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Approach to Muscle and Neuromuscular Junction Disorders

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ABSTRACT

PURPOSE OF REVIEW: Muscle and neuromuscular junction disorders are a diverse group of disorders that can be difficult to diagnose. This article provides a diagnostic approach based on clinical history and neurologic examination leading to a narrow set of diagnostic tests.

RECENT FINDINGS: Numerous discoveries in recent years have facilitated clinician access to more advanced laboratory and genetic testing to pinpoint the exact diagnosis in patients with muscle or neuromuscular junction disorders. Large-scale genetic testing has become much less expensive, and free testing has become available for many of the rare conditions because of increased research and the availability of effective therapies for these rare disorders.

SUMMARY: The approach to muscle and neuromuscular junction disorders depends on the clinical pattern of muscle weakness. By classifying patients into one of 10 muscle patterns, diagnostic testing can be targeted and gene testing yield will be optimized. With the increased accessibility and reduced cost of genetic testing (eg, gene panels, whole-exome sequencing, whole-genome sequencing, and chromosomal microarray), this clinical approach to muscle weakness and targeted gene testing will ensure a cost-effective investigational plan. This clinical approach should also assist clinicians in making a timely and accurate diagnosis.

INTRODUCTION

Muscle diseases constitute a variety of both acquired and hereditary disorders that can alter muscle structure, metabolism, or muscle channel function. Neuromuscular junction disorders are caused by diseases of the presynaptic terminal, synaptic cleft, or postsynaptic membrane and can be either acquired or inherited. The approach to patients with muscle and neuromuscular junction disorders is challenging.[1] As with other neurologic disorders, localization of the lesion is key.[1–3] A thorough history of the patient's type (positive or negative) and distribution of symptoms, temporal data (progression rate, age of onset), triggering events, associated systemic signs and symptoms, past medical and family history, and a detailed neurologic examination are important to diagnose these conditions.[2,4] Electrodiagnostic

examination, laboratory data, ultrasonography, muscle biopsies, and genetic tests assist in the diagnosis. However, the history and clinical examination provide essential guidance for selection of appropriate confirmatory tests to make an accurate diagnosis.

The main feature that distinguishes neuromuscular junction defects from myopathies is the fluctuation in symptoms and signs. Patients with myasthenia gravis (MG) typically report fatigue during repetitive activity, but this is not a specific finding. Patients with Lambert-Eaton myasthenic syndrome (LEMS) will, at times, report transient strength improvement after brief exercise. Extraocular muscles are more commonly involved in neuromuscular junction disorders than in myopathies, although mitochondrial cytopathies and oculopharyngeal muscular dystrophy are clear exceptions. Although myopathies and neuromuscular junction disorders are associated with proximal muscle weakness, certain myopathies and, rarely, neuromuscular junction disorders can manifest with primarily distal weakness.[5]

KEY POINTS

- Thorough history of onset and progression is fundamentally important for the diagnosis of myopathies and neuromuscular junction disorders.
- The main features that distinguish neuromuscular junction defects from myopathies are fluctuation in symptoms and signs, as well as ocular manifestations.
- Identification of triggering factors for weakness or stiffness is useful for diagnosis of muscle and neuromuscular junction disorders.

APPROACH TO A MUSCLE OR NEUROMUSCULAR JUNCTION DISORDER

A comprehensive history and detailed neuromuscular examination are the most important first steps in the approach to a muscle or neuromuscular junction disorder. Once these narrow the differential diagnostic possibilities, ancillary testing is used to confirm the clinical impression and accurate diagnosis. Early and correct diagnosis of a neuromuscular disorder is essential, particularly in treatable disorders (eg, inflammatory myopathies, MG, and LEMS). With the advent of gene-directed therapies, some of the chronic muscle diseases, such as Duchenne muscular dystrophy, have mutation-specific therapies available or in development. Even in chronic genetic disorders in which progression cannot be stopped, accurate diagnosis is very important as it brings closure, allows for supportive care management, and leads to appropriate genetic counseling.

Medical History

It is fundamental that clinicians define the onset and course of the illness as well as the distribution of symptoms. Weakness is typically the main symptom that all patients with myopathies or neuromuscular junction disorders present with. Other negative symptoms are fatigue and atrophy. The so-called positive symptoms in myopathic disorders include stiffness/inability to relax (myotonia), pain (myalgia), cramps, contractures, rippling/mounding, and muscle hypertrophy.

Once the symptoms are identified (TABLE 1-1),[6] their temporal pattern is important: acute, subacute, or chronic; constant or episodic; monophasic or relapsing; age at onset or lifelong (suggesting congenital disorders); progressive or static.

The distribution of the weakness or stiffness is determined based on the history and neuromuscular examination: proximal arms/legs; distal arms/legs; proximal and distal; neck; cranial nerves (ocular [ptosis], extraocular muscle motility [diplopia], pharyngeal [dysarthria/dysphagia], facial); and muscle atrophy/hypertrophy.

Triggering events may further narrow the differential diagnosis according to patterns of occurrence of stiffness or weakness: during or immediately after exercise; after brief or prolonged exercise; after exercise followed by rest or after a high-carbohydrate meal (as in periodic paralysis); relieved by exercise (eg, stiffness in myotonic dystrophy); use of drugs/exposure to toxins (eg, statins) (CASE 1-1); or related to internal or external temperature.

Family history of a myopathic disorder helps classify disorders as X-linked, autosomal dominant, autosomal recessive, or maternally transmitted (mitochondrial). Associated systemic signs and symptoms to look for in a patient with a suspected myopathic disorder include rash, baldness, fever, dark/red urine, dysmorphic features, cardiac dysfunction, pulmonary dysfunction, arthritis and other connective tissue disease findings, cataracts, developmental delay/dementia, skeletal contractures, skeletal deformities, Paget disease, neuropathy, and gastrointestinal dysfunction.

Identifying the symptoms, their temporal pattern, the distribution of weakness, triggering events, family history, and associated symptoms and signs may help clinicians narrow the broad differential diagnosis into 10 muscle/neuromuscular junction patterns.[1] This efficient method may yield a correct diagnosis in most cases (TABLE 1-2).

TABLE 1-1

Symptoms Typically Associated With Myopathies and Neuromuscular Junction Disorders[a]

Neuromuscular Junction Disorders

- **Ptosis**
- **Diplopia**
- **Ophthalmoplegia**
- **Dyspnea**
- **Dysarthria**
- **Weakness in extremities**
- **Fatigue**
- **Vision abnormalities in botulism**
- **Paresthesia in Lambert-Eaton myasthenic syndrome**

Myopathies

- **Negative**
  - Exercise intolerance
  - Fatigue
  - Muscle atrophy
  - Weakness
- **Positive**
  - Cramps
  - Contracture (electrically silent)
  - Muscle hypertrophy
  - Myalgia
  - Myoglobinuria
  - Stiffness

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6] © 2006 Academy of Neurology.

If this first-pass approach does not yield a specific diagnosis, a broader list should be considered. The differential diagnosis of weakness associated with muscle disease and neuromuscular junction disorders is broad and differs with age (TABLE 1-3, TABLE 1-4, and TABLE 1-5).[8]

The onset and rate of progression are important to pursue. Some disorders progress acutely over days or weeks (TABLE 1-6), whereas others progress over several months to years and are referred to as chronic (TABLE 1-7).

The symptoms (TABLE 1-1) depend on the muscles involved and rate of disease progression. Patients with proximal muscle weakness report difficulty in

CASE 1-1

A 65-year-old man was admitted to the hospital with a 6-month history of progressive proximal leg weakness resulting in three falls in the past month. He had started using a walker to ambulate. He had been prescribed pravastatin 6 months earlier because of high cholesterol. Two months earlier, the pravastatin was stopped for 1 month without any improvement in leg weakness, so it was restarted. His weakness progressively worsened after restarting the medication, which was ultimately discontinued upon his admission to the hospital.

Examination revealed intact cranial nerves, moderate neck flexor weakness, and marked proximal weakness of the arms and legs with inability to stand up from a chair without using his arms, and his gait was slow and unsteady.

His creatine kinase level was 8000 U/L upon admission. Nerve conduction studies and EMG demonstrated no evidence of neuropathy, but spontaneous activity and motor unit action potential (MUAP) changes suggestive of an irritative myopathy were seen. Muscle biopsy demonstrated severe myofiber necrosis and myophagocytosis with diffuse expression of major histocompatibility complex (MHC) class I antigens on the surface of myofibers. Serology was positive for autoantibodies to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, consistent with the clinical impression of statin-associated necrotizing autoimmune myopathy. He was treated with corticosteroids, IV immunoglobulin (IVIg), and methotrexate and demonstrated clinical improvement over the next several months.

COMMENT

This patient's pattern (muscle pattern 1 in TABLE 1-2) is the most common muscle pattern.[1] Statins are associated with side effects of myalgia or myopathic symptoms in up to 5% of cases. These side effects usually improve after stopping the statin; however, a much smaller proportion of patients develop symmetric weakness that progresses for more than 2 months after stopping the statin, with muscle enzyme elevation up to 25,000 U/L or even 30,000 U/L and necrotizing myopathy on muscle biopsy (with MHC class I expression).[7] Autoantibodies to HMG-CoA reductase are detectable in two-thirds of these cases. Treatment of this condition requires multiple immunosuppressive agents, including corticosteroids, IVIg, and other adjuvant medications.

TABLE 1-2 **Muscle Patterns**[a]

	Weakness						
Pattern	**Proximal**	**Distal**	**Asymmetric**	**Symmetric**	**Episodic**	**Trigger**	**Diagnosis**
Muscle pattern 1: Limb-girdle	+			+			Most myopathies, both hereditary and acquired
Muscle pattern 2: Distal		+		+			Distal myopathies (also neuropathies)
Muscle pattern 3: Proximal arm and distal leg (also known as *scapuloperoneal*)	+ Arm	+ Leg	+ (facioscapulohumeral muscular dystrophy [FSH])	+ (others)			FSH, Emery-Dreifuss muscular dystrophy, acid maltase deficiency, congenital scapuloperoneal syndrome
Muscle pattern 4: Distal arm/ proximal leg	+ Leg	+ Arm	+				Inclusion body myositis, myotonic dystrophy
Muscle pattern 5: Ptosis/ ophthalmoplegia	+		+ (myasthenia gravis)	+ (others)			Oculopharyngeal muscular dystrophy, myasthenia gravis, myotonic dystrophy, mitochondrial myopathies
Muscle pattern 6: Neck extensor	+			+			Isolated neck extensor myopathy, myasthenia gravis
Muscle pattern 7: Bulbar (tongue, pharyngeal, diaphragm)	+			+			Myasthenia gravis, Lambert-Eaton myasthenic syndrome, oculopharyngeal muscular dystrophy (also amyotrophic lateral sclerosis)
Muscle pattern 8: Episodic weakness/pain/ rhabdomyolysis + trigger	+			+	+	+	McArdle disease, carnitine palmitoyltransferase deficiency, drugs, toxins
Muscle pattern 9: Episodic weakness, delayed or unrelated to exercise	+			+	+	+/-	Primary periodic paralysis, channelopathies (sodium, calcium), secondary periodic paralysis
Muscle pattern 10: Stiffness/inability to relax					+	+/-	Myotonic dystrophy, channelopathies, proximal myotonic myopathy, rippling muscle disease (also stiff person syndrome, neuromyotonia)

[a] Modified with permission from Barohn R, et al, Neurol Clin.[1] © 2014 Elsevier Inc.

climbing stairs and rising from a chair, commode, or floor. They use their arms to push themselves out of the chair. Weakness of the anterior compartment of the leg causes footdrop. These patients report frequent tripping or stubbing of the toes because of the inability to dorsiflex the foot. Posterior compartment weakness causes difficulty in standing on toes. Weakness of the shoulder girdle may cause difficulty in raising the arms above the head. Distal upper extremity weakness usually causes progressive difficulty with grip or finger elevation. With neck flexor weakness, patients have difficulty lifting their head off a pillow, and with head drop, neck extensors are weak. Involvement of the cranial muscles causes ptosis, diplopia, dysarthria, and difficulty with chewing and swallowing. The presence of fluctuations in strength is suggestive of a neuromuscular junction disorder.[9] Muscle bulk enlargement, whether due to hypertrophy or pseudohypertrophy of the muscles, is seen in certain muscular dystrophies.

Muscle and Neuromuscular Junction Disorders That Present in Infants as "Floppy Infant"[a] TABLE 1-3

Neuromuscular Junction Disorders

- **Infantile botulism**
- **Infantile myasthenia gravis**
- **Congenital myasthenic syndrome**

Myopathies

- **Congenital myopathies**
- **Muscular dystrophies**
  - Congenital muscular dystrophies
  - Dystrophinopathy/sarcoglycanopathy
  - Congenital myotonic dystrophy
- **Metabolic myopathies**
  - Glycogen storage defects
    - Acid maltase deficiency
    - Debrancher deficiency
    - Branching enzyme deficiency
    - Myophosphorylase deficiency (rare)
  - Disorder of lipid metabolism
    - Carnitine deficiency
    - Fatty acid–acyl-coenzyme A dehydrogenase deficiencies
- **Mitochondrial myopathies**
  - Benign and fatal infantile myopathy
  - Leigh syndrome
- **Endocrine myopathies**

[a] Modified with permission from Amato AA, Russell JA.[4] © 2016 McGraw-Hill.

The past medical history of patients should be addressed because many medical diseases are associated with neuromuscular disorders. Inflammatory myopathies may be seen in association with connective tissue disease. MG may be seen in patients with other autoimmune conditions, and half of LEMS cases are associated with small cell lung cancer. Review of systems may reveal systemic symptoms that may be associated with a specific neuromuscular disorder (eg, arthralgia for underlying connective tissue disease in myositis, weight loss for paraneoplastic syndromes or severe dysphagia). Family history is very important to define the possible mode of inheritance or degree of penetrance (TABLE 1-8). When a hereditary disorder is suspected, it is valuable to examine affected family members also. Some family members who are asymptomatic may have mild signs of the disease on thorough examination.

In patients with progressive weakness, a history regarding possible toxin exposure is important. Toxin exposure can be related to work environment, medications, home environment, or food. Toxins can cause damage of the muscle[7] or neuromuscular junction (TABLE 1-9).[10]

TABLE 1-4

Muscle and Neuromuscular Junction Disorders Presenting With Weakness in Childhood or Early Adulthood[a]

Neuromuscular Junction Disorders

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

Myopathies

- **Congenital myopathies**
  - Central core
  - Multicore
  - Centronuclear
  - Nemaline
  - Myofibrillar
- **Muscular dystrophies**
  - Dystrophinopathy (Duchenne muscular dystrophy or Becker muscular dystrophy)
  - Limb-girdle muscular dystrophies
  - Congenital muscular dystrophy (partial merosin deficiency)
  - Myotonic dystrophy
  - Other dystrophies (eg, facioscapulohumeral muscular dystrophy, Emery-Dreifuss muscular dystrophy)

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When assessing children, it is important to obtain a detailed history from the parents, including asking for details on developmental milestones, as a child being described as "clumsy" or not athletic may be an early clue.

Examination

After obtaining the history, a complete neurologic examination should be performed. The distribution of the symptoms and pattern of weakness are very important. Most myopathies affect the proximal muscles more than the distal muscles. However, certain myopathies more often affect distal muscles (TABLE 1-10).[11] Neuromuscular junction disorders also more often affect proximal muscles than distal muscles and have a predilection for the ocular muscles.

Extraocular, facial, jaw, pharyngeal, tongue, and neck weakness (TABLE 1-11) may be apparent by just observing the patient while taking the history; ptosis or ophthalmoparesis may be apparent during the interview of a patient with a mitochondrial myopathy[12] or MG, and ptosis may be apparent in

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- **Metabolic myopathies**
  - Glycogen storage defects
    - Acid maltase deficiency
    - Debrancher and branching enzyme deficiency
  - Disorders of lipid metabolism
    - Carnitine deficiency
    - Fatty acid–acyl-coenzyme A dehydrogenase deficiencies
  - Mitochondrial myopathies
  - Periodic paralysis
  - Electrolyte imbalance
    - Hyperkalemia
    - Hypokalemia
    - Hypophosphatemia
    - Hypercalcemia
  - Endocrine myopathies
  - Toxic myopathies
  - Inflammatory myopathies
    - Dermatomyositis
    - Polymyositis
    - Necrotizing myopathy (autoimmune or toxic)
    - Infectious myositis (such as parasitic)

[a] Modified with permission from Amato AA.[8] © Anthony Amato.

oculopharyngeal muscular dystrophy (TABLE 1-12) (CASE 1-2). The presence of a characteristic rash (heliotrope, Gottron sign, or papules) may lead to the diagnosis of dermatomyositis.[13] Patients with myotonic dystrophy have facial weakness, hatchet face, frontal balding, and temporal muscle atrophy and weakness.[14] Thus, some neuromuscular conditions can be suggested while observing the patient during history taking.

For adequate examination, all patients should be asked to undress (except for undergarments) and wear a gown. Muscles should be examined in the proper anatomic position to elicit antigravity strength or better. The patient's posture should be assessed while sitting, standing, and walking. Weakness of the spine extensors may require the patient to lean forward on his or her arms or rest against the examining table to maintain an upright posture. Neck extensor weakness may present as head drop. Excessive lumbar lordosis, hyperextension of the knee, and ankle contractures may be seen in patients with proximal muscle weakness. An excessive lordosis is also seen with hip extensor muscle weakness. With quadriceps weakness, knee extensors are unable to lock the knee joint thus

TABLE 1-5

Muscle and Neuromuscular Junction Disorders Presenting With Weakness in Late Adulthood[a]

Neuromuscular Junction Disorders

- **Botulism**
- **Myasthenia gravis**
- **Lambert-Eaton myasthenic syndrome**

Myopathies

- **Congenital myopathies**
  - Myofibrillar myopathy
- **Muscular dystrophies**
  - Dystrophinopathy (Becker muscular dystrophy)
  - Myotonic muscular dystrophy
  - Facioscapulohumeral muscular dystrophy
  - Limb-girdle muscular dystrophies
  - Oculopharyngeal muscular dystrophy
  - Dropped head/bent spine syndrome
- **Metabolic myopathies**
  - Glycogen storage defects
    - → Acid maltase deficiency
    - → Debrancher deficiency
  - Disorders of lipid metabolism (rare)
  - Mitochondrial myopathies

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leading to falls; patients may try to compensate by hyperextension of the knee (*genu recurvatum*).

Patients with proximal weakness may have a wide-based waddling gait, hyperlordosis, genu recurvatum, or, in the setting of Achilles tendon contractures, toe walking. A waddling gait is due to hip abductor weakness. A positive Trendelenburg sign occurs due to the pelvis dropping down excessively during ambulation. Patients with weakness of the anterior compartment of the leg have footdrop and a high steppage gait to prevent falls. Distal lower extremity strength should be assessed by asking the patient to perform the heel and toe walk. Weakness of the shoulder girdle can result in winging of the scapula. In addition, a "trapezius hump" is caused by rising up of the shoulder secondary to poor fixation and is seen in patients with facioscapulohumeral muscular dystrophy (**CASE 1-3**).[15] Proximal arm weakness also may result in drooping of the shoulders and inward rotation on the arms. In addition, shoulder girdle weakness can cause the horizontal displacement of the anterior axillary lines and the dorsum of the hands to face forward rather than to the side.

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- Periodic paralysis
  - Familial hypokalemic periodic paralysis (manifests within the first 3 decades)
  - Familial hyperkalemic periodic paralysis (usually manifests in the first decade)
- Electrolyte imbalance
  - Hyperkalemia
  - Hypokalemia
  - Hypophosphatemia
  - Hypercalcemia
- Endocrine myopathies
- Toxic myopathies
- Myopathy associated with systemic disease (eg, cancer), poor nutrition, disuse
- Amyloid myopathy
- Inflammatory myopathies
  - Inclusion body myositis (most common inflammatory myopathy after the age of 50)
  - Dermatomyositis
  - Polymyositis (after age 20)
  - Necrotizing myopathy (autoimmune or toxic)

[a] Modified from Amato AA.[8] © Anthony Amato.

TABLE 1-6

Muscle and Neuromuscular Junction Disorders Presenting Acutely[a]

Neuromuscular Junction Disorders

- **Botulism**
- **Lambert-Eaton myasthenic syndrome**
- **Myasthenia gravis**

Myopathies

- **Periodic paralysis**
- **Electrolyte imbalance**
- **Endocrinopathies**
- **Inflammatory myopathies**
  - Dermatomyositis
  - Polymyositis
  - Necrotizing myopathy
  - Infectious myositis
- **Toxic myopathies**
- **Metabolic myopathies**
  - Glycogen and lipid disorders in association with myoglobinuria

[a] Modified with permission from Amato AA, Russell JA.[4] © 2016 McGraw Hill.

TABLE 1-7

Muscle and Neuromuscular Junction Disorders Presenting With Chronic Progressive Weakness[a]

Neuromuscular Junction Disorders

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

Myopathies

- **Channelopathy**
- **Electrolyte imbalance**
- **Endocrinopathies**
- **Inflammatory myopathies**
  - Dermatomyositis
  - Polymyositis
  - Necrotizing myopathy
  - Infectious myositis
- **Toxic myopathies**
- **Metabolic myopathies**
  - Glycogen and lipid disorders in association with myoglobinuria

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Muscles should be inspected for wasting or hypertrophy, not only of the extremities, but also of the head and neck. Muscle cramping and the presence of continuous muscle activity (eg, myokymia) should be noted, and the tone and tenderness of muscles should be assessed. Myotonia can affect proximal or distal muscles depending on the specific myopathy type, although it is typically seen in distal muscles. In myotonic disorders, direct percussion of the muscle may lead to pronounced contraction of the muscle with delayed relaxation (*percussion myotonia*).[14] Action myotonia can be assessed by having the patient sustain a grip for a brief period and then release the grip; in action myotonia, slow relaxation will be seen. Myotonia generally improves with repetition. In contrast, paramyotonia worsens with repetitive activity. This may be demonstrated in patients with paramyotonia congenita[16] by having them repeatedly open and close their eyelids; eventually patients will have difficulty completely opening their eyes. Both paramyotonia and myotonia worsen with cold temperature.[14,17] Other abnormalities can be noted on percussion. A peculiar wave of muscle contraction emanating from the site of percussion or biceps muscle pinching is seen in so-called rippling muscle disease. Occasionally, a "mounding" of the

Diagnosis of Myopathy Based on Pattern of Inheritance[a] TABLE 1-8

X-Linked

- Becker muscular dystrophy
- Duchenne muscular dystrophy
- Emery-Dreifuss muscular dystrophy

Autosomal Dominant

- Myotonic dystrophy
- Facioscapulohumeral muscular dystrophy
- Limb-girdle muscular dystrophy type 1
- Oculopharyngeal muscular dystrophy
- Central core myopathy
- Paramyotonia congenita
- Periodic paralysis
- Thomsen disease
- Autosomal dominant Emery-Dreifuss muscular dystrophy
- Mitochondrial myopathies

Autosomal Recessive

- Limb-girdle muscular dystrophy type 2
- Becker myotonia
- Metabolic myopathies

Maternal Transmission

- Mitochondrial myopathies

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6] © 2006 American Academy of Neurology.

TABLE 1-9

Drugs That Can Cause Toxic Myopathies and Neuromuscular Junction Disorders[a]

Neuromuscular Junction Disorders

- **Botulinum toxin**
- **Snake venom**
- **Organophosphates**
- **Curare**
- **Magnesium (hypermagnesemia)**

Myopathies

- **Inflammatory**
  - Cimetidine
  - D-penicillamine
  - Procainamide
  - L-tryptophan
  - L-dopa
- **Noninflammatory necrotizing or vacuolar**
  - Cholesterol-lowering agents
  - Chloroquine
  - Colchicine
  - Emetine
  - ε-Aminocaproic acid
  - Labetalol
  - Cyclosporine and tacrolimus
  - Isoretinoic acid (vitamin A analogue)
  - Vincristine
  - Alcohol
- **Rhabdomyolysis and myoglobinuria**
  - Cholesterol-lowering drugs
  - Alcohol
  - Heroin
  - Amphetamine
  - Toluene
  - Cocaine
  - ε-Aminocaproic acid
  - Pentazocine
  - Phencyclidine
- **Myosin loss**
  - Nondepolarizing neuromuscular blocking agents
  - Steroids

[a] Modified with permission from Barohn RJ.[10] © 2000 Elsevier, Inc.

muscle is observed, rather than a contraction indentation; this phenomenon is called *myoedema*[18] and can be observed in patients with hypothyroidism.

Manual muscle testing is extremely important; the Medical Research Council (MRC) scale is commonly used for uniformity. The grading is on a scale of 1 to 5: 1 is trace contraction of the muscle, 2 is the ability to move with gravity eliminated, 3 is active movement against gravity, 4 is the ability to move the joint against combination of gravity and some resistance, and 5 is normal power. A plus sign (eg, 4+) or minus sign (eg, 3–) is added to the numbers for a finer distinction of degrees of muscle weakness between the larger grades, but this has poor interrater reliability.

Muscle testing should include the head, neck, eyes, jaw, and face. All strength testing should be performed with the muscle positioned to perform against gravity. Thus, neck flexion should be assessed with patient supine, whereas neck extension, hip extension, and knee flexion should be tested with the patient prone. Hip girdle weakness can be assessed by asking the patient to rise from the floor without holding on to nearby objects; patients may show the Gowers sign

Neuromuscular Junction and Muscle Disorders Causing Distal Weakness[a] **TABLE 1-10**

Neuromuscular Junction Disorders

- **Myasthenia gravis (distal myasthenia gravis is rare)**
- **Congenital myasthenic syndrome (eg, slow [to close] ion channel defect)**

Intrinsic Muscle Disorders

- **Distal myopathies**
  - Late adult-onset distal myopathy type 1 (Welander)
  - Late adult-onset distal myopathy type 2 (LGMD2A [Udd] and LGMD2B [Markesbery-Griggs])
  - Early adult-onset distal myopathy type 1 (Nonaka)
  - Early adult-onset distal myopathy type 2 (Miyoshi)
  - Early adult-onset distal myopathy type 3 (Laing)
- **Centronuclear myopathy**
- **Debrancher myopathy**
- **Hereditary inclusion body myopathy**
- **Inclusion body myopathy**
- **Myofibrillary myopathy**
- **Myotonic dystrophy**
- **Scapuloperoneal syndrome**
- **Emery-Dreifuss muscular dystrophy**
- **Oculopharyngodistal myopathy**
- **Acid maltase deficiency**
- **Phosphorylase b kinase deficiency**
- **Focal myositis**

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TABLE 1-11

Muscle and Neuromuscular Junction Disorders With Prominent Neck Weakness[a]

Neuromuscular Junction Disorders

- Myasthenia gravis

Myopathies

- Isolated neck extensor myopathy
- Polymyositis
- Inclusion body myositis
- Dermatomyositis
- Carnitine deficiency
- Facioscapulohumeral muscular dystrophy
- Myotonic dystrophy
- Congenital myopathy
- Hyperparathyroidism

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TABLE 1-12

Muscle and Neuromuscular Junction Disorders That Cause Ptosis and Ophthalmoparesis[a]

Neuromuscular Junction Disorders

- Botulism
- Lambert-Eaton myasthenic syndrome
- Myasthenia gravis
- Congenital myasthenic syndrome

Myopathies

- **Mitochondrial myopathies**
  - Kearns-Sayre syndrome
  - Progressive external ophthalmoplegia and progressive external ophthalmoplegia plus
- **Oculopharyngeal muscular dystrophy and oculopharyngodistal myopathy**
- **Myotonic dystrophy (ptosis only)**
- **Congenital myopathy**
  - Myotubular
  - Nemaline (ptosis only)
- Hyperthyroidism/Graves disease (ophthalmoplegia/proptosis without ptosis)

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(ie, using their hands and arms to stand up). Patients may be asked to perform a deep knee bend, rise from a squat or chair, climb stairs, run, or hop on one leg to detect subtle weakness.

Recording the time it takes to perform specific tasks (eg, climbing 10 steps, walking 30 feet, the modified Timed Up and Go test) is helpful,[19] especially in monitoring a functional response to therapy or in following the progression of the disorder. In MG, it is useful to measure and record the distance between the upper and lower eyelids and the time it takes for ptosis to appear after sustained upgaze.

Muscle tone should be assessed as normal, decreased, or increased. In most myopathies and neuromuscular junction disorders, muscle tone is usually normal or sometimes decreased. Patients with MG have normal reflexes, whereas patients with LEMS have diminished reflexes. During the early phases of

CASE 1-2

A 65-year-old woman presented for evaluation of a 7-year history of progressive dysphagia and weakness. She denied any diplopia and reported that her symptoms did not fluctuate during the day. She reported similar symptoms in family members, without definite diagnosis.

On examination, her cranial nerve testing showed bilateral ptosis, incomplete restriction of eye movements laterally, and mild bulbar weakness (orbicularis oris weakness and mild tongue weakness). Motor examination revealed mild proximal weakness with 4+/5 neck flexion and 4/5 shoulder abduction, 4+/5 elbow flexion, 5/5 finger extension, 4/5 hip flexion, 5/5 knee extension, and 5/5 ankle dorsiflexion and plantar flexion bilaterally. The rest of the neurologic examination, including sensory, cerebellar, and reflex examinations, was normal.

Her creatine kinase level was 300 U/L, and acetylcholine receptor antibody was negative. Nerve conduction studies were normal, EMG showed evidence of myopathic units in proximal muscles, and single-fiber EMG was normal.

COMMENT

The weakness pattern in this patient (ptosis, ophthalmoparesis, dysphagia, and proximal weakness) is consistent with a combination of muscle patterns 5 and 7 in **TABLE 1-2**. Ptosis with ophthalmoplegia but without diplopia may occur in oculopharyngeal dystrophy, mitochondrial myopathy, and centronuclear myopathy. Bulbar weakness may be seen in myasthenia gravis, Lambert-Eaton myasthenic syndrome, oculopharyngeal dystrophy, limb-girdle muscular dystrophy type 1A, myotonic dystrophy, and inclusion body myositis. The late age of onset and presence of a similar family history are most suggestive of a diagnosis of oculopharyngeal muscular dystrophy. The slowly progressive course of the condition and the absence of fatigability make a neuromuscular junction disorder a less likely etiology in this patient. A triplet repeat expansion (GCG) in the *PABPN1* gene causes mostly autosomal dominant oculopharyngeal muscular dystrophy. Targeted gene testing is appropriate in this case. Muscle biopsy would also confirm the diagnosis by demonstrating rimmed cytoplasmic vacuoles.

CASE 1-3

A 46-year-old right-handed man presented with persistent neck and lower back pain. He had initially been treated with conservative management and anti-inflammatory medications. After multiple tests to assess his symptoms, his primary care physician obtained a creatine kinase (CK) level, which was mildly elevated at 324 U/L. He was then referred to a neurologist for further workup.

The patient reported some right lower extremity weakness and atrophy. He attributed this to an old injury while playing soccer. He also reported some difficulty walking. He mentioned he had difficulty lifting his arms overhead and some inability to whistle for many years.

Examination revealed an asymmetric smile, minimal right lateral scapular winging, and a steppage gait. Atrophy of the right pectoralis major, trapezius, and gastrocnemius and of the tibialis anterior bilaterally was also noted. In addition to atrophy, he had weakness of orbicularis oculi and orbicularis oris bilaterally, right pectoralis major, tibialis anterior bilaterally, peroneus longus, gastrocnemius, and hamstrings, with slightly worse weakness in the right than the left leg.

Electrodiagnostic testing showed normal nerve conduction studies of the right arm and leg. However, EMG showed myopathic units and abnormal spontaneous activity in the form of fibrillation potentials and positive sharp waves in various muscles.

Given his clinical presentation and electrodiagnostic findings, facioscapulohumeral muscular dystrophy (FSHD) was suspected and genetic testing was ordered. It confirmed D4Z4 contraction in the subtelomeric region of chromosome 4q35, which causes marked hypomethylation. He was diagnosed with FSHD type 1.

COMMENT

The distribution of weakness is very important in making a clinical diagnosis. This patient had weakness in his facial and scapular muscles, consistent with muscle pattern 3 in **TABLE 1-2**. This is commonly caused by FSHD. The CK level may be mildly elevated or even normal in some of the muscular dystrophies, as seen in this patient. With the availability of genetic testing, muscle biopsy has become the second choice and is used if genetic testing is negative or indeterminate. Muscle biopsies can help resolve variants of uncertain significance, which are commonly found on multigene panels. In FSHD, some patients that do not harbor D4Z4 contraction may instead have FSHD type 2. FSHD type 2 shows digenic inheritance, requiring a mutation in the *SMCHD1* gene that results in D4Z4 chromatin relaxation and an FSHD-permissive DUX4 allele on chromosome 4.

myopathic disorders, reflexes are usually present. As the disease progresses, they may diminish or become unobtainable. Specific myopathies are associated with decreased or absent reflexes and may have a predilection for certain muscle groups. For example, the knee jerk is reduced early in the course of inclusion body myositis (IBM) when other reflexes are still relatively normal. On the other hand, certain reflexes appear to be spared even late in the course of some diseases (eg, ankle jerks are frequently present in patients with Duchenne muscular dystrophy despite severe generalized weakness). Plantar responses are usually normal in myopathies and neuromuscular junction disorders. Sensation to various modalities is usually normal with patients with muscle and neuromuscular junction disorders except for mild sensory symptoms and signs in LEMS and IBM.[20,21]

Examining children for a muscle or neuromuscular junction disorder can be difficult, especially infants. Neck extensor muscle weakness can be assessed in infants by holding them in a prone position and observing their ability to extend their head. Neck flexion weakness is observed by pulling infants from the supine to a sitting position using their arms. Infants' voice and fatigability of voice can be assessed by listening to them cry. Muscle weakness in infants is associated with an overall decrease in tone; therefore, the term *floppy infant* is used to describe them. It is important to also examine the parents of these children for a possible neuromuscular disorder. Weakness can transiently develop in 15% of infants born to mothers with MG.

In addition to taking the history and performing the neurologic examination, it is important to identify other organ involvement. Cardiac disease can be associated with a number of myopathies (TABLE 1-13), whereas respiratory involvement is seen not only in Pompe disease but also in many myopathies and neuromuscular junction disorders (TABLE 1-14).

KEY POINTS

- The 10 patterns of muscle involvement are an extremely valuable starting point to formulate the initial diagnoses and guide ordering of confirmatory tests.
- Family history and pattern of inheritance provide information for the efficient diagnosis of genetic conditions.
- Examination of children can be challenging in comparison with that of adults with neuromuscular disease. Examination of the parent may provide a valuable clue to the diagnosis (eg, grip myotonia in a mother of a hypotonic infant).
- Assessment for other organ involvement is important for diagnosis and prognosis of muscle and neuromuscular junction disorders.

Laboratory Testing

In patients in whom the diagnosis is still unclear after the history and examination, further testing is required.

MYOPATHIES. CK is the most useful blood test for myopathy evaluation. The normal level depends on the sex and race of the patient (TABLE 1-15).[22] Elevated CK may not be seen in all myopathies. The degree of muscle weakness in any given patient may not correlate with the serum CK level. Other enzymes that are routinely screened (eg, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase [LDH]) can also be elevated in muscle disorders. Many physicians initially suspect liver disease upon seeing an elevated AST, ALT, and LDH. However, AST, ALT, and LDH are expressed in muscle as well as the liver, and in the case of aldolase, it is elevated in hepatitis. To distinguish elevation of these enzymes due to liver disease versus a myopathic process, a serum CK and γ-glutamyltransferase (GGT) should be obtained. CK is specific for muscle disease, whereas GGT is specific for liver disease. Aldolase is selectively elevated, whereas CK is normal, in diseases that spare myofibers (eg, antisynthetase syndrome, dermatomyositis, and fasciitis) or involve myofiber regeneration (aldolase is first to be elevated) and in critical illness myopathy. However, aldolase is also increased with hepatitis, and CK/CK-myocardial band (MB) increase with stroke.

Electrolytes are also routinely tested in patients suspected of having a myopathy. Electrolyte disturbances such as high or low potassium levels and

calcium levels can cause generalized weakness. High or low thyroid hormone levels can cause myopathy; therefore, thyroid function tests should be obtained. Erythrocyte sedimentation rate and antinuclear antibody level should be obtained for patients suspected to have an inflammatory myopathy. Serum immunofixation is useful for evaluation of monoclonal gammopathy and acquired amyloidosis. With increased awareness of molecular genetics and availability of DNA testing, many hereditary myopathies can now be diagnosed, including various types of muscular dystrophies, mitochondrial myopathies, metabolic disorders, congenital myopathies, and hereditary forms of periodic paralysis.

NEUROMUSCULAR JUNCTION DISORDERS. Acetylcholine receptor antibodies, muscle-specific tyrosine kinase (MuSK) antibodies, low-density lipoprotein receptor–related protein 4 antibodies, and antibodies directed against the voltage-gated muscle calcium channel (in LEMS) can be assayed in patients with suspected neuromuscular junction disorders (CASE 1-4). Although these

TABLE 1-13 **Myopathies Associated With Cardiac Disease**

Arrhythmias

- **Andersen-Tawil syndrome**
- **Kearns-Sayre syndrome**
- **Polymyositis**
- **Sarcoid myopathy**
- **Muscular dystrophies**
  - Myotonic
  - Limb-girdle muscular dystrophy types 1B, 2C through 2G
  - Emery-Dreifuss muscular dystrophy

Congestive Heart Failure

- **Acid maltase deficiency**
- **Carnitine deficiency**
- **Muscular dystrophies**
  - Duchenne muscular dystrophy
  - Becker muscular dystrophy
  - Emery-Dreifuss muscular dystrophy
  - Myotonic dystrophy
  - Limb-girdle muscular dystrophy types 1B, 2C through 2G, and 2J
- **Nemaline myopathy**
- **Polymyositis**
- **Mitochondrial myopathy (hypertrophic cardiomyopathy)**
- **Myofibrillar myopathies**

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6] © 2006 American Academy of Neurology.

Muscle and Neuromuscular Junction Disorders With Respiratory Muscle Involvement

TABLE 1-14

Neuromuscular Junction Disorders

- **Myasthenia gravis**
- **Botulism**

Myopathies

- **Muscular dystrophies**
  - Becker muscular dystrophy
  - Duchenne muscular dystrophy
  - Congenital muscular dystrophy
  - Emery-Dreifuss muscular dystrophy
  - Limb-girdle muscular dystrophy types 2A and 2I
  - Myotonic dystrophy
- **Metabolic myopathies**
  - Acid maltase deficiency
  - Debrancher deficiency
- **Mitochondrial myopathies**
- **Congenital myopathies**
  - Centronuclear myopathy
  - Nemaline myopathy
- **Myofibrillar myopathy**
- **Critical illness myopathy**
- **Amyloid myopathy**
- **Inflammatory myopathies**

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6]

Effects of Race and Gender on Creatine Kinase Measurements[a]

TABLE 1-15

Group	Constituents	Upper Limit of Normal (U/L)
High	Black men	1201
Intermediate	Nonblack men	504
	Black women	621
Low	Nonblack women	325

[a] Modified with permission from Silvestri NJ, Wolfe GI, Muscle Nerve.[22]

CASE 1-4

A 30-year-old woman was seen in neurologic consultation after she developed limb weakness and difficulty breathing, chewing, and swallowing after the delivery of her second child. In retrospect, she reported intermittent weakness and fatigue with exertion for the past 2 years and difficulty breathing with activity for about a year. These symptoms improved with rest.

On examination, her palpebral fissures were normal at 10 mm. Mild to moderate orbicularis oculi and orbicularis oris muscle weakness was evident without any diplopia or ptosis. She had severe neck flexor and extensor muscle weakness. Her extremity strength testing revealed moderate fatigable weakness of the deltoid, triceps, and iliopsoas muscles. Sensation, reflexes, and gait were normal on examination. Forced vital capacity was 1.5 liters or 40% of predicted.

Laboratory testing was obtained, including acetylcholine receptor antibody binding titer (to confirm a previously negative titer obtained by the referring provider) and muscle-specific tyrosine kinase (MuSK) antibodies. While these tests were pending, EMG showed 1+ fibrillation potentials and myopathic motor unit potentials in the deltoid. Repetitive stimulation of the ulnar nerve was normal, but a 30% decrement in the spinal accessory nerve study and a 17% decrement in the facial nerve study were seen.

Based on the clinical presentation and electrophysiologic testing, a presumptive diagnosis of myasthenia gravis (MG) was made. She was started on pyridostigmine bromide 60 mg orally 3 times a day, prednisone 60 mg/d, and plasma exchange; she was later started on azathioprine. She improved significantly and was discharged home on prednisone, tapered 2 weeks later to 60 mg orally every other day.

At clinic follow-up, her acetylcholine receptor antibody binding titer returned negative, but her MuSK antibody test was positive. Chest CT showed no thymic abnormalities. Her final diagnosis was MuSK antibody–positive MG.

COMMENT

This case demonstrates a combination of features of muscle patterns 6 and 7 of **TABLE 1-2**, characteristic of one of the presenting phenotypes of MuSK MG. MuSK MG has a female predominance and prominent bulbar and respiratory weakness with proximal muscle weakness. Frequently, patients with MuSK MG either do not respond to or may even worsen after treatment with pyridostigmine. Although they may need more than one treatment, they ultimately do respond to plasma exchange or corticosteroids and, to a lesser extent, to IV immunoglobulin (IVIg) and other immunosuppressive medications. Case series suggest efficacy of B-cell depletion therapy with rituximab.

antibodies are quite specific, they are not 100% sensitive. A chest CT should be obtained in patients with MG to look for thymoma (present in 10%). A chest CT should also be obtained in patients with LEMS to look for small cell lung carcinoma.

Botulism is caused by a toxin produced by *Clostridium botulinum*. Ingestion of bacterial spores, colonization of the gut, and release of toxin leads to infantile botulism. Colonization of deep wounds, such as fractures or injection sites in people using drugs, leads to wound botulism. Botulism outbreaks have resulted from ingestion of the toxin from improperly cooked or canned foods. Serum and stool samples can be assayed for the toxin in suspected cases. Polymerase chain reaction (PCR) can identify the organism in biological specimens and food.

Electrodiagnostic Examination

Electrodiagnostic studies continue to be an important and established diagnostic tool for neuromuscular disorders, especially for muscle and neuromuscular junction disorders. In some cases, this may be the only confirmatory diagnostic testing to establish the correct diagnosis, (eg, in seronegative MG).

NERVE CONDUCTION STUDIES. Motor nerve conduction studies can be normal or may show low amplitudes in patients with myopathies or neuromuscular junction disorders, especially in LEMS, but sensory nerve conduction studies are normal in myopathies and neuromuscular junction diseases, with few exceptions such as in LEMS and IBM. A motor conduction study before and after 10 to 20 seconds of exercise may show significant increase of the amplitude in LEMS and botulism.

REPETITIVE STIMULATION. Repetitive stimulation studies are useful in distinguishing neuromuscular junction disorders (ie, botulism, LEMS, and MG) from myopathies, which they can resemble. In patients with MG, baseline motor responses are of normal amplitude. However, a decremental response is seen following slow rates (2 Hz to 3 Hz) of repetitive stimulation.[9] Ten seconds of exercise may correct this decrement (postexercise facilitation), while 1 minute of exercise will result in an increase of the decrement (postexercise exhaustion). However, decrement may be seen in some cases of centronuclear myopathy.

In botulism and LEMS, the baseline motor amplitudes are low. Decrement may be seen following low rates of repetitive stimulation.[23,24] An incremental response may be seen following fast rates of repetitive stimulation (20 Hz to 50 Hz). Fast repetitive stimulation is a painful procedure and is rarely necessary because 10 to 20 seconds of exercise can usually reproduce a significant increase in amplitude from baseline in these disorders.

NEEDLE EMG. Needle EMG is a useful test for diagnosing neuromuscular conditions. Evaluation of multiple proximal and distal arm, leg, paraspinal, and even cranial nerve-innervated muscles may be necessary, especially in mild disease conditions. The first part of EMG testing includes assessment for abnormal insertional and spontaneous activity. The second part looks at the motor unit action potential (MUAP) duration, amplitude, morphology, and recruitment. Small amplitude and duration of MUAPs point to a diagnosis of myopathy. Electrodiagnostic medicine consultants can usually determine the

presence of myopathy on this testing. Quantitative EMG may be required for diagnosis of some difficult cases.

In patients with normal repetitive nerve stimulation for suspected MG, single-fiber EMG is useful in diagnosis.[9] Single-fiber EMG measures the "jitter" between two single muscle fibers belonging to the same motor unit. Although jitter analysis is sensitive for MG diagnosis, it is not specific as it can be seen in other conditions that remodel the neuromuscular junction (eg, motor neuron disease, neuropathies, necrotizing myopathies).

Histologic Evaluation

In general, many patients with a myopathy will require a muscle biopsy, particularly for acquired diseases but for hereditary disorders only when gene testing is negative or equivocal. The clinical examination, laboratory workup, and electrophysiologic studies may indicate a myopathy is present but usually do not indicate the exact type of myopathy. In some scenarios, the clinical phenotype, in combination with the appropriate laboratory and electrophysiologic studies, allows diagnosis without need for a biopsy (eg, myotonic dystrophy), especially with the increasing availability of genetic testing.

Although muscle histopathologic evaluation is being slowly replaced by gene testing for hereditary disorders, it still is the cornerstone of the evaluation of the idiopathic inflammatory myopathies. Two types of muscle biopsies can be conducted: open and needle. With open muscle biopsies, several large samples can be obtained and processed for routine histochemical stains. In some cases,

TABLE 1-16 **Utility of Muscle Biopsy Stains and Histochemical Reactions**[a]

Histochemical Reactions and Stains	Clinical Utility
ATPase	Distribution of fiber types
Gomori trichrome	General histology and mitochondrial disease
Hematoxylin and eosin (H&E)	General histology
Nicotinamide adenine dinucleotide (NADH), succinate dehydrogenase, cytochrome oxidase	Myofibrillar and mitochondrial abnormalities
Oil red O	Lipid storage disease
Periodic acid-Schiff	Glycogen and lysosomal storage disease
Congo red, crystal violet	Detection of amyloid deposition
Myophosphorylase	McArdle disease
Phosphofructokinase	Phosphofructokinase deficiency
Myoadenylate deaminase	Myoadenylate deaminase deficiency
Dysferlin immunostaining	Limb-girdle muscular dystrophy type 2B
Membrane attack complex immunostaining	Dermatomyositis

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6] © 2006 American Academy of Neurology.

immunostains to specific muscle targets may be done; in other cases, protein analysis (Western blot), metabolic analysis, or even electron microscopy may be conducted. With needle muscle biopsies, individual samples sizes are small, but many more areas of potentially affected muscle tissue can be accessed via smaller incisions. Open muscle biopsies are useful for multifocal processes, such as inflammatory myopathies[13] and myopathic disorders that require electron microscopy for confirming a diagnosis. In chronic myopathies, a mildly weak muscle (grade 4) should be selected for biopsy. In a weak muscle with a grade of less than 3, the tissue may show end-stage muscle disease, making it difficult to distinguish a myopathic disorder from severe neurogenic atrophy. Needle EMG or muscle MRI can be helpful in selecting the muscle to biopsy in patients with mild muscle weakness. If affected, the biceps brachii is the best muscle to biopsy, followed by the quadriceps and possibly the deltoid. The gastrocnemius is usually avoided because of the neurogenic changes that can be seen in this muscle related to radiculopathy.

Light microscopy is used routinely for analysis. Biochemical assays on the biopsy specimens are useful for various enzyme deficiencies (eg, glycogen and lipid storage diseases). Western blot is useful for specific protein abnormalities (eg, dystrophin) and DNA analysis for genetic mutations (eg, mitochondrial myopathies) (TABLE 1-16). Congo red or crystal violet staining is used to detect amyloid deposition. Immunostaining techniques are employed for the diagnosis of specific muscular dystrophies (eg, dystrophin staining for Duchenne muscular dystrophy and Becker muscular dystrophy, merosin staining for congenital muscular dystrophy, sarcoglycan stains for limb-girdle muscular dystrophies, emerin stain for Emery-Dreifuss muscular dystrophy). Immunostaining has made it possible for early diagnosis and understanding of the pathogenesis of the different inflammatory myopathies and vasculitis (eg, stains for complement, membrane attack complex, immunoglobulins, common leukocyte antigens, and inflammatory cell surface markers). Detailed evaluation of the ultrastructural components of muscle fibers can be performed using electron microscopy.

Molecular Genetic Studies

Peripheral blood testing and saliva DNA analysis have been useful to identify mutations that are associated with hereditary muscle diseases. Many specific molecular genetic defects associated with muscle diseases have been identified in recent years. Examples of commonly available genetic studies for muscle and neuromuscular junction disorders are included in TABLE 1-17; it is important to emphasize that the list of available gene tests is constantly evolving and being updated.

Many inherited disorders and phenotypes are genetically heterogeneous (ie, pathogenic variants in more than one gene can cause the same phenotype). Before the development of massively parallel sequencing (next-generation sequencing[25]), the only cost-effective way to test more than one gene was serial single-gene testing, which was expensive and time consuming, with a low yield of 15% to 19%. In the past few years, improvements in massively parallel sequencing techniques have led to the widespread clinical use of multigene panels that allow testing of more than 150 genes. These panels include sequence analysis, deletion/duplication analysis, and other non–sequencing-based panels and have a yield of 46%. Multigene panels can be of two types. In the first, the panel of genes is already included based on the broad phenotype (eg, a

KEY POINTS

- Muscle biopsies are mostly useful for acquired myopathies and hereditary myopathies with negative genetic testing or with variants of unknown significance.
- Needle EMG or MRI can be used to identify the most useful muscle site to biopsy.
- Commercial genetic testing has significantly improved in recent years with increased efficiency and reduced cost.

cardiomyopathy panel); the second type is custom designed, so the physician chooses the genes he or she would like to be tested.

Next-generation sequencing is a DNA sequencing technology in which an entire human genome can be sequenced within a day. This is used to sequence many fragments of DNA at the same time, and special computer techniques are used to put together these DNA fragments by mapping the individual reads to the human reference genome. Accurate data and insight into unexpected DNA variation can be obtained. It is useful to sequence the entire genome, the specific area of interest, and small numbers of individual genes to capture a broader spectrum of mutations. Next-generation sequencing is unselective and is used to interrogate full genomes or exomes to discover entirely novel mutations and disease-causing genes. Next-generation sequencing also allows detection of mosaic mutations acquired as postfertilization events. The main disadvantages are the infrastructure, computer capacity and storage, and expertise required to analyze and interpret the data. Significant numbers of variants of uncertain significance are identified during the sequencing as this is the most common finding. The variants can be benign, having no impact on the health or function

TABLE 1-17

Muscle and Neuromuscular Junction Disorders With Commercially Available Molecular Genetic Studies[a]

Neuromuscular Junction Disorders

- Congenital myasthenic syndrome (*DOK7*, *COLQ*, *SCN4A*, *GFPT1*, *CHRNE*, *CHRNA1*, *CHAT*)

Muscle Disorders

- Chronic progressive external ophthalmoplegia (*POLG*, *TWINK*, *SLC25A4*, *OPA1*)
- Collagen VI disorders (*COL6A1*, *COL6A2*, *COLA63*)
- Congenital muscular dystrophy (*FKRP*, *FKTN*, *LAMA2*, *POMGNT1*, *POMT1*, *POMT2*)
- Duchenne muscular dystrophy and Becker muscular dystrophy (*DMD* sequencing)
- Emery-Dreifuss muscular dystrophy (*EMD*, *FHL1*)
- Facioscapulohumeral muscular dystrophy (*FSHD1*, *FSHD2*)
- Periodic paralysis (*CACNA1S*, *KCNJ2*, *RYR1*, *SCN4A*)
- Limb-girdle muscular dystrophy (*ANO5*, *CAPN3*, *CAV3*, *CRPPA*, *DAG1*, *DES*, *DMD*, *DNAJB6*, *DYSF*, *FKRP*, *FKTN*, *GAA*, *GMPPB*, LMNA, MYOT, PLEC, *PNPLA2*, *POMGNT1*, *POMK*, *POMT1*, *POMT2*, *SGCA*, *SGCB*, *SGCD*, *SGCG*, *TCAP*, *TNPO3*, *TOR1AIP1*, *TRAPPC11*, *TRIM32*, *TTN*)
- Mitochondrial myopathy, including myoclonic epilepsy with ragged red fibers (MERRF) and mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) (*A8344G* [frequent], *G8361A*, *G8363A*, *MELAS*, *POLG, T8356C, etc*)
- Myotonic dystrophy (*CNBP*, *DMPK*)
- Myofibrillar myopathy (*BAG3*, *CRYAB*, *DES*, *DNAJB6*, *FHL1*, *FLNC*, *LDB3*, *MYOT*)
- Myotubular myopathy (*MTM1* mutations)
- Nemaline myopathy (*ACTA1*, *CFL2*, *KBTBD13*, *KLHL40*, *KLHL41*, *LMOD3*, *MYPN*, *NEB*, *TNNT1*, *TPM2*, *TPM3*)
- Oculopharyngeal muscular dystrophy (*PABPN1*)

[a] Updated from Jackson CE, Continuum (Minneap Minn).[6] © 2006 American Academy of Neurology.

of an organism, or they can be pathogenic (ie, associated with the disease). Genetic counseling is offered in many clinics and by companies that perform genetic testing to assist patients and ordering physicians with understanding the results of the testing. Evaluating the frequency of a variant of uncertain significance in the general population, whether it induced a missense or nonsense mutation, and its known and modeled effects on the gene product are helpful clues to triage variants of uncertain significance as benign or disease causing. Equally important are correlation with patient phenotype and investigating healthy and affected relatives regarding segregation of the variant of uncertain significance with a phenotype. Additional novel methods for measuring the gene products in situ are available on a research basis.

The resolution of variants of uncertain significance requires intense work and coordination between the testing laboratory and the requesting clinician so that a variant of uncertain significance can be truly and reliably classified as a benign or disease-causing variant.

More comprehensive genomic testing includes several methods, one of which is whole-exome sequencing. Whole-exome sequencing is used to identify and analyze the sequence of all protein-coding nuclear genes in the genome. Approximately 95% of the exome can be sequenced with currently available techniques. With whole-exome sequencing, diagnostic utility for neuromuscular disease is about 37%, which is lower than the 46% yield of multigene panels. Many reasons exist for why whole-exome testing has a lower yield than multigene panels. Whole-exome testing would miss copy number variation (as in two-thirds of Duchenne muscular dystrophy cases that harbor deletions), large truncations (as in FSHD), and repeat sequences (as in myotonic dystrophy), thereby detecting only 11% of the three most common muscular dystrophies. Combined approaches in gene testing are reducing that gap in Duchenne muscular dystrophy.

Whole-genome sequencing is a laboratory test designed to identify and analyze the sequence of all coding and noncoding nuclear DNA. Mitochondrial DNA is part of the genome; however, mitochondrial sequencing is often ordered as a separate laboratory test. This is more expensive than whole-exome sequencing, and the diagnostic utility is disappointing compared to that of whole-exome sequencing, despite the identification of additional variants outside the coding region.

Chromosomal microarray is a molecular genetic test that is used to detect copy number variations, which are deletions (loss) or duplications (gain) of chromosome material that range in size from approximately one kilobase to multiple megabases, with the largest copy number variation resulting in a loss or gain of an entire chromosome. Copy number variations may be benign, pathogenic, or of uncertain significance.

While on the surface, it seems that muscle biopsies should become obsolete with advances in genetics, the facts are contrary to that. Indeed, muscle biopsies are critically important to triage the numerous variants of uncertain significance. One approach for resolution is to examine enough family members, both affected and unaffected. This approach is logistically complicated and inefficient. With the help of muscle histopathology, variants of uncertain significance can be easily and reliably triaged as either benign or disease causing, thereby aiding in the diagnosis and advancing our knowledge of the pathogenicity of these genetic alterations.

KEY POINT

- **Despite genetic testing becoming more readily available and affordable, the resolution of variants of uncertain significance requires the implementation of a careful and thoughtful pattern approach, support from electrophysiology, and muscle biopsy.**

CONCLUSION

The pattern recognition approach to myopathy can be extremely helpful in narrowing the differential diagnosis, thus minimizing the number of laboratory studies needed to confirm the diagnosis. While this approach will help with recognizing the majority of muscle and neuromuscular junction disorders, limitations exist, and some patients may not fit into any of the patterns. In addition, certain neuropathies or motor neuron diseases may present similarly to these patterns. Along with recognition of the patterns, the patient's history is useful to determine the diagnosis. Muscle biopsy is helpful not only in the inflammatory myopathies but also in genetic dystrophies in which variants of uncertain significance require resolution or when genetic testing is unrevealing.

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