The Office Evaluation of Weakness

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ABSTRACT

The office evaluation of weakness can be a daunting task. Many different disorders affecting many different parts of the nervous system can manifest with "weakness," and several nonneurologic conditions may present with complaints of weakness. It is the job of the neurologist to determine whether a patient has neurologic weakness or suffers simply from fatigue. The physician then must properly localize the pathophysiologic site of weakness. The author focuses on neuromuscular causes of weakness affecting muscle, the neuromuscular junction, peripheral nerve, or the anterior horn cell. General historical and examination clues to localization will be discussed. A localization-based evaluation will be outlined, with more specific recommendations regarding the evaluation of a few specific disorders offered. Localization-specific laboratory, electrodiagnostic, imaging, and pathologic investigations will be presented.

KEYWORDS: Weakness, myopathy, myasthenia gravis, multifocal motor neuropathy, amyotrophic lateral sclerosis

"Weakness" is a common presenting symptom in the office of the practicing neurologist. It is often a vague complaint that can be a manifestation of a wide variety of neurologic and nonneurologic conditions. Occasionally, the cause of weakness is readily apparent, but many times it is elusive and requires a more extensive evaluation to identify. This article will review the approach to the patient with weakness as a primary presenting complaint, and will discuss clinical features of several of the more commonly encountered neuromuscular disorders that manifest primarily as weakness.

GENERAL PRINCIPLES

The steps in the evaluation of the patient with weakness are the following: (1) define what is meant by "weakness," (2) determine if the weakness is the result of a primary neurologic problem, (3) localize the weakness to the correct region of the neuraxis, and (4) identify the possible cause. The term "weakness" may have various and very different meanings to different patients. Patients may use the term "weakness" to describe fatigue, sleepiness, unsteadiness, or loss of muscle strength. Often patients who complain of being "weak" are describing "fatigue," which according to the *Merriam-Webster Medical Dictionary* is "weariness or exhaustion from labor, exertion, or stress."[1] Fatigue generally manifests as a tiredness or lack of energy, although from a patient's perspective feeling "weak" seems to be a simpler descriptive term. Fatigue has a variety of causes, including metabolic disorders; endocrine abnormalities (e.g., thyroid, adrenal, etc.); psychiatric conditions (e.g., depression); toxic or drug exposure (e.g., alcohol); side effects of medications, infections, and general systemic conditions.[2–32]

In contrast to fatigue, true muscle weakness refers to loss of muscle power or strength from a disorder involving the motor pathways. True weakness may be the result of dysfunction involving the motor cortex,

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subcortical corticospinal tracts, spinal cord, anterior horn cells or lower motor neurons, neuromuscular junction (NMJ), or muscle. Patients with neuromuscular disorders that produce true weakness will often also commonly experience fatigue, underscoring the importance of separating out these two symptoms. Once the neurologist identifies the patient's complaint as one of true muscle weakness, localization of the process is necessary to determine the potential cause. The remainder of this article will focus on the evaluation of neuromuscular disorders that manifest solely or primarily as muscle weakness.

LOCALIZATION OF WEAKNESS

The information obtained from the neurologic history and examination should allow for accurate localization of the site of motor pathway dysfunction and the development of a differential diagnosis based on the identified localization. Information such as the temporal profile, presence or absence of other nonmotor neurologic and nonneurologic symptoms, and the pattern and distribution of weakness help to identify the underlying disorder.

Temporal Profile

The time course of the onset and progression of weakness may be acute, subacute, or chronic. Acute neuromuscular disorders are those that occur abruptly, typically over hours to days, and are usually caused by vascular (e.g., vasculitis), inflammatory, or toxic etiologies. An acute presentation of weakness from a neuromuscular disorder is uncommon, but can occur with disorders such as acute motor axonal neuropathy (AMAN) or Guillain-Barre syndrome, porphyric polyradiculopathy, or a fulminant inflammatory myopathy. Disorders that develop subacutely over weeks often indicate an inflammatory, infectious, toxic, or sometimes metabolic process. Most neuromuscular disorders are chronic in onset and progression, and evolve gradually over months to years. Chronic disorders may be inherited, degenerative, metabolic, or from chronic toxic exposures.

Historical Features

As with any neurologic disorder, a careful exploration of symptoms referable to other systems, such as cardiac, pulmonary, endocrine, or dermatologic provides clues to a possible etiology. For example, skin abnormalities in a myopathy may suggest dermatomyositis; polydipsia and polyuria in a polyradiculopathy may suggest diabetes; and cardiomyopathy in a myopathy or polyradiculopathy may suggest amyloidosis. A careful medication history is important to identify those that can cause weakness due to injury to the peripheral nerves or muscle fibers (Table 1).[4,9–19,21,33,34] Furthermore, because many neuromuscular disorders may be inherited, a careful and complete family history can reveal a pattern consistent with an inherited disorder. Clues to unrecognized familial weakness include relatives requiring assistance with ambulation even late in life, spinal or skeletal abnormalities, or early death or familial cardiac disease.

Associated Nonmotor Neurologic Symptoms

The presence or absence of associated nonmotor symptoms, such as pain, cramps, muscle stiffness, and sensory loss, can assist in localizing the underlying process and sometime provide clues to the underlying condition (Table 2). Most neuromuscular disorders are painless; however, certain myopathies may be associated with myalgias, and some polyradiculopathies may be painful. Cramps are nonspecific and do not necessarily indicate a neuromuscular disorder. Patients with disorders of the lower motor neuron (LMN), peripheral nerve, and sometimes muscle, however, may be more predisposed to muscle cramps. Muscle stiffness is similarly nonspecific, but true difficulty relaxing the muscle after use may be an indicator of myotonia, which may be seen in myotonic myopathies. Sensory abnormalities, such as

Table 1 Selected Drugs Causing Myopathy or Peripheral Neuropathy

Myopathy	Neuropathy	Both
Cholesterol-lowering agents	Bortezomib	Amiodarone
Corticosteroids	Cisplatinum	Chloroquine/hydroxychloroquine
Cyclosporine	Disulfiram	Colchicine
D-penicillamine	Infliximab	Interferons
Emetine	Isoniazid	
Procainamide	Metronidazole	
L-tryptophan	Paclitaxel	
Zidovudine	Phenytoin	
	Pyridoxine	
	Thalidomide	
	Vincristine	

Table 2 Positive Symptom Clues for Neuromuscular Localization

Muscle	Neuromuscular Junction	Peripheral Nerve	Anterior Horn Cell
Myalgia	Dry mouth*	Paresthesias	Cramps
Cramps	Orthostatic hypotension*	Pain	Fasciculations
Myotonia		Cramps	
Muscle rippling		Fasciculations	

*In Lambert-Eaton myasthenic syndrome.

dysesthetic pain or sensory loss, indicate a process involving the peripheral nerves or spinal cord.

Pattern of Weakness

Features obtained during the history about performance of routine daily activities can be early clues to identifying the pattern and distribution of weakness. For example, "catching of toes on the ground" and falls, or difficulty with turning keys, manipulating buttons, or opening jars or doors may be indicators of distal leg or arm weakness. Similarly, difficulty rising from a low, seated position, such as a couch or toilet, walking up stairs, carrying heavy objects, or raising the arms above the head to place items on shelves or brush hair may indicate proximal weakness. Dysphagia, dysarthria, diplopia, or ptosis suggests facial and bulbar weakness.

In performing a careful neurologic examination, the distribution of weakness, symmetry of muscle involvement, presence of muscle atrophy or fasciculations, abnormalities of muscle stretch reflexes, and presence and distribution of sensory loss will help to distinguish among diseases of the muscle, neuromuscular junction, peripheral nerve, or central nervous system (CNS). Most diseases that fall within each of these localizations have a fairly typical pattern of findings on the neurologic examination (Table 3). The severity of weakness should be quantified to allow for tracking over time and objectively assessing response to therapy.[35,36]

MUSCLE

In most myopathies, weakness occurs in a symmetric and proximal pattern with little or no muscle atrophy, preserved or mildly reduced reflexes, and normal sensation. Subtle proximal weakness in mild myopathies may not be easily identified with direct manual muscle testing, but can be revealed by noting difficulty rising from a seated position with arms crossed or difficulty squatting and rising. Distal weakness is less common, but can occur in certain myopathies, such as inclusion body myositis or myotonic dystrophy (Table 4). Similarly, facial weakness, ptosis, or ophthalmoparesis occur in only a small group of muscle diseases (Table 5).[37–41] In

Table 3 Pattern of Clinical Examination Findings Associated by Localization

Localization	Typical Distribution of Weakness	Atrophy	Reflexes	Sensation
Muscle	Proximal > distal	No (unless severe or end stage)	Normal	Normal
Neuromuscular junction	Ocular, bulbar, or proximal	Rare	Normal or reduced	Normal
Peripheral nerve	Distal or proximal (symmetric or asymmetric)	Yes	Reduced	Abnormal
Anterior horn cell (motor neuron disease)	Any	Yes	Reduced (increased in ALS)	Normal
Spinal cord	Upper limb extensors; lower limb flexors	No	Increased	Abnormal

Table 4 Myopathies with Distal Weakness

Category of Myopathy	Examples
Inflammatory	Inclusion body myositis, severe polymyositis/ dermatomyositis
Myotonic disorders	Myotonic dystrophy type 1
Distal muscular dystrophies and myopathies	Early onset distal myopathy, late onset distal myopathies, dysferlinopathy, distal myopathy with rimmed vacuoles, oculopharyngodistal myopathy
Other	Myofibrillar myopathy, caveolinopathy, debrancher enzyme deficiency, phosphorylase b kinase deficiency, congenital myopathies, scapuloperoneal syndromes, facioscapulohumeral dystrophy

Table 5 Myopathies Associated with Facial Weakness

Facioscapulohumeral dystrophy
Oculopharyngeal muscular dystrophy*
Mitochondrial myopathies (ocular predominant)*
Congenital myopathies
Myotonic dystrophy
Inclusion body myositis

*Extraocular muscle involvement.

addition to testing strength, percussing the muscle or testing for relaxation following tight grip may identify percussion or grip myotonia, which may not be recognized by patients with myotonic myopathies.[42]

NEUROMUSCULAR JUNCTION

Disorders of neuromuscular transmission classically cause fatigable weakness (i.e., weakness that objectively worsens following repetitive use of the muscle), although patients often have some degree of fixed or even slowly progressive weakness. In myasthenia gravis (MG), the pattern of weakness is primarily in cranial and proximal muscles, although distal weakness, particularly in finger extensors, may be present. Fatigable ptosis or extraocular weakness can be identified by maintaining sustained upgaze or lateral gaze, and fatigable limb weakness by testing strength following sustained or repetitive arm elevation or rising from a low seated position. In contrast to MG, in Lambert-Eaton myasthenic syndrome (LEMS) proximal and distal limb weakness, particularly in the legs, is the most common pattern. Muscle atrophy is rarely a feature of neuromuscular junction diseases apart from some patients with myasthenia associated with antimuscle-specific receptor tyrosine kinase (MuSK) antibodies.[43,44]

Reflexes are usually normal in myasthenia gravis and reduced in LEMS. In LEMS, "facilitation" or an improvement in muscle strength and reflexes may be seen on examination following 10 to 20 seconds of isometric contraction.[45,46] Autonomic findings, such as orthostatic hypotension, impotence, and dry mouth are frequently associated findings in LEMS.[45–47] Sensation is normal in neuromuscular junction disorders.

POLYRADICULOPATHY

The distribution of weakness in polyradiculopathies is classically proximal and distal, and may be symmetric or asymmetric. If longstanding, atrophy may develop. Muscle stretch reflexes are reduced or absent and sensation may be diminished or absent in the affected distributions.

ANTERIOR HORN CELL AND MOTOR NEURON

In pure lower motor neuron disorders, weakness can be focal or multifocal, affecting any region including the limbs or cranial muscles. Muscle atrophy, fasciculations, and cramps are common associated features. Muscle stretch reflexes are generally reduced in weak limbs. Sensation should be normal in pure motor neuron disorders, although patients may occasionally have mild sensory complaints.

In motor neuron disorders in which there is involvement of the corticospinal tracts as well as the lower motor neurons, such as amyotrophic lateral sclerosis (ALS), a combination of upper and LMN involvement may be present. In these disorders, muscle tone and reflexes may be increased, or may be normal in an atrophic and weak limb. Thus, the presence of relative hyperreflexia and spasticity in an atrophic limb should raise the possibility of motor neuron disease.

SPINAL CORD (MYELOPATHY)

Weakness from a CNS disorder, such as myelopathy, may be generalized or focal. The classic upper motor neuron (UMN) distribution of weakness is in the extensor muscle groups (triceps and finger and wrist extensors) in the upper extremities and flexor muscle groups (iliopsoas, hamstrings, and anterior tibialis) in the lower extremities. Muscle tone is increased, often with spasticity that may be subtle or prominent, and reflexes are typically increased. Proprioceptive sensory loss may also be seen, although some pure UMN syndromes, such as primary lateral sclerosis, will not have sensory abnormalities.

EVALUATION OF WEAKNESS

Once the site of motor pathway dysfunction is suspected based on the neurologic history and examination, ancillary tests are often required to confirm localization and identify potential causes. A combination of laboratory, electrodiagnostic, and pathologic tests may be needed to determine the etiology. The type of studies selected should be based on the general type of disease and suspected potential etiologies.

Laboratory Studies

Localization and historical features help to define the laboratory studies needed to assess for etiology. Because a variety of general medical disorders can be associated with myopathies, polyradiculopathies, and motor neuropathies, screening for these conditions with a complete blood count, electrolytes, renal and liver function tests, vitamin levels, uric acid, monoclonal protein studies, and markers of connective tissue diseases or vasculitis are important. If clinical features lead to a suspicion of a myopathy, serum creatine kinase (CK) should be obtained, and if a defect of neuromuscular transmission is suspected, acetylcholine receptor antibodies, anti-MuSK antibodies, or voltage-gated calcium channel antibodies

should be considered. Several genetic studies are commercially available to confirm several underlying inherited neuromuscular disorders, including myotonic disorders, muscular dystrophies, and peripheral neuropathies.

Electrodiagnostic Studies

Another essential component of the evaluation of weakness is an electrodiagnostic study. Nerve conduction studies (NCS) and needle electromyography (EMG) should be performed to confirm the clinically suspected localization and exclude other potential localizations; detect subclinical disease in clinically unaffected body regions; determine the distribution, severity, and time course of disease; provide clues to the etiology of disease; and assess response to treatment. The needle examination can also efficiently examine muscles in a suspected myopathy that may not be amenable to biopsy as well as guide the neurologist's decision on selecting an appropriate muscle for biopsy. In most cases, a complete electrodiagnostic study in a patient with weakness should consist of a combination of motor and sensory NCS, repetitive nerve stimulation studies when a neuromuscular junction disorder is possible, and a thorough needle examination.

Pathologic Studies

In some instances, further evaluation with a nerve or muscle biopsy may provide a definite diagnosis. The decision of whether to perform a biopsy depends on the suspicion of the type of underlying disorder and the results of other noninvasive tests. Because a nerve biopsy usually consists of biopsy of a sensory nerve, it is rarely needed in the patient with a pure motor neuropathy. However, in some patients with a polyradiculopathy in which mild sensory abnormalities are detected clinically or by electrodiagnostic studies, a nerve biopsy may be useful. A muscle biopsy is often necessary to determine the cause of a myopathy, and will be discussed in more detail below. In patients with suspected motor neuron disease, there is no indication for muscle biopsy. In these cases, the muscle biopsy will only demonstrate nonspecific features indicative of a neurogenic process, information that can be obtained less invasively with electrodiagnostic studies.

COMMON NEUROMUSCULAR DISORDERS PRESENTING WITH WEAKNESS

In an office-based neurology practice, a wide variety of neuromuscular disorders that manifest as weakness may be encountered. A review of each of the many different disorders is beyond the scope of this article. In the following sections, I will discuss important clinical features, approach to the evaluation, and treatment issues related to several of the diseases that are more commonly encountered in an adult clinical practice.

MYOPATHIES

In a typical outpatient adult neurology practice, acquired myopathies are more commonly encountered than inherited myopathies and are usually due to inflammatory or autoimmune, metabolic, endocrine, or toxic (i.e., medication) processes. Inherited myopathies, such as the dystrophinopathies, congenital muscular dystrophies, storage diseases, and morphologically distinct myopathies often present in the neonatal period or early childhood, and are often encountered initially in a pediatric neurology practice.[38,39,48–53] Adult-onset inherited myopathies run the gamut of diseases from dystrophies to myotonic disorders to metabolic myopathies and other structurally distinct myopathies.[39,51,53] Of these, the inherited disorders that may be more commonly encountered in a general practice include myotonic dystrophy, myotonia congenita, and limb girdle muscular dystrophies.

Clinical Features

Weakness is most often symmetric and proximal, a common pattern in both inherited and acquired myopathies. Several myopathies, however, can manifest with distal (with or without proximal) weakness (Table 4). Prominent facial weakness and ophthalmoplegia is rare (Table 5).[37–41] Atrophy of involved muscles is evident in most chronic myopathies, although selective atrophy can provide a clue to diagnosis (such as scapulohumeral atrophy in facioscapulohumeral dystrophy or quadriceps and forearm flexor muscle atrophy in inclusion body myositis).

The temporal course is variable in myopathic disorders. Congenital myopathies are characterized by a chronic, nonprogressive course, whereas dystrophies are slowly progressive. Inflammatory myopathies can present acutely or subacutely.[54] Episodic weakness occurs in metabolic myopathies and channelopathies, such as the periodic paralyses.[39,55]

Muscle pain is a variable and nonspecific feature and may be more common in acquired myopathies, but is also prominent in many patients with type 2 myotonic dystrophy, while cramps are common features of myopathies associated with impaired glucose or glycogen utilization.[39,56] Myotonia, clinically manifested as a tightening of the muscle that can occur following rest, with activity ("paradoxical" myotonia), or following percussion of the muscle, is associated with channelopathies and myotonic disorders. Myoglobinuria can result from many disorders including metabolic and mitochondrial myopathies, rarely inherited myopathies,

trauma, or toxic or environmental exposure, although repeated bouts suggest a metabolic cause.

Laboratory Features

Serum creatine kinase (CK) level is the most commonly abnormal serologic marker in myopathy, but reliance on CK in establishing a diagnosis should be used with caution. Modest elevations in CK can be seen in a wide variety of myopathies. Extremely high levels (>10 times the upper limit of normal) are indicative of a few specific muscular dystrophies involving dystrophin, dysferlin, calpain, caveolin, the sarcoglycans, and fukutin-related protein.[51,57,58] Inflammatory myopathies can have highly elevated serum CK values, particularly in the acute phase. However, normal CK levels are not uncommon, and therefore, it is important to note that normal serum CK and inflammatory markers do *not* exclude an inflammatory myopathy.[54,59] Partially treated inflammatory myopathies, chronic muscle disease with significant atrophy, steroid myopathy, and some toxic myopathies such as alcoholic myopathy can have a normal serum CK.

Mild CK elevation is not specific for myopathies and can occur in disorders of the LMN (e.g., ALS), muscle trauma, recent exercise, dehydration, and even in asymptomatic patients with increased muscle bulk. Serum CK levels can also be higher than the laboratory range of normal in African Americans.[60]

Aldolase is another muscle enzyme that may be elevated in myopathies, but is not likely to be positive if the CK is negative, and mainly adjunctive to serum CK. Other serum enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) or lactate dehydrogenase (LDH) that are typically considered as being of liver origin can also arise from muscle and be elevated in myopathies. Most neuromuscular specialists have seen more than one patient who has had a liver biopsy due to elevation in these enzymes.[61] When these enzymes are elevated during a general screening, serum CK should be checked to ensure that an underlying muscle disease is not missed, and that unnecessary and potentially invasive testing is not performed.

Other laboratory studies can be helpful in some situations. If an inflammatory myopathy is suspected, autoimmune serologies should be obtained including an erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), antibodies to extractable nuclear antigen (ENA), and possibly anti-Jo-1, antisignal recognition particle (SRP), anti-Mi-2, or anti-Mas.[54] Although some are often given the moniker "muscle-specific antibodies" none of these antibodies are strictly specific to the presence or type of muscle disease, but can provide guidance as to the presence of coexistent rheumatologic disease. In patients with myopathy and suspected rhabdomyolysis, elevated urine myoglobin should alert the physician to hydrate and potentially alkalinize the urine to prevent kidney damage. Serum myoglobin levels are generally of no benefit in the evaluation of muscle disease.

Laboratory assessment for other systemic causes, including TSH (hypo- or hyperthyroidism) and potassium and magnesium should be included in the evaluation.[4] In the patient with true episodic weakness in which periodic paralysis may be a consideration, potassium levels during attacks of paralysis can assist in the diagnosis, although nonspecific changes in potassium level are not necessarily diagnostic.[2,3,55] Sporadic late-onset nemaline myopathy and amyloid myopathy can be heralded by a monoclonal gammopathy, and both serum protein electrophoresis and serum immunofixation should be obtained.[62–65]

If there is high suspicion for muscle disease, particularly an inherited or metabolic myopathy, there should be concern for associated cardiac disease. Muscle disease-associated cardiac disease can take the form of a hypertrophic, dilated, or arrhythmogenic cardiomyopathy.[66] Monitoring for cardiac disease should include a chest radiograph, electrocardiography, echocardiogram, and event monitor.

Electrodiagnostic Evaluation

Nerve conduction studies are usually normal in myopathies. Abnormalities in sensory NCS may indicate a coexistent and possibly related peripheral nerve involvement. On motor NCS, amplitudes may be low in chronic, severe, or distal myopathies. Needle examination at rest can be normal, but myopathies that are characterized by muscle fiber necrosis, splitting, or vacuolar changes within the muscle may produce fibrillation potentials. The presence of myotonic discharges can narrow the differential diagnosis. With voluntary activation, the classic finding in myopathies is short duration, low amplitude, polyphasic motor unit potentials. However, in some congenital, metabolic, endocrine, and steroid myopathies the needle examination may be normal. In a few chronic myopathies, classically inclusion body myositis, a mixture of large and small motor unit potentials may be seen.

In general, electrodiagnostic abnormalities in muscle diseases are not specific for any particular disorder, may show minimal findings in early or very mild disease, can have patchy abnormalities (particularly in inflammatory myopathies), and the severity of findings may not correlate with the clinical severity. Disorders associated with specific findings on EMG are outlined in Table 6.

Muscle Biopsy

Determining the exact etiology of many muscle diseases requires a pathologic diagnosis. One of the most

Table 6 Specific Electrophysiological Findings in Myopathies

Finding	Examples
Abnormal sensory nerve conductions (Neuromyopathies)	Vasculitis, sarcoidosis, amyloidosis, toxic, medications, alcohol, mitochondrial disease, myofibrillar myopathy
Low compound muscle action potential amplitudes	Distal myopathies and dystrophies, severe or chronic inflammatory myopathies, acid maltase deficiency, acute quadriplegic myopathy, periodic paralysis (while symptomatic)
Fibrillation potentials	Inflammatory and infiltrative myopathies, muscular dystrophies, myofibrillar myopathy, myotonic disorders, toxic, acid maltase deficiency, necrotizing myopathies, rhabdomyolysis
Myotonic discharges (with clinical myotonia)	Myotonic dystrophy types 1 and 2, myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, potassium aggravated myotonia, chondrodystrophic myotonia (Schwartz-Jampel syndrome)
Myotonic discharges (without clinical myotonia)	Acid maltase deficiency, myofibrillar myopathy, hypothyroid myopathy, toxic, amyloid myopathy, inflammatory myopathies

important indications for a muscle biopsy is to confirm an inflammatory or infiltrative myopathy prior to initiating immunosuppressant medications. A patient should not be treated "empirically" with immunosuppressant medications for a presumed inflammatory myopathy until tissue has been secured because immunosuppressants may suppress the inflammatory reaction in muscle, leading to a falsely negative biopsy.

Appropriately selecting a muscle for biopsy is important to increase the yield of identifying the pathologic abnormalities. A mild to moderately weak muscle should be selected because severely weak or atrophied muscles may yield only end-stage changes. If there is no clinical weakness on examination, an electrodiagnostically abnormal muscle should then be selected. If neither is present, then a symptomatic muscle is appropriate. Muscles that have had a recent needle examination performed should be avoided because pathologic abnormalities mimicking disease can occur as a result of needle trauma to muscle tissue.

Recently, immunohistochemical techniques have become available to assist in diagnosing inherited disorders. Biochemical testing on muscle tissue is essential in diagnosing many metabolic myopathies. Many muscle diseases are now diagnosed definitively by molecular genetic or biochemical studies. This can serve to confirm a clinical or histological diagnosis. Symptomatic or asymptomatic carrier status can also be defined.

DERMATOMYOSITIS

The typical clinical features of dermatomyositis are acute to subacute symmetric, proximal weakness, and cutaneous abnormalities. Dysphagia and respiratory failure can occur when severe. Cutaneous manifestations include a malar, periorbital, shawl distribution, chest, or extensor surface rash and periungual erythema and telangiectasias. Serum CK may be elevated or normal. Muscle biopsy shows perifascicular atrophy and muscle fiber structural abnormalities, and perivascular and perimysial inflammation. Because there is an increased risk for associated malignancy with dermatomyositis, evaluation for an underlying tumor should be considered in high-risk patients. Treatment includes corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and less commonly cyclosporine, cyclophosphamide, or rituximab.[54]

POLYMYOSITIS

The presentation of polymyositis is similar to that of dermatomyositis, but without the associated skin changes. Serum CK is more persistently elevated, and the associated malignancy risk is lower than dermatomyositis. Muscle biopsy typically shows endomysial inflammation with invasion of nonnecrotic muscle fibers. Treatment options are similar to those of dermatomyositis.[54]

INCLUSION BODY MYOSITIS

The most common "inflammatory" myopathy in individuals over age 50 is inclusion body myositis. In contrast to dermatomyositis and polymyositis, the distribution of weakness often involves distal muscles and is more often asymmetric. The most involved muscles are classically the knee extensors and forearm finger flexors, but other limb muscles may be affected. Weakness of facial muscles is not uncommon and dysphagia may be a prominent symptom. Serum CK is normal or mildly elevated. Muscle biopsy is characterized by autoaggressive inflammation with invasion of nonnecrotic fibers, vacuolated fibers, and congophilic deposits. Treatment is focused on providing supportive care because there is no evidence for improvement with immunosuppressant medications or intravenous immunoglobulin (IVIg).[54]

STEROID MYOPATHY

Patients taking corticosteroids may develop a progressive myopathy. Steroid myopathy can present at any time during steroid administration, and painless weakness typically involves proximal muscles symmetrically. Serum CK and EMG typically are normal, reflecting the pathologic changes of type II fiber atrophy without muscle fiber necrosis or inflammation. Tapering or withdrawal of steroids leads to resolution, but recovery can be prolonged.[4,9]

CHOLESTEROL-LOWERING AGENT MYOPATHY

The most common iatrogenic cause of myopathy is cholesterol-lowering-agent myopathy (CLAM). The most common effect of statin medications is myalgia without weakness, but proximal, symmetric muscle weakness and frank rhabdomyolysis also occur less frequently. Serum CK may be elevated and EMG may demonstrate fibrillation potentials, rarely myotonic discharges, and short duration motor unit potentials. Discontinuation of the offending agent usually leads to improvement, but can take several months. Some patients have inflammatory changes on muscle biopsy and require immune suppression with corticosteroids.[9,11,12]

NEUROMUSCULAR JUNCTION DISEASES

The two classic neuromuscular junction disorders are myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). Congenital myasthenic syndromes are much rarer and typically present in infancy or childhood, although disorders such as the slow channel syndrome can present initially in adults.[67,68]

Myasthenia Gravis

Clinical features. Myasthenia gravis is an autoimmune disease caused by an antibody-mediated attack directed toward the acetylcholine receptor (AChR).[69] The age at presentation in MG is bimodal with most patients presenting in their 20s or after the age of 40; women generally present at an earlier age than men.[70,71] The classic presenting feature is painless weakness that worsens with activity and improves with rest of the exerted muscles. The majority of patients present with ocular involvement such as fluctuating asymmetric ptosis or diplopia.[71] Common presenting complaints include vision problems due to ocular involvement, including the description simply of "blurry vision." This worsens with such activities as reading, driving, watching television, or being in bright light. Generalized weakness involving bulbar or limb muscles (oculobulbar or generalized MG) is not uncommon, and involvement of axial muscles can cause head drop.[72] Bulbar weakness may manifest as difficulty chewing foods such as steak or other meats, swallowing, nasal regurgitation of liquids, or dysarthria after prolonged speaking. Limb weakness may occur following repetitive activities such as brushing the teeth or hair or walking up flights of stairs. Distal limb weakness may occur but is uncommon.[73,74] Weakness of respiratory muscles can occur in severe MG, manifesting as dyspnea on exertion, progressing to orthopnea, rapid shallow breathing, and eventually respiratory failure requiring mechanical ventilation ("myasthenic crisis"). Rarely, patients may present with respiratory failure.[75]

Several patients previously thought to have "seronegative" generalized MG have been found to have antibodies directed against the muscle-specific receptor tyrosine kinase (MuSK).[76] Anti-MuSK myasthenia gravis occurs most commonly in women in their 20s or 30s, but can be much later.[43,44,77] These patients tend to have more significant facial, bulbar, and respiratory weakness. Ocular involvement is less common and less severe.[43,44,77] Weakness at baseline can be quite severe and thus makes elicitation of fatigability difficult.

Because fatigable weakness on neurologic examination in a patient with suspected MG may be subtle, testing strength following provocative maneuvers is important. For example, the neurologist can assess for fatigable ptosis during one minute of sustained upgaze, extraocular movement weakness with sustained lateral or upgaze, dysarthria with prolonged counting or reading, or limb weakness after repetitive arm abduction or rising from a seated position 10 times. When ptosis is identified, restful closing of the eyes or cooling the brow with an ice pack should improve ptosis (the "ice-pack test").[78–80]

Electrodiagnostic features. Routine motor NCS are usually normal, but may demonstrate low CMAP (compound muscle action potential) amplitudes in severe MG. Repetitive nerve stimulation (RNS) at 2 to 3 Hz before and following one minute of exercise will demonstrate a decrement (usually $> 10\%$) in amplitude and area between the 1st and 4^{th} or 5^{th} stimuli. Abnormal decrement is more likely to be found in proximal nerve muscle combinations, such as the spinal accessory nerve/trapezius or facial nerve/nasalis, and in clinically weak muscles, but the test is not 100% sensitive.[79,80] Needle examination may demonstrate varying, normal, or short-duration motor unit potentials. If the above are normal and the clinical suspicion is high, single-fiber electromyography (SFEMG) or concentric needle jitter analysis may be necessary to confirm the diagnosis. SFEMG is the most sensitive test for a defect of neuromuscular transmission with a sensitivity of 82 to 99% when several muscles are tested.[80] Single-fiber EMG can also be useful to exclude a NMJ disorder in a patient with fatigue or nonspecific weakness because normal jitter in a weak muscle effectively excludes a defect of neuromuscular transmission as a cause of weakness.

Antibody and other testing. Laboratory testing in suspected MG mainly focuses on identifying the presence of acetylcholine receptor (AChR) antibodies to

confirm the diagnosis. A combination of AChR binding, blocking, and modulating antibodies may be present. Binding antibodies are elevated in up to 90% of patients with generalized MG, but only ~50% of patients with ocular MG.[71] They do not correlate with disease severity or an individual's disease activity, and are therefore not useful to follow response to therapy.[71] Rare patients have elevated blocking antibodies in isolation, although they usually are present in association with binding antibodies.[80,81] A slightly higher percentage of patients will have an elevated modulating antibody titer in isolation.[80,81] Antistriated muscle antibodies may also be present, and are most useful in younger patients; their presence suggests thymoma, but can be seen in MG without thymoma.[80]

In seronegative generalized MG suspects or patients with severe facial weakness, MuSK antibodies should be obtained, and ~40% of seronegative patients with generalized MG will have anti-MuSK antibodies.[76,82] Patients with purely ocular MG are unlikely to have anti-MuSK antibodies.[76] In patients who remain seronegative for all antibodies, but in whom the diagnosis is clinically highly suspected, repeat AChR antibody assay should be considered because ~15% of patients seroconvert after presentation.[71,82] Because MG often coexists with autoimmune disorders, such as thyroid disease, other autoimmune markers and thyroid function tests should be obtained.[83]

Once the diagnosis of MG is made, a computed tomography (CT) scan of the chest should be performed to evaluate for the presence of a thymoma, which is present in ~15% of patients with MG. Noncontrast studies are preferred as iodinated contrast may lead to exacerbation of MG.[84] The discovery of thymic abnormality is an indication for thymectomy. Anti-MuSK myasthenia is not commonly associated with thymic abnormality or cancer.[44]

If immunosuppressive therapy, particularly azathioprine or mycophenolate mofetil, is being considered, baseline testing of renal function, liver function, and complete blood counts should be obtained. Thiopurine-methyl transferase activity should be assessed if azathioprine is to be prescribed, as reduced activity makes adverse reactions more likely.[85] Serum IgA level should also be determined if IVIg may be administered.

Treatment. Treatment of MG includes symptomatic therapy and disease-modifying immune-based therapy. Symptomatic therapy with cholinesterase inhibitors, such as pyridostigmine, is used to temporarily reduce the degree and duration of weakness.[86,87] Muscarinic side effects of pyridostigmine include diarrhea, abdominal pain, diaphoresis, and cramps; overtreatment with cholinesterase inhibitors has the potential for exacerbation of weakness.[86,87]

In some patients, pyridostigmine alone is sufficient to control the symptoms; however, the addition of immune-based therapy is necessary for many patients. Corticosteroids, plasma exchange, IVIg, azathioprine, and less commonly cyclosporine or cyclophosphamide are potential effective options.[86,87] Methotrexate has also been successful in treating MG, although evidence in MG is lacking.[87] Recently, rituximab has emerged as a potentially useful treatment.[88] Despite two controlled trials failing to demonstrate added efficacy of mycophenolate mofetil over prednisone alone or a steroid-sparing effect of mycophenolate mofetil, it remains a popular and effective treatment for MG as several case reports and retrospective studies have shown benefit.[89–91]

Thymectomy is indicated if a thymoma is detected on chest CT, but remains controversial in patients without thymoma.[87] In nonthymomatous seropositive MG thymectomy remains an option but the benefit is unclear, and any improvement can be delayed by several years.[87,92,93] A trial of thymectomy in nonthymomatous MG is currently underway.[94]

Lambert-Eaton Myasthenic Syndrome

Clinical features. Clinical features of LEMS differ from MG in several aspects. The onset is usually after the fifth decade and men are preferentially affected.[45] Unlike MG, weakness involves mainly the proximal extremities, particularly the lower extremities, and oculobulbar muscles are less commonly and minimally involved.[45] In contrast to MG, strength may improve during exercise in LEMS.[45,46] Muscle stretch reflexes are often reduced or absent, although brief improvement (facilitation) following exercise or repeated testing of the reflex may occur.[45,46] Autonomic dysfunction, including dry mouth, erectile dysfunction, orthostatic intolerance, and gastrointestinal motility disturbances, is common.[45–47]

Electrodiagnostic features. In LEMS, routine motor NCS show low amplitude CMAPs (usually < 50% of normal).[45,80,95] Repetitive nerve stimulation demonstrates decrement at rest, with facilitation (usually >100%) following brief exercise.[80,95] Varying motor unit potentials and increased jitter and impulse blocking are also seen on needle examination and SFEMG.[45,80]

Antibody and other testing. Lambert-Eaton myasthenic syndrome is associated with antibodies against the presynaptic voltage-gated calcium channels (VGCC).[96] In patients with typical clinical and electrodiagnostic features of LEMS, the presence of P/Q type VGCC confirms the diagnosis.[80,96] AChR and striated muscle antibodies may also be found.[45,46] Lambert-Eaton myasthenic syndrome is associated with small cell lung cancer in ~50% of patients, and a higher percentage of male smokers. Therefore, chest CT and possibly a positron emission tomography (PET) scan should be considered.[45,87,95,96]

Treatment. For symptomatic treatment, pyridostigmine may improve strength.[87] The medication

3,4-diaminopyridine (3,4-DAP) is beneficial in many patients, but is not approved by the Food and Drug Administration (FDA) for LEMS and therefore is currently only available through compassionate use protocols. Because 3,4-DAP increases the propensity for seizures, an electroencephalogram (EEG) should be obtained prior to initiation.[87,97,98] Treatment with IVIg, plasmapheresis, or immunosuppressant medication may lead to improvement or remission of the disease.[87] If a small cell lung cancer is identified, treatment directed against the tumor may lead to improvement of LEMS.[87]

PERIPHERAL NEUROPATHIES (MOTOR PREDOMINANT)

Disorders of the peripheral nerve, including mononeuropathies, brachial and lumbosacral plexopathies, or focal radiculopathies can manifest as focal weakness, whereas diffuse peripheral neuropathies or polyradiculopathies may manifest with generalized weakness. Most of these disorders typically have associated sensory symptoms, but certain disorders can have little or no sensory involvement. Diffuse disorders of the peripheral nerve that have predominant motor nerve abnormalities include acute inflammatory demyelinating polyneuropathy (AIDP), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), paraproteinemic and paraneoplastic neuropathies, multifocal motor neuropathy with conduction block (MMN), some inherited neuropathies such as hereditary neuropathy with liability to pressure palsies (HNPP), and brachial plexus neuropathy. Many of these more typically have findings outside of the motor system, and careful attention to sensory and autonomic symptoms and signs will lead to proper localization. Peripheral nerve diseases are addressed in a separate article in this issue, but a motor neuropathy that presents only with weakness – multifocal motor neuropathy with conduction block – will be reviewed.

Multifocal Motor Neuropathy with Conduction Block

Clinical features. Multifocal motor neuropathy (MMN) usually presents in younger adulthood as asymmetric slowly progressive weakness, typically in the distal upper extremities.[99–101] Although weakness often fits single-nerve distributions, there is often variable weakness in different muscles supplied by the same nerve.[100] Rarely, the phrenic nerve and cranial nerves are affected, and scapular winging has been reported.[102] There may be muscle atrophy later in the course of the disease.[99,101,102] Pain and sensory loss are not features of MMN, although up to 50% of patients may experience cramps and fasciculations.[99–103] Reflexes are commonly reduced, most often in affected regions.[99,101–103]

As the most concerning differential diagnosis is motor neuron disease, a thorough neurologic examination is essential and should focus on determination of UMN signs, such as pathologic reflexes and increased muscle tone. A detailed history of sensory symptoms and examination of sensation should help differentiate MMN from acute and chronic inflammatory demyelinating polyradiculopathy, hereditary neuropathy with liability to pressure palsies, and brachial plexus neuropathy.

Electrodiagnostic features. The electrophysiologic hallmark of MMN is the presence of focal, partial conduction block without temporal dispersion of motor fibers, but not sensory fibers in the same region of conduction block, and not at common sites of compression. Stimulation may need to be performed more proximally (e.g., through the axilla and Erb's point) to identify a proximal conduction block. Because technical issues can produce findings that mimic conduction block, interpretation of conduction block on NCS should follow published consensus criteria.[104,105]

Laboratory testing. Monoclonal protein studies may show a monoclonal gammopathy.[106,107] Serum CK may be slightly elevated.[108] Cerebrospinal fluid examination may demonstrate a mild elevation of protein, but should not lead the practitioner away from the diagnosis.[99,101,103,107] Antiganglioside antibodies, specifically anti-GM1 IgM antibodies, have been found in 31 to 85% of patients with MMN.[99,101,108] Although not specific for MMN, they likely are helpful in confirming the diagnosis, but their absence does not exclude it. Magnetic resonance imaging (MRI) of the cervical spine due to the predominant upper extremity weakness should be performed in patients without clear conduction block to rule out structural abnormalities leading to cervical radiculopathy or the rare distal segmental muscular atrophy (Hirayama disease).

Treatment. Intravenous immunoglobulin is the most extensively studied therapy in MMN and is the treatment of choice.[109–112] The majority of patients respond to IVIg infusions, but long-term treatment must be individually tailored.[113] Cyclophosphamide has also proven effective in MMN.[106,114–117] Various other immune therapies are of limited to no benefit.

MOTOR NEURON DISEASE

Amyotrophic lateral sclerosis is the most common disease of motor neurons, but several other disorders listed in Table 7 can mimic ALS.

Clinical features. Patients with ALS typically present with either slowly progressive, painless asymmetric limb weakness or bulbar weakness with difficulty speaking or swallowing. Rarely patients will seek attention

Table 7 Motor Neuron Disease Mimickers

Category	Upper Motor Neuron Syndromes (With or Without Lower Motor Neuron Involvement)	Lower Motor Neuron Syndromes
Sporadic	Amyotrophic lateral sclerosis, Primary lateral sclerosis	Progressive muscular atrophy, Juvenile monomelic amyotrophy (Hirayama disease)
Hereditary	Hereditary amyotrophic lateral sclerosis, Adrenomyeloneuropathy, Hereditary spastic paraparesis	Spinal muscular atrophy, X-linked spinobulbar muscular atrophy (Kennedy disease), Hexosaminidase A deficiency
Metabolic / Toxic	B_{12} deficiency, copper deficiency, vitamin E deficiency	Heavy metal toxicity, B_{12} deficiency, copper deficiency, hyperthyroidism, vitamin E deficiency
Infectious	HIV, HTLV, syphilis	HIV, HTLV
Inflammatory or neoplastic	Lymphoma	Multifocal motor neuropathy, CIDP, lymphoma

HIV, human immunodeficiency virus, HTLV, human T-lymphotropic virus; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy

for isolated respiratory compromise, muscle twitching, or possibly head drop. Additional features may include muscle twitching or cramping, or emotional lability, which is an indicator of the pseudobulbar affect seen in many patients with ALS. Orthopnea and shortness of breath with even limited exertion indicate respiratory muscle weakness.

Classic examination findings include upper (hyperreflexia, spasticity, Babinski signs, spastic dysarthria, hyperactive jaw jerk reflex) and LMN (atrophy, fasciculations) signs. With bulbar involvement, dysarthria classically has a mixed spastic and flaccid character, and tongue fasciculations may be present. The strength of cough and forced exhalation can provide information regarding respiratory muscle strength. Cognitive impairment is not uncommon, and frontotemporal dementia is increasingly recognized in patients with ALS, but may require formal neuropsychologic testing to define.[118] The El Escorial criteria for the diagnosis of ALS provide guidance for research and requires UMN and LMN findings in at least three body segments (bulbar, cervical, thoracic, or lumbosacral) for the diagnosis of "clinically definite" ALS.[119] These criteria are probably overly restrictive for routine clinical use, and an experienced physician will not require strict El Escorial criteria fulfillment to diagnose ALS.

Ancillary testing. In classic presentations of ALS, few additional studies may be necessary. Imaging with MRI should be performed, at least of segments rostral to the uppermost UMN finding and possibly of segments with LMN findings (usually of the cervical spine and/or brain) to exclude structural intracranial or cervical spine abnormalities, such as a brainstem mass, cervical stenosis, or syringomyelia. Ultimately, the decision to obtain imaging should be determined based on the individual patient's presentation and findings.

Although there is no single laboratory test to confirm or exclude ALS, laboratory studies should be used to rule out various mimickers. Serum chemistry, blood count, calcium, TSH, and CK may be all that is necessary.[120] Mild serum CK elevation is not uncommon with ALS and should not lead the physician to suspect a primary myopathy. If calcium is elevated, a parathyroid hormone level should be obtained as some patients with parathyroid adenoma have presented with a syndrome mimicking motor neuron disease, although these patients may have had simply coexistent disease.[121] Disorders that can manifest with UMN dysfunction, include B12, vitamin E, copper deficiencies, human immunodeficiency virus, human T-lymphotropic virus (HTLV), syphilis, and CNS lymphoma although many of these disorders typically produce some degree of sensory abnormalities.[122–125] A pure LMN syndrome may be due to heavy metal toxicity, inflammatory or infiltrative polyradiculopathy, lymphoma, or (in young patients less than 40 to 50-years-old) hexosaminidase A deficiency. Spinal fluid examination, assessing cell count, protein, glucose, and cytology should be considered in patients with a suspicion of an inflammatory or infiltrating polyradiculopathy.

Electrodiagnostic testing. In evaluating patients with suspected ALS, EMG is useful to confirm the distribution and extent of the findings and to search for an alternate diagnosis. Nerve conduction studies may show low motor amplitudes if there has been sufficient axon loss. In patients with apparent LMN weakness, careful NCS evaluation for conduction block should be made to identify CIDP or MMN. Needle examination demonstrates fibrillation and fasciculation potentials and long duration, high amplitude, varying motor unit potentials with reduced recruitment in muscles in which LMN degeneration has occurred.[119] In patients with primarily UMN features, only minimal or patchy findings may be seen on needle EMG; however, subsequent examinations months apart will usually identify evolution of LMN involvement. Rarely the needle examination can disclose previously unrecognized myopathies, such as with inclusion body myositis.

Treatment. Currently, there is no curative treatment for ALS. Riluzole is the only FDA approved medication that has been shown to be effective for slowing disease progression. The mainstay of treatment focuses on supportive and symptomatic treatment. The American Academy of Neurology recently published a practice parameter addressing treatment of ALS that provided treatment recommendations in several realms.[126,127] For patients with dysphagia, enteral nutrition via percutaneous endoscopic gastrostomy can help maintain weight and muscle mass and may prolong survival. Noninvasive positive pressure ventilation may also prolong survival and should be offered when there is evidence for respiratory impairment. Sialorrhea can be treated with anticholinergics or botulinum toxin injected into the parotid and submandibular glands. Dextromethorphan with quinidine is effective in treating pseudobulbar affect. Benzodiazepines, baclofen, tizanidine, and stretching exercises can help with spasticity and may benefit cramps. Augmentative communication devices should be considered when dysarthria interferes with effective communication. When possible, referral to a multidisciplinary ALS clinic should be considered in which physical, occupational, speech and respiratory therapy, nutrition, social work, and cognitive evaluation can be addressed and coordinated during the visit.

CONCLUSION

Weakness can be the presenting feature of many diverse neuromuscular disorders. These disorders may affect the motor unit at any level from muscle through the anterior horn cell. Although presentations can be similar on the surface, there are important features of the history and neurologic examination that should direct the evaluation in a more focused fashion. Localizing the problem accurately and tailoring the investigation for specific disorders within that localization can lead to the correct diagnosis in a timely, cost-effective manner.

REFERENCES

1. Merriam-Webster. Fatique. Available at: http://www.merriam-webster.com/medlineplus/fatigue. Accessed June 1, 2010
2. Baker SB, Worthley LI. The essentials of calcium, magnesium and phosphate metabolism: part II. Disorders. Crit Care Resusc 2002;4(4):307–315
3. Riggs JE. Neurologic manifestations of electrolyte disturbances. Neurol Clin 2002;20(1):227–239, vii
4. Alshekhlee A, Kaminski HJ, Ruff RL. Neuromuscular manifestations of endocrine disorders. Neurol Clin 2002; 20(1):35–58, v–vi
5. Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. Am Fam Physician 2009;80(8):841–846
6. Ziambaras K, Dagogo-Jack S. Reversible muscle weakness in patients with vitamin D deficiency. West J Med 1997;167(6): 435–439
7. Hinshaw DB, Carnahan JM, Johnson DL. Depression, anxiety, and asthenia in advanced illness. J Am Coll Surg 2002;195(2):271–277; discussion 277–278
8. Ruttenber AJ, McAnally HB, Wetli CV. Cocaine-associated rhabdomyolysis and excited delirium: different stages of the same syndrome. Am J Forensic Med Pathol 1999;20(2): 120–127
9. Walsh RJ, Amato AA. Toxic myopathies. Neurol Clin 2005;23(2):397–428
10. Dresser LP, Massey EW, Johnson EE, Bossen E. Ipecac myopathy and cardiomyopathy. J Neurol Neurosurg Psychiatry 1993;56(5):560–562
11. Mastaglia FL. Drug induced myopathies. Pract Neurol 2006;6:4–13
12. Gaist D, Rodríguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology 2001;12(5):565–569
13. Bradley WG, Lassman LP, Pearce GW, Walton JN. The neuromyopathy of vincristine in man. Clinical, electrophysiological and pathological studies. J Neurol Sci 1970;10(2): 107–131
14. Srinivasan J, Wu CJ, Amato AA. Inflammatory myopathy associated with imatinib mesylate therapy. J Clin Neuromuscul Dis 2004;5(3):119–121
15. Pulipaka U, Lacomis D, Omalu B. Amiodarone-induced neuromyopathy: three cases and a review of the literature. J Clin Neuromuscul Dis 2002;3(3):97–105
16. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. Pharmacotherapy 2004;24(12): 1784–1792
17. Casado E, Gratacós J, Tolosa C, et al. Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. Ann Rheum Dis 2006; 65(3):385–390
18. Kwon J-B, Kleiner A, Ishida K, Godown J, Ciafaloni E, Looney RJ Jr. Hydroxychloroquine-induced myopathy. J Clin Rheumatol 2010;16(1):28–31
19. Authier FJ, Chariot P, Gherardi RK. Skeletal muscle involvement in human immunodeficiency virus (HIV)-infected patients in the era of highly active antiretroviral therapy (HAART). Muscle Nerve 2005;32(3):247–260
20. Tunn UW, Wiedey K. Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. Prostate Cancer Prostatic Dis 2009;12(1):83–87
21. Sobaci G, Erdem U, Durukan AH, et al. Safety and effectiveness of interferon alpha-2a in treatment of patients with Behcet's uveitis refractory to conventional treatments. Ophthalmology. Available at: http://dx.doi.org/10.1016/j.ophtha.2009.11.022. Accessed June 1, 2010
22. Shaiova L. The management of opioid-related sedation. Curr Pain Headache Rep 2005;9(4):239–242
23. Aapro MS, Cella D, Zagari M. Age, anemia, and fatigue. Semin Oncol 2002;29(3, Suppl 8):55–59
24. Meeus M, Mistiaen W, Lambrecht L, Nijs J. Immunological similarities between cancer and chronic fatigue syndrome: the common link to fatigue? Anticancer Res 2009;29(11): 4717–4726
25. Clauw DJ. Fibromyalgia: an overview. Am J Med 2009; 122(12, Suppl):S3–S13

26. Mioxham J, Jolley C. Breathlessness, fatigue and the respiratory muscles. Clin Med 2009;9(5):448–452
27. Shizukuda Y, Plummer SL, Harrelson A. Customized exercise echocardiography: beyond detection of coronary artery disease. Echocardiography 2010;27(2):186–194
28. Newton JL. Systemic symptoms in non-alcoholic fatty liver disease. Dig Dis 2010;28(1):214–219
29. Stenholm S, Kronholm E, Sainio P, et al. Sleep-related factors and mobility in older men and women. J Gerontol A Biol Sci Med Sci 2010;65(6):649–657
30. Dhruva A, Dodd M, Paul SM, et al. Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. Cancer Nurs 2010;33(3):201–212
31. Vernon SD, Whistler T, Cameron B, Hickie IB, Reeves WC, Lloyd A. Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr virus. BMC Infect Dis 2006; 6:15
32. Banning M. Influenza: incidence, symptoms and treatment. Br J Nurs 2005;14(22):1192–1197
33. Dalakas MC. Toxic and drug-induced myopathies. J Neurol Neurosurg Psychiatry 2009;80(8):832–838
34. Toyooka K, Fujimura H. Iatrogenic neuropathies. Curr Opin Neurol 2009;22(5):475–479
35. Members of the Mayo Clinic Department of Neurology, Mayo Clinic and Mayo Foundation. Mayo Clinic Examinations in Neurology. 7th ed. St. Louis, MO: Mosby; 1998
36. The Guarantors of Brain. Aids to the Examination of the Peripheral Nervous System. 4th ed. Edinburgh: W.B. Saunders; 2000
37. Tawil R, Van Der Maarel SM. Facioscapulohumeral muscular dystrophy. Muscle Nerve 2006;34(1):1–15
38. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry 2010;81(4):358–367
39. van Adel BA, Tarnopolsky MA. Metabolic myopathies: update 2009. J Clin Neuromuscul Dis 2009;10(3):97–121
40. Bogousslavsky J, Perentes E, Regli F, Deruaz JP. Polymyositis with severe facial involvement. J Neurol 1982;228(4):277–281
41. Brais B. Oculopharyngeal muscular dystrophy: a polyalanine myopathy. Curr Neurol Neurosci Rep 2009;9(1):76–82
42. Ptáček LJ, Tawil R, Griggs RC, et al. Sodium channel mutations in acetazolamide-responsive myotonia congenita, paramyotonia congenita, and hyperkalemic periodic paralysis. Neurology 1994;44(8):1500–1503
43. Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. Neurology 2003;60(12):1978–1980
44. Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in MuSK-antibody positive myasthenia gravis: a U.S. experience. Muscle Nerve 2010;41(3):370–374
45. O'Neill JH, Murray NMF, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain 1988;111(Pt 3):577–596
46. Katz JS, Wolfe GI, Bryan WW, Tintner R, Barohn RJ. Acetylcholine receptor antibodies in the Lambert-Eaton myasthenic syndrome. Neurology 1998;50(2):470–475
47. O'Suilleabhain P, Low PA, Lennon VA. Autonomic dysfunction in the Lambert-Eaton myasthenic syndrome: serologic and clinical correlates. Neurology 1998;50(1):88–93
48. Reed UC. Congenital muscular dystrophy. Part I: a review of phenotypical and diagnostic aspects. Arq Neuropsiquiatr 2009;67(1):144–168
49. Sewry CA, Jimenez-Mallebrera C, Muntoni F. Congenital myopathies. Curr Opin Neurol 2008;21(5):569–575
50. Ozawa E, Noguchi S, Mizuno Y, Hagiwara Y, Yoshida M. From dystrophinopathy to sarcoglycanopathy: evolution of a concept of muscular dystrophy. Muscle Nerve 1998;21(4): 421–438
51. Norwood F, de Visser M, Eymard B, Lochmüller H, Bushby K; EFNS Guideline Task Force. EFNS guideline on diagnosis and management of limb girdle muscular dystrophies. Eur J Neurol 2007;14(12):1305–1312
52. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008;371(9631):2201–2212
53. Selcen D, Ohno K, Engel AG. Myofibrillar myopathy: clinical, morphological and genetic studies in 63 patients. Brain 2004;127(Pt 2):439–451
54. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. J Neurol Neurosurg Psychiatry 2009;80(10):1060–1068
55. Miller TM, Dias da Silva MR, Miller HA, et al. Correlating phenotype and genotype in the periodic paralyses. Neurology 2004;63(9):1647–1655
56. Day JW, Ricker K, Jacobsen JF, et al. Myotonic dystrophy type 2: molecular, diagnostic and clinical spectrum. Neurology 2003;60(4):657–664
57. Hoffman EP, Fischbeck KH, Brown RH, et al. Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. N Engl J Med 1988;318(21):1363–1368
58. Guglieri M, Magri F, D'Angelo MG, et al. Clinical, molecular, and protein correlations in a large sample of genetically diagnosed Italian limb girdle muscular dystrophy patients. Hum Mutat 2008;29(2):258–266
59. Pautas E, Chérin P, Piette JC, et al. Features of polymyositis and dermatomyositis in the elderly: a case-control study. Clin Exp Rheumatol 2000;18(2):241–244
60. Wong ET, Cobb C, Umehara MK, et al. Heterogeneity of serum creatine kinase activity among racial and gender groups of the population. Am J Clin Pathol 1983;79(5):582–586
61. Wakefield SE, Dimberg EL, Moore SA, Tseng BS. Dystrophinopathy presenting with arrhythmia in an asymptomatic 34-year-old man: a case report. J Med Case Reports 2009;3:8625
62. Eymard B, Brouet JC, Collin H, Chevallay M, Bussel A, Fardeau M. Late-onset rod myopathy associated with monoclonal gammopathy. Neuromuscul Disord 1993;3 (5-6):557–560
63. Milone M, Katz A, Amato AA, et al. Sporadic late onset nemaline myopathy responsive to IVIg and immunotherapy. Muscle Nerve 2010;41(2):272–276
64. Sundblad A, Porwit A, Ostad M, et al. Antibody reactivities to skeletal muscle proteins in a patient with lambda light chain secreting multiple myeloma, generalised amyloidosis and rhabdomyolysis. Eur J Haematol 2001; 67(3):189–193
65. Chapin JE, Kornfeld M, Harris A. Amyloid myopathy: characteristic features of a still underdiagnosed disease. Muscle Nerve 2005;31(2):266–272
66. Wexler RK, Elton T, Pleister A, Feldman D. Cardiomyopathy: an overview. Am Fam Physician 2009;79(9):778–784
67. Engel AG, Ohno K, Sine SM. Congenital myasthenic syndromes: progress over the past decade. Muscle Nerve 2003;27(1):4–25

68. Engel AG, Shen XM, Selcen D, Sine SM. Further observations in congenital myasthenic syndromes. Ann N Y Acad Sci 2008;1132:104–113
69. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest 2006;116(11): 2843–2854
70. Grob D. Course and management of myasthenia gravis. J Am Med Assoc 1953;153(6):529–532
71. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37(2):141–149
72. D'Amelio M, Di Benedetto N, Ragonese P, et al. Dropped head as an unusual presenting sign of myasthenia gravis. Neurol Sci 2007;28(2):104–106
73. Nations SP, Wolfe GI, Amato AA, Jackson CE, Bryan WW, Barohn RJ. Distal myasthenia gravis. Neurology 1999;52(3):632–634
74. Renard D, Castelnovo G, Labauge P. Distal myasthenia gravis. Acta Neurol Belg 2008;108(3):107–108
75. Kim WH, Kim JH, Kim EK, et al. Myasthenia gravis presenting as isolated respiratory failure: a case report. Korean J Intern Med 2010;25(1):101–104
76. McConville J, Farrugia ME, Beeson D, et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. Ann Neurol 2004;55(4):580–584
77. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 2003;126(Pt 10):2304–2311
78. Larner AJ. The place of the ice pack test in the diagnosis of myasthenia gravis. Int J Clin Pract 2004;58(9):887–888
79. Benatar M. A systematic review of diagnostic studies in myasthenia gravis. Neuromuscul Disord 2006;16(7): 459–467
80. Meriggioli MN, Sanders DB. Advances in the diagnosis of neuromuscular junction disorders. Am J Phys Med Rehabil 2005;84(8):627–638
81. Howard FM Jr, Lennon VA, Finley J, Matsumoto J, Elveback LR. Clinical correlations of antibodies that bind, block, or modulate human acetylcholine receptors in myasthenia gravis. Ann N Y Acad Sci 1987;505: 526–538
82. Chan KH, Lachance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. Muscle Nerve 2007;36(5):651–658
83. Kiessling WR, Finke R, Kotulla P, Schleusener H. Circulating TSH-binding inhibiting immunoglobulins in myasthenia gravis. Acta Endocrinol (Copenh) 1982;101(1):41–46
84. Chagnac Y, Hadani M, Goldhammer Y. Myasthenic crisis after intravenous administration of iodinated contrast agent. Neurology 1985;35(8):1219–1220
85. Richard VS, Al-Ismail D, Salamat A. Should we test TPMT enzyme levels before starting azathioprine? Hematology 2007;12(4):359–360
86. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004;29(4):484–505
87. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2006;13(7):691–699
88. Lebrun C, Bourg V, Tieulie N, Thomas P. Successful treatment of refractory generalized myasthenia gravis with rituximab. Eur J Neurol 2009;16(2):246–250
89. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 2008;71(6):394–399
90. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 2008;71(6):400–406
91. Hehir MK, Burns TM, Alpers J, Conaway MR, Sawa M, Sanders DB. Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: outcomes in 102 patients. Muscle Nerve 2010;41(5):593–598
92. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000; 55(1):7–15
93. Masaoka A, Yamakawa Y, Niwa H, et al. Extended thymectomy for myasthenia gravis patients: a 20-year review. Ann Thorac Surg 1996;62(3):853–859
94. Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy. Available at:http://clinicaltrials.gov/ct2/show/study/NCT00294658. Accessed June 4, 2010
95. Tim RW, Massey JM, Sanders DB. Lambert-Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. Neurology 2000;54(11):2176–2178
96. Lennon VA, Lambert EH. Autoantibodies bind solubilized calcium channel-ω-conotoxin complexes from small cell lung carcinoma: a diagnostic aid for Lambert-Eaton myasthenic syndrome. Mayo Clin Proc 1989;64(12): 1498–1504
97. McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. N Engl J Med 1989;321(23):1567–1571
98. Wirtz PW, Verschuuren JJ, van Dijk JG, et al. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert-Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. Clin Pharmacol Ther 2009;86(1):44–48
99. Nobile-Orazio E. Multifocal motor neuropathy. J Neuroimmunol 2001;115(1-2):4–18
100. Slee M, Selvan A, Donaghy M. Multifocal motor neuropathy: the diagnostic spectrum and response to treatment. Neurology 2007;69(17):1680–1687
101. Taylor BV, Wright RA, Harper CM, Dyck PJ. Natural history of 46 patients with multifocal motor neuropathy with conduction block. Muscle Nerve 2000;23(6):900–908
102. Magistris M, Roth G. Motor neuropathy with multifocal persistent conduction blocks. Muscle Nerve 1992;15(9): 1056–1057
103. Kaji R, Shibasaki H, Kimura J. Multifocal demyelinating motor neuropathy: cranial nerve involvement and immunoglobulin therapy. Neurology 1992;42(3 Pt 1):506–509
104. Olney RK; American Association of Electrodiagnostic Medicine. Guidelines in electrodiagnostic medicine. Consensus criteria for the diagnosis of partial conduction block. Muscle Nerve Suppl 1999;8(Suppl 8):S225–S229
105. Olney RK, Lewis RA, Putnam TD, Campellone JV Jr; American Association of Electrodiagnostic Medicine. Consensus criteria for the diagnosis of multifocal motor neuropathy. Muscle Nerve 2003;27(1):117–121
106. Pestronk A, Cornblath DR, Ilyas AA, et al. A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. Ann Neurol 1988;24(1):73–78
107. Nobile-Orazio E, Cappellari A, Meucci N, et al. Multifocal motor neuropathy: clinical and immunological features and

response to IVIg in relation to the presence and degree of motor conduction block. J Neurol Neurosurg Psychiatry 2002;72(6):761–766
108. Chaudhry V, Corse AM, Cornblath DR, et al. Multifocal motor neuropathy: response to human immune globulin. Ann Neurol 1993;33(3):237–242
109. Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology 1994;44(3 Pt 1):429–432
110. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 1995;59(3):248–252
111. Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. Neurology 2000;55(9):1256–1262
112. Léger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain 2001;124(Pt 1):145–153
113. Baumann A, Hess CW, Sturzenegger M. IVIg dose increase in multifocal motor neuropathy: a prospective six month follow-up. J Neurol 2009;256(4):608–614
114. Krarup C, Stewart JD, Sumner AJ, Pestronk A, Lipton SA. A syndrome of asymmetric limb weakness with motor conduction block. Neurology 1990;40(1):118–127
115. Feldman EL, Bromberg MB, Albers JW, Pestronk A. Immunosuppressive treatment in multifocal motor neuropathy. Ann Neurol 1991;30(3):397–401
116. Tan E, Lynn DJ, Amato AA, et al. Immunosuppressive treatment of motor neuron syndromes. Attempts to distinguish a treatable disorder. Arch Neurol 1994;51(2):194–200
117. Brannagan TH III, Alaedini A, Gladstone DE. High-dose cyclophosphamide without stem cell rescue for refractory multifocal motor neuropathy. Muscle Nerve 2006;34(2): 246–250
118. Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2009;10(3):131–146
119. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1(5):293–299
120. Fisher M, Mateer JE, Ullrich I, Gutrecht JA. Pyramidal tract deficits and polyneuropathy in hyperthyroidism, Combination clinically mimicking amyotrophic lateral sclerosis. Am J Med 1985;78(6 Pt 1):1041–1044
121. Jackson CE, Amato AA, Bryan WW, Wolfe GI, Sakhaee K, Barohn RJ. Primary hyperparathyroidism and ALS: is there a relation? Neurology 1998;50(6):1795–1799
122. Weihl CC, Lopate G. Motor neuron disease associated with copper deficiency. Muscle Nerve 2006;34(6):789–793
123. Di Rocco A, Simpson DM. AIDS-associated vacuolar myelopathy. AIDS Patient Care STDS 1998;12(6):457–461
124. Hemmer B, Glocker FX, Kaiser R, Lücking CH, Deuschl G. Generalised motor neuron disease as an unusual manifestation of Borrelia burgdorferi infection. J Neurol Neurosurg Psychiatry 1997;63(2):257–258
125. Baud P, Parant E, Loison F, Ménage JJ. [IgM kappa lymphoma with antisulfatide antibodies revealed by cervical motor neuropathy simulating amyotrophic lateral sclerosis]. Rev Med Interne 1998;19(4):275–278
126. Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009;73(15):1218–1226
127. Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009;73(15):1227–1233