third of patients, removes 4977 bp of contiguous mtDNA. Monitoring for cardiac conduction defects is critical. Prophylactic pacemaker implantation is indicated when ECGs demonstrate a bifascicular block. Progressive External Ophthalmoplegia (PEO) PEO can be caused by nuclear DNA mutations affecting mtDNA and thus inherited in a Mendelian fashion or by mutations in mtDNA. Onset is usually after puberty. Fatigue, exercise intolerance, dysphagia, and complaints of muscle weakness are typical. The neurologic examination confirms the ptosis and ophthalmoplegia, usually asymmetric in distribution. Patients do not complain of diplopia. Mild facial, neck flexor, and proximal weakness is typical. Rarely, respiratory muscles may be pro gressively affected and may be the direct cause of death. Serum CK and lactate can be normal or mildly elevated. The EMG can be myopathic. Ragged red and COX-negative fibers are promi nently displayed in the muscle biopsy. This autosomal dominant form of CPEO is most commonly caused by mutations in the genes encoding adenine nucleotide translocator 1 (ANT1), twinkle gene (C10orf2), and mtDNA polymerase 1 (POLG1). Autosomal recessive PEO can also be caused by mutations in POLG1. Point mutations have been identified within various mitochondrial tRNA (Leu, Ile, Asn, Trp) genes in families with maternal inheritance of PEO. There is no specific medical treatment available; exercise may improve function, but this will depend on the patient's ability to participate. Myoclonic Epilepsy with Ragged Red Fibers (MERRF) The onset of MERRF is variable, ranging from late childhood to middle adult life. Characteristic features include myoclonic epilepsy, cerebellar ataxia, and progressive proximal muscle weakness. The seizure disor der is an integral part of the disease and may be the initial symptom. Cerebellar ataxia precedes or accompanies epilepsy. Other more vari able features include dementia, peripheral neuropathy, optic atrophy, hearing loss, and diabetes mellitus. Serum CK levels and lactate may be normal or elevated. EMG is myopathic, and in some patients, NCS show a neuropathy. The electroencephalogram is abnormal, corroborating clinical findings of epilepsy. Typical ragged red fibers are seen on muscle biopsy. MERRF is caused by maternally inherited point mutations of mitochondrial

tRNA genes. The most common mutation found in 80% of MERRF patients is an A to G substitution at nucleotide 8344 of tRNA lysine (A8344G tRNAlys). Only supportive treatment is possible, with special attention to epilepsy.

Mitochondrial Myopathy, Encephalopathy, Lactic Acido sis, and Stroke-like Episodes (MELAS) MELAS is the most common mitochondrial encephalomyopathy. The term stroke-like is appropriate because the cerebral lesions do not conform to a strictly vascular distribution. The onset in the majority of patients is before age 20. Seizures, usually partial motor or generalized, are common and may represent the first clearly recognizable sign of disease. The cerebral insults that resemble strokes cause hemiparesis, hemianopia, and cortical blindness. A presumptive stroke occurring before age 40 should place this mitochondrial encephalomyopathy high in the differential diagnosis. Associated conditions include hearing loss, diabetes mellitus, hypothalamic pituitary dysfunction causing growth hormone deficiency, hypothyroidism, and absence of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and a fatal outcome. Serum lactic acid is typically elevated. PART 13 Neurologic Disorders The CSF protein is also increased but is usually ≤1 g/L (100 mg/dL). Muscle biopsies show ragged red fibers. Neuroimaging demonstrates basal ganglia calcification in a high percentage of cases. Focal lesions that mimic infarction are present predominantly in the occipital and parietal lobes. Strict vascular territories are not respected, and cerebral angiography fails to demonstrate lesions of the major cerebral blood vessels. MELAS is usually caused by maternally inherited point muta tions of mitochondrial tRNA genes. The A3243G point mutation in tRNALeu(UUR) is the most common, occurring in ~80% of MELAS cases. No specific treatment is available. Supportive treatment is essential for the stroke-like episodes, seizures, and endocrinopathies. Mitochondrial DNA Depletion Syndromes Mitochondrial DNA depletion syndrome (MDS) is a heterogeneous group of disorders that are inherited in an autosomal recessive fashion and can present in infancy or in adults. MDS can be caused by mutations in several genes (TK2, DGUOK, RRM2B, TYMP, SUCLA1, and SUCLA2) that lead to depletion of mitochondrial deoxyribonucleotides (dNTP) necessary for mtDNA replication. The other major cause of MDS is a set of mutations in genes essential for mtDNA replication (e.g., POLG1 and C10orf2). The clinical phenotypes associated with MDS vary. Patients may develop a severe encephalopathy (e.g., Leigh’s syndrome), PEO, an isolated myopathy, myo-neuro-gastrointestinal encephalopathy (MNGIE), and a sensory neuropathy with ataxia. DISORDERS OF MUSCLE MEMBRANE EXCITABILITY Muscle membrane excitability is affected in a group of disorders referred to as channelopathies. These disorders usually present with episodic muscle weakness (periodic paralysis) and sometimes myoto nia or paramyotonia (Table 460-1). ■ ■CALCIUM CHANNEL DISORDERS OF MUSCLE Hypokalemic Periodic Paralysis (HypoKPP) This is an auto somal dominant disorder with onset in adolescence. Males are more often affected because of decreased penetrance in females. Episodic weakness with onset after age 25 is almost never due to periodic paralyses, with the exception of thyrotoxic periodic paralysis. Attacks are often provoked by meals high in carbohydrates or sodium and may accompany rest following prolonged exercise. Weakness usually affects proximal limb muscles more than distal. Ocular and bulbar muscles are less likely to be affected. Respiratory muscles are usually spared, but when they are involved, the condition may prove fatal. Weakness may take as long as 24 h to resolve. Life-threatening cardiac arrhythmias related to hypokalemia may occur during attacks. As a late

complication, patients commonly develop severe, disabling proximal lower extremity weakness. Attacks of thyrotoxic periodic paralysis resemble those of primary HypoKPP. Despite a higher

incidence of thyrotoxicosis in women, men, particularly those of Asian descent, are more likely to manifest this complication. Attacks abate with treatment of the underlying thy roid condition. A low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis. In the midst of an attack of weak ness, motor conduction studies may demonstrate reduced amplitudes, whereas EMG may show electrical silence in severely weak muscles. In between attacks, the EMG and routine NCS are normal. However, a long exercise NCS test may demonstrate decrementing amplitudes. HypoKPP type 1 is the most common form and is caused by muta tions in the voltage-sensitive, skeletal muscle calcium channel gene, CALCL1A3. Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (SCN4A). In both forms, the mutations lead to an abnormal gating pore current that predisposes the muscle cell to depolarize when potassium levels are low. TREATMENT Hypokalemic Periodic Paralysis Mild attacks usually do not require medical treatment. However, severe attacks of weakness can be improved by the administration of potassium. Oral KCl (0.2–0.4 mmol/kg) can be given every 30 min. Only rarely is IV therapy necessary (e.g., when swallowing prob lems or vomiting is present). The long-term goal of therapy is to avoid attacks. Patients should be made aware of the importance of a low-carbohydrate, low-sodium diet and consequences of intense exercise. Prophylactic administration of acetazolamide or dichlor phenamide can reduce attacks of periodic weakness. However, in patients with HypoKPP type 2, attacks of weakness can be exacer bated with these medications. ■ ■SODIUM CHANNEL DISORDERS OF MUSCLE Hyperkalemic Periodic Paralysis (HyperKPP) The term hyperkalemic is misleading because patients are often normokalemic during attacks. That attacks are precipitated by potassium administra tion best defines the disease. The onset is usually in the first decade; males and females are affected equally. Attacks are brief and mild, usually lasting 30 min to several hours. Weakness affects proximal muscles, sparing bulbar muscles. Attacks are precipitated by rest fol lowing exercise and fasting. Potassium may be slightly elevated or normal during an attack. As in HypoKPP, NCS in HyperKPP muscle may demonstrate reduced motor amplitudes and the EMG may be silent in very weak muscles. A long exercise NCS test can reveal diminished amplitudes as well. The EMG may demonstrate myotonic discharges. HyperKPP is caused by mutations of the voltage-gated sodium channel SCN4A gene. Acetazol amide or dichlorphenamide can reduce the frequency and severity of attacks. Mexiletine may be helpful in patients with significant clinical myotonia. Paramyotonia Congenita In PC, the attacks of weakness are coldinduced or occur spontaneously and are mild. Myotonia is a prominent feature but worsens with muscle activity (paradoxical myotonia). This is in contrast to classic myotonia in which exercise alleviates the condition. Attacks of weakness are seldom severe enough to require emergency room treatment. Over time, patients develop inter-attack weakness as they do in other forms of periodic paralysis. Serum CK is usually mildly elevated. Routine NCS are normal. Short exercise NCS tests may be abnormal, however, and cooling of the muscle often dramatically reduces the amplitude of the compound muscle action potentials. EMG reveals diffuse myotonic potentials in

PC. Upon local cooling of the muscle, the myotonic discharges disap pear as the patient becomes unable to activate MUAPs. PC is inherited as an autosomal dominant condition; voltage-gated sodium channel mutations are responsible, and thus, this disorder is allelic with HyperKPP. Mexiletine is reported to be helpful in reducing the myotonia. ■ ■POTASSIUM CHANNEL DISORDERS Andersen-Tawil Syndrome This rare disease is characterized by episodic weakness, cardiac arrhythmias, and dysmorphic features (short stature, scoliosis, clinodactyly, hypertelorism, small or promi nent low-set ears, micrognathia, and broad forehead). The cardiac arrhythmias are

potentially serious and life threatening. They include long QT, ventricular ectopy, bidirectional ventricular arrhythmias, and tachycardia. The disease is most commonly caused by mutations of the inwardly rectifying potassium channel (Kir 2.1) gene that heighten muscle cell excitability. The episodes of weakness may differ between patients because of potassium variability. Acetazolamide may decrease the attack frequency and severity. ■ ■CHLORIDE CHANNEL DISORDERS Two forms of this disorder, autosomal dominant (Thomsen disease) and autosomal recessive (Becker disease), are both caused by muta tions in the chloride channel 1 gene (CLCN1). Symptoms are noted in infancy and early childhood. The severity lessens in the third to fourth decade. Myotonia is worsened by cold and improved by activity. The gait may appear slow and labored at first but improves with walking. In Thomsen disease, muscle strength is normal, but in Becker disease, which is usually more severe, there may be muscle weakness. Muscle hypertrophy is usually present. Myotonic dis charges are prominently displayed by EMG recordings. Serum CK is normal or mildly elevated. Mexiletine is helpful in relieving the myotonia. ENDOCRINE AND METABOLIC MYOPATHIES Endocrinopathies can cause weakness, but fatigue is more common than true weakness. The serum CK level is often normal (except in hypothyroidism), and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopa thies respond to treatment. ■ ■THYROID DISORDERS Hypothyroidism (Chap. 395) Patients with hypothyroidism have frequent muscle complaints, and about one-third have proximal muscle weakness. Muscle cramps, pain, and stiffness are common. Some patients have enlarged muscles. Features of slow muscle con traction and relaxation occur in 25% of patients; the relaxation phase of muscle stretch reflexes is characteristically prolonged and best observed at the ankle or biceps brachii reflexes. The serum CK level is often elevated (up to 10 times normal). EMG is typically normal. Muscle biopsy shows no distinctive morphologic abnormalities. Hyperthyroidism (Chap. 396) Patients who are thyrotoxic commonly have proximal muscle weakness, but they rarely complain of myopathic symptoms. Activity of deep tendon reflexes may be enhanced. Fasciculations may be apparent and, when coupled with increased muscle stretch reflexes, may lead to an erroneous diagnosis of amyotrophic lateral sclerosis. A form of hypokalemic periodic paral ysis can occur in patients who are thyrotoxic. Mutations in the KCNJ18 gene that encodes for the inwardly rectifying potassium channel, Kir 2.6, have been discovered in up to a third of cases. ■ ■PARATHYROID DISORDERS (SEE ALSO CHAP. 422) Hyperparathyroidism Proximal muscle weakness, muscle wast ing, and brisk muscle stretch reflexes are the main features of this

endocrinopathy. Some patients develop neck extensor weakness (part of the dropped head syndrome). Serum CK levels are usually normal or slightly elevated. Serum parathyroid hormone levels are elevated, while vitamin D and calcium levels are usually reduced. Muscle biopsies show only mild type 2 fiber atrophy.

Hypoparathyroidism An overt myopathy due to hypocalce mia rarely occurs. Neuromuscular symptoms are usually related to localized or generalized tetany. Serum CK levels may be increased secondary to muscle damage from sustained tetany. Hyporeflexia or areflexia is usually present and contrasts with the hyperreflexia in hyperparathyroidism. ■ ■ADRENAL DISORDERS (SEE ALSO CHAP. 398) Conditions associated with glucocorticoid excess cause a myopathy; steroid myopathy is the most commonly diagnosed endocrine muscle disease. Proximal muscle weakness combined with a cushingoid appearance are the key clinical features. Serum CK and EMG are normal. Muscle biopsy, not typically done for diagnostic purposes, reveals type 2b muscle fiber atrophy. In primary hyperaldosteron ism (Conn’s syndrome), neuromuscular complications are due to potassium

depletion. The clinical picture is one of persistent muscle weakness. Long-standing hyperaldosteronism may lead to proximal limb weakness and wasting. Serum CK levels may be elevated, and a muscle biopsy may demonstrate necrotic fibers. These changes relate to hypokalemia and are not a direct effect of aldosterone on skeletal muscle. CHAPTER 460 Muscular Dystrophies and Other Muscle Diseases ■ ■PITUITARY DISORDERS (SEE ALSO CHAP. 392) Patients with acromegaly usually have mild proximal weakness. Mus cles often appear enlarged but exhibit decreased force generation. The duration of acromegaly, rather than the serum growth hormone levels, correlates with the degree of myopathy. ■ ■DIABETES MELLITUS (SEE ALSO CHAP. 417) Neuromuscular complications of diabetes mellitus are most often related to neuropathy. The only notable myopathy is ischemic infarc tion of leg muscles, usually involving one of the thigh muscles but on occasion affecting the distal leg. This condition occurs in patients with poorly controlled diabetes and presents with the abrupt onset of pain, tenderness, and edema of a thigh or calf. The area of muscle infarction is hard and indurated. The muscles most often affected include the vastus lateralis, thigh adductors, and biceps femoris. Computed tomography (CT) or MRI can demonstrate focal abnor malities in the affected muscle. Diagnosis by imaging is preferable to muscle biopsy, if possible, as hemorrhage into the biopsy site can occur. MYOPATHIES OF SYSTEMIC ILLNESS Systemic illnesses such as chronic respiratory, cardiac, or hepatic failure are frequently associated with severe muscle wasting and com plaints of weakness. Fatigue is usually a more significant problem than weakness, which is typically mild. DRUG-INDUCED OR TOXIC MYOPATHIES The most common toxic myopathies are caused by the cholesterollowering agents and glucocorticoids. Others impact practice to a lesser degree but are important to consider in specific situations. Table 460-8 provides a comprehensive list of drug-induced myopathies with their distinguishing features. ■ ■MYOPATHY FROM LIPID-LOWERING AGENTS All classes of lipid-lowering agents have been implicated in muscle toxicity, including HMG-CoA reductase inhibitors (statins) and, to a much lesser extent, fibrates, niacin, and ezetimibe. Myalgia and elevated CKs are the most common manifestations. Rarely, patients exhibit proximal weakness or myoglobinuria. Concomitant use of statins with fibrates and cyclosporine increases the risk of severe

TABLE 460-8 Drug-Induced Myopathies DRUGS MAJOR TOXIC REACTION Drugs belonging to all three of the major classes of lipid-lowering agents can produce a spectrum of toxicity: asymptomatic serum creatine kinase elevation, myalgias, exercise-induced pain, rhabdomyolysis, and myoglobinuria. Lipid-lowering agents HMG-CoA reductase inhibitors Fibric acid derivatives Niacin (nicotinic acid) Glucocorticoids Acute, high-dose glucocorticoid treatment can cause acute quadriplegic myopathy. These high doses of steroids are often combined with nondepolarizing neuromuscular blocking agents, but the weakness can occur without their use. Chronic steroid administration produces predominantly proximal weakness. Nondepolarizing neuromuscular blocking agents Acute quadriplegic myopathy can occur with or without concomitant glucocorticoids. PART 13 Neurologic Disorders Zidovudine Mitochondrial myopathy with ragged red fibers. All drugs in this group can lead to widespread muscle breakdown, rhabdomyolysis, and myoglobinuria. Local injections cause muscle necrosis, skin induration, and limb contractures. Drugs of abuse Alcohol Amphetamines Cocaine Heroin Phencyclidine Meperidine Use of statins may cause an immune-mediated necrotizing myopathy associated with HMG-CoA reductase antibodies. Checkpoint inhibitors can be complicated by myositis, myocarditis, myasthenia gravis, and immune-mediated neuropathies. Myasthenia gravis has also been reported with penicillamine. Autoimmune myopathy Statins Checkpoint inhibitors D-Penicillamine All amphophilic drugs have the potential to produce painless, proximal weakness associated with necrosis and autophagic

vacuoles in the muscle biopsy. Amphophilic cationic drugs Amiodarone Chloroquine Hydroxychloroquine This drug produces painless, proximal weakness especially in the setting of renal failure. Muscle biopsy shows necrosis and fibers with autophagic vacuoles. Antimicrotubular drugs Colchicine myotoxicity. EMG demonstrates irritability, and myopathic units and muscle biopsies reveal necrotic muscle fibers in weak muscles. Severe myalgia, weakness, marked elevations in serum CK (>3–5 times baseline), and myoglobinuria are indications for stopping the drug. Patients usually improve with drug cessation, although this may take several weeks. Rare cases continue to progress after the offending agent is discontinued. It is possible that in such cases the statin may have triggered an immune-mediated necrotizing myopathy, as these individuals require immunotherapy (e.g., intravenous immunoglobulin or immunosuppressive agents) to improve and often relapse when these therapies are discontinued (Chap. 377). Autoantibodies directed against HMG-CoA reductase have been identified in many of these cases. ■ ■GLUCOCORTICOID-RELATED MYOPATHIES Glucocorticoid myopathy occurs with chronic treatment or as “acute quadriplegic” myopathy secondary to high-dose IV glucocorticoid use. Chronic administration produces proximal weakness accompanied by cushingoid manifestations, which can be quite debilitating; the chronic use of prednisone at a daily dose of ≥30 mg/d is most often associated with toxicity. Patients taking fluorinated glucocorticoids (triamcinolone, betamethasone, dexamethasone) appear to be at especially high risk for myopathy. In chronic steroid myopathy, the serum CK is usually normal. Serum potassium may

be low. The muscle biopsy in chronic cases shows preferential type 2 muscle fiber atrophy; this is not reflected in the EMG, which is usually normal. Patients receiving high-dose IV glucocorticoids for status asthmaticus, chronic obstructive pulmonary disease, organ transplantation, or other indications may develop severe generalized weakness (critical illness myopathy). This myopathy, also known as acute quadriplegic myopathy, can also occur in the setting of sepsis. Involvement of the diaphragm and intercostal muscles causes ventilatory muscle weakness and is usually appreciated when patients are unable to be weaned off a ventilatory in the intensive care unit. NCS demonstrate reduced compound muscle action potentials in the setting of relatively preserved sensory potentials. EMG can demonstrate abnormal insertional and spontaneous activity and early recruitment of myopathic appearing units in those muscles that can be activated. Muscle biopsy can show a distinctive loss of thick filaments (myosin) by electron microscopy. Treatment is withdrawal of glucocorticoids and physical therapy, but the recovery is slow. Patients require supportive care and rehabilitation. ■ ■OTHER DRUG-INDUCED MYOPATHIES Certain drugs produce painless, largely proximal muscle weakness. These drugs include the amphophilic cationic drugs (amiodarone, chloroquine, hydroxychloroquine) and antimicrotubular drugs (colchicine) (Table 460-6). Muscle biopsy can be useful in the identification of toxicity because autophagic vacuoles are prominent pathologic features of these toxins. ■ ■GLOBAL ISSUES As previously discussed, certain dystrophies have an increased prevalence in different parts of the world. LGMD2A/LGMDR1 is the most common LGMD in individuals from Spain, France, Italy, and Great Britain; LGMD2I/LGMDR9 is more common in those with northern European ancestry. GNE myopathy is the most common form of distal myopathy in Japan but is also prevalent in the Ashkenazi population. OPMD is most common in those with ancestry from Spain and French-Canada as well as among Ashkenazi. Epidemiologic studies are lacking regarding other forms of myopathy and their prevalence in different areas of the world. ■ ■FURTHER READING Amato AA et al: Amato and Russell’s Neuromuscular Disorders, 3rd ed. McGraw Hill, 2025. Chin HL et al: A clinical approach to diagnosis and management of mitochondrial myopathies. Neurotherapeutics 21:e00304, 2024. Doughty CT, Amato AA: Toxic myopathies. Continuum (Minneap Minn) 25:1712, 2019. Heller SA et al: Emery-

Dreifuss muscular dystrophy. Muscle Nerve 61:436, 2020. Johnson NE: Myotonic muscular dystrophies. Continuum (Minneap Minn) 25:1682, 2019. Johnson NE, Statland JM: The limb-girdle muscular dystrophies. Continuum (Minneap Minn) 28:1698, 2022. Mah JK et al: A systematic review and meta-analysis on the epidemiology of the muscular dystrophies. Can J Neurol Sci 43:163, 2016. Mul K: Facioscapulohumeral Muscular Dystrophy. Continuum (Minneap Minn) 28:1735, 2022. Rodolico C et al: Endocrine myopathies: Clinical and histopathological features of the major forms. Acta Myol 39:130, 2020. Rosow LK, Amato AA: The role of electrodiagnostic testing, imaging, and muscle biopsy in the investigation of muscle disease. Continuum (Minneap Minn) 22:1787, 2016. Straub V et al: LGMD Workshop Study Group. 229th ENMC international workshop: Limb girdle muscular dystrophies—Nomenclature and reformed classification Naarden, the Netherlands, 17-19 March 2017. Neuromuscul Disord 28:702, 2018.

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