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. 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,
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). 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.

Table 1 Selected Drugs Causing Myopathy or Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Myopathy</th>
<th>Neuropathy</th>
<th>Both</th>
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<tbody>
<tr>
<td>Cholesterol-lowering agents</td>
<td>Bortezomib</td>
<td>Amiodarone</td>
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<td>Corticosteroids</td>
<td>Cisplatinum</td>
<td>Chloroquine/hydroxychloroquine</td>
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<td>Cyclosporine</td>
<td>Disulfiram</td>
<td>Colchicine</td>
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<td>D-penicillamine</td>
<td>Infliximab</td>
<td>Interferons</td>
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<td>Emetine</td>
<td>Isoniazid</td>
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<td>Procainamide</td>
<td>Metronidazole</td>
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<td>L-tryptophan</td>
<td>Paclitaxel</td>
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<td>Zidovudine</td>
<td>Phenytoin</td>
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<td></td>
<td>Pyridoxine</td>
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<td></td>
<td>Thalidomide</td>
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<td></td>
<td>Vincristine</td>
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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.

**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

<table>
<thead>
<tr>
<th>Table 2 Positive Symptom Clues for Neuromuscular Localization</th>
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<tbody>
<tr>
<td><strong>Muscle</strong></td>
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<tr>
<td>Myalgia</td>
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<td>Cramps</td>
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<td>Myotonia</td>
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<td>Muscle rippling</td>
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*In Lambert-Eaton myasthenic syndrome.

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<th>Table 3 Pattern of Clinical Examination Findings Associated by Localization</th>
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<tr>
<td><strong>Localization</strong></td>
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<tr>
<td>Muscle</td>
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<tr>
<td>Neuromuscular junction</td>
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<tr>
<td>Peripheral nerve</td>
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<tr>
<td>Anterior horn cell (motor neuron disease)</td>
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<td>Spinal cord</td>
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<th>Table 4 Myopathies with Distal Weakness</th>
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<td><strong>Category of Myopathy</strong></td>
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<tr>
<td>Inflammatory</td>
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<tr>
<td>Myotonic disorders</td>
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<tr>
<td>Distal muscular dystrophies and myopathies</td>
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<tr>
<td>Other</td>
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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, electrophysiologic, 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

<table>
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<th>Table 5 Myopathies Associated with Facial Weakness</th>
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<tr>
<td>Facioscapulohumeral dystrophy</td>
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<td>Oculopharyngeal muscular dystrophy*</td>
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<tr>
<td>Mitochondrial myopathies (ocular predominant)*</td>
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<tr>
<td>Congenital myopathies</td>
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<tr>
<td>Myotonic dystrophy</td>
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<tr>
<td>Inclusion body myositis</td>
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*Extraocular muscle involvement.
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. 

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). 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 quadriiceps 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. Episodic weakness occurs in metabolic myopathies and channelopathies, such as the periodic paralyses.

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. 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.54 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.8 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.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.64 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
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, peri-orbital, shawl distribution, chest, or extensor surface rash and periangual 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.

**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.

**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).

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**Table 6 Specific Electrophysiological Findings in Myopathies**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Abnormal sensory nerve conduction</td>
<td>Vasculitis, sarcoidosis, amyloidosis, toxic, medications, alcohol, mitochondrial disease, myofibrillar myopathy</td>
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<tr>
<td>(Neuromyopathies)</td>
<td></td>
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<tr>
<td>Low compound muscle action potential</td>
<td>Distal myopathies and dystrophies, severe or chronic inflammatory myopathies, acid maltase deficiency, acute quadriplegic myopathy, periodic paralysis (while symptomatic)</td>
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<tr>
<td>amplitudes</td>
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<td>Fibrillation potentials</td>
<td>Inflammatory and infiltrative myopathies, muscular dystrophies, myofibrillar myopathy, myotonic disorders, toxic, acid maltase deficiency, necrotizing myopathies, rhabdomyolysis</td>
</tr>
<tr>
<td>Myotonic discharges (with clinical myotonia)</td>
<td>Myotonic dystrophy types 1 and 2, myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, potassium aggravated myotonia, chondrodystrophic myotonia (Schwartz-Jampel syndrome)</td>
</tr>
<tr>
<td>Myotonic discharges (without clinical myotonia)</td>
<td>Acid maltase deficiency, myofibrillar myopathy, hypothyroid myopathy, toxic, amyloid myopathy, inflammatory myopathies</td>
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</table>
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.5,11,12

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 4th or 5th 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. They do not correlate with disease severity or an individual’s disease activity, and are therefore not useful to follow response to therapy. Rare patients have elevated blocking antibodies in isolation, although they usually are present in association with binding antibodies. A slightly higher percentage of patients will have an elevated modulating antibody titer in isolation. 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.

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. Patients with purely ocular MG are unlikely to have anti-MuSK antibodies. 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. Because MG often coexists with autoimmune disorders, such as thyroid disease, other autoimmune markers and thyroid function tests should be obtained.

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. The discovery of thymic abnormality or cancer is an indication for thymectomy. Anti-MuSK myasthenia is not commonly associated with thymic abnormality or cancer.

If immunosuppressive therapy, particularly azathioprine or mycophenolate mofetil, is 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. Serum IgA level should also be determined if IV Ig 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. Muscarinic side effects of pyridostigmine include diarrhea, abdominal pain, diaphoresis, and cramps; overtreatment with cholinesterase inhibitors has the potential for exacerbation of weakness.

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, IV Ig, azathioprine, and less commonly cyclosporine or cyclophosphamide are potential effective options. Methotrexate has also been successful in treating MG, although evidence in MG is lacking. Recently, rituximab has emerged as a potentially useful treatment. 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.

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

### 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. Unlike MG, weakness involves mainly the proximal extremities, particularly the lower extremities, and oculobulbar muscles are less commonly and minimally involved.

In contrast to MG, strength may improve during exercise in LEMS. Muscle stretch reflexes are often reduced or present, although brief improvement (facilitation) following exercise or repeated testing of the reflex may occur. Autonomic dysfunction, including dry mouth, erectile dysfunction, orthostatic intolerance, and gastrointestinal motility disturbances, is common.

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

**Antibody and other testing.** Lambert-Eaton myasthenic syndrome is associated with antibodies against the presynaptic voltage-gated calcium channels (VGCC).

In patients with typical clinical and electrophysiological features of LEMS, the presence of P/Q type VGCC confirms the diagnosis. AChR and striated muscle antibodies may also be found. 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.

**Treatment.** For symptomatic treatment, pyridostigmine may improve strength. 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. Treatment with IV Ig, plasmapheresis, or immunosuppressant medication may lead to improvement or remission of the disease. If a small cell lung cancer is identified, treatment directed against the tumor may lead to improvement of LEMS.

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. Although weakness often fits single-nerve distributions, there is often variable weakness in different muscles supplied by the same nerve. Rarely, the phrenic nerve and cranial nerves are affected, and scapular winging has been reported. There may be muscle atrophy later in the course of the disease. Pain and sensory loss are not features of MMN, although up to 50% of patients may experience cramps and fasciculations. Reflexes are commonly reduced, most often in affected regions.

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.

Laboratory testing. Monoclonal protein studies may show a monoclonal gammapathy. Serum CK may be slightly elevated. Cerebrospinal fluid examination may demonstrate a mild elevation of protein, but should not lead the practitioner away from the diagnosis. Antiganglioside antibodies, specifically anti-GM1 IgM antibodies, have been found in 31 to 85% of patients with MMN. 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. The majority of patients respond to IV Ig infusions, but long-term treatment must be individually tailored. Cyclophosphamide has also proven effective in MMN. 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.
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 dysthria, hyperactive jaw jerk reflex) and LMN (atrophy, fasciculations) signs. With bulbar involvement, dysthria 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.\(^ {122\text{-}125}\) 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.

**Table 7  Motor Neuron Disease Mimickers**

<table>
<thead>
<tr>
<th>Category</th>
<th>Upper Motor Neuron Syndromes (With or Without Lower Motor Neuron Involvement)</th>
<th>Lower Motor Neuron Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td>Amyotrophic lateral sclerosis, Primary lateral sclerosis</td>
<td>Progressive muscular atrophy, Juvenile monomelic amyotrophy (Hirayama disease)</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Hereditary amyotrophic lateral sclerosis, Adrenomyeloneuropathy, Hereditary spastic paraparesis</td>
<td>Spinal muscular atrophy, X-linked spinobulbar muscular atrophy (Kennedy disease), Hexosaminidase A deficiency</td>
</tr>
<tr>
<td>Metabolic / Toxic</td>
<td>B12 deficiency, copper deficiency, vitamin E deficiency</td>
<td>Heavy metal toxicity, B12 deficiency, copper deficiency, hyperthyroidism, vitamin E deficiency</td>
</tr>
<tr>
<td>Infectious</td>
<td>HIV, HTLV, syphilis</td>
<td>HIV, HTLV</td>
</tr>
<tr>
<td>Inflammatory or neoplastic</td>
<td>Lymphoma</td>
<td>Multifocal motor neuropathy, CIDP, lymphoma</td>
</tr>
</tbody>
</table>

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

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1. 118
2. 119
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6. 123
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8. 125
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. 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.

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