A Clinical Approach to Muscle Diseases

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ABSTRACT

Muscle diseases constitute a large variety of both acquired and hereditary disorders that can affect muscle structure, metabolism, or the function of the muscle channel. A successful clinical approach to a patient with a suspected myopathy is based on a thorough medical history and neurological examination. Associated clinical symptoms such as myoglobinuria, contractures, myotonia, cardiac disease, and respiratory insufficiency can be extremely helpful in limiting the differential diagnosis. In addition, a phenotypic approach to diagnosis according to the patient's predominant pattern of weakness is essential for guiding the physician in selecting the most appropriate diagnostic studies. Although muscle biopsy remains a useful tool, molecular genetic studies are now available for the noninvasive diagnosis of many muscle diseases.

KEYWORDS: Myopathy, myalgia, myoglobinuria, myotonia, cardiomyopathy, creatine kinase

Muscle diseases are disorders in which there is a structural or functional abnormality of skeletal muscle. Muscle diseases can be distinguished from other disorders of the motor unit—including motor neuron diseases, neuromuscular junction disorders, and peripheral neuropathies—by characteristic clinical and laboratory features. The first goal, therefore, in approaching a patient with a suspected muscle disease is to identify the correct site of the lesion. The second goal is to determine whether the muscle disease is due to an acquired or a hereditary disorder to provide accurate genetic counseling. Finally, the third goal in our clinical approach is to determine if there is a specific treatment. Certainly in most hereditary muscle diseases, there is no curative therapy, and the clinician's focus must be on aggressive symptom management and the provision of appropriate adaptive equipment to maximize the patient's functional abilities and enhance quality of life.

CLINICAL EVALUATION

Despite the tremendous increase in the number and sophistication of diagnostic tests, the most important element of evaluating a patient with a suspected muscle disease remains a thorough history and physical examination.[1] The history should allow the physician to make a reasonable preliminary diagnosis that places the patient into one of the categories in Table 1. The findings on the physical examination, particularly the distribution of muscle weakness, should provide additional information in determining the correct diagnosis. Many muscle diseases have features so characteristic that they can be diagnosed with relative certainty at the bedside. The results of laboratory studies, including creatine kinase, electrodiagnostic studies, muscle biopsy, and/or molecular genetic studies should play a *confirmatory* diagnostic role rather than serving as a "fishing expedition."

Although the basic components of the history are similar for patients with other medical conditions,

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Table 1 Classification of Myopathies

Hereditary
Channelopathies
Congenital myopathies
Metabolic myopathies
Mitochondrial myopathies
Muscular dystrophies
Myotonias
Acquired
Drug-induced myopathies
Endocrine myopathies
Inflammatory myopathies
Myopathies associated with systemic disease
Toxic myopathies

certain features are unique to the patient with a suspected myopathy. Therefore, the first step is to ask six key questions based on specific symptoms and signs that may direct the clinician to the correct diagnosis.

1. Which "Negative" and/or "Positive" Symptoms and Signs does the Patient Demonstrate?

Symptoms and signs of muscle disease (Table 2) can be divided into "positive" complaints, such as myalgias, cramps, contractures, myoglobinuria, and muscle stiffness, and "negative" complaints, such as weakness, exercise intolerance, fatigue, and muscle atrophy. Myalgia, like fatigue, is a nonspecific symptom of some myopathies[2] (Table 3). Diffuse myalgia may occur with viral infection or in association with polymyositis, dermatomyositis, toxic or infectious myopathies, and a few rare endocrine myopathies. Myalgias, which occur episodically in association with exercise, may suggest a metabolic myopathy. However, muscle pain is usually not associated with most other muscle diseases, and is more likely to be due to orthopedic, psychiatric, or rheumatological disorders. It is rare for a muscle disease to cause vague aches and muscle discomfort in the presence of a normal neuromuscular examination and laboratory studies.[3]

A specific type of muscle pain is the involuntary muscle cramp. Unlike contractures, cramps may occur at rest, last from seconds to minutes, and often be localized to a particular muscle region. They are typically benign, occurring frequently in normal individuals, and are seldom a feature of a primary myopathy. Cramps are characterized by rapidly firing motor unit discharges on needle electromyography similar to a maximal contraction.[4] Cramps can occur with dehydration, hyponatremia, azotemia, hypothyroidism, adrenal insufficiency, renal/hepatic failure, and pregnancy, as well as in peripheral neuropathies, radiculopathies, and motor neuron diseases.

Muscle contractures are uncommon but can superficially resemble a cramp. They are typically provoked by exercise in patients with glycolytic enzyme defects. Contractures differ from cramps in that they may persist for hours and are electrically silent with needle electromyography. Muscle disorders that are associated with contractures are listed in Table 4.

Myotonia is a phenomenon of impaired relaxation of muscle after forceful voluntary contraction and most commonly involves the hands and eyelids. Myotonia is due to repetitive depolarization of the muscle membrane and is characterized on electrophysiological studies by waxing and waning rhythmical discharges. Patients may complain of muscle stiffness or tightness resulting in difficulty releasing their handgrip after a handshake, unscrewing a bottle top, or opening their eyelids if they forcefully shut their eyes. Myotonia classically

Table 2 Symptoms and Signs Associated with Myopathies

Negative	Positive
Weakness	Myalgias
Fatigue	Cramps
Exercise intolerance	Contractures
Muscle atrophy	Myotonia
	Myoglobinuria

Table 3 Muscle Disorders Associated with Diffuse Myalgias

Endocrine myopathies (especially hypothyroidism)
Eosinophilia-myalgia syndrome
Inflammatory myopathies (polymyositis, dermatomyositis)
Infectious myositis (viral, parasitic, or bacterial)
Mitochondrial myopathies
Myoadenylate deaminase deficiency
Toxic myopathies (lovastatin, chloroquine, alcohol)
Tubular aggregate myopathy
X-linked myalgia and cramps (Becker dystrophy variant)

Table 4 Myopathies Associated with Muscle Contractures

Brody's disease
Glycolytic/glycogenolytic enzyme defects
Myophosphorylase deficiency (McArdle's disease)
Phosphofructokinase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Debrancher enzyme deficiency
Hypothyroid myopathy
Paramyotonia congenita
Rippling muscle disease

Table 5 Myopathies Associated with Muscle Stiffness

Brody's disease
Hyperkalemic periodic paralysis
Hypothyroid myopathy
Myotonic disorders
Myotonic dystrophy types 1 and 2
Myotonia congenita
Paramyotonia congenita
Polymyalgia rheumatica

improves with repeated exercise. In contrast, patients with paramyotonia congenita demonstrate "paradoxical myotonia" in that symptoms are typically worsened by exercise or repeated muscle contractions. Exposure to cold results in worsening of both myotonia and paramyotonia. The muscle disorders associated with muscle stiffness are listed in Table 5.

Myoglobinuria is a relatively uncommon manifestation of muscle disease and is caused by the excessive release of myoglobin from muscle during periods of rapid muscle destruction (rhabdomyolysis). Severe myoglobinuria can result in renal failure due to acute tubular necrosis. Patients who complain of exercise-induced weakness and myalgias should be asked if their urine has ever turned coke-colored or red during or after these episodes. Recurrent myoglobinuria is usually due to an underlying metabolic myopathy (Table 6), whereas isolated episodes, particularly those occurring after unaccustomed strenuous exercise, are frequently idiopathic.

Weakness is by far the most common negative symptom reported by a patient with muscle disease. If the weakness involves the lower extremities, patients will complain of difficulty going up or down stairs, arising from a chair or toilet, arising from a squatted position, or getting off of the floor. When the upper extremities are involved, patients notice trouble lifting objects over their head, reaching to get things from top shelves, brushing teeth, shaving, dressing, and brushing their hair. These symptoms in the arms and legs indicate proximal muscle weakness, which is probably the most common site of weakness in a myopathic disorder (discussed later). Less commonly, patients with myopathies can complain of distal weakness manifested as difficulty opening jars, buttoning clothes, or turning a key in the ignition. Patients with distal lower extremity weakness may complain of tripping over curbs, difficulty walking on uneven ground or "foot slapping." Some myopathies may also result in cranial muscle weakness resulting in complaints of dysarthria, dysphagia, or ptosis.

Table 6 Causes of Myoglobinuria

Acquired causes
Drugs and toxins (especially alcohol, clofibrate, opiates, statins)
Heat stroke or prolonged fever
Neuroleptic malignant syndrome
Prolonged, intensive exercise
Serotonin syndrome
Severe metabolic disturbances
Snake venoms
Trauma (crush injuries, electric shock)
Viral and bacterial infections
Familial causes
Hypokalemic periodic paralysis
Limb-girdle MD 2C-F (sarcoglycanopathies)
Metabolic myopathies
Glycogenoses (myophosphorylase deficiency)
Lipid disorders (carnitine palmitoyltranferase deficiency)
Malignant hyperthermia (central core myopathy, Duchenne dystrophy)
Myoadenylate deaminase deficiency
Inflammatory myopathies (rare)
Muscular dystrophies (Duchenne and Becker)

Fatigue is a much less useful negative symptom because it is nonspecific and may reflect a patient's cardiopulmonary status, level of conditioning, overall health, sleeping habits or emotional state.[4,5] Many patients who complain of diffuse global weakness or fatigue do not have a disorder of muscle, particularly if the neurological examination is normal. On the other hand, abnormal fatigability after exercise can result from certain metabolic and mitochondrial myopathies and neuromuscular junction disorders, and it is important to define the duration and intensity of exercise that provokes the fatigue.

2. Are There Precipitating Factors that Trigger Episodic Weakness or Myotonia?

A history of precipitating factors that might trigger or exacerbate symptoms of weakness or myotonia should be explored. It is important to ask the patient if there is any history of either illegal drug or prescription medication use that might produce a myopathy. A history of weakness, pain, and/or myoglobinuria, which is provoked by exercise, might suggest the possibility of a glycolytic pathway defect. Episodes of weakness, which occur in association with a fever, would be supportive of a diagnosis of carnitine palmityl transferase deficiency. Attacks of periodic paralysis are characteristically provoked by exercise and ingestion of a carbohydrate meal followed by a period of rest. Patients with paramyotonia congenita frequently report that cold exposure may precipitate their symptoms of muscle stiffness.

3. Is There a Family History of a Myopathic Disorder?

Because many myopathies are inherited, obtaining a thorough family history is obviously of great importance in making a correct diagnosis. A detailed family tree

Table 7 Diagnosis of Myopathy Based on Pattern of Inheritance

Autosomal-dominant
FSH, LGMD, oculopharyngeal MD, myotonic dystrophy, periodic paralysis, paramytonia congenita, Thomsen's disease, central core myopathy
Autosomal-recessive
LGMD, metabolic myopathies, Becker's myotonia
Maternal transmission
Mitochondrial myopathies
X-linked
Duchenne's MD, Becker's MD, Emery-Dreifuss MD

FSH, facioscapulohumeral; MD, muscular dystrophy; LGMD, limb-girdle muscular dystrophy; MD, muscular dystrophy.

should be completed to look for evidence of autosomal-dominant, autosomal-recessive, and X-linked patterns of transmission. Questions regarding family members' use of canes or wheelchairs, skeletal deformities, functional limitations, and associated medical conditions are usually more informative than vague questions such as, "Does any member of your family have a muscle disease?" Particularly in some autosomal-dominant disorders, such as myotonic dystrophy and facioscapulohumeral (FSH) dystrophy, phenotypic variability may be such that even affected parents can be asymptomatic. In this situation, examination of other family members may be necessary to distinguish an acquired from a hereditary disorder. Identifying a particular hereditary pattern cannot only help in correctly diagnosing the specific myopathy (Table 7), but is also of tremendous importance in providing appropriate genetic counseling.

4. What is the Temporal Evolution?

It is obviously important to determine the onset, duration, and evolution of the patient's symptoms and signs of muscle disease. Did the weakness (or other symptoms) first manifest at birth or was the onset in the first, second, third, or later decade (Table 8)? Identifying the age that symptoms began can provide crucial information leading to the correct diagnosis. For example, symptoms of Duchenne's muscular dystrophy usually are identified by 3 years of age, whereas most FSH and limb-girdle muscular dystrophies (LGMDs) begin in adolescence or later. Of the inflammatory myopathies, dermatomyositis occurs in children and adults, polymyositis rarely occurs in children but at any decade in the adult years, and inclusion body myositis occurs most commonly in the elderly.

It is also imperative to determine the evolution and duration of the disease. Myopathies can present with either *constant* weakness (muscular dystrophies, inflammatory myopathies) or *episodic* periods of weakness with normal strength interictally (periodic paralysis, metabolic myopathies due to certain glycolytic pathway disorders). The episodic disorders have acute weakness that can return to normal strength within hours or days. Patients presenting with fluctuating weakness that is provoked by fatigue may also have a neuromuscular junction disorder. The tempo of the disorders with constant weakness can vary from: (1) acute or subacute progression in some inflammatory myopathies (dermatomyositis and polymyositis), (2) chronic slow progression over years (most muscular dystrophies), or (3) nonprogressive weakness with little change over decades (congenital myopathies). Finally, both constant and episodic myopathic disorders can have symptoms that may be monophasic or relapsing. For example, polymyositis can occasionally have an acute monophasic

Table 8 Diagnosis of Myopathy Based on Age of Onset

Myopathies presenting at birth
Congenital myotonic dystrophy
Congenital myopathies
Centronuclear myopathy
Congenital fiber-type disproportion
Central core disease
Nemaline myopathy
Congenital muscular dystrophy
Glycogen storage diseases (acid maltase and phosphorylase deficiencies)
Lipid storage diseases (carnitine deficiency)
Myopathies presenting in childhood
Congenital myopathies: nemaline myopathy, centronuclear myopathy, central core
Endocrine-metabolic disorders: hypokalemia, hypocalcemia, hypercalcemia
Glycogen storage disease (acid maltase deficiency)
Inflammatory myopathies: dermatomyositis, polymyositis (rarely)
Lipid storage disease (carnitine deficiency)
Mitochondrial myopathies
Muscular dystrophies: Duchenne, Becker, Emery-Dreifuss, facioscapulohumeral, limb-girdle, congenital
Myopathies presenting in adulthood
Distal myopathies
Centronuclear myopathy
Endocrine myopathies: thyroid, parathyroid, adrenal, pituitary disorders
Inflammatory myopathies: polymyositis, dermatomyositis, inclusion body myositis, viral (HIV)
Metabolic myopathies (acid maltase deficiency, lipid storage diseases, debrancher)
Deficiency, phosphorylase b kinase deficiency
Muscular dystrophies: limb-girdle, facioscapulohumeral, Becker, Emery-Dreifuss, myotonic
Mitochondrial myopathies
Nemaline myopathy
Toxic myopathies: alcohol, corticosteroids, local injections of narcotics, colchicine, chloroquine

Table 9 Myopathies Associated with Respiratory Insufficiency

Muscular dystrophies
Becker
Congenital
Duchenne
Emery-Dreifuss
Limb-girdle 2A, 2I
Myofibrillar myopathy
Myotonic dystrophy
Ullrich scleroatonic
Metabolic myopathies
Acid maltase deficiency
Carnitine deficiency
Debrancher deficiency
Mitochondrial myopathies
Progressive external ophthalmoplegia
Leigh's
Congenital myopathies
Nemaline
Centronuclear
Acquired myopathies
Acute quadriplegic myopathy
Amyloid myopathy
Polymyositis (especially Jo-1)
Sarcoid

course with complete resolution of strength within weeks or months. Patients with periodic paralysis or metabolic myopathies can have recurrent attacks of weakness over many years, whereas a patient with acute rhabdomyolysis due to cocaine may have a single episode.

5. Are There Associated Systemic Symptoms or Signs?

Involvement of organs or tissues other than muscle may also provide helpful clues in making the appropriate diagnosis. Respiratory failure may be the presenting symptom of myotonic dystrophy, centronuclear myopathy, nemaline myopathy, or acid maltase deficiency (Table 9).[6–8] Eventually, most myopathies will affect respiratory muscle strength, highlighting the need for consistent monitoring of pulmonary function studies throughout the disease course. The earliest manifestations of hypoventilation usually result in frequent nocturnal arousals, morning headaches, excessive daytime sleepiness, and vivid dreams. Patients usually do not report dyspnea or orthopnea until the forced vital capacity falls below 50% of predicted. Once symptoms of hypoventilation are evident, supportive care with noninvasive positive pressure ventilation and assistive devices for clearance of upper airway secretions should be employed.

Table 10 Myopathies Associated with Cardiac Disease

Arrythmias
Andersen's syndrome
Bethlem myopathy
Kearns-Sayre syndrome
Muscular dystrophies: Myotonic, Limb-girdle, 1B, 1E, 2C–F, 2G, Emery-Dreifuss
Polymyositis
Congestive heart failure
Acid maltase deficiency
Amyloid mopathy
Branching enzyme deficiency
Carnitine disorders
Debrancher enzyme deficiency
Lamp-2
Mitochondrial disorders
Muscular dystrophies: Duchenne, Becker, Emery-Dreifuss, Myotonic, Limb-girdle 1A, 1B, 1E, 2C–F, 2G, 2I, 2L
Nemaline myopathy
Polymyositis/dermatomyositis

Cardiac disease, in the form of congestive heart failure or arrhythmias, is a common feature of many myopathies (Table 10) including: myotonic dystrophy, Duchenne's or Becker's muscular dystrophies, LGMD 1B (laminopathy), LGMD 2I (fukutin-related protein [FKRP]), LGMD 2C-F (sarcoglycanopathies), LGMD 2G (telethoninopathy), Emery-Dreifuss muscular dystrophy, and Andersen's syndrome. It is critical to identify cardiac disease early because it may be amenable to therapy, including afterload reduction and pacemakers.

Hepatomegaly may be seen in myopathies associated with deficiencies in acid maltase, debranching enzyme, and carnitine. The presence of cataracts, frontal balding, and mental retardation strongly suggests the diagnosis of myotonic dystrophy. Optic atrophy and/or pigmentary retinopathy may be associated with a mitochondrial myopathy. The presence of a rash is extremely helpful in confirming the diagnosis of dermatomyositis and vasculitis, and multiple lipomas may lead to a diagnosis of a mitochondrial disorder. Musculoskeletal contractures can occur in many myopathies of long-standing duration. However, contractures developing early in the course of the disease, especially at the elbows, can be a clue to Emery-Dreifuss dystrophy, LGMD 1B (laminopathy), and Bethlem myopathy.

Central nervous system (CNS) involvement is frequently seen in the mitochondrial myopathies and may include strokelike episodes, headache, myoclonus, epilepsy, deafness, ataxia, and encephalopathy. CNS involvement in the form of a lower intelligence quotient occurs in some patients with Duchenne's dystrophy and in congenital myotonic dystrophy. Magnetic resonance imaging (MRI) in congenital muscular dystrophy with

Table 11 Conditions That May Affect Both Muscle and Peripheral Nerve

Alcohol abuse
Amyloidosis (acquired or familial)
Chronic renal failure
Collagen vascular disorders (rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosis)
Congenital muscular dystrophy associated with merosin deficiency
Endocrine disorders (hypothyroidism, acromegaly)
HIV infection
Inclusion body myositis
Lamin A/C mutations
Medications
Malnutrition
Mitochondrial myopathies
Paraneoplastic disease
Sarcoidosis

laminin α-2 chain deficiency shows hypomyelination, but patients rarely have intellectual impairment.[9] Peripheral nervous system (PNS) involvement can occur in some myopathies as well; in these rare situations, the differential diagnosis is rather limited (Table 11) and includes alcohol abuse, amyloidosis, sarcoidosis, collagen vascular disorders, endocrine disorders, HIV infection, malnutrition, and mitochondrial myopathies.

6. What is the Distribution of Weakness?

The distribution of weakness is in many respects the most essential information to be determined from the history and physical examination, as it provides critical clues to the diagnosis. To determine the distribution of muscle weakness, it is important to know which muscles to test and how to grade their power. Muscle strength can be tested by manual testing and from observation of functional activity (Table 12). Functional testing is particularly informative in young children, who cannot usually cooperate with formal manual muscle testing, and in adults with "give-way" weakness who present with complaints of muscle pain.[10]

In performing manual muscle testing of the upper extremities, it is necessary to assess shoulder abduction, external and internal rotation; elbow flexion and extension; wrist flexion and extension; and finger and thumb extension, flexion, and abduction. Muscle groups that should be tested in the lower extremities include hip flexion, extension, and abduction; knee flexion and extension; ankle dorsiflexion, plantar flexion, inversion, and eversion; and toe extension and flexion. All muscle groups should be tested bilaterally, and preferably against gravity. Neck flexors should be assessed in the supine position and neck extensors in the prone position. Knee extension and hip flexion should be tested in the seated position, knee flexion should be tested prone, and hip abduction should be tested in the lateral decubitus position. If testing against gravity is not done, the presence of significant muscle weakness can escape recognition. Assessment of muscle strength is usually based on the expanded MRC (Medical Research Council of Great Britain) grading scale of 0 to 5 (Table 13).[11]

Table 12 Functional Assessment of Muscle Weakness

Location	Signs or Symptoms of Weakness
Facial	Inability to ''bury eyelashes,'' ''horizontal smile,'' inability to whistle
Ocular	Double vision, ptosis, dysconjugate eye movements
Bulbar	Nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals
Neck	Poor head control
Trunk	Scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up
Shoulder girdle	Difficulty lifting objects overhead, scapular winging
Forearm/hand	Inability to make a tight fist, finger or wrist drop
Pelvic girdle	Difficulty climbing stairs, waddling gait, Gower's sign
Leg/foot	Foot drop, inability to walk on heels or toes
Respiratory	Use of accessory muscles

Finally, cranial nerve muscles such as the orbicularis oculi and oris, extraocular muscles, tongue, masseters, and palate should be examined. These may be best tested by observation of functional activities such as asking the patient to whistle, suck from a straw, and smile broadly. Mild ptosis may be subtle and difficult to detect on examination, and some patients may tilt their head backward, raise their eyebrows or wrinkle their foreheads in an attempt to compensate. When assessing ptosis and extraocular muscle function, it is also critical to check for fatigability. Evaluating the patient's speech is also an excellent method for assessing palatal and tongue strength. Palatal weakness produces speech that is nasal, with difficulty pronouncing sounds such as *k* and the hard *g*. In contrast, tongue weakness produces slurred speech, and patients have difficulty with sounds such as *d*, *l*, *n*, and *t*. Swallowing can be assessed by timing how long it takes to swallow a certain amount of fluid or by documenting the number of swallows taken.

In addition to manual muscle testing and functional testing, muscles should be inspected for evidence of atrophy or hypertrophy. Atrophy of proximal limb muscles is common in most chronic myopathies. However, certain myopathies may demonstrate atrophy in specific groups that correspond to severe weakness in those muscles and provide additional diagnostic clues.

Table 13 Expanded MRC* Scale for Manual Muscle Testing

Modified MRC Grade	Degree of Strength
5	Normal power
5 –	Equivocal, barely detectable weakness
4 +	Definite but slight weakness
4	Able to move the joint against combination of gravity and some resistance
4 –	Capable of minimal resistance
3 +	Capable of transient resistance but collapses abruptly
3	Active movement against gravity
3 –	Able to move against gravity but not through full range
2	Able to move with gravity eliminated
1	Trace contraction
0	No contraction

*Medical Research Council of Great Britain.

For example, atrophy of the parascapular muscles associated with scapular winging is characteristic of FSH dystrophy. Scapular winging is also seen in patients with LGMD 1B (laminopathy), LGMD 2A (calpainopathy), and LGMD 2C-F (sarcoglycanopathies). Selective atrophy of the quadriceps muscles and forearm flexor muscles is highly suggestive of inclusion body myositis. Distal myopathies may have profound atrophy of the anterior or posterior lower extremity compartments. On the other hand, muscles can show evidence of hypertrophy in some myotonic conditions such as myotonia congenita and neuromyotonia. Muscle hypertrophy is also characteristic of disorders including amyloidosis, sarcoidosis, debrancher enzyme deficiency, and hypothyroid myopathy. In Duchenne's and Becker's dystrophy, the calf muscles demonstrate "pseudohypertrophy" due to replacement with connective tissue and fat. Calf muscle hypertrophy is also characteristically seen in LGMD 2C-F (sarcoglycanopathies) and LGMD 2I (FKRP). In LGMD 2G (telethoninopathy), 50% of patients will show calf hypertrophy and 50% will have calf atrophy.[12] Focal muscle enlargement can also be due to a neoplastic or inflammatory process, ectopic ossification, tendon rupture, or partial denervation.

PATTERN RECOGNITION APPROACH TO MYOPATHIC DISORDERS

After answering the six key questions obtained from the history and neurological examination outlined previously, a myopathic disorder can be classified into one of six distinctive patterns of muscle weakness.[13] Although there are certainly exceptions to any rule concerning the distribution of involved muscles, using this classification system allows the practitioner to be able to substantially restrict the differential diagnosis. The final diagnosis can then be confirmed based on information from a *selective* number of laboratory studies.

Pattern 1: Proximal Limb-Girdle Weakness

The most common pattern of muscle weakness in myopathies is symmetric weakness affecting predominantly the proximal muscles of the legs and arms, or the so-called "limb-girdle" distribution. The distal muscles are usually involved, but to a much lesser extent. Neck extensor and flexor muscles are also frequently affected. This pattern of weakness is seen in most hereditary and acquired myopathies and, therefore, is the least specific in arriving at a particular diagnosis.[12,14]

Pattern 2: Distal Weakness

The distal pattern of weakness predominantly involves the distal muscles of the upper or lower extremities (anterior or posterior compartment muscle groups) (Table 14).[15] Depending on the diagnosis and severity of disease, proximal muscles may also be affected. The involvement is usually, although not invariably, symmetric. Selective weakness and atrophy in distal extremity muscles is more commonly a feature of neuropathies; therefore, a careful sensory and reflex examination must always be performed in patients presenting with this phenotype.

Pattern 3: Proximal Arm/Distal Leg Weakness (Scapuloperoneal)

The scapuloperoneal pattern of weakness affects the parascapular muscles of the proximal arm and the anterior compartment muscles of the distal lower extremity, or the so-called "scapuloperoneal" distribution (Table 14). The scapular muscle weakness is usually characterized by scapular winging. Weakness can be very *asymmetric*. These patients often relate a history of prominent "sloped shoulders" or "poor posture" and may have difficulty climbing a rope, throwing a ball, or swinging a golf club. When this pattern is associated with facial weakness, it is highly suggestive of a diagnosis of FSH dystrophy. Asymmetric facial weakness in FSH dystrophy results in an odd, twisted smile with dimpling at the corner of the mouth and a depressed and "flat" appearance to the patient's face. Other hereditary myopathies that are associated with a scapuloperoneal distribution of weakness include scapuloperoneal dystrophy, Emery-Dreifuss dystrophy, LGMD 1B (laminopathy), LGMD 2A (calpainopathy), and LGMD 2C-F (sarcoglycanopathies), LGMD 2I (FKRP), congenital myopathies, phosphorylase deficiency, and acid maltase deficiency.[12]

Table 14 Myopathies Characterized By Predominantly Distal Weakness

Childhood onset distal myopathy
Congenital myopathies
Nemaline myopathy*
Central core myopathy*
Centronuclear myopathy
Cytoplasmic body myopathy
Distal myopathies
Desmin myopathy
Emery-Dreifuss humeroperoneal dystrophy*
Facioscapulohumeral dystrophy*
Inclusion body myositis
Inflammatory myopathies
Metabolic myopathies
Debrancher deficiency
Phosphorylase b kinase
Acid-maltase deficiency*
Myotonic dystrophy
Oculoparyngeal dystrophy
Oculopharyngodistal myopathy
Scapuloperoneal myopathy*

*Scapuloperoneal pattern can occur.

Pattern 4: Distal Arm/Proximal Leg Weakness

The distal arm/proximal leg pattern is associated with distal arm weakness involving the distal forearm muscles (wrist and finger flexors) and proximal leg weakness involving the knee extensors (quadriceps). Patients commonly complain of falls caused by their "knees giving out" and difficulty walking *down* stairs. They may also complain of difficulty picking up coins, winding their wrist watch, or knitting. The facial muscles are usually spared. Involvement of other muscles is extremely variable. In addition, the weakness is often *asymmetric* between the two sides, which is uncommon in most myopathies. This pattern is essentially pathognomonic for inclusion body myositis.[16] The pattern may also represent an uncommon presentation of myotonic dystrophy; however, unlike inclusion body myositis, muscle weakness is symmetric.

Pattern 5: Ptosis With or Without Ophthalmoplegia

Myopathies presenting with predominant involvement of ocular and/or pharyngeal muscles represent a relatively limited group of disorders (Table 15). The eye involvement principally results in ptosis and ophthalmoplegia, which usually, although not always, occurs *without* symptoms of diplopia.[17] Facial weakness is not uncommon and questioning may elicit a history of having a "funny smile" or having difficulty blowing up balloons, drinking through a straw or clearing food caught between the lips and gums. Extremity weakness is extremely variable, depending on the diagnosis.

Table 15 Myopathies with Ptosis or Ophthalmoplegia

Ptosis without ophthalmoplegia
Congenital myopathies
Centronuclear myopathy
Nemaline myopathy
Central core myopathy
Desmin (myofibrillary) myopathy
Myotonic dystrophy
Ptosis with ophthalmoplegia
Chronic progressive external ophthalmoplegia
Oculopharyngeal muscular dystrophy
Oculopharyngodistal myopathy
Neuromuscular junction disease (myasthenia gravis, Lambert-Eaton, botulism)

The combination of ptosis, ophthalmoplegia without diplopia, and dysphagia should suggest the diagnosis of oculopharyngeal dystrophy, especially if the onset is in middle age or later. Ptosis and ophthalmoplegia without prominent pharyngeal involvement is a hallmark of many of the mitochondrial myopathies. Ptosis and facial weakness without ophthalmoplegia is a common feature of myotonic dystrophy and fascioscapulohumeral dystrophy.

Pattern 6: Prominent Neck Extensor Weakness

The prominent neck extensor weakness pattern is characterized by severe weakness of the neck extensor muscles. The term "dropped head syndrome" has been used in this situation (Table 16).[18] Involvement of the neck flexors is variable. Extremity weakness depends on the diagnosis and may follow one of the previously outlined phenotypic patterns. For example, a patient with a limb-girdle pattern of weakness may also have significant neck extensor involvement. Isolated neck

Table 16 Myopathies with Prominent Neck Extensor Weakness

Acid maltase deficiency
Carnitine deficiency
Desmin myopathy
Dermatomyositis
Facioscapulohumeral dystrophy
Hyperparathyroidism
Hypothyroidism
Hypokalemic periodic paralysis (acute)
Inclusion body myositis
Isolated neck extensor myopathy
Myotonic dystrophy types 1 and 2
Nemaline rod myopathy
Polymyositis

extension weakness represents a distinct muscle disorder called isolated neck extensor myopathy (INEM). Prominent neck extensor weakness is also common in two other neuromuscular diseases: amyotrophic lateral sclerosis and myasthenia gravis.

LABORATORY APPROACH IN THE EVALUATION OF A SUSPECTED MYOPATHY

At the conclusion of the history and physical examination, a relatively short list of possible diagnoses should be under consideration. Laboratory studies can then be judiciously used to make a final diagnosis. It is important to recognize that laboratory testing in myopathies may serve different purposes, depending on the type of test and the nature of the problem. Some tests, such as DNA analyses in genetic disorders and enzyme assays in the metabolic myopathies, will provide a specific diagnosis. Other tests, such as electromyography and the ischemic forearm test, suggest the type of problem but not an exact diagnosis.

Creatine Kinase

Creatine kinase (CK) is the single most useful laboratory study for the evaluation of patients with a suspected myopathy. The CK is elevated in the majority of patients with muscle disease but may be normal in slowly progressive myopathies. The degree of CK elevation can also be helpful in distinguishing different forms of muscular dystrophy. For example, in Duchenne dystrophy, the CK is invariably at least 10 times (and often up to 100 times) normal, whereas in most other myopathies there are lesser elevations. The other exceptions are LGMD 1C (caveolinopathy), LGMD 2A (calpainopathy), and LGMD 2B (dysferlinopathy), where CK may also be markedly elevated. The CK level may not be elevated in some myopathies or may even by lowered by several factors including profound muscle wasting, corticosteroid administration, collagen diseases, alcoholism, or hyperthyroidism.

In the inflammatory myopathies, the CK is usually, but not always, elevated, more so in polymyositis and dermatomyositis than inclusion body myositis. It is important, however, to recognize that the degree of CK elevation in these disorders has an imprecise relationship to muscle strength and therefore should not be relied on completely in following a patient's response to therapy. It is also important to remember that an elevation of serum CK does not necessarily imply a primary myopathic disorder (Table 17). Many times the CK will rise modestly (usually to less than 10 times normal) in motor neuron disease and uncommonly, CK elevations may be seen in Guillain Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. Endocrine disorders such as hypothyroidism and hypoparathyroidism can also be associated with high CK levels. Causes of CK elevation other than neuromuscular disease include muscle trauma (falls, intramuscular or subcutaneous injections, EMG studies, electric shock), viral illnesses, hypothermia, cardiac injury, seizures, severe dyskinesias, or vigorous exercise. In these cases, CK elevations are usually transient and less than 5x normal.

Table 17 Differential Diagnosis of Creatine Kinase Elevation

Myopathies
Carrier state (dystrophinopathies)
Channelopathies
Congenital myopathies
Drug/toxin-induced
Inflammatory myopathies
Metabolic myopathies
Muscular dystrophies
Motor neuron diseases
Amyotrophic lateral sclerosis
Postpolio syndrome
Spinal muscular atrophy
Neuropathies
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyneuropathy
Nonneuromuscular
Hypothyroidism/hypoparathyroidism
''Idiopathic hyperCKemia''
Increased muscle mass
Malignant hyperthermia
Medications
Race
Sex
Strenuous exercise
Surgery
Trauma (EMG studies, IM, or SQ injections)
Viral illness

EMG, electromyography; IM, intramuscular; SQ, subcutaneously.

Medications can cause serum CK elevations either with or without associated muscle weakness (Table 18). Race and gender can also affect serum CK (Table 19).[19] CK levels are frequently above the "normal" range in some African-American individuals and in patients with enlarged muscles. Occasionally, benign elevations of CK appear on a hereditary basis. It is extremely unusual for a slightly elevated CK (threefold or less) to be associated with an underlying myopathy in the absence of objective muscle weakness or pain.

Serum tests for other muscle enzymes are significantly less helpful than the determination of the CK. Enzymes such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), and lactate dehydrogenase (LDH) may be slightly elevated in myopathies. Because AST, ALT, and LDH are often

Table 18 Medications Associated with Creatine Kinase Elevations

Amiodarone
Cimetidine
Clofibrate
Chloroquine
Colchicine
Cyclosporine
Heroin
Labetalol
Lipid-lowering drugs
HMG-CoA reductase inhibitors (statins)
Fibric acid derivatives (gemfibrozil)
Niacin
Nifedipine
Procainamide
D-Penicillamine
Zidovudine

HMG-CoA, beta-hydroxy-beta-methylglutaryl-coenzyme A.

measured in screening chemistry panels, their elevation should prompt CK measurement to determine if the source is muscle or liver. If a patient with an inflammatory myopathy is treated with an immunosuppressive agent that may cause hepatoxicity, the liver specific enzyme, gamma glutamic transferase (GGT) should be followed.

In general, CK isoenzymes are not helpful in evaluating myopathies. CK-MM elevations are typical of muscle disease, but CK-MB is also elevated in myopathies and does not indicate that cardiac disease is present. In mitochondrial disorders, serum lactate can be a useful screening test because it is commonly elevated at rest. Blood and urine carnitine and acylcarnitine assays can be helpful in the diagnosis of a disorder of lipid metabolism.

ELECTROPHYSIOLOGICAL STUDIES

Electrodiagnostic studies, consisting of both nerve conduction studies (NCS) and electromyography (EMG), should be part of the routine evaluation of a patient with a suspected myopathy.[20] These studies are helpful in confirming that the muscle is indeed the correct site of the lesion and that weakness is not the result of an underlying motor neuron disease, neuropathy, or neuromuscular junction disorder. Nerve conduction studies are typically normal in patients with myopathy. Needle EMG examination showing evidence of brief duration, small amplitude motor units with increased recruitment can be extremely helpful in confirming the presence of a myopathy. Needle EMG can also provide a clue to which muscles have had recent or ongoing muscle injury and can be a guide to which muscle to biopsy. It is important to realize, however, that the EMG can be normal in a patient with myopathy, and the results of electrodiagnostic studies need to be evaluated in the context of the patient's history, neurological examination, and other laboratory studies. For example, there are some diseases that mainly produce a myopathy but that may also be associated with a subclinical neuropathy such as mitochondrial disorders, myotonic dystrophy, and inclusion body myositis.

Table 19 Effect of Race and Gender on Creatine Kinase Measurements

Group	Constituents	ULN (97.5%)
High	Black males	520 IU/L
Intermediate	Nonblack males Black females	345 IU/L
Low	Nonblack females	145 IU/L

ULN, upper limit of normal.

THE MUSCLE BIOPSY

If the clinical features and/or electrodiagnostic features suggest the possibility of a myopathy, a muscle biopsy may be an appropriate test to confirm the diagnosis. However, many forms of hereditary muscle disorders can now be diagnosed with molecular genetic testing, thereby eliminating the need for performing a muscle biopsy in every patient. Similar to the use of electrophysiological studies, biopsy results must be interpreted in the light of the clinical history and other laboratory studies. It is also important to recognize that pathological changes may be focal, both between muscles and within a given muscle. This is particularly true for all of the inflammatory myopathies.

A muscle specimen can be obtained through either an open or closed (needle or punch) biopsy procedure. The advantage of a needle or punch biopsy is that it is minimally invasive, is cosmetically more appealing, and multiple specimens can be obtained. The disadvantage of the closed biopsy procedure is that not all laboratories have the expertise to adequately process the muscle tissue acquired with this approach for all the necessary studies. Selection of the appropriate muscle to biopsy is critical. Muscles that are severely weak (MRC grade 3 or less) should be not be biopsied because the results are likely to show only evidence of "end-stage" muscle. In addition, muscles that have recently been studied by needle EMG should be avoided due to the possibility of artifacts created by needle insertion. Biopsies should generally be taken from muscles that demonstrate MRC grade 4 strength. For practical purposes, in the upper extremities, the muscles of choice are either the biceps or deltoid; in the lower extremities, the best choice is the vastus lateralis. The gastrocnemius should be avoided because its tendon insertion extends throughout the muscle and inadvertent

Table 20 Utility of Muscle Biopsy Stains and Histochemical Reactions

Histochemical Reactions and Stains	Clinical Utility
Hematoxylin and Eosin	General histology
Gomori trichrome	General histology and mitochondrial disease
ATPase	Distribution of fiber types
NADH, SDH, cytochrome oxidase	Myofibrillar and mitochondrial abnormalities
Periodic acid-Schiff	Glycogen storage diseases
Oil Red O	Lipid storage diseases
Congo Red, Crystal Violet	Detection of amyloid deposition
Myophosphorylase	McArdle's disease
Phosphofructokinase	Phosphofructokinase deficiency
Myoadenylate deaminase	Myoadenylate deaminase deficiency
Dystrophin immunostain	Duchenne's and Becker's muscular dystrophy
Dysferlin immunostain	Limb-girdle MD 2B
Membrane attack complex immunostain	Dermatomyositis, polymyositis

ATPase, adenosine triphosphatase; NADH, nicotinamide adenine dinucleotide; SDH, succinate dehydrogenase; MD, muscular dystrophy.

sampling of a myotendinous junction may cause difficulty with interpretation. Occasionally, an imaging procedure such as muscle ultrasound, computed tomography, or MRI can be used to guide selection of the appropriate muscle to biopsy.

Muscle biopsy specimens can be studied through histological, histochemical, immunocytochemical, biochemical, electron microscopic, or genetic techniques (Table 20).[21,22] In most instances, light microscopic observations of frozen muscle tissue specimens are sufficient to make a pathological diagnosis. Typical myopathic abnormalities include central nuclei, both small and large hypertrophic round fibers, split fibers, and degenerating and regenerating fibers. Inflammatory myopathies are characterized by the presence of mononuclear inflammatory cells in the endomysial and perimysial connective tissue between fibers, and occasionally around blood vessels. In addition, in dermatomyositis, atrophy of fibers located on the periphery of a muscle fascicle, perifascicular atrophy, is a common finding. Chronic myopathies frequently show evidence of increased connective tissue and fat.

For general histology, hematoxylin and eosin (H&E) and modified Gomori trichrome are the most useful. The latter is particularly helpful in identifying ragged-red fibers, which might suggest a mitochondrial disorder. In addition to these standard stains, other histochemical reactions can be used to gain additional information (Table 20). The myosin adenosine triphosphatase (ATPase) stains (alkaline - pH 9.4 and acidic - pH 4.3 and 4.6) allow a thorough evaluation of histochemistry fiber types. Type 1 fibers (slow-twitch, fatigue-resistant, oxidative metabolism) stain lightly at alkaline and darkly at acidic pHs. Type 2 fibers (fast-twitch, fatigue-prone, glycolytic metabolism) stain darkly at alkaline and lightly at acidic pHs. Normally, there is a random distribution of the two fiber types, and there are generally twice as many type 2 as type 1 fibers. In several myopathies, there is a nonspecific type 1 fiber predominance. Oxidative enzyme stains (nicotinamide adenine dinucleotide [NADH] dehydrogenase, succinate dehydrogenase, cytochrome-c oxidase) are useful for identifying myofibrillar and mitochondrial abnormalities. Periodic acid-Schiff (PAS) stains can be helpful in identifying glycogen storage diseases, and oil red O stains may assist with the diagnosis of a lipid storage disease. Acid and alkaline phosphatase reactions can highlight necrotic and regenerating fibers, respectively. Qualitative biochemical enzymes stains can be performed for myophosphorylase (McArdle's disease), phosphofructokinase (PFK) deficiency, and myoadenylate deaminase (MAD) deficiency. Amyloid deposition can be assayed with Congo red or crystal violet staining. Finally, immunohistochemical techniques can stain for muscle proteins that are deficient in some muscular dystrophies (e.g., dystrophin in Duchenne's and Becker's dystrophies) or for products that are increased in certain inflammatory myopathies such as the membrane attack complex in dermatomyositis.

Electron microscopy (EM) evaluates the ultrastructural components of muscle fibers and is not required in the majority of myopathies to make a pathological diagnosis. Electron microscopy is important, however, in the diagnosis of some congenital myopathies and mitochondrial disorders. Findings detected only by EM are seldom of clinical importance.

MOLECULAR GENETIC STUDIES

The specific molecular genetic defect is now known for a large number of hereditary myopathies, and mutations can be identified by peripheral blood DNA analysis. Molecular genetic studies that are commercially available

Table 21 Commercially Available Molecular Genetic Studies Performed with Peripheral Blood Samples

Congenital muscular dystrophy (FKRP, FCMD, MEB, SGCA, and POMT1 mutations)
Duchenne and Becker muscular dystrophy (Dystrophin)
Facioscapulohumeral muscular dystrophy
Kearns Sayre syndrome/chronic progressive external ophthalmoplegia
Limb-girdle muscular dystrophy 1B (Lamin A/C), 1C (Caveolin), 2A (CAPN3), 2B (Dysferlin), 2C–F (Sarcoglycan), and 2I (FKRP)
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS)
Myotubular myopathy (MTM1 mutations)
Myoclonic epilepsy and ragged red fibers (MERRF)
Myotonic dystrophy (types 1 and 2)
Myotonia congenita (CLCN1)
Nemaline myopathy (ACTA1)
Nonaka myopathy/inclusion body myopathy type 2
Oculopharyngeal muscular dystrophy

FKRP, fukutin-related protein; FCMD, Fukuyama-type congenital muscular dystrophy; MEB, muscle-eye-brain; SGCA, alpha-sarcoglycan; POMT1, protein O-mannosyltransferase 1.

are included in Table 21. Molecular genetic testing frequently eliminates the need for muscle biopsy or additional laboratory testing. This technology is also extremely helpful for determining carrier status, identifying presymptomatic or at-risk individuals, and for performing prenatal testing. Occasionally, as in myotonic dystrophy, it may suggest phenotypic expression and severity of disease. Recently, molecular genetic studies have been useful for identifying patients for gene therapy trials.

OTHER TESTS

In addition to CK determinations, other blood tests that can be extremely helpful in the evaluation of a patient with a suspected myopathy include serum electrolytes, thyroid function tests, parathyroid hormone levels, and HIV tests. In patients with an inflammatory myopathy, serological determinations for systemic lupus erythematosus, rheumatoid arthritis, and other immunological markers (e.g., Jo-1 antibodies) can occasionally be useful. A urine analysis can also be performed to detect the presence of myoglobinuria. This should be suspected if the urine tests positive for blood but no red blood cells are identified.

Forearm exercise testing can be a critical part of the evaluation of a patient with a suspected metabolic myopathy. The exercise test should be performed without the blood pressure cuff because ischemic exercise may be hazardous in patients with defects in the glycolytic enzyme pathway. The test is performed by asking the patient to do isometric contractions using a hand grip dynamometer for 1.5 seconds separated by rest periods of 0.5 second for 1 minute. A resting blood sample for venous lactate and ammonia is obtained at baseline and subsequently at 1, 2, 4, 6, and 10 minutes following the completion of exercise. A threefold increase in lactate level represents a normal response. The characteristic elevation of serum lactate after exercise is absent (phosphofructokinase deficiency, myophosphorylase deficiency) or reduced (phosphoglycerate mutase deficiency). Conversely, myoadenylate deaminase deficiency results in a normal lactate rise but little or no increase in ammonia. Forearm testing is normal in all disorders of fat metabolism and also in some glycolytic disorders with fixed muscle weakness such as acid maltase deficiency. With submaximal effort, neither lactate nor ammonia will increase.[23]

CONCLUSION

Although this pattern recognition approach to myopathy may have limitations, it can be extremely helpful in narrowing the differential diagnosis and therefore minimizing the number of laboratory studies that must be ordered to confirm the diagnosis. There will always be patients with muscle disease who will not fit neatly into any of these six categories. In addition, patients with involvement of other areas of the neuroaxis such as the motor neuron, peripheral nerve, or neuromuscular junction may also frequently present with one of these patterns. For example, although proximal greater than distal weakness is most often seen in a myopathy, patients with acquired demyelinating neuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy) often have proximal as well as distal muscle involvement. Careful consideration of the distribution of muscle weakness and attention to these common patterns of involvement in the context of other aspects of the neurological examination and laboratory evaluation will usually, however, lead the clinician to a timely and accurate diagnosis.

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