REVIEW ARTICLE

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A Symptoms and Signs Approach to the Patient With Neuromuscular Weakness

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ABSTRACT

PURPOSE OF REVIEW: Muscle weakness is a common feature of many neuromuscular disorders. This article outlines a symptoms and signs approach to the patient presenting with neuromuscular weakness, highlighting key aspects of the clinical history and examination.

RECENT FINDINGS: The past several years have seen a dramatic increase in the ability to test for many inherited and autoimmune neuromuscular disorders more reliably and accurately. Similarly, numerous targeted therapies have been recently approved to treat previously untreatable disorders. Therefore, timely and accurate diagnosis is essential so that patients can receive appropriate therapy, ultimately leading to better clinical outcomes.

SUMMARY: Muscle weakness is a common symptom resulting from dysfunction that can occur at any level of the neuraxis and is a cardinal feature of many neuromuscular disorders. An accurate and meticulous history and a thorough neurologic examination are paramount in localizing the lesion in order to generate a differential diagnosis and guide appropriate ancillary testing. The patient's age at symptom onset, any identified inciting factors, tempo of symptom progression, pattern of weakness, and associated symptoms and signs are all important diagnostic clues in the evaluation of a patient presenting with muscle weakness.

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INTRODUCTION

Muscle weakness is a common presenting concern in neurologic practice. The differential diagnosis of weakness is extensive and includes both central and peripheral etiologies. The key to determining the diagnosis is performance of a thorough and hypothesis-driven history and neurologic examination to localize the lesion in the neuraxis and determine its cause through targeted ancillary testing. Reaching an accurate diagnosis requires eliciting and synthesizing key factors in the case, such as the patient's age at symptom onset, the tempo of symptom development, the pattern of weakness, the patient's

comorbid medical conditions, the presence or absence of other neurologic symptoms, and the findings on the neurologic examination. This article delineates a symptoms and signs approach to the patient presenting with muscle weakness.

THE CLINICAL HISTORY

Patients often seek neurologic consultation with a chief concern of weakness. First and foremost, it is crucial to differentiate true muscle weakness from other symptoms that people may confuse with an actual loss of strength. These may include generalized fatigue or malaise; physical limitations due to arthralgia, myalgia, or deconditioning; and even the effects of depression. Weakness is most simply defined as a reduction in muscle strength. When discussing a patient's concern about weakness, it is instructive to ask about the impact of the symptoms on routine activities to differentiate true weakness from the aforementioned conditions.[1] For instance, patients with loss of proximal muscle strength often report difficulty combing their hair, brushing their teeth, reaching for objects overhead, rising from chairs, getting out of a car, or climbing stairs. When weakness affects more distal muscles, patients frequently describe difficulty with dexterity such as buttoning, typing, or texting, or frequent trips, ankle injuries, or falls secondary to footdrop or flail feet. Patients with ocular muscle weakness describe blurred vision which in this context is due to unrecognized diplopia, frank diplopia, or eyelid ptosis. Those with bulbar muscle weakness experience dysarthria, dysphonia, dysphagia, chewing difficulty, and trouble manipulating their tongues, often resulting in frequent tongue or cheek bites.[2]

As the examples in this line of questioning indicate, a detailed history is essential to accurately pinpoint a particular patient's source of weakness. In addition to the pattern of weakness and the impact of weakness on the person's day-to-day activities, identifying the underlying cause requires determining the age at which symptoms first manifested, the tempo of symptom development, and the presence or absence of associated symptoms.

Muscle weakness can develop acutely over hours to days, subacutely over weeks, or chronically over months. Extrapolating from the categorization of autoimmune neuropathies such as acute and chronic inflammatory polyradiculoneuropathies, acute onset and progression of weakness can be defined as occurring for up to 4 weeks, subacute for 4 to 8 weeks, and chronic for longer than 8 weeks.[3] Most, if not all, patients who experience the subacute onset of weakness go on to experience chronic symptoms, highlighting the somewhat artificial nature of this categorization.

Along these lines, it is important to determine whether weakness is progressive or static. In most neurologic disorders, weakness is fixed; however, in certain disorders such as those affecting the neuromuscular junction, muscle channelopathies, and certain metabolic myopathies, weakness may be episodic and is typically provoked by physical activity.[4,5] Causes of episodic weakness are listed in TABLE 1-1. In cases of neuromuscular junction disorders, episodic weakness is often referred to as fatigability and must be differentiated from generalized fatigue.[6] For instance, a patient with myasthenia gravis (MG) who is experiencing fatigability will note decreased strength with sustained activity, such as the development of diplopia with prolonged reading or more difficulty chewing as a meal progresses (CASE 1-1). This symptom must be distinguished

KEY POINTS

- It is important to differentiate true muscle weakness from other symptoms such as generalized fatigue or malaise, or physical limitations due to arthralgia, myalgia, or deconditioning.
- When evaluating a patient for muscle weakness, it is instructive to ask about the impact of the symptoms on routine activities to differentiate true weakness from other conditions.
- Muscle weakness can develop acutely over hours to days, subacutely over weeks, or chronically over months.
- Fatigability is often seen in neuromuscular junction disorders and must be differentiated from generalized fatigue or malaise.

from that of a patient reporting feeling generally weak or tired or having the urge to nap later in the day.

Most causes of fixed weakness are progressive if left untreated; for many causes of neuromuscular weakness, effective treatment does not yet exist. With continued progression, however, the weakness may seem to become static as muscles reach their end stage and can no longer contract. This may be the case in the later stages of amyotrophic lateral sclerosis (ALS) or Duchenne muscular dystrophy. Several causes of weakness are truly static, including traumatic nerve injuries or those involving permanent axonal loss, as well as most forms of congenital myopathy.

It is also important to determine the age of the patient at symptom onset, which directly affects the differential diagnosis. Although some patients come to medical attention early in the course of their illness, others may have experienced

TABLE 1-1

Causes of Episodic Weakness

Neuropathies

- **Acute intermittent porphyria**
- **Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (relapsing form)**

Disorders of neuromuscular transmission

- **Myasthenia gravis**
- **Congenital myasthenic syndromes**
- **Lambert-Eaton myasthenic syndrome**

Metabolic myopathies

- **Glycogen storage disorders**
  - Myophosphorylase deficiency
  - Phosphorylase *b* kinase deficiency
  - Phosphofructokinase deficiency
  - Phosphoglycerate kinase deficiency
  - Phosphoglycerate mutase deficiency
  - Lactate dehydrogenase deficiency
- **Disorders of fatty acid oxidation**
  - Carnitine palmitoyltransferase type 2 deficiency
  - Trifunctional protein deficiency
  - Very-long-chain acyl-coenzyme A dehydrogenase deficiency
  - Medium-chain acyl-coenzyme A dehydrogenase deficiency
- **Myoadenylate deaminase deficiency**
- **Mitochondrial cytopathies**

Muscle channelopathies

- **Hyperkalemic periodic paralysis**
- **Hypokalemic periodic paralysis**
- **Andersen-Tawil syndrome**

more subtle symptoms over a longer time, sometimes decades, before presentation. Asking a patient or the parents about the pace of development of motor milestones during childhood, athletic ability during childhood or adolescence, and any physical limitations experienced over the life course is important. Comparison with peers or siblings of similar age can be very helpful in this regard.

It is also important to elicit a history of inciting events or triggers. For example, a history of antecedent vaccinations or illnesses in the weeks before symptom onset, recently started medications, or exposure to environmental toxins may be relevant in cases of acute onset and rapid progression of weakness. Vaccine reactions or gastrointestinal or upper respiratory tract infections occur 2 to 3 weeks before the development of neurologic symptoms in roughly two-thirds of patients diagnosed with Guillain-Barré syndrome (GBS).[3] Medications known to cause muscle weakness include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), corticosteroids (if used chronically), amiodarone, and several chemotherapeutic agents.

CASE 1-1

A 27-year-old woman presented with a 2-month history of intermittent ptosis and diplopia, which was most noticeable at night and after working on her computer for extended periods of time. Three weeks before presentation, she experienced dysarthria with prolonged conversation and dysphagia toward the end of meals, with occasional regurgitation of liquid through her nose and choking spells. One week later, she began to have trouble drying her hair and climbing stairs.

On examination, she had bilateral ptosis at rest, which was accentuated after 1 minute of sustained upgaze. Similarly, she developed dysconjugate gaze and diplopia with sustained upgaze. She had mild bifacial weakness and fatigable weakness in both of her deltoids and iliopsoas muscles. The remainder of her neurologic examination was normal, including sensory, coordination, reflex, and gait testing.

Serum acetylcholine receptor antibodies were elevated, and chest imaging did not demonstrate evidence of thymoma.

COMMENT

The weakness in this patient was both oculobulbar and proximally predominant in distribution and was fatigable, all pointing to a disorder of neuromuscular transmission, specifically myasthenia gravis (MG). MG has a bimodal age distribution, affecting women more than men in the second and third decades and both sexes roughly equally in the sixth and seventh decades. Acetylcholine receptor antibodies are present in 85% of patients with generalized MG. Thymomas occur in 15% of patients with MG, and chest imaging is recommended at the time of diagnosis. Acetylcholinesterase inhibitors, steroids, and immunosuppressants are all available treatment options. Thymectomy is typically performed in patients with thymoma and in patients aged 50 years or younger with acetylcholine receptor–positive MG.

In cases of episodic weakness, associations of symptoms with diet, exercise, rest after exercise, ambient temperature, and underlying illnesses such as infections are important clues to the diagnosis. Conditions that commonly lead to weakness after exercise include not only MG but also metabolic myopathies such as myophosphorylase deficiency, phosphofructokinase deficiency, carnitine palmitoyltransferase type 2 deficiency, and mitochondrial cytopathies. Muscle channelopathies including hyperkalemic periodic paralysis are known to cause episodes of weakness after a period of rest following exercise. Episodes of hypokalemic periodic paralysis are frequently triggered by exercise, cold

CASE 1-2

A 23-year-old man presented with a 10-year history of intermittent episodes of generalized muscle weakness that occurred with prolonged physical activity, such as playing soccer. The episodes lasted anywhere from 5 to 60 minutes and resolved with rest. The episodes had become more frequent over time and were not associated with changes in temperature, emotional stress, alcohol intake, or eating specific foods. The patient's mother reported that she also suffered from similar but less severe attacks as a child, as did her sister, mother, and uncle.

The patient's neurologic examination was completely normal. Routine laboratory evaluation including complete blood cell count, comprehensive metabolic panel, and thyroid function studies yielded normal results; in addition, creatine kinase level was normal, and acetylcholine receptor antibodies were negative.

Nerve conduction studies were normal, but myotonia was found in all muscles sampled on EMG. Genetic testing revealed a pathogenic mutation in the *SCN4A* gene, consistent with a diagnosis of hyperkalemic periodic paralysis.

COMMENT

This patient had intermittent episodes of weakness following physical activity, suggestive of either a disorder of neuromuscular transmission, a muscle channelopathy, or a metabolic myopathy. The family history of similarly, albeit mildly, affected relatives suggested a genetic disorder with an autosomal dominant pattern of inheritance. The presence of myotonia on EMG can be seen in myotonic dystrophy types 1 and 2, which are also autosomal dominant disorders, but are also accompanied by progressive weakness and involvement of other organ systems such as the cardiac, pulmonary, and gastrointestinal systems. Myotonia can also be seen in nondystrophic myotonic disorders such as myotonia congenita, paramyotonia congenita, and hyperkalemic periodic paralysis. Genetic testing can differentiate among these disorders. Advanced nerve conduction study techniques such as the long-exercise test can also help distinguish the periodic paralyses on electrophysiologic grounds. This patient had a pathogenic mutation in the *SCN4A* gene, which encodes sodium channels. Serum potassium levels are usually elevated only during an attack of weakness. Treatment includes dietary modification or use of carbonic anhydrase inhibitors.

temperature, emotional stress, alcohol intake, or carbohydrate-rich meals. Increased ambient temperature characteristically worsens symptoms in patients with MG. Although any underlying illness or infection that increases the body's inflammatory milieu can conceivably make symptoms due to any number of neurologic disorders more prominent, this is especially true in MG and in metabolic disorders of fatty acid oxidation, including carnitine palmitoyltransferase type 2 deficiency.

Many neuromuscular disorders including ALS, phrenic nerve injury, MG, and acid maltase deficiency can lead to early weakness of the muscles of respiration, including the diaphragm, intercostals, and accessory muscles. Patients may therefore experience dyspnea at rest or on exertion. Orthopnea is often an early symptom, as the diaphragm is placed at a mechanical disadvantage in the supine position. Therefore, lying in the supine position often results in nocturnal hypoventilation early on, leading to nonrefreshing sleep, daytime sleepiness, and morning headaches due to hypercarbia. Patients may also experience weak cough and difficulty handling their secretions and are at risk for aspiration, particularly if concomitant bulbar muscle involvement is present.[7] A thorough past medical history should be obtained to identify any concomitant diseases that may cause or be associated with muscle weakness, such as organ system dysfunction (eg, thyroid, liver, kidney, or cardiac disease), malignancy, connective tissue disorders, or autoimmune disorders. Hypothyroidism can cause myopathy or carpal tunnel syndrome and, less commonly, generalized neuropathy. The hypothyroid state in and of itself may lead to a sense of fatigue, malaise, and generalized weakness, which must be differentiated from actual loss of strength. Chronic kidney disease has been associated with the development of mononeuropathies, and both this condition and liver disease, if severe or chronic, can lead to generalized cachexia. Cardiac dysfunction can limit one's ability to perform physical activity because of pump failure and the development of edema, which can affect either the peripheral tissues or the lungs, the latter leading to dyspnea on exertion. Underlying malignancies or their treatment with systemic chemotherapy or radiation therapy often leads to generalized fatigue, malaise, and cachexia with muscle wasting. Connective tissue disorders can also be associated with the development of neuropathy or myopathy. Systemic lupus erythematosus, for example, can predispose a person to the development of an inflammatory myopathy as part of an overlap syndrome. Connective tissue disorders may also lead to significant joint involvement, and the resultant deformities or pain due to arthritis can also cause functional limitations, which must be differentiated from muscle weakness. The presence of one autoimmune disorder predisposes a person to the development of another at a higher rate than the general population.

Because many neurologic diseases leading to muscle weakness are inherited, obtaining a detailed and accurate family history is imperative. However, as other family members may not have an identified neurologic diagnosis, it is key to ask not only about those relatives who have been formally diagnosed with a particular neurologic disorder but also about any family members with potentially undiagnosed conditions, such as those with functional limitations or difficulty walking or who have been described as "clumsy" or not athletic. Although these characteristics are not always signs of an underlying neurologic disorder, they can be helpful clues, especially in determining mode of inheritance after constructing a pedigree, as they differ from disorder to disorder (CASE 1-2). Examining a potentially similarly affected family member can prove invaluable.

KEY POINTS

- The age of the patient at the onset of muscle weakness is also important to accurately determine, as it directly affects the differential diagnosis.
- Vaccinations, gastrointestinal symptoms, or upper respiratory tract infections occur 2 to 3 weeks before the development of neurologic symptoms in roughly two-thirds of patients diagnosed with Guillain-Barré syndrome.
- With episodic weakness, the associations of symptoms with diet, exercise, rest after exercise, ambient temperature, and underlying illnesses such as infections are important clues to the diagnosis.
- Orthopnea is often an early symptom of neuromuscular respiratory failure, as the diaphragm is placed at a mechanical disadvantage in the supine position.
- A thorough past medical history is necessary to identify any concomitant diseases that may be associated with muscle weakness, such as organ system dysfunction, malignancy, connective tissue disorders, or autoimmune disorders.
- Examining a similarly affected family member with muscle weakness can prove invaluable when eliciting a family history.

Other potential issues to consider when eliciting a family history include the possibilities of spontaneous mutations, incomplete penetrance, or false paternity.

ASSESSMENT FOR MUSCLE WEAKNESS

The detailed history should lead to a reasonable hypothesis regarding the source of the lesion responsible for a patient's weakness. Next, a complete neurologic examination should be performed to further localize the process and refine the differential diagnosis.

Muscle strength can be objectively assessed on examination using the MRC scale (TABLE 1-2[8]). The pattern of weakness must be determined using both the history and the physical examination. Using a modified version of the framework previously developed by Barohn and colleagues,[9,10] muscle weakness can be categorized into one of only a few patterns, which can aid greatly in refining the differential diagnosis. These patterns of muscle weakness include proximal predominance, distal predominance, proximal and distal involvement, proximal involvement in the upper extremities and distal involvement in the lower extremities, oculobulbar predominance, and isolated neck flexor or extensors.

Proximally predominant muscle weakness is that involving the muscles of the shoulder and pelvic girdles. In the upper extremities, it usually includes involvement of the deltoids, periscapular muscles, biceps brachii, and triceps brachii. In the lower extremities, the iliopsoas, hip abductors, and hip adductors are most often affected. The neck flexors and extensors are also often involved to some extent. Most myopathies and disorders of the neuromuscular junction, including Lambert-Eaton myasthenic syndrome (LEMS) and MG, present with this pattern, although in the latter instance the weakness may fluctuate. Rare forms of neuropathy such as porphyric neuropathy can also be proximally predominant, as are most forms of motor neuron disorders such as spinal muscular atrophy (SMA). TABLE 1-3 outlines common causes of proximal weakness based on localization.

Distally predominant weakness most often involves the muscles of the forearms and hands, ankle and toe dorsiflexors, and plantar flexors. This is the pattern most often seen initially in ALS, as well as in most neuropathies such as Charcot-Marie-Tooth disease and rare myopathies (such as certain congenital "distal" myopathies, myotonic dystrophy type 1 and inclusion body myositis

TABLE 1-2 Medical Research Council Scale[a]

- 5: Full strength
- 4: Active movement against gravity and resistance
- 3: Active movement against gravity
- 2: Active movement with gravity eliminated
- 1: Flicker of movement or contraction
- 0: No contraction

[a] Data from O'Brien M, Elsevier.[8]

[IBM]); it occurs rarely in MG. TABLE 1-4 outlines the common causes of distal weakness based on localization.

In some instances, weakness can affect both proximal and distal muscles equally. This pattern is most often seen eventually in motor neuronopathies such as ALS and SMA, autoimmune demyelinating neuropathies such as GBS and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and the later stages of progressive myopathies, such as dystrophinopathies and limb-girdle muscular dystrophies.

Some disorders can lead to proximal weakness in the upper extremities and distal weakness in the lower extremities, in what has been referred to as a humeroperoneal distribution. These disorders include Emery-Dreifuss muscular dystrophy and facioscapulohumeral muscular dystrophy. Conversely, IBM characteristically leads to distal upper extremity weakness (preferentially involving wrist and finger flexors) and proximal lower extremity weakness (predominantly affecting quadriceps). TABLE 1-5 lists common causes of proximal and distal weakness based on localization.

Oculobulbar-predominant weakness leading to ptosis, dysconjugate gaze and diplopia, dysarthria, dysphagia, or dysphonia is typical of MG, certain mitochondrial myopathies, and oculopharyngeal muscular dystrophy. Bulbar weakness occurs eventually but may be the presenting location in up to one-third of people with ALS as well as those with spinobulbar muscular atrophy.[11] TABLE 1-6 lists common causes of oculobulbar weakness.

Isolated involvement of the neck flexors or extensors, often referred to as "dropped head syndrome," can be the first and an early manifestation of ALS, MG, various congenital myopathies, and, rarely, myotonic dystrophy type 1. It can also occur alone because of isolated neck extensor myopathy, which can be inflammatory or degenerative in etiology.[12]

Causes of Proximally Predominant Weakness TABLE 1-3

Motor neuron

- Spinal muscular atrophy
- Spinobulbar muscular atrophy

Nerve

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Acute intermittent porphyria
- Tick paralysis

Neuromuscular junction

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome

Muscle

- Most myopathies, including muscular dystrophies
- Inflammatory, congenital, toxic, and endocrinologic myopathies
- Periodic paralyses

Whether the weakness is symmetric or asymmetric at onset also has important diagnostic implications. Notable disorders that often begin with an asymmetric onset of weakness include most forms of adult-onset motor neuron disease such as ALS, multifocal motor neuropathy (MMN), vasculitic neuropathy, entrapment or traumatic neuropathies, IBM, and facioscapulohumeral muscular dystrophy. The distribution of weakness in ALS is initially myotomal in nature and then spreads in a contiguous fashion. The weakness in MMN, on the other hand, is in the distribution of named nerves, most often in the upper extremities (CASE 1-3). Vasculitic neuropathy most often presents in a sequential asymmetric mononeuritis multiplex pattern but can take on a symmetric or confluent pattern with continued progression if left untreated.[13] TABLE 1-7 outlines common causes of asymmetric weakness.

Similarly, focal, as opposed to generalized, muscle weakness has a restricted differential diagnosis and includes rare forms of motor neuron disorder such as monomelic amyotrophy, brachial or lumbosacral plexopathies, and entrapment or traumatic neuropathies.

ASSOCIATED SYMPTOMS AND SIGNS

In many conditions leading to weakness, there are other associated symptoms and signs that must be considered. From the standpoint of the motor system, muscle tone, bulk, and the presence of abnormal movements are important features. In most disorders of the peripheral nervous system, muscle tone is reduced, as would be expected with a lesion of any portion of the lower motor neuron or motor unit. In most patients, tone can be easily assessed by an examiner by asking the patient to relax and allow passive movement of the limbs.

Muscle atrophy, or reduction in bulk, is also generally seen in the distribution of muscle involvement in most lower motor neuron disorders. In general, weakness occurs before atrophy in myopathies, as the degenerating tissue is frequently first replaced by fat. The reverse is true in neurogenic disorders, in which atrophy often occurs before clinical weakness. Occasionally, muscle hypertrophy is seen in rare disorders of increased muscle excitation such as

TABLE 1-4 **Causes of Distally Predominant Weakness**

Motor neuron

- Amyotrophic lateral sclerosis in early stages
- Distal spinal muscular atrophy (hereditary motor neuronopathy)

Nerve

- Most neuropathies

Neuromuscular junction

- Rare presentations of myasthenia gravis

Muscle

- Inclusion body myositis
- Myotonic dystrophy type 1
- Welander, Udd, Markesbery-Griggs, Nonaka, Laing, Miyoshi distal myopathies

myotonia congenita, and pseudohypertrophy is observed in the gastrocnemius-soleus complex in patients with Duchenne muscular dystrophy.

The presence or absence of abnormal muscle movements can also provide useful diagnostic clues. Fasciculations or muscle cramps are frequently encountered in motor neuron disorders but may also be observed in neuropathies such as MMN.[14] Fasciculations are most easily observed in the tongue and the first dorsal interosseous muscle. Myokymia, visible vermicular movements of a muscle, is most often observed with a lesion of the nerve root or the plexus, as can occur in radiation-induced brachial plexopathy. Distinguishing between fasciculations and myokymia on clinical inspection can be difficult. Whereas fasciculations are generally brief and irregular movements of muscle, myokymia is a slower contraction of portions of muscle occurring in a more regular manner, giving the overlying skin an undulating appearance. Myotonia, or delayed relaxation following muscle contraction, is often seen in myotonic dystrophy types 1 and 2, as well as in the nondystrophic myotonic disorders, including myotonia congenita. Grip myotonia can be assessed by evaluating how easily a patient can release their hand following a handshake. Percussion myotonia can be elicited by using a reflex hammer to strike a group of muscles such as the thenar eminence, third digit extensor, or trapezius, which briskly contract and then slowly relax.[15] Finally, muscle rippling is rare but can be observed in Brody disease and as a manifestation of caveolinopathy, a form of limb-girdle muscular dystrophy.

All patients presenting with muscle weakness should be examined with the patient in a gown so that the examiner can directly observe the affected muscles, with appropriate attention paid to proper draping techniques. Direct inspection also allows for the identification of scapular winging, joint deformities, or kyphoscoliosis.

Sensory symptoms can occur in cases of disorders of the nerve root, plexus, or nerves. Patients may experience numbness, paresthesia, or dysesthesia in the distribution of the territory of the lesion. Involvement of small-diameter sensory fibers, as in diabetic or amyloid polyneuropathy, for instance, or in up to two-thirds of cases of GBS, can lead to autonomic symptoms and signs such as dry eyes, dry mouth, orthostasis and resultant presyncope, early satiety due to gastroparesis, constipation, or erectile dysfunction. Symptoms and signs of cholinergic dysautonomia are also frequently reported in patients with LEMS

Causes of Combined Proximal and Distal Weakness TABLE 1-5

Motor neuron

- Later-stage amyotrophic lateral sclerosis

Nerve

- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Neuromuscular junction

- Botulism

Muscle

- Later-stage muscular dystrophies

because of impaired release of acetylcholine from preganglionic autonomic nerves. Ataxia and loss of balance may also occur in the context of a generalized polyneuropathy involving large-diameter sensory fibers. As such, examination of gait and stance is imperative. Patients with severe proprioceptive loss often exhibit a steppage or "slapping" gait to activate pain fibers in the feet to compensate for loss of joint position sense. People with severe footdrop do the same to avoid tripping over their feet or toes. Proximal muscle weakness in the lower extremities often leads to a waddling gait with Trendelenburg sign. Patients also demonstrate Gowers sign (in this maneuver, a patient first rises to their hands and knees from a prone position and next walks their hands progressively up their legs and thighs to a standing position) under these circumstances. Concomitant upper motor neuron involvement may lead to a spastic or scissoring gait.

In infants, several maneuvers can be employed that are also helpful in assessing for the presence of frank weakness. These include lifting an infant by the arms from the supine position to evaluate for head lag, using vertical suspension to determine if an infant will slip through the examiner's hands, and using horizontal suspension to evaluate for draping of the body. Hypotonic infants also often take on a "frog-legged" posture with both lower extremities externally rotated and abducted when lying supine.[16]

TABLE 1-6

Causes of Oculobulbar Weakness

Motor neuron (bulbar weakness only)

- Amyotrophic lateral sclerosis
- Spinal muscular atrophy
- Spinobulbar muscular atrophy

Nerve

- Guillain-Barré syndrome
- Miller Fisher syndrome
- Compressive, infiltrative, or inflammatory cranial neuropathies

Neuromuscular junction

- Myasthenia gravis
- Congenital myasthenic syndromes
- Botulism

Muscle

- Chronic progressive external ophthalmoplegia
- Kearns-Sayre syndrome
- Oculopharyngeal muscular dystrophy
- Myotubular myopathy
- Ptosis only
  - Myotonic dystrophy type 1
  - Nemaline myopathy

In disorders with an upper motor neuron component, such as ALS or myeloneuropathies (eg, vitamin B_{12} or copper deficiencies, adrenomyeloneuropathy), an increase in tone, or spasticity, may also be present. Similarly, muscle stretch reflexes are reduced in the distribution of a lower motor neuron lesion regardless of cause but can be exaggerated if there is concomitant upper motor neuron involvement (eg, ALS).

CASE 1-3

A 55-year-old man presented with an 8-month history of right hand weakness that had slowly progressed since onset. The patient noticed difficulty buttoning his shirts, writing, and texting on his phone. He denied experiencing numbness, tingling, or pain, but endorsed occasional muscle cramps in his right forearm and twitching movements of several muscles in his right hand.

Cranial nerve examination was normal. On motor examination, he had 4-/5 strength in finger flexion of the fourth and fifth digits and 4/5 strength in both the first dorsal interosseous and abductor digiti minimi on the right. Strength in the right finger extensors was 4+/5. The right thumb abductors and flexors had full strength. Mild atrophy and frequent fasciculations of both the right first dorsal interosseous and abductor digiti minimi were seen. Sensation was normal throughout, and reflexes, coordination, and gait were normal.

Nerve conduction studies of the right upper extremity demonstrated slowing of conduction velocity with conduction block and temporal dispersion with stimulation of the right ulnar nerve at Erb point and at the axilla; there was no slowing across the elbow. Motor nerve conduction studies of the right radial nerve also demonstrated slowed conduction velocity and conduction block in the forearm. Motor nerve conduction studies of the right median nerve were normal. All sensory nerve conduction studies were normal, as was EMG. Serum anti-GM1 antibodies were elevated.

COMMENT

This patient developed progressive weakness, atrophy, and fasciculations in his right upper extremity in the absence of sensory symptoms, and without involvement of other limbs. While the symptoms were initially concerning for motor neuron disease, on examination the patient demonstrated weakness in a named nerve pattern (involving the ulnar and radial nerves), rather than in a myotomal pattern as would be seen in amyotrophic lateral sclerosis. The presence of signs of demyelination including slowed conduction velocities and conduction block and temporal dispersion in motor but not sensory branches of named nerves, along with the absence of ongoing denervation or chronic reinnervation on EMG, is diagnostic for multifocal motor neuropathy, a rare autoimmune demyelinating neuropathy. Anti-GM1 antibodies are present in 50% of cases. The standard treatment for multifocal motor neuropathy is IV immunoglobulin (IVIg).

SYSTEMIC SYMPTOMS

Finally, systemic symptoms and signs should be carefully elicited and considered. Involvement of the respiratory system was discussed earlier. Cardiac involvement can also lead to dyspnea on exertion or orthopnea and can be seen in many forms of myopathy, including several dystrophies and congenital forms.[17] Characteristic skin rashes including a malar rash, shawl sign, and Gottron papules can be observed in cases of dermatomyositis. Inquiring about a history of pigmenturia is also important, as several metabolic or congenital myopathies, most notably including central core disease, can lead to rhabdomyolysis and myoglobinuria.[18] Gynecomastia often occurs in spinobulbar muscular atrophy as a result of androgen insensitivity. Hair loss can be a sign of underlying thyroid dysfunction or, less commonly, arsenic toxicity. Arsenic toxicity is also associated with characteristic changes to the hands and feet, which can appear erythematous and swollen and feature Mees lines on the nails. Foot deformities such as pes cavus and hammer toe are frequently seen in Charcot-Marie-Tooth disease.

DIAGNOSTIC EVALUATION

As highlighted previously, the diagnostic evaluation for a patient's muscle weakness depends entirely on the history and detailed physical examination. The ordering of tests should be hypothesis-driven based on the differential diagnosis arrived at by the history and examination, rather than a "shotgun approach."

Laboratory Evaluation

Laboratory evaluation is often a critical initial step in the workup. Most, if not all, patients will have already had a complete blood cell count and comprehensive metabolic profile obtained by the time they reach neurologic consultation. Generalized weakness can be caused by severe anemia, hypokalemia or

TABLE 1-7 **Causes of Asymmetric Weakness**

Motor neuron

- Amyotrophic lateral sclerosis in early stages

Nerve

- Multifocal motor neuropathy
- Vasculitic neuropathy
- Most entrapment or traumatic neuropathies
- Radiculopathies
- Plexopathies

Neuromuscular junction

- Myasthenia gravis (oculobulbar)

Muscle

- Inclusion body myositis
- Facioscapulohumeral muscular dystrophy

hyperkalemia, hypomagnesemia or hypermagnesemia, hypophosphatemia, or acute renal or hepatic failure.

In patients with a suspected motor neuron disorder, a creatine kinase level is often obtained; although it is often mildly elevated, this finding is neither sensitive nor specific enough to diagnose these disorders. Thyroid-stimulating hormone (TSH) and parathyroid hormone levels, serum protein electrophoresis with immunofixation electrophoresis, and urine protein electrophoresis should also be sent as hypothyroidism or hyperthyroidism and hematologic malignancies have been reported to cause motor neuron dysfunction. Anti-GM1 antibodies are also often assessed in lower motor neuron–predominant disease to evaluate for the possibility of MMN.

In cases of suspected generalized polyneuropathy with a subacute to chronic course, glycosylated hemoglobin, vitamin B_{12}, methylmalonic acid and homocysteine, and TSH levels, as well as serum protein electrophoresis and urine protein electrophoresis, are a part of the recommended evaluation.[19] In more acutely developing cases of polyneuropathy not consistent with GBS, consideration should be given to checking a 24-hour urine collection for the presence of heavy metals and, in the appropriate clinical context, evaluation for urine porphyrins.

If upper motor neuron–predominant motor neuron disorder or myeloneuropathy is suspected, vitamin B_{12}, methylmalonic acid and homocysteine, copper, zinc, and ceruloplasmin levels should be assessed; in males with a family history of similar disorders, testing for very-long-chain fatty acids may be considered to evaluate for adrenomyeloneuropathy. Testing for human T-cell lymphotropic virus (HTLV) and human immunodeficiency virus (HIV) can also be performed in the appropriate clinical context.

In cases of suspected MG, acetylcholine receptor antibody testing should be performed. Evaluation for muscle-specific tyrosine kinase (MuSK) and lipoprotein-related protein antibodies should be included in those patients with suspected MG and negative acetylcholine receptor antibodies, particularly in those with profound bulbar involvement. Evaluation of TSH, as well as thyroxine levels, should also be performed in patients with MG, as dysthyroid disease can rarely lead to neuromuscular junction dysfunction. Antibodies to voltage-gated calcium channels, which cause LEMS, can also be tested. Finally, in cases of suspected myopathy, serum creatine kinase and aldolase levels should be obtained; these are elevated in most instances of inflammatory, dystrophic, and toxic disease. Alanine transaminase (ALT) and aspartate transaminase (AST) levels can also be elevated in myopathy; however, unlike with elevations seen in liver disease, γ-glutamyl transferase (GGT) level will not be elevated.

Electrodiagnostic Testing

Electrodiagnostic studies including nerve conduction studies and EMG are also invaluable tools to aid in the diagnosis of many neuromuscular disorders causing weakness. They are best conceptualized as extensions of the history and neurologic examination.[20] The diagnosis of motor neuron disorders is greatly aided by these studies. Although SMA and spinobulbar muscular atrophy can be diagnosed with genetic testing, this is not the case for most patients with ALS. Therefore, EMG and nerve conduction studies play a pivotal role in making this diagnosis once all other reasonable possibilities have been ruled out with other testing. In the right clinical context, the presence of ongoing denervation in the

KEY POINTS

- The pattern of muscle weakness must be determined using both the history and the neurologic examination.
- Most myopathies and disorders of the neuromuscular junction cause proximally predominant weakness.
- Distally predominant weakness is often seen initially in motor neuron disorders and neuropathies; it occurs rarely in myopathies and disorders of the neuromuscular junction.
- Oculobulbar-predominant weakness leading to ptosis, dysconjugate gaze and diplopia, dysarthria, dysphagia, or dysphonia is typical of myasthenia gravis.
- The symmetry or asymmetry of involvement is an important diagnostic clue in the evaluation of muscle weakness.
- It is necessary to directly inspect a patient's muscles to evaluate for the presence of atrophy, hypertrophy, or abnormal movements.
- Sensory symptoms can co-occur with muscle weakness and indicate involvement of the spinal cord, nerve roots, or nerves.
- Ancillary tests should be ordered using a hypothesis-driven approach based on the differential diagnosis arrived at by the history and examination.

form of fibrillation potentials and positive sharp waves, and chronic reinnervation in the form of large-amplitude, long-duration, polyphasic motor units, in more than one craniospinal level on EMG can facilitate this diagnosis. Cervical and lumbosacral radiculopathies can be identified with EMG findings corresponding to the affected myotome(s), whereas brachial and lumbosacral plexopathies can be diagnosed with the appropriate changes on sensory and motor nerve conduction studies, as well as the pattern of muscle involvement on EMG. The presence, severity, chronicity, and pathophysiology (axonal or demyelinating) of a generalized polyneuropathy can also be reliably determined with electrodiagnostic testing. Single-fiber EMG and repetitive nerve stimulation are useful in the diagnosis of neuromuscular junction disorders. While not specific, increased jitter on single-fiber EMG is seen in MG, LEMS, and botulism. Slow (3-Hz) repetitive nerve stimulation can demonstrate a decrement of greater than 10% by the fourth potential in a train of 6 to 10 responses in MG, and fast (50-Hz) repetitive stimulation or postexercise facilitation demonstrates an increment of more than 100% in LEMS and botulism. In cases of suspected generalized MG, electrodiagnosis is most helpful in cases in which antibody testing is negative, which occurs in roughly 7% to 8% of cases.[21] Electrodiagnostic studies are even more important in cases of ocular MG, in which antibodies are present only in roughly 50% of cases. Finally, EMG often demonstrates small-amplitude, short-duration, polyphasic motor units in affected muscles in myopathies. Electrical myotonia on EMG is another feature that can be helpful in making the diagnosis of disorders such as myotonic dystrophy.

Muscle Biopsy

Muscle biopsy continues to be an essential element in the diagnostic evaluation of myopathy, particularly in cases of suspected inflammatory etiologies. When inherited forms of myopathy such as muscular dystrophies and metabolic myopathies are considered, genetic testing has largely obviated the need for biopsy. Nerve biopsies can be especially helpful in the diagnosis of amyloid and vasculitic neuropathies; they can also be useful in cases of CIDP that are not otherwise straightforward. Combined muscle and nerve biopsies are recommended for the diagnosis of vasculitic neuropathy.

Imaging

MRI may also have a role in the evaluation of muscle weakness. In cases of concomitant upper motor neuron involvement, imaging is often performed to evaluate for compressive or inflammatory disorders of the spinal cord. Nerve ultrasound has gained widespread use in the diagnosis of compressive neuropathies and generalized polyneuropathies over the past decade.[22] MRI of peripheral nerves and muscles is also emerging as a useful and less invasive diagnostic tool.

CONCLUSION

Muscle weakness is a common symptom resulting from dysfunction that can occur at any level of the motor system and is a cardinal feature of most neuromuscular disorders. An accurate and meticulous history and a thorough neurologic examination are paramount in localizing the lesion to generate a differential diagnosis and guide appropriate ancillary testing. The patient's age at

symptom onset, inciting factors, the tempo of symptom progression, the pattern of weakness, and associated symptoms and signs on examination are all important diagnostic clues in the evaluation of a patient presenting with muscle weakness.

KEY POINT

- **Nerve conduction studies and EMG are invaluable tools to aid in the diagnosis of neuromuscular disorders and are best conceptualized as extensions of the history and neurologic examination.**

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