# Evaluation of the Patient with Muscle Weakness

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**Muscle weakness is a common complaint among patients presenting to family physicians. Diagnosis begins with a patient history distinguishing weakness from fatigue or asthenia, separate conditions with different etiologies that can coexist with, or be confused for, weakness. The pattern and severity of weakness, associated symptoms, medication use, and family history help the physician determine whether the cause of a patient's weakness is infectious, neurologic, endocrine, inflammatory, rheumatologic, genetic, metabolic, electrolyte-induced, or drug-induced. In the physical examination, the physician should objectively document the patient's loss of strength, conduct a neurologic survey, and search for patterns of weakness and extramuscular involvement. If a specific cause of weakness is suspected, the appropriate laboratory or radiologic studies should be performed. Otherwise, electromyography is indicated to confirm the presence of a myopathy or to evaluate for a neuropathy or a disease of the neuromuscular junction. If the diagnosis remains unclear, the examiner should pursue a tiered progression of laboratory studies. Physicians should begin with blood chemistries and a thyroid-stimulating hormone assay to evaluate for electrolyte and endocrine causes, then progress to creatine kinase level, erythrocyte sedimentation rate, and antinuclear antibody assays to evaluate for rheumatologic, inflammatory, genetic, and metabolic causes. Finally, many myopathies require a biopsy for diagnosis. Pathologic evaluation of the muscle tissue specimen focuses on histologic, histochemical, electron microscopic, biochemical, and genetic analyses; advances in technique have made a definitive diagnosis possible for many myopathies. (Am Fam Physician 2005;71:1327-36. Copyright© 2005 American Academy of Family Physicians.)**

See page 1245 for strength-of-evidence labels.

The online-only version of this article, which offers more detailed information on additional selected causes of muscle weakness, is available at: http://www.aafp.org/afp/URL.

Muscle weakness is a common complaint among patients presenting to the family physician's office. Although the cause of weakness occasionally may be apparent, often it is unclear, puzzling the physician and frustrating the patient. A comprehensive evaluation of these patients includes a thorough examination and coordination of appropriate laboratory, radiologic, electrodiagnostic, and pathologic studies.

## Definitions

Determining the cause of muscle weakness involves distinguishing primary weakness from fatigue or asthenia, common conditions that differ from, but often overlap with, muscle weakness.[1] Fatigue describes the inability to continue performing a task after multiple repetitions; in contrast, a patient with primary weakness is unable to perform the first repetition of the task. Asthenia is a sense of weariness or exhaustion in the absence of muscle weakness. This condition is common in people who have chronic fatigue syndrome, sleep disorders, depression, or chronic heart, lung, and kidney disease.[1] Because these conditions are prevalent in the ambulatory population, family physicians can expect to encounter patients with asthenia and fatigue more frequently than those with intrinsic muscle weakness.[1] Selected causes of asthenia and fatigue are listed in *Table 1*.[1]

Unfortunately, the distinction between asthenia, fatigue, and primary weakness often is unclear. Patients frequently confuse the terms, and the medical literature sometimes uses them interchangeably.[2] In addition, a patient's condition may cause progression from one syndrome to another; for example, asthenia in a patient with heart failure may progress to true muscle weakness through deconditioning. Further, asthenia and fatigue can coexist with weakness, such as in patients with multiple sclerosis and concomitant depression. Because depression is so prevalent, it is essential to consider it as a possible cause of a patient's symptoms; diagnosis can be facilitated by using one of the several validated screening tools designed for the outpatient setting.[3,4] This article discusses only intrinsic muscle weakness in adults.

**Strength of Recommendations**

| *Key clinical recommendation* | *Label* | *References* |
|---|---|---|
| It is essential to consider depression as a possible diagnosis; several screening tools for depression have been validated for use in outpatient settings. | A | 3,4 |
| Primary muscle weakness must be distinguished from the more common conditions of fatigue and asthenia. | C | 1 |
| If the diagnosis is still inconclusive after the history, physical examination, and laboratory, radiologic, and electromyographic evaluation, a muscle biopsy is required for patients who have a suspected myopathy. | C | 41 |

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 1245 for more information.*

## Differential Diagnosis

Conditions that result in intrinsic weakness can be divided into several main categories: infectious, neurologic, endocrine, inflammatory, rheumatologic, genetic, metabolic, electrolyte-induced, or drug-induced.

In adults, medications *(Table 2*[5,6]*)*, infections, and neurologic disorders are common causes of muscle weakness. The use of alcohol or steroids can cause proximal weakness with characteristic physical and laboratory findings.[5,7,8] Infectious agents that are most commonly associated with muscle weakness include influenza and Epstein-Barr virus *(Table 3*[6,9-12]*)*. Human immunodeficiency virus (HIV) is a less common cause of muscle weakness but should be considered in patients with associated risk factors or symptoms.[6,9] Neurologic conditions that can cause weakness include cerebrovascular disease (i.e., stroke, subdural/epidural hematomas), demyelinating disorders (i.e., multiple sclerosis, Guillain-Barré syndrome), and neuromuscular disorders (i.e., myasthenia gravis, botulism). Localizing neurologic deficits can help the physician focus the diagnostic work-up[6,10-12] *(Table 3*[6,9-12]*)*.

Less common myopathies include those caused by endocrine, inflammatory, rheumatologic, and electrolyte syndromes *(Tables 4*[5-8,13-26] *and 5*[6,8,15,16,18,20,24-38]*)*. Of the endocrine diseases, thyroid disease is common, but thyroid-related myopathy is uncommon; parathyroid-related myopathy should be suspected in a patient with muscle weakness and chronic renal failure.[14,15,32] Inflammatory diseases typically affect older adults and include both proximal (polymyositis and dermatomyositis) and distal myopathies (inclusion body myositis); the proximal inflammatory myopathies respond to steroids.[21-23] Rheumatologic disorders causing weakness, such as systemic lupus and rheumatoid arthritis, can occur in young and elderly persons.[17,18] Disorders of potassium balance are among the more common electrolyte myopathies and may be primary (such as in hypokalemic or hyper-

TABLE 1
**Causes of Asthenia and Fatigue**

| | |
|---|---|
| Addison's disease | Heart disease |
| Anemia | Hypothyroidism |
| Anxiety | Infections (such as influenza, Epstein-Barr virus, HIV, hepatitis C, tuberculosis) |
| Chemotherapy | Medications |
| Chronic fatigue syndrome | Narcotics |
| Chronic pain | Paraneoplastic syndrome |
| Deconditioning/sedentary lifestyle | Pregnancy/postpartum |
| Dehydration and electrolyte disorders | Pulmonary disease |
| Depression | Renal disease |
| Diabetes | Sleep disorders |
| Fibromyalgia | |

*HIV = human immunodeficiency virus.*

*Adapted with permission from Hinshaw DB, Carnahan JM, Johnson DL. Depression, anxiety, and asthenia in advanced illness. J Am Coll Surg 2002;195:276.*

TABLE 2
**Medications and Narcotics that Can Cause Muscle Weakness**

| |
|---|
| Amiodarone (Cordarone) |
| Antithyroid agents: methimazole (Tapazole); propylthiouracil |
| Antiretroviral medications: zidovudine (Retrovir); lamivudine (Epivir) |
| Chemotherapeutic agents |
| Cimetidine (Tagamet) |
| Cocaine |
| Corticosteroids |
| Fibric acid derivatives: gemfibrozil (Lopid) |
| Interferon |
| Leuprolide acetate (Lupron) |
| Nonsteroidal anti-inflammatory drugs |
| Penicillin |
| Sulfonamides |
| Statins |

*Information from references 5 and 6.*

kalemic periodic paralysis) or secondary (such as in renal disease or angiotensin-converting enzyme inhibitor toxicity). Patients in whom these disturbances are suspected should have electrocardiography to screen for cardiac sequelae.[13,27-30]

Rare causes of muscle weakness include genetic (muscular and myotonic dystrophies), metabolic (glycogenoses, lipidoses, and mitochondrial defects), and sarcoid- and amyloid-associated myopathies[24-26,34-38] *(Tables 4*[5-8,13-26] *and 5*[6,8,15,16,18,20,24-38]*)*.

## History

Once muscle weakness has been differentiated from asthenia and fatigue, the physician should ask the patient about disease onset and progression. Acute onset may indicate infection or stroke. Subacute onset may implicate drugs, electrolytes, or inflammatory or rheumatologic disease. Chronic progressive weakness is the classic presentation in genetic and metabolic myopathies. Despite these generalizations, there is considerable variation in the time courses of different classes of myopathy, and even within the individual disorders. For instance, although typically subacute, myasthenia gravis may present with rapid, generalized weakness or remain confined to a single muscle group for years (as in ocular myasthenia).[12]

Because of this variability, the pattern of muscle weakness is crucial in differentiating the etiology. The physician should establish whether the loss of strength is global (e.g., bilateral; may be proximal, distal, or both) or focal. Focal processes (those that are unilateral or involve specific nerve distributions or intracranial vascular areas) tend to be neurologic—although not all neurologic processes are focal—and may require a different approach than that used with global strength loss.

**The use of alcohol or steroids can cause proximal weakness with characteristic physical and laboratory findings.**

In patients with diffuse weakness, the physician should determine whether the loss of function is proximal or distal by noting which physical activities muscle weakness limits. If the patient has difficulty rising from a chair (hip muscles) or combing his or her hair (shoulder girdle), the weakness is proximal; if the patient has difficulty standing on his or her toes (gastrocnemius/soleus) or

TABLE 3
**Infectious and Neurologic Causes of Muscle Weakness**

| |
|---|
| **Infectious** |
| Epstein-Barr virus |
| Human immunodeficiency virus |
| Influenza |
| Lyme disease |
| Meningitis (multiple agents) |
| Polio |
| Rabies |
| Syphilis |
| Toxoplasmosis |
| **Neurologic** |
| Amyotrophic lateral sclerosis |
| Cerebrovascular disease |
| Stroke |
| Subdural/epidural hematomas |
| **Neurologic** *(continued)* |
| Demyelinating disorders |
| Guillain-Barré syndrome |
| Multiple sclerosis |
| Neoplasm |
| Neuromuscular disorders |
| Botulism |
| Lambert-Eaton myasthenic syndrome |
| Myasthenia gravis |
| Organophosphate intoxication |
| Radiculopathies |
| Cervical spondylosis |
| Degenerative disc disease |
| Spinal cord injury |
| Spinal muscle atrophy |

*Information from references 6 and 9 through 12.*

TABLE 4

## Selected Causes of Primary Muscle Weakness

| *Cause* | *Weakness* | *Age of onset/diagnosis* | *Systemic symptoms and findings* |
|---|---|---|---|
| **Drugs** | | | |
| Alcohol | Proximal (may be distal) | Variable | Change in mental status; telangiectasia; peripheral neuropathy |
| **Endocrine** | | | |
| Adrenal insufficiency | Generalized | Variable | Hypotension; hypoglycemia; bronzing of the skin |
| Glucocorticoid excess | Proximal | Variable | Buffalo hump; striae; osteoporosis |
| Parathyroid hormone (secondary hyperparathyroidism§) | Proximal, lower extremity more than upper extremity | Variable, older adult | Usually has associated comorbidities (cardiovascular disease, diabetes) |
| Thyroid hormone (hyperthyroidism) | Proximal, bulbar | 40 to 49 years | Weight loss; tachycardia; increased perspiration; tremor |
| Thyroid hormone (hypothyroidism) | Proximal | 30 to 49 years | Menorrhagia; bradycardia; goiter; delayed relaxation of deep tendon reflexes |
| **Inflammatory** | | | |
| Dermatomyositis | Proximal | Variable, increased incidence with age | Gottron papules; heliotrope rash; calcinosis; interstitial lung disease; disordered GI motility |
| Inclusion body myositis | Distal, especially forearm and hand | At least 50 years (younger than 50 years: rare) | Dysphagia; extramuscular involvement not as common |
| Polymyositis | Proximal | Variable, increased incidence with age | Interstitial lung disease, disordered GI motility; overlap with rheumatologic diseases more common |
| **Rheumatologic** | | | |
| Rheumatoid arthritis | Focal, periarticular, or diffuse | Adult | Symmetric joint inflammation (especially MCP, PIP joints); dry eyes and mouth |
| Systemic lupus erythematosus | Proximal | Adult | Malar rash; nephritis; arthritis |
| **Genetic** | | | |
| Becker muscular dystrophy | Hip; proximal leg and arm | Late childhood to adulthood | Mental retardation; cardiomyopathy |
| Limb-girdle muscular dystrophies** | Variable, usually proximal limb, pelvic, and shoulder girdle muscles | Variable | Variable, may have cardiac abnormalities |
| Myotonic dystrophy type 1 | Distal greater than proximal; foot drop; temporal and masseter wasting | Adolescence to adulthood | Conduction abnormalities; mental retardation; cataracts; insulin resistance |
| **Metabolic** | | | |
| Glycogen and lipid storage diseases; mitochondrial disease | Proximal | Variable | Variable; exercise intolerance and cardiomyopathy more common |

*GGT = gamma-glutamyltransferase; ACTH = adrenocorticotropin hormone; MUAPs = motor unit action potentials; $T_3$ = triiodothyronine; $T_4$ = thyroxine; TSH = thyroid-stimulating hormone; GI = gastrointestinal; ANA = antinuclear antibodies; MCP = metacarpophalangeal; PIP = proximal interphalangeal; EMG = electromyogram; FIET = forearm ischemic exercise testing.*

**—Myopathic changes are nonspecific and include atrophy, degeneration, and regeneration of muscle fibers.*

*†—Myotonic discharges are a type of prolonged burst of activity seen on insertion of the EMG needle.*

*‡—Myopathic MUAPs are shorter in duration, lower in amplitude, and polyphasic when compared to MUAPs from normal muscle.*

*§—Secondary hyperparathyroidism usually caused by renal failure.*

*Information from references 5 though 8 and 13 through 26.*

| *Laboratory abnormalities* | *Creatine kinase* | *Electromyogram* | *Muscle biopsy* |
|---|---|---|---|
| Elevated transaminase and GGT levels; anemia; decreased vitamin $B_{12}$ | Normal to elevated | Normal | Myopathic changes*; selected atrophy of type II muscle fibers |
| Hyponatremia; hyperkalemia; ACTH assay; ACTH stimulation test | Normal | Myotonic discharges† | Diminished glycogen content |
| Elevated urine-free cortisol, dexamethasone suppression, or corticotropin-releasing hormone stimulation tests | Normal | Myopathic MUAPs‡ | Selective atrophy of type II muscle fibers |
| Hypocalcemia; uremia | Normal | Myopathic MUAPs‡ | Atrophy of type II muscle fibers; increased lipofuscin beneath cell membrane; calcium deposits in muscle |
| Elevated $T_4$ and $T_3$; TSH variable, depending on cause | Normal or elevated | Myopathic MUAPs‡ with or without fibrillation potentials‖ | Usually normal |
| TSH | Elevated | With or without myopathic MUAPs‡ and fibrillation potentials‖ | Myopathic changes*; glycogen accumulation |
| Elevated myoglobin; ANA positive; myositis autoantibodies may be present | Greater than 10 times normal elevations | Myopathic MUAPs‡ with fibrillation potentials‖ | Inflammatory infiltrate with myopathic changes* and replacement by adipose and collagen |
| Elevated myoglobin; positive ANA less common; myositis autoantibodies may be present | Elevated | Myopathic MUAPs‡ with fibrillation potentials‖ | Inflammatory infiltrate with vacuoles containing eosinophilic inclusions |
| Elevated myoglobin; ANA positive; myositis autoantibodies may be present | Greater than 10 times normal elevations | Myopathic MUAPs‡ with fibrillation potentials‖ | Inflammatory infiltrate with myopathic changes* and replacement by adipose and collagen |
| Elevated rheumatoid factor | Normal or elevated | No data | Atrophy of type II muscle fibers; may have overlap syndrome with polymyositis |
| ANA, anti-DNA antibodies, depressed C3 and C4¶ | Normal to elevated | No data | Type II fiber atrophy; lymphocytic vasculitis; myositis |
| None | Elevated | Myopathic MUAPs‡ with fibrillation potentials‖ | Myopathic changes*; decreased and patchy staining of dystrophin |
| None | Variable, normal, or elevated | Myopathic MUAPs‡ +/- fibrillation potentials‖ | Myopathic changes*; may demonstrate absence of specific protein on immunohistochemical staining |
| None | Normal to minimally elevated | Myopathic MUAPs‡; myotonic discharges‖ | Less necrosis and remodeling than in muscular dystrophies; atrophy of type I muscle fibers; ring fibers |
| Some glycogenoses associated with abnormal FIET†† | Variable, may increase with exercise | Normal or myopathic MUAPs‡ +/- fibrillation potentials‖ | Myopathic changes* with glycogen deposits, lipid deposits, or ragged red fibers (for glycogen, lipid, or mitochondrial disease, respectively) |

‖—*Fibrillation potentials represent spontaneous activity on the part of single muscle fibers (not usually noted with nondiseased muscle).*

¶—*C3 and C4 are complement components.*

**—*Including facioscapulohumeral dystrophy.*

††—*FIET evaluates the rise of ammonia and lactate in the forearm during exertion.*

**Focal processes tend to be neurologic and may require a different approach than that used in patients with global strength loss.**

doing fine work with the hands (intrinsics), the muscle weakness is distal. Although many myopathies are associated with proximal weakness, a small number are associated predominantly with distal weakness; these include myotonic dystrophy, inclusion body myositis, and the genetic distal myopathies.[21,34] Patients with statin or alcohol toxicity can present with either proximal or distal weakness.[5,7,39]

Other areas to address in the patient's history are associated symptoms, family history, and pharmaceutical use. Common drugs associated with muscle weakness are listed in *Table 2*.[5,6] Associated symptoms are found in many myopathies and can be especially helpful in narrowing the differential diagnosis among endocrine, rheumatologic, and inflammatory disorders. For example, dysphagia may accompany weakness in inclusion body myositis and systemic sclerosis, whereas menorrhagia may attend the weakness that occurs in hypothyroidism. A family history, which almost always is present in genetic myopathies, may also be present in other causes of weakness, including lupus, rheumatoid arthritis, dermatomyositis, polymyositis, and the potassium-related paralyses[27] *(Table 6*[5,7-15,17,18,21,24-27,34,36,38]*)*.

TABLE 5
**Additional Selected Causes of Muscle Weakness**

| |
|---|
| **Electrolyte** |
| Hypercalcemia |
| Hyperkalemia/hypokalemia |
| Hypermagnesemia/hypomagnesemia |
| **Endocrine** |
| Acromegaly |
| Primary hyperparathyroidism |
| Hypopituitarism |
| Vitamin D deficiency (osteomalacia) |
| **Rheumatologic** |
| Polymyalgia rheumatica |
| Systemic sclerosis/scleroderma |
| **Genetic** |
| Distal myopathies |
| Oculopharyngeal muscular dystrophy |
| Myotonic dystrophy type 2 (proximal myotonic myopathy) |
| **Metabolic** |
| Glycogenoses |
| Acid maltase deficiency |
| Aldolase A deficiency |
| Brancher enzyme deficiency |
| Myophosphorylase deficiency |
| Phosphofructokinase deficiency |
| Lipidoses |
| Carnitine deficiency |
| Carnitine palmitoyltransferase II deficiency |
| Trifunctional protein deficiency |
| Mitochondrial defects |
| **Miscellaneous** |
| Amyloidosis |
| Sarcoidosis |

*Information from references 6, 8, 15, 16, 18, 20, and 24 through 38.*

## Physical Examination

The physical examination begins with an objective confirmation of the subjective severity and distribution of muscle weakness. In addition to individual muscles, the physician should survey functional activities such as standing and writing to determine whether the weakness is proximal, distal, or both.

Next, a thorough neurologic survey should accompany motor testing. The physician should note patterns and relations among defects and narrow the differential by determining whether the deficits are referable to the central or peripheral nervous system. The pattern is important. A neurologic examination that shows deficits in a single nerve or radicular distribution indicates a possible mononeuritis, entrapment neuropathy, or radiculopathy, and calls for a different workup than that required for a limb paresis in a patient with cerebrovascular risk factors.

If the neurologic examination is unrevealing, a more general physical examination, searching for extramuscular signs, is warranted *(Table 6*[5,7-15,17,18,21,24-27,34,36,38]*)*. Mental status testing may reveal changes suggestive of a myopathy-inducing electrolyte disorder (calcium or magnesium) or an arrest of

TABLE 6
**Diagnostic Clues for Muscle Weakness**

| *Finding* | *Suggested diagnoses* |
|---|---|
| **History** | |
| Abdominal pain; excessive urination; renal stones | Hypercalcemia; hyperparathyroidism |
| Acute weakness with neurologic deficit(s) | Spinal cord injury; stroke |
| Arthralgia; malaise; myalgia; respiratory symptoms | Epstein-Barr virus; HIV; influenza |
| Chronic neck or back pain, with or without sharp shooting pains | Cervical spondylosis; degenerative disc disease |
| Distal weakness | Genetic distal myopathies; inclusion body myositis |
| Dysphagia; rash around eyelids; shortness of breath | Dermatomyositis |
| Easy bruising; emotional lability; obesity | Glucocorticoid excess; steroid-induced myopathy |
| Exercise-provoked weakness | Glycogen and lipid storage diseases; mitochondrial myopathies; myasthenia gravis |
| Family history of myopathy | Hyper- or hypokalemic periodic paralysis; inflammatory disease; muscular dystrophies; rheumatologic disease |
| Heat-induced symptoms; multiple neurologic deficits spread over space and time | Multiple sclerosis |
| Legal problems; memory loss; repeated trauma; sexual dysfunction | Alcoholism |
| Positive medication history | Medication-induced myopathy (esp. anti-retrovirals, statins, steroids) |
| Sexually transmitted disease | HIV; syphilis |
| **Physical examination** | |
| Arthritis; malar rash; nephritis | Systemic lupus erythematosus |
| Cardiomyopathy | Alcohol; amyloid; glycogen storage disease; inflammatory myopathies; muscular dystrophies; sarcoid |
| Dry eyes and mouth; joint inflammation (especially MCP, PIP joints) | Rheumatoid arthritis |
| Facial weakness; fatigable weakness; ptosis | Myasthenia gravis |
| Neurologic deficits | |
| Focal | |
| Central | Multiple sclerosis; stroke |
| Peripheral | Peripheral neuropathy; radiculopathy |
| Diffuse | |
| Central | Amyotrophic lateral sclerosis |
| Peripheral | Guillain-Barré syndrome; polyneuropathy |
| Orthostatic hypotension; skin bronzing | Hypoadrenalism |

*HIV = human immunodeficiency virus; MCP = metacarpophalangeal; PIP = proximal interphalangeal.*

*Information from references 5, 7 through 15, 17, 18, 21, 24 through 27, 34, 36, and 38.*

mental development as occurs in genetic myopathies.[25,29] The cardiovascular assessment may elicit changes consistent with a cardiomyopathy—a nonspecific consequence of many myopathy-inducing disorders—or a pericarditis, as occurs with some of the infectious and rheumatologic causes of muscle weakness.[5,7,8,9,18,21,24,25,29,36,38]

Pulmonary testing may reveal the crackles of a restrictive lung defect, found in some inflammatory and rheumatologic myopathies.[17,21] Gastrointestinal examination may reveal hepatomegaly, associated with metabolic storage diseases and amyloidosis.[24,38] Skin findings are possible in multiple categories of disease (e.g., skin bronzing in adrenal insufficiency; Gottron's papules and heliotrope rash in dermatomyositis; and erythema nodosum in sarcoidosis). The skeletal examination may reveal the leg bowing and pseudofractures of osteomalacia or the symmetric joint swelling of lupus and rheumatoid arthritis.[8,17,18,21,25,35]

**In a patient whose muscle weakness is suggestive of neurologic disease, early neuroimaging (for suspected cerebrovascular disease) or lumbar puncture (for possible meningitis, encephalitis, or multiple sclerosis) is indicated.**

## Laboratory and Radiologic Evaluation

The sequence and timing of the ancillary investigations varies with the clinical scenario. In a patient whose muscle weakness is suggestive of neurologic disease, early neuroimaging (for suspected cerebrovascular disease) or lumbar puncture (for possible meningitis, encephalitis, or multiple sclerosis) is indicated. If infectious disease is suspected, appropriate titers or cultures should be obtained. When a specific class or type of myopathy is suspected, appropriate testing should be performed.

If the cause of muscle weakness is unclear, serum chemistries (electrolytes, calcium, phosphate, magnesium, glucose) should be obtained, as well as a thyroid-stimulating hormone assay to evaluate for electrolyte and endocrine myopathies. If an endocrinopathy is suspected, more specific assays can be performed based on clinical suspicion (e.g., 24-hour urine cortisol testing to rule out Cushing's disease; oral glucose load/growth hormone assay to rule out acromegaly; vitamin D assay to rule out osteomalacia).[8,13-15,28,29,32]

Next, investigations looking for inflammatory, rheumatologic, or genetic myopathies can be performed sequentially or concurrently. Although nonspecific, the creatine kinase (CK) level usually is normal in the electrolyte and endocrine myopathies (notable exceptions are thyroid and potassium disorder myopathies).[8,16,28,29] However, the CK level may be highly elevated (10 to 100 times normal) in the inflammatory myopathies and can be moderately to highly elevated in the muscular dystrophies.[16,23,25] Other conditions that can be associated with elevated CK levels include sarcoidosis, infections, alcoholism, and adverse reactions to medications. Metabolic (storage) myopathies tend to be associated with only mild to moderate elevations in CK levels.[7,16]

In addition to CK, an erythrocyte sedimentation rate (ESR) and an antinuclear antibody assay (ANA) may help determine if a rheumatologic myopathy exists. If either ESR or ANA assay is positive, additional studies may be obtained, including rheumatoid factor (rheumatoid arthritis); anti–double-stranded DNA or antiphospholipid antibodies (lupus); or anticentromere antibodies (scleroderma).[17-19] Patients with idiopathic inflammatory myopathies also tend to have elevated ESR and ANA levels; many of these same patients have overlap syndromes, in which an inflammatory myopathy and a rheumatologic disease coexist. An antisynthetase antibody, when positive, may help confirm the presence of an inflammatory myopathy.[23]

## Electromyography

If the presence of myopathy is uncertain, electromyography may be indicated. Although changes seen on electromyography are not pathognomonic for any specific disease process, an abnormal electromyogram can indicate if a neuropathy or neuromuscular disease is present or can help solidify the diagnosis of a primary myopathy.


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Electromyography assesses several components of muscle electrical activity: the muscle's spontaneous activity; its response to the insertion of a probe; the character of the muscle's individual motor unit action potentials; and the rapidity with which additional motor units are recruited in response to an electrical signal. Muscle inflammation, atrophy, necrosis, denervation, or neuromuscular disease can alter these components, giving rise to patterns that may help illuminate the underlying pathology. Although the procedure can cause minor discomfort, most patients tolerate it well.[16,24,40]

## Muscle Biopsy

If the diagnosis is still inconclusive after the history, physical examination, and laboratory, radiologic, and electromyographic evaluations, a muscle biopsy is required for patients who have a suspected myopathy.[41] The technology of this method, especially regarding the use of genetic markers, is advancing rapidly, making a definitive diagnosis possible for a wider range of myopathies.[24,25]

The biopsy site should be an affected muscle that is not diseased to the point of necrosis. Common biopsy sites are the vastus lateralis of the quadriceps for proximal myopathies and the gastrocnemius for distal myopathies; in patients without involvement of these muscles, an affected group is chosen.[24] The muscle biopsy can be accomplished as an outpatient procedure and carries the attendant risks of pain, bleeding, infection, and sensory loss. As with electromyography, patients should avoid using anticoagulants before the procedure, and the site chosen for biopsy should be free of overlying infection.

The pathologic analysis of biopsy specimens focuses on the histologic, histochemical, electron microscopic, genetic, and biochemical changes that are found in the affected muscle. Histology may show atrophic, degenerating, and regenerating muscle fibers (general findings referred to as myopathic changes), or it may show more specific findings such as accumulations of glycogen (glycogen storage diseases), ragged red fibers (mitochondrial myopathies), noncaseating granulomas (sarcoidosis), and amyloid deposits (amyloidosis). Histochemical techniques assay for specific enzymes and proteins, and may reveal deficiencies as in disorders of carbohydrate or fatty acid metabolism or the muscular dystrophies. Electron microscopy and biochemical assays may help to uncover subtle changes not detectable by other techniques, further aiding in the diagnosis of metabolic and protein-deficiency myopathies.[7,18-20,21,24,25,27,28,35,37]

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