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An Approach to Myopathy for the Primary Care Clinician

Rose M. Domingo-Horne, MD, Mohammad Kian Salajegheh, MD

VA Boston Healthcare System, Neurology Service/Division of Neuromuscular Medicine, Harvard Medical School, Boston, Mass.

ABSTRACT

Patients with muscle weakness are frequently encountered in the primary care clinic; however, the identification of an underlying disorder of muscle can pose a significant challenge. The aim of this review article is to provide a clinical and diagnostic framework to aid the primary care clinician in the detection and evaluation of suspected myopathies.

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INTRODUCTION

Myopathies are a heterogeneous collection of disorders characterized by the abnormal structure or functioning of skeletal muscle. Such disorders are frequently encountered in primary care practices; however, the recognition and diagnosis of these conditions can be challenging. In this review, we will discuss the symptoms and signs that may alert practitioners to the possibility of underlying muscle disease, as well as the basic elements of an appropriate diagnostic workup, and when to refer to a specialist.

SYMPTOMS

As with most neurologic disorders, the diagnosis of myopathy begins with taking a careful and thorough history. Patients often report symptoms of fatigue, exercise intolerance, generalized weakness, and muscle pain; however, these symptoms are relatively nonspecific and may reflect nonmyopathic conditions, including cardiopulmonary disorders, orthopedic conditions, rheumatologic diseases, medication use, deconditioning, and even depression. In contrast, symptoms that should raise suspicions of an underlying myopathy include discrete patterns of muscle weakness, fatigable weakness, muscle atrophy, myotonia, and recurrent myoglobinuria.[1]

The evaluation of a patient with suspected myopathy should include a discussion of the duration of symptoms and history—including developmental and early childhood history—as well as a family history of similar symptoms or diagnosed myopathy. Certain congenital, metabolic, and mitochondrial myopathies may present at birth or in early childhood, with such issues as failure to thrive, delayed motor milestones, and contractures, whereas other hereditary and acquired myopathies may not present until adolescence or adulthood. Inflammatory myopathies such as polymyositis and dermatomyositis may occur at any age, whereas inclusion body myositis often presents in late adulthood.

A discussion regarding the tempo of symptom onset and progression, as well as any provoking or exacerbating factors, may also provide diagnostic clues when evaluating patients with presumed muscle disease. For example, patients reporting the onset of symptoms after the initiation of a lipid-lowering therapy may be experiencing an acquired medication-induced myopathy, whereas those with symptoms after a carbohydrate-rich meal may have a periodic paralysis. For patients who describe a family history of disease, one should attempt to determine an inheritance pattern, because this can help guide future genetic testing and counseling.

SIGNS: PATTERNS OF WEAKNESS AND A HEAD-TO-TOE APPROACH

It is critical for clinicians to determine the pattern and distribution of deficits in patients with muscle weakness. Ten

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Requests for reprints should be addressed to Mohammad Kian Salajegheh, MD, VA Boston Healthcare System, Neurology Service/Division of Neuromuscular Medicine, Harvard Medical School, 150 S. Huntington Avenue, Boston, MA 02130.

E-mail address: Mohammad.Salajegheh@va.gov

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basic patterns of muscle weakness have been described by Barohn and colleagues,[2] most recently in 2014, and have been taught to countless medical trainees and practicing physicians. Despite broad advancements in specialized testing over the years, the ability of the clinician to recognize and categorize patients by these basic patterns of weakness can greatly improve diagnostic accuracy with less, or more targeted, ancillary testing.

Fixed weakness of the proximal limb-girdle musculature is the most common, and therefore least specific, pattern of weakness in patients with underlying myopathies, such as limb girdle muscular dystrophies and acquired myopathies. Patients with limb-girdle weakness of the upper extremities may describe difficulties in raising their arms up to lift objects overhead, whereas those with proximal weakness of the lower limbs may describe difficulty arising from a chair without pushing off with their arms.

Intermittent or fatigable weakness may predominate in metabolic myopathies, periodic paralyses, or other neuromuscular conditions (eg, myasthenia gravis), with return to near-normal strength levels between episodes. Episodic symptoms with muscle pain, weakness, and myoglobinuria may also be experienced by patients without myopathy in the setting of exercise.

Distal-predominant weakness can occur in various distal myopathies, metabolic myopathies, congenital myopathies, and myotonic and muscular dystrophies; however, more commonly it may be a sign of a length-dependent polyneuropathy (particularly when there are coexisting sensory symptoms and deficits).

A scapuloperoneal distribution of weakness, affecting the proximal arms and distal legs, may be appreciated in patients with facioscapulohumeral muscular dystrophy and other hereditary myopathies, and may be associated with scapular winging.

The pattern of distal arm and proximal leg weakness is uncommon in general in cases of myopathy, but is pathognomonic for inclusion body myositis, particularly when asymmetrical and involving deep finger flexors.

Patients with weakness of the cranial-innervated musculature may present with ptosis, ophthalmoplegia, dysarthria, and dysphagia. Certain combinations of these features should concern clinicians for the possibility of an underlying myopathy, such as oculopharyngeal muscular dystrophy, or myotonic dystrophy, but may also herald other neuromuscular conditions, including myasthenia gravis and motor neuron disease (which may also mimic myopathy when prominent neck extensor weakness is evident). Patients who experience defective muscle relaxation may have a hereditary condition, such as myotonia, paramyotonia, or myotonic dystrophy.

Associated systemic symptoms, such as cardiopulmonary disease, dysmorphic features, and cognitive impairment, may also help clinicians in determining an underlying cause for myopathy or may aid in the diagnosis of a nonmyopathic condition.

Muscle power can be tested manually or by observation of functional ability in patients who are unable to cooperate with formal examination or in those who demonstrate intermittent voluntary activation on strength testing. It is important for the clinician to grade the strength of cranial-innervated, proximal, and distal limb musculature in a systematic manner so that future intra-rater and inter-rater comparative assessments are considered reliable.

Clinicians often develop their own methods for examination over time, and there is no "right way" to conduct a neurologic assessment, provided that the key components are included in an efficient, focused manner that maximizes diagnostic yield and minimizes patient discomfort. In our practice, we tend to take a "head-to-toe" approach to strength testing, evaluating for patterns of weakness that may help to narrow down a differential diagnosis of disease or exonerate a primary muscle disorder as a cause for symptoms (**Table 1**).

Several different hereditary and acquired forms of muscle disease that may be of importance to the primary care clinician are listed in **Tables 2 and 3**; however, an exhaustive discussion of these disorders is beyond the scope of this review (please refer to the Reference list for additional recommended readings).[3-11]

CLINICAL SIGNIFICANCE

- Myopathies are a broad and heterogeneous collection of diseases frequently encountered in primary care practices.
- The detection and diagnosis of muscle disorders require a high level of clinical suspicion and the recognition of various patterns of weakness.
- Supplemental laboratory, electrodiagnostic, genetic, and histopathologic testing can aid in the diagnosis of myopathy.
- Early referral to a neuromuscular medicine specialist should be considered when evaluating patients with suspected muscle disease.

LABORATORY TESTING

The creatine kinase level is the most useful initial laboratory study in the evaluation of the patient with suspected myopathy; however, it is important to recognize that it may be normal in patients with myopathy (eg, those with slowly progressive conditions, those with profound muscle atrophy, or those using corticosteroid therapy) and may be elevated in those without myopathy (eg, after heavy physical exertion or in patients with endocrinopathies, such as hypothyroidism).[1,2] The degree to which a creatine kinase level is elevated may provide a clue to its clinical significance (eg, a marked, sustained creatine kinase elevation would be expected in untreated polymyositis, whereas a transient, minor elevation may be expected after an electromyogram or other muscle trauma). Certain ethnic and

Table 1 Head-to-Toe Approach to Strength Testing

Body Segment	Motor Assessment
Cranial-Innervated Musculature	Listening for speech quality/dysarthria
	Inspection for ptosis
	Eyelid closure/ability to bury lashes
	Eye movements
	Mouth closure/ability to smile/puff out cheeks
	Ability to whistle/drink from a straw
	Lateral tongue movements against resistance
	Palatal elevation
	Ability to swallow
	Inspection for accessory respiratory muscle use
	Inspection for facial/tongue fasciculations
	Inspection for muscle atrophy
Cervical-Innervated Musculature	Neck flexion/extension
	Shoulder abduction/rotation
	Inspection for scapular winging
	Arm flexion/extension
	Wrist flexion/extension
	Finger flexion/extension
	Finger abduction/adduction
	Grip strength
	Inspection for grip myotonia
	Inspection for accessory respiratory muscle use
	Inspection for upper limb fasciculations
	Inspection for muscle atrophy
Thoracic-Innervated Musculature	Inspection for scoliosis
	Ability to sit upright
	Inspection for accessory respiratory muscle use
	Inspection for truncal fasciculations
	Inspection for muscle atrophy
Lumbar-Innervated Musculature	Ability to stand from a seated position without arms
	Ability to arise from a low squat
	Inspection for Gower sign
	Ability to climb and descend stairs
	Hip flexion/extension
	Hip abduction/adduction
	Leg flexion/extension
	Ankle dorsiflexion/plantar flexion
	Ankle inversion/eversion
	Ability to ambulate
	Ability to walk on toes and heels
	Inspection for lower limb fasciculations
	Inspection for muscle atrophy/(pseudo)hypertrophy

demographic groups are also prone to creatine kinase levels at the upper end or in excess of "normal" laboratory ranges, in the absence of a myopathy, including African Americans and military recruits.[12,13] Therefore, laboratory values should be interpreted on an individual basis and correlated clinically. In general, patients with nonspecific symptoms, a normal neurologic examination, and normal-to-mildly elevated creatine kinase levels (up to 3× normal) are less likely to have an underlying myopathy.

Less useful serologic tests for myopathy include aldolase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and gamma glutamic transferase (when attempting to differentiate between muscle and liver pathology). Creatine kinase isoenzymes are not considered helpful when evaluating patients with suspected myopathy. Additional laboratory studies that may be considered in the evaluation of the patient with myopathy, as well as to exclude other systemic conditions, include serum electrolytes, thyroid function tests, inflammatory markers, immunologic markers, human immunodeficiency virus testing, and urinalysis.[1,2]

A SPECIAL WORD ON STATINS

Certain medications are known to cause creatine kinase elevations and may predispose one to the development of an iatrogenic myopathy.[14] Perhaps most recognized among these myotoxic medications in recent years are the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins). The development of a toxic myopathy in the setting of statin use has been well described in the literature and may include the development of myalgias, creatine kinase elevations, muscle weakness, and rhabdomyolysis (which can, in rare instances, be fatal).[15] Generally, these symptoms are relatively mild and may reverse with discontinuation of the offending agent. In patients without rhabdomyolysis, a rechallenge with a less myotoxic statin, once the symptoms of myopathy resolve, can be successful.[16] However, a small subgroup of patients exposed to statins may go on to develop an hydroxymethylglutaryl-coenzyme A receptor antibody-mediated necrotizing myopathy,[17,18] similar to the necrotizing myopathy uncommonly experienced by patients with connective tissue disorders or paraneoplastic syndromes. The incidence of statin-induced autoimmune necrotizing myopathy is estimated to be 2 cases per million per year.[18] Such a condition, although rare, should be considered and more fully evaluated by muscle biopsy in patients who develop marked creatine kinase elevations and muscle weakness that persist beyond the discontinuation of a statin, because treatment with immunosuppression may be indicated.[19,20]

ELECTRODIAGNOSTIC TESTING

An electromyogram should be considered in all patients with suspected myopathy. Nerve conduction studies are typically normal in cases of myopathy, and they are useful in that they can exclude a coexisting or mimicking neuromuscular condition, such as neuropathy or a disorder of neuromuscular junction transmission. The needle electrode portion of the examination can confirm the presence of a myopathy when low-amplitude, brief-duration, polyphasic motor units with early recruitment are appreciated and can confirm electrical myotonia. It can also be used as an extension of the clinical neurologic examination to determine which muscles are best

suited for biopsy, if indicated. Motor neuron disease, which in certain cases can mimic myopathy, can be tested for and excluded by a needle electrode examination. In certain patients with myopathy, an electromyogram study may be unrevealing.

MUSCLE BIOPSY

Muscle biopsy is thought of as the cornerstone for diagnosing myopathies. Other than in patients in whom the cause is clear from the initial evaluation (e.g., presence of a myotoxic agent or hyperthyroidism), a muscle biopsy may be necessary. In

Table 2 Hereditary Myopathies

Category	Distinguishing Features
Congenital myopathies	• Genotypically and phenotypically diverse • Generalized or proximal-predominant weakness • May be associated with dysmorphisms • Cardiorespiratory weakness • Characteristic myofiber abnormalities
Muscular dystrophies	
Dystrophinopathies	• Proximal-predominant weakness, calf pseudohypertrophy • Motor delays or regression, loss of ambulation • Cardiorespiratory weakness • CK markedly elevated • Abnormal muscle dystrophin immunostaining • Supportive therapies include corticosteroids, gene therapy
Limb-Girdle Muscular Dystrophy	• Genotypically and phenotypically diverse • Proximal-predominant weakness; distal-predominant in some • May be associated with scapular winging, contractures, myalgias, calf hypertrophy, cardiomyopathy • Inflammatory biopsy features may be mistaken for polymyositis • Abnormal protein expression on immunostaining
Congenital Muscular Dystrophy	• Genotypically and phenotypically diverse • Generalized weakness, motor delays • May be associated with contractures, calf hypertrophy, respiratory weakness, central/peripheral dysmyelination, mental retardation, seizures, optic atrophy • Inflammatory biopsy features may be mistaken for polymyositis
Facioscapulohumeral Muscular Dystrophy	• Facial weakness, scapular winging, biceps and triceps weakness; often asymmetric • Peroneal-distribution weakness with foot drop in some • Inflammatory biopsy features may be mistaken for polymyositis
Oculopharyngeal Muscular Dystrophy	• Ptosis and extraocular muscle weakness without diplopia • Facial weakness, dysphonia, dysphagia • Neck and limb weakness may occur • Rimmed vacuoles similar to inclusion body myopathy may be seen
Emery–Dreifuss Muscular Dystrophy	• Humeroperoneal-predominant weakness • Early contractures, spine rigidity, pes cavus deformities • Often associated with cardiomyopathy, conduction defects
Distal myopathy	• Genotypically diverse • Distal-predominant weakness; often presents with foot drop • Limb-girdle distribution weakness, cardiomyopathy may occur • Rimmed vacuoles similar to inclusion body myopathy may be seen • Some overlap with myofibrillar myopathy
Myofibrillar myopathy	• Genotypically and phenotypically diverse • May be associated with cardiomyopathy, spine rigidity, neuropathy, smooth muscle involvement (intestinal pseudo-obstruction) • Spectrum of histologic abnormalities • Rimmed vacuoles similar to inclusion body myopathy may be seen
Hereditary inclusion body myopathy	• Genotypically and phenotypically diverse • May be associated with respiratory weakness, Paget disease of bone, frontotemporal dementia, arthrogryposis, ophthalmoparesis, cerebral hypomyelination • Differentiated from sporadic inclusion body myositis by earlier age at onset, variable distribution of weakness, lack of endomysial inflammation on muscle biopsy

Table 2 Continued

Category	Distinguishing Features
Metabolic myopathies	
Disorders of carbohydrate metabolism	• Genotypically and phenotypically diverse • Motor examination may be normal between attacks; "second wind" in some • May be associated with exertional myalgias, rhabdomyolysis, cardiorespiratory involvement, central nervous system disturbances • Forearm exercise testing can help distinguish among types • Biochemical assays demonstrate enzyme deficiencies • Glycogen-containing vacuoles present in myofibers • Supportive therapies include enzyme replacement, frequent low carbohydrate/high protein meals, aerobic conditioning
Disorders of lipid metabolism	• Genotypically and phenotypically diverse • Motor examination may be normal between attacks • May be associated with exertional myalgias, rhabdomyolysis, nonketotic hypoglycemia, aciduria, cardiorespiratory involvement, encephalopathy • Forearm exercise testing should be normal • Lipid-containing vacuoles present in myofibers • Supportive therapies include carnitine, frequent low fat/high protein meals, avoidance of fasting/cold/prolonged strenuous activity
Mitochondrial myopathies	• Genotypically and phenotypically diverse • Multisystemic disorders also affecting cardiac, respiratory, endocrine, ophthalmologic, gastrointestinal, central nervous systems • Ragged red fibers and abnormal oxidative enzyme staining; ultrastructural mitochondrial abnormalities may be seen
Muscle channelopathies	• Genotypically diverse • Characterized by clinical or electrical myotonia and/or episodic weakness in the absence of muscle dystrophy • Motor examination may be normal between attacks; progressive proximal weakness may occur • Cardiac manifestations, arrhythmias, developmental abnormalities possible in some • Myotonia generally improves with repeated muscle contraction ("warm-up" phenomenon), but can worsen in certain forms • Changes in ambient temperature or diet may worsen myotonia • Long and short exercise nerve conduction testing may aid diagnosis • Treatment includes antiarrhythmics and antiepileptics for myotonia and acetazolamide and dichlorphenamide for periodic paralysis • Supportive therapies include avoidance of dietary/environmental triggers
Myotonic dystrophies	
Myotonic dystrophy type 1 (DM1) Myotonic dystrophy type 2 (DM2)	• Genotypically and phenotypically diverse; anticipation in DM1 but not DM2 • Multisystemic disorders also affecting cardiac, respiratory, endocrine, ophthalmologic, reproductive, gastrointestinal (in DM1) systems • May be associated with cognitive impairment, neurobehavioral abnormalities • DM1: facial and distal-predominant limb weakness, atrophy, myotonia • DM2: progressive proximal and distal limb weakness, atrophy, myotonia

CK = creatine kinase; DM = myotonic dystrophy.

addition to determining the presence of an inflammatory myopathy (that would necessitate the use of immunomodulatory medication), it may, in some cases, demonstrate features that would help in the diagnosis of specific hereditary forms. Neuromuscular specialists can assist in guiding surgeons and neuropathologists before biopsy, both in regard to the most appropriate sites for biopsy and any special preparations, stains, or techniques that may be needed for a specific histologic diagnosis.

OTHER DIAGNOSTIC TESTS

Muscle imaging with T1-weighted and fat-suppressed T2-weighted or short-tau inversion–recovery images may help in determining the presence of myopathy and its pattern. Genetic testing is key for the definitive diagnosis of hereditary myopathies. The most cost-effective way is to determine the gene(s) to be tested using clinical and electrodiagnostic features, as well as muscle biopsy findings. With the advent of next-generation sequencing becoming more affordable, more

Table 3 Acquired Myopathies

Category	Distinguishing Features
Idiopathic inflammatory myopathies	
Polymyositis	• Proximal-predominant weakness; dysphagia in some • May be associated with connective tissue disease, myocarditis, interstitial lung disease, malignancy • CK markedly elevated; may also have elevation in ANA, myositis-specific antibodies • Endomysial inflammation on biopsy, often with invasion of non-necrotic muscle fibers • Treatment with immunosuppressive therapies
Dermatomyositis	• Proximal-predominant weakness; dysarthria, dysphagia in some • May be associated with connective tissue disease, myocarditis, interstitial lung disease, vasculitis, malignancy (screening is imperative) • Pathognomonic skin manifestations include heliotrope rash, Gottron papules, shawl sign (absence does not preclude diagnosis) • CK may be markedly elevated; may also have elevation in ANA, myositis-specific antibodies • Perifascicular atrophy, perivascular inflammation on biopsy • Treatment with immunosuppressive therapies
Inclusion body myositis	• Weakness of wrist and deep finger flexors, knee extensors, ankle dorsiflexors; often asymmetric • Dysphagia • May be associated with autoimmune disease • Endomysial inflammation, rimmed vacuoles containing amyloid, TDP43 or P62 on muscle biopsy • Lack of response to treatment with immunosuppressive agents
Myopathies in systemic disease	
Thyrotoxic myopathy	• Proximal-predominant weakness; distal-predominant in some • Extraocular muscle and bulbar involvement in Graves' disease • Brisk deep tendon reflexes, fasciculations, myokymia possible • Myasthenia gravis (in association with Graves' disease) or thyrotoxic (hypokalemic) periodic paralysis may develop
Hypothyroid myopathy	• Proximal-predominant weakness • Delayed relaxation of deep tendon reflexes possible • Myasthenia gravis may be associated
Steroid myopathy	• Proximal-predominant weakness • Cushingoid appearance • May develop from pituitary/adrenal tumor or iatrogenic source • EMG needle electrode examination generally normal and can help differentiate steroid-induced from other forms of myopathy • Predominant type 2B fiber atrophy on biopsy
Critical illness myopathy	• Generalized weakness; respiratory muscle involvement • Atrophic and necrotic muscle fibers; absence of myosin thick filaments on biopsy • Corticosteroids (increase the risk)
Amyloid myopathy	• Proximal-predominant weakness; macroglossia may occur • Can occur in primary or familial amyloidosis; multisystemic disorders also affecting cardiac, renal, and other organ systems • May be associated with polyneuropathy, entrapment neuropathies • Endomysial, perimysial, epineurial, vascular amyloid deposition
Toxic myopathies	
Necrotizing myopathy	• Proximal-predominant weakness • CK may be markedly elevated • Necrotic muscle fibers with inflammation limited to them (no evidence of endomysial inflammatory cell infiltrate invading non-necrotic muscle fibers to be differentiated from polymyositis) • Causes include: HMG-CoA reductase inhibitors, other lipid-lowering agents, cyclosporine
Amphiphilic drug myopathy	• Generalized or proximal-predominant weakness • May be associated with neuropathy ("neuromyopathy") • Autophagic vacuoles and inclusions on muscle/nerve biopsies • Causes include chloroquine, hydroxychloroquine, amiodarone

Table 3 Continued

Category	Distinguishing Features
Antimicrotubular myopathy	• Proximal-predominant weakness • May be associated with neuropathy ("neuromyopathy"), clinical myotonia • Autophagic vacuoles and inclusions on muscle biopsy; axonal degeneration on nerve biopsy • Causes include colchicine, vincristine (mostly neuropathy)
Drug-induced mitochondrial myopathy	• Proximal-predominant weakness • CK normal to mildly elevated (marked elevation more likely to be related to HIV-associated myositis) • Ragged red fibers on muscle biopsy without significant endomysial inflammation • Causes include: zidovudine and other anti-retroviral agents (neuropathy more common)
Drug-induced inflammatory myopathies	• Proximal-predominant weakness • Endomysial, perimysial, perivascular inflammatory infiltrates • Treatment requires immunosuppressive agents • Causes include: cholesterol-lowering agents, L-tryptophan, D-penicillamine, alpha-interferon, imatinib mesylate
Alcoholic myopathy	• Proximal-predominant; may manifest as acute necrotizing myopathy, acute hypokalemic myopathy, cardiomyopathy • Atrophic and necrotic muscle fibers on biopsy (depending by the type) • Polyneuropathy more common than myopathy

ANA = antinuclear antibody; CK = creatine kinase; EMG = electromyogram; HIV = human immunodeficiency virus; HMG-CoA = hydroxymethylglutaryl-coenzyme A.

genes can be tested concurrently; however, this also increases the chance of identifying "variants of uncertain significance," which may pose a challenge in determining their pathogenicity and reaching a definitive diagnosis. Referral to a neuromuscular specialist may help avoid sending unnecessary tests and in determining the clinical significance of these variants of uncertain significance.

CONCLUSIONS

Patients with myopathy are encountered frequently in primary care practices. Although myopathic disorders may be diagnostically challenging, it is important for the general medical practitioner to have a high level of suspicion for an underlying disorder of muscle when such patients present, to recognize the patterns of weakness and laboratory abnormalities that support a disorder of muscle, and to know when to refer patients for specialized testing and neuromuscular evaluation.

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