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A PATTERN RECOGNITION APPROACH TO THE PATIENT WITH A SUSPECTED MYOPATHY

Richard J. Barohn, MD,
Gertrude and Dewey Ziegler Professor, Chairman, Department of Neurology, University Distinguished Professor, University of Kansas Medical Center, 3901 Rainbow Blvd, Mail Stop 2012, Kansas City, KS 66160, Phone: 913.588.6970

Mazen M. Dimachkie, MD, and
Professor of Neurology, Director, Neurophysiology Division, Director, Neuromuscular Section, Department of Neurology, University of Kansas Medical Center, 3901 Rainbow Blvd, Mail Stop 2012, Kansas City, KS 66160

Carlayne E. Jackson, MD, FAAN
Professor of Neurology and Otolaryngology, Assistant Dean of Ambulatory Services, Chief Medical Officer – UT Medicine San Antonio, University of Texas Health Science Center, 8300 Floyd Curl Drive, Mail Code 7883, San Antonio, Texas 78229-3900

Abstract

Myopathies are a heterogeneous group of disorders that can be challenging to diagnose. The purpose of this review is to provide a diagnostic approach based predominantly upon the clinical history and neurologic examination. Laboratory testing that can be subsequently used to confirm the suspected diagnosis based upon this pattern recognition approach will also be discussed. Over the past decade, there have been numerous discoveries allowing clinicians to diagnose myopathies with genetic testing. Unfortunately, some of the testing, particularly molecular genetics, is extremely expensive and frequently not covered by insurance. Careful consideration of the distribution of muscle weakness and attention to common patterns of involvement in the context of other aspects of the neurologic examination and laboratory evaluation should assist the clinician in making a timely and accurate diagnosis, and sometimes can minimize the expense of further testing

Corresponding Author: Richard J. Barohn, MD, Gertrude and Dewey Ziegler Professor, Chairman, Department of Neurology, University Distinguished Professor, University of Kansas Medical Center, 3901 Rainbow Blvd, Mail Stop 2012, Kansas City, KS 66160, rbarohn@kumc.edu, Phone: 913.588.6970.

WEBSITES:
NIH/Gene Reviews: genetic testing and reviews: http://www.ncbi.nlm.nih.gov/sites/GeneTests/review
Muscular Dystrophy Association http://mdausa.org/
Washington University Neuromuscular Disease Center http://neuromuscular.wustl.edu/

Keywords

Myopathy; limb-girdle; distal myopathy; inflammatory myopathy; metabolic myopathy; myotonia

Introduction

Myopathies are disorders affecting either the channel, structure or metabolism of skeletal muscle. Myopathies can be distinguished from other disorders of the motor unit, including the neuromuscular junction, peripheral nerve, or motor neuron, by characteristic clinical and laboratory features. Therefore, the first goal in approaching a patient with a suspected muscle disease is to determine the correct *site* of the lesion. Once the lesion is localized to the muscle, the next step is to identify whether the myopathy is due to a defect in the muscle channel, muscle structure, or a dysfunction in muscle metabolism. The second goal is to determine the *cause* of the myopathy. In general, myopathies can be classified into acquired or hereditary disorders (Box 1). Finally, the third goal in our approach is to determine if there is a specific treatment, and if not, to optimally manage the patient's symptoms in order to maximize their functional abilities and enhance their quality of life.

Clinical Evaluation

The most important component of evaluating a patient with a suspected myopathy is obtaining a comprehensive medical history. The history should allow the clinician to make a reasonable preliminary diagnosis that places the patient into one of the categories in Box 1. The findings on the physical examination, and in particular the distribution of muscle weakness, should provide additional information in determining the correct diagnosis. The results of laboratory studies (blood tests, electrodiagnostic studies, muscle biopsy, molecular genetic studies) then play a confirmatory diagnostic role. (Amato AA, Russell JA. Neuromuscular Disorders. New York: McGraw Hill, 2008. Barohn RJ. General Approach to Muscle Diseases. Cecil Textbook of Medicine, 23rd ed. Goldman & Bennett, 2008, p. 2816-2834. Brooke MH. A Clinician's View of Neuromuscular Disease, 2nd ed. Baltimore: Williams & Wilkins, 1986. Griggs RC, Mendell JR, Miller RG. Evaluation and Treatment of Myopathies. Philadelphia: FA Davis, 1995.) The first step in this clinical approach is to ask six key questions regarding the patient's symptoms.

1. Which "negative" and/or "positive" symptoms does the patient demonstrate?

Symptoms of muscle disease (Box 2) can be divided into "negative" complaints such as exercise intolerance, fatigue, muscle atrophy and weakness and "positive" complaints such as contractures, cramps, myalgias, muscle stiffness and myoglobinuria.

Weakness is by far the most common "negative" symptom reported by a patient with muscle disease—When the upper extremities are involved, patients notice trouble brushing their teeth, combing their hair or lifting objects overhead. If the weakness involves the lower extremities, patients will complain of difficulty arising from a low chair or toilet, getting up from a squatted position, or climbing stairs. These symptoms in the arms and legs indicate proximal muscle weakness, which is probably the most common

distribution of weakness in a myopathic disorder (see below). Less commonly, patients with myopathies can complain of distal weakness manifested as difficulty turning a key in the ignition, opening jars, or gait instability due to foot drop. Some myopathies may also result in cranial muscle weakness resulting in complaints of slurred speech, difficulty swallowing or double vision. Fatigue is a much less useful “negative” symptom since it is may be a result of a patient’s overall health, cardiopulmonary status, level of conditioning, sleeping habits or emotional state. Many patients who complain of generalized weakness or fatigue do not have a myopathy, particularly if the neurologic examination is normal. On the other hand, it is important to define the intensity and duration of exercise that provokes the fatigue since metabolic and mitochondrial myopathies can cause abnormal fatigability after exercise.

“Positive” symptoms associated with myopathies may include cramps, contractures, myalgias, muscle stiffness or myoglobinuria. Myalgia, like fatigue, is another non-specific symptom of some myopathies (Box 3). Myalgias may be episodic such as in metabolic myopathies or nearly constant such as in inflammatory muscle diseases. However, muscle pain is usually not common in most muscle diseases and pain is more likely to be due to orthopedic or rheumatologic disorders. It is extremely uncommon for a myopathy to be responsible for vague aches and muscle discomfort in the presence of a normal neuromuscular examination and laboratory studies.

Muscle cramps are a specific type of muscle pain. They are typically benign, occurring frequently in normal individuals, and are seldom a feature of a primary myopathy. Cramps commonly occur due to dehydration, hyponatremia, azotemia, myxedema and disorders of the nerve or motor neuron (especially amyotrophic lateral sclerosis), or most often are benign and not related to an underlying disease process. Cramps may last from seconds to minutes and are usually localized to a particular muscle region, typically the calves. Cramps are characterized by rapidly firing motor unit discharges on needle electromyography.

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 usually last longer and are electrically silent with needle electromyography. Muscle contractures should not be confused with fixed tendon contractures. Muscle disorders which are associated with contractures are listed in Box 4.

Myotonia is due to repetitive depolarization of the muscle membrane and results in impaired relaxation of muscle after forceful voluntary contraction. Myotonia most commonly involves the eyelids and hands. As a result, 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 improves with repeated exercise. In contrast, patients with paramyotonia congentia 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 Box 5. Sometimes patients with myotonia also complain of myalgias and fatigue.

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

2. 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 (Box 7)? 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 age three, whereas most Facioscapaulohumeral and Limb-girdle dystrophies (LGMD) begin in adolescence or later. For further discussion of these diseases, the reader is referred to the corresponding chapters in this issue. Of the inflammatory myopathies, dermatomyositis occurs in children and adults, polymyositis rarely occurs in children as a benign childhood myositis but is primarily 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 (inflammatory myopathies, muscular dystrophies) or *episodic* periods of weakness with normal strength interictally (metabolic myopathies due to certain glycolytic pathway disorders, periodic paralysis). The episodic disorders are characterized by acute loss of strength that can return to normal within hours or days. The tempo of the disorders with constant weakness can vary from: (1) acute or sub-acute progression in some inflammatory myopathies (dermatomyositis and polymyositis); (2) chronic slow progression over years (most muscular dystrophies); or (3) non-progressive 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 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, while a patient with acute rhabdomyolysis due to cocaine may have a single episode.

3. Is there a family history of a myopathic disorder?

Since many myopathies are inherited, obtaining a thorough family history is of tremendous importance in making a correct diagnosis. A detailed family tree should be completed to evaluate for evidence of autosomal dominant, autosomal recessive and X-linked patterns of transmission. Questions regarding family members' use of canes or wheelchairs, skeletal deformities or functional limitations are usually more informative than vague questions such as, "Does any member of your family have a muscle disease?" Identifying a particular

hereditary pattern can not only help in correctly diagnosing the specific myopathy (Box 8), but is also of critical importance in providing appropriate genetic counseling.

4. Are there precipitating factors that trigger episodic weakness or stiffness?

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 using either illegal drugs or prescription medications that might produce a myopathy. Drugs that can cause toxic myopathies are listed in Box 9 and further discussion of this topic is found in the Toxic Myopathy chapter in this issue. A history of weakness, pain, and/or myoglobinuria that is provoked by exercise might suggest the possibility of a glycolytic pathway defect. Episodes of weakness that occur in association with a fever would be supportive of a diagnosis of Carnitine Palmityl Transferase deficiency. Periodic paralysis is 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.

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. Cardiac disease (Box 10) may be associated with Andersen-Tawil Syndrome, Duchenne’s or Becker’s muscular dystrophies, Emery-Dreifuss muscular dystrophy, LGMD 1B (Laminopathy), LGMD 2I (Fukutin related protein), LGMD 2C-F (sarcoglycanopathies), LGMD2G (telethoninopathies), and Myotonic dystrophy (types 1 and 2).

Respiratory failure may be the presenting symptom of Acid Maltase deficiency, Centronuclear myopathy, Myotonic dystrophy, or Nemaline myopathy (Box 11). Eventually, many myopathies will affect respiratory muscle strength, highlighting the need for consistent monitoring of pulmonary function studies throughout the disease course. Once symptoms of hypoventilation are evident, supportive care should be initiated with non-invasive positive pressure ventilation and assistive devices for clearance of upper airway secretions.

Hepatomegaly may be seen in myopathies associated with deficiencies in acid maltase, carnitine, and debranching enzyme. The presence of cataracts, frontal balding, and mental retardation strongly suggests the diagnosis of myotonic dystrophy. Dysmorphic features may be associated with the congenital myopathies. The presence of a rash is extremely helpful in confirming the diagnosis of dermatomyositis. Musculoskeletal contractures can occur in many myopathies of a longstanding duration. However, contractures developing early in the course of the disease, especially at the elbows, can be a clue to Bethlem myopathy, Emery-Dreifuss dystrophy, and LGMD 1B (laminopathy). Evidence of diffuse systemic disease can indicate amyloidosis, sarcoidosis, an endocrinopathy, collagen-vascular disease, infectious disease, or a mitochondrial disorder.

6. What is the distribution of weakness?

In order 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 (Box 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.

Assessment of muscle strength is usually based on the expanded MRC (Medical Research Council of Great Britain) grading scale of 0 to 5 (Box 13). 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 (Medical Research Council. Aids to the Examination of the Peripheral Nervous System. London: Balliere Tindall, 1986.). 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.

The MRC grading system has being criticized due to the unequal width of response options. For instance, a one point change from MRC 2 to 1 does not have the same significance as far as amount of motor unit or muscle loss as a change from 5 to 4. Using Rasch analysis (Vanhoutte EK1, Faber CG, van Nes SI, Jacobs BC, van Doorn PA, van Koningsveld R, Cornblath DR, van der Kooi AJ, Cats EA, van den Berg LH, Notermans NC, van der Pol WL, Hermans MC, van der Beek NA, Gorson KC, Eurelings M, Engelsman J, Boot H, Meijer RJ, Lauria G, Tennant A, Merkies IS; PeriNomS Study Group. Modifying the Medical Research Council grading system through Rasch analyses. Brain. 2012 May;135(Pt 5):1639-49.) in over a thousand patients with a variety of neuromuscular disorders, disordered thresholds were demonstrated in 74-79% of the muscles examined, indicating physicians’ inability to discriminate between most Medical Research Council categories regardless of physicians’ experience or illness type. Thresholds were restored after rescoring the Medical Research Council grades from six to four options (0, paralysis; 1, severe weakness; 2, slight weakness; 3, normal strength). The modified Medical Research Council sum score acceptably fulfilled Rasch model expectations.

Finally, cranial nerve muscles such as the orbicularis oculi and oris, extraocular muscles, tongue, 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.

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. For example, atrophy of the peri-scapular muscles associated with scapular winging is characteristic of facioscapulohumeral dystrophy. Scapular winging is also seen in patients with LGMD 1B (laminopathy), LGMD 2A (calpainopathy), Pompe disease 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. Muscle hypertrophy is also characterized by disorders including amyloidosis, sarcoidosis, and hypothyroid myopathy. In Duchenne's and Becker's dystrophy, the calf muscles demonstrate "pseudo-hypertrophy" due to replacement with connective tissue and fat. Calf muscle hypertrophy is also characteristically seen in LGMD 2C-F (sarcoglycanopathies), early on in the course of Miyoshi myopathy and anoctamin-5 defect and in LGMD 2I (fukutin-related protein). In LGMD 2G (telethoninopathy), 50% of the patients will show calf hypertrophy and 50% will demonstrate calf atrophy. 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 outlined above from the history and neurologic examination, one can attempt to classify a myopathic disorder into one of ten distinctive patterns of muscle weakness, each with a specific differential diagnosis. The final diagnosis can then be confirmed based on information from a *selective* number of laboratory evaluations.

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.

Pattern 2: Distal Weakness

This pattern of weakness predominantly involves the distal muscles of the upper or lower extremities (anterior or posterior compartment muscle groups) (Box 14) (Dimachkie and Barohn. Distal Myoapthies. N Clin N Am 2014 in current issue). 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 and 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)

This pattern of weakness affects the peri-scapular muscles of the proximal arm and the anterior compartment muscles of the distal lower extremity, or the so-called "scapuloperoneal" distribution (Box 15). The scapular muscle weakness is usually characterized by scapular winging. Weakness can be very *asymmetric*. When this pattern is associated with facial weakness, it is highly suggestive of a diagnosis of facioscapulohumeral muscular dystrophy (need statland tawil n clin ref). More detailed discussion of this entity can be found in the section of this issue titled "Facioscapulohumeral Muscular Dystrophy" by Statland and Tawil. Other hereditary myopathies that are associated with a scapuloperoneal distribution of weakness include acid maltase deficiency, congenital myopathies, Emery-Dreifuss dystrophy, LGMD 1B (laminopathies), LGMD 2A (calpain), and LGMD 2C-F (sarcoglycans), and scapuloperoneal dystrophy.

Pattern 4: Distal Arm/Proximal Leg Weakness

This 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). The facial muscles are typically spared and 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*. For further discussion of this disease, the reader is referred to the chapter in this issue titled "Inclusion Body Myositis." This pattern may also represent an uncommon presentation of myotonic dystrophy, however, unlike inclusion body myositis, muscle weakness is symmetric. (Barohn RJ. Myotonic dystrophy with quadriceps and finger flexor weakness: the inclusion body myositis phenotype. J Child Neurol 2002; 17:15.)

Case 1—A 68 y/o male without significant past medical history is referred for evaluation of slowly progressive muscle weakness for the past 5 years. His symptoms initially began with difficulty walking down stairs due to his right knee "giving out". He currently has difficulty arising from a chair and grasping objects with his right hand. He was evaluated by a neurologist two years ago whose workup included a CPK of 500 IU/L and a left quadriceps muscle biopsy which was consistent with "polymyositis". The patient has been treated with a variety of immunosuppressive medications including prednisone, methotrexate, and azathioprine with continued progression of his weakness. Current examination reveals intact cranial nerves, sensation, and muscle stretch reflexes. Motor exam in the right upper extremity shows MRC grade 5 shoulder abduction, 5 elbow flexion/extension, 4 wrist flexion, 5 wrist extension, and 3- finger flexion. Strength in the left upper extremity is normal except for grade 4+ finger flexion. In the left lower extremity, the patient exhibits grade 4+ hip flexion, 3+ knee extension, and 4+ ankle dorsiflexion with thigh muscle atrophy. In the right lower extremity, strength is normal except for grade 4+ knee extension.

Comment—The chronic onset, asymmetric distribution of weakness and selective involvement of wrist/finger flexion and knee extension is most consistent with a diagnosis of inclusion body myositis (IBM). In many cases, initial muscle biopsy fails to identify vacuoles and patients are inappropriately treated with immunosuppressant medications for

presumptive “polymyositis”. In patients with a phenotype consistent with IBM, particularly if they are “refractory” to immunosuppressive treatment, a repeat biopsy may be necessary to clarify the diagnosis.

Pattern 5: Ptosis With or Without Ophthalmoparesis

Myopathies presenting with predominant involvement of ocular and/or pharyngeal muscles represent a relatively limited group of disorders (Box 16). The ocular involvement principally results in ptosis and ophthalmoparesis which usually, although not always, occurs *without* symptoms of diplopia. Facial weakness is not uncommon and extremity weakness is extremely variable, depending on the diagnosis.

The combination of ptosis, ophthalmoparesis without diplopia, and dysphagia should suggest the diagnosis of oculopharyngeal dystrophy, especially if there is a positive family history and the onset is in middle-age or later. Ptosis and ophthalmoparesis without prominent pharyngeal involvement is a hallmark of many of the mitochondrial myopathies. Ptosis and facial weakness without ophthalmoparesis is a common feature of myotonic dystrophy and fascioscapulohumeral dystrophy. Ptosis has diurnal variation in ocular myasthenia gravis and is often associated with diplopia.

Case 2—A 70 y/o white female with a family history of “myasthenia gravis” presents for evaluation of an 10 year history of progressive dysphagia and weakness. She specifically denies any symptoms of diplopia and states that her symptoms do not fluctuate during the day or when she becomes fatigued. She has noted no improvement with a course of prednisone 60 mg/d and pyridostigmine 60mg QID. Cranial nerve examination is remarkable for bilateral ptosis, incomplete abduction /adduction of both eyes, mild orbicularis oris weakness, and mild tongue weakness. Motor exam reveals MRC grade 4 neck flexion, 4 shoulder abduction, 4+ elbow flexion, 5 finger extension, 4 hip flexion, 5 knee extension, and 5 ankle dorsiflexion and plantar flexion. Sensory, cerebellar, and reflex examinations are normal. Workup by a referring physician was remarkable for a CK of 350 IU/L and a negative acetylcholine receptor antibody.

Comment—The patient’s distribution of weakness (ptosis, ophthalmoparesis, dysphagia, and proximal weakness), age of onset, and positive family history would be most suggestive of a diagnosis of oculopharyngeal muscular dystrophy (OPMD). The absence of symptoms of diplopia and muscle fatigueability and the patient’s slowly progressive course strongly argues against of diagnosis of a neuromuscular junction disorder such as myasthenia gravis.

Pattern 6: Prominent Neck Extensor Weakness

This pattern is characterized by severe weakness of the neck extensor muscles. The term “dropped head syndrome” has been used in this situation (Box 17). Involvement of the neck flexors is variable. Extremity weakness is dependent 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 extension weakness represents a distinct muscle disorder called isolated neck extensor myopathy (INEM) (Need Katz NEM ref) (Katz JS, Wolfe GI, Burns DK, Bryan WW,

Fleckenstein JL, Barohn RJ. Isolated neck extensor myopathy: A common cause of dropped head syndrome. Neurology 1996;46:917 921.). Prominent neck extensor weakness is also common in two other neuromuscular diseases: amyotrophic lateral sclerosis and myasthenia gravis.

Pattern 7: Bulbar Weakness

Bulbar weakness, i.e. tongue and pharyngeal weakness, is manifested by symptoms of dysarthria and dysphagia. While a number of myopathies can have some bulbar involvement, the muscular dystrophy that has bulbar involvement as a primary manifestation is oculopharyngeal muscular dystrophy. Limb girdle muscular dystrophy type 1A (myotilinopathy) can present with isolated bulbar weakness and the inflammatory myopathies may rarely present in this manner. Neuromuscular junction disorders such as myasthenia gravis and Lambert-Eaton myasthenic syndrome also frequently have bulbar symptoms and signs. This pattern is considered an “overlap” pattern with amyotrophic lateral sclerosis and other motor neuron disorders which can have significant bulbar involvement.

Pattern 8: Episodic Pain, Weakness and Myoglobinuria

This is the pattern characterized by a history of episodic pain, weakness, and myoglobinuria and may be related to a variety of conditions, many of which are not due to an underlying muscle disorder (Box 18). When these symptoms are triggered by exercise, a metabolic myopathy is most likely. However, a number of patients may develop myoglobuinuria because they are inactive individuals who are suddenly required to do an overwhelming amount of exercise, i.e. the “couch potato” syndrome.

Pattern 9: Episodic Weakness Delayed or Unrelated to Exercise

This pattern applies to the disorders of periodic paralysis – both the genetic autosomal dominant channelopathies (Box 19) and the secondary periodic paralyses, such as those due to thyrotoxicosis. Also, for completeness sake, it is reasonable to include the neuromuscular junction disorders in this pattern. In all of these conditions, the weakness can occur during or after exercise, or often the weakness is unrelated to physical exertion.

Pattern 10: Stiffness and Decreased Ability to Relax

This pattern includes all of the disorders that produce myotonia and paramyotonia and includes the hereditary disorders involving sodium and chloride channelopathies (Boxes 20 and 21), as well as myotonic dystrophy types 1 and 2 (trivedi in this issue and thornton in this issue). Both myotonic dystrophies usually have fixed muscle weakness as well, with predominantly distal weakness in myotonic dystrophy type 1 and proximal weakness in myotonic dystrophy type 2. The autosomal recessive form of chloride channelopathies, Becker’s disease, also has fixed proximal weakness. In addition, other less common disorders that fit this pattern include Brody’s disease, neuromyotonia, and the central nervous system disorder, stiff-person syndrome (Box 20). Box 22 summarizes these 10 patterns of presentation of muscle disease. Once the key questions reviewed above have

been answered, and the patient has been placed into one of these 10 patterns of weakness, laboratory studies can then be used to confirm the diagnosis.

Laboratory Approach in the Evaluation of a Suspected Myopathy

Creatine kinase

Creatine kinase (CK) is an extremely useful laboratory study for the evaluation of patients with a suspected myopathy (Box 23). 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 less significant elevations. The other exceptions are LGMD 1C (caveolinopathy), 2A (calpainopathy), and 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 a number of factors including profound muscle wasting, corticosteroid administration, collagen diseases, alcoholism, or hyperthyroidism.

It is also important to remember than an elevation of serum CK does not necessarily imply a primary myopathic disorder. 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 Charcot-Marie Tooth and Guillain Barre syndrome. 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), viral illnesses, seizures, or strenuous exercise. In these cases, CK elevations are usually transient and less than 5x normal.

Race and gender can also affect serum CK (Box 24). CK levels are frequently above the “normal” range in some black 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 CPK (threefold or less) to be associated with an underlying myopathy in the absence of objective muscle weakness or pain. Recent data suggests that even higher cutoff values than those listed in Box 24 may be found in otherwise normal individuals based on gender and ethnicity (Silvestri NJ, Wolfe GI. Asymptomatic/pauci-symptomatic creatine kinase elevations (hyperckemia). Muscle Nerve. 2013 Jun;47(6):805-15.). For black males, an upper normal limit of 1,201 IU/L was suggested, for black females 621, nonblack males 504 and the lowest cutoff is for nonblack females of 325 IU/L. In the absence of muscle weakness on examination, these patients can be observed as long as the history does not suggest a metabolic myopathy (Martin A, Haller RG, Barohn RJ. Metabolic myopathies. Curr Opin Rheumatol 1994;6:552 558.).

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

Electrophysiologic Studies

Electrophysiologic 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 (Amato, A.A. & James A. Russell J.A. (2008). Testing in Neuromuscular Disease – Electrodiagnosis and Other Modalities. In A.A. Anthony, J. A. Russell (Eds.), Neuromuscular Disorders. (pp.17-70). The McGraw-Hill Companies Inc. Preston, D.C. & Shapiro, B.E (1998). Myopathy. In D.C. Preston, B. E. Shapiro. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiological Correlations (pp.525-539). Butterworth-Heinemann.). 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. NCS are typically normal in patients with myopathy except in distal myopathies. 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 as to which muscles have had recent or ongoing muscle injury and can be a guide as 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 exam, and other laboratory studies.

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 (Dubowitz, V., Sewery, C.A (2007). Muscle biopsy: a practical approach, third ed. London: Saunders.). However, many forms of hereditary muscle disorders can now be diagnosed with molecular genetic testing, eliminating the need for performing a muscle biopsy in every patient. 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 since the results are likely to show only evidence of "end-stage" muscle. In addition, muscles which 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 which 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 since its tendon insertion extends throughout the muscle and inadvertent sampling of a myotendinous junction may cause difficulty with interpretation. Occasionally, an imaging procedure such as muscle ultrasound, computed tomography, or magnetic resonance imaging can be used to guide selection of the appropriate muscle to biopsy.

Biopsy specimens can be analyzed by light microscopy, electron microscopy, biochemical studies and immune staining (Box 25). In most instances, light microscopic observations of frozen muscle tissue specimens are sufficient to make a pathologic 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, the 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 (Box 25). The myosin 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 a number of myopathies, there is a non-specific type 1 fiber predominance. Oxidative enzyme stains (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 (eg. dystrophin in Duchenne and Becker dystrophy) or for products that are increased in certain inflammatory myopathies such as the membrane attack complex in dermatomyositis or p62 in inclusion body myositis. (Dubourg O, Wanschitz J, Maisonobe T, et al. Diagnostic value of markers of muscle degeneration in sporadic inclusion body myositis. Acta Myol. 2011 Oct;30(2):103-8).

Electron microscopy (EM) evaluates the ultrastructural components of muscle fibers and is not required in the majority of myopathies to make a pathologic diagnosis. EM is important,

however, in the diagnosis of some congenital myopathies and mitochondrial disorders. Findings detected only by EM are seldom of clinical importance.

The muscle tissue can also be processed for biochemical analysis to determine a specific enzyme defect in the evaluation of a possible metabolic or mitochondrial myopathy. In addition, Western blot determinations from muscle tissue can be performed for certain muscle proteins. This type of analysis is usually limited to the dystrophin assays when the immune stains and the molecular genetic studies are inconclusive in establishing a diagnosis of either Duchenne or Becker dystrophy. This method has recently been expanded to calpainopathies and dysferlin defect though gene sequencing is more definitive.

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. Examples of molecular genetic studies which are commercially available are included in Box 26. This list continually updated on www.genetests.org. Molecular genetic testing frequently eliminates the need for muscle biopsy. This technology is also extremely helpful for determining carrier status and for performing prenatal testing. For Pompe disease, dry blood spot assay is a good screening test that must be followed by confirmation of acid alpha-glucosidase enzymatic activity in blood lymphocytes or other tissues (muscle or skin fibrobalsts) or through gene sequencing (please refer to the Pompe chapter in this issue).

Other Tests

In addition to creatine kinase determinations, additional 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, Vitamin D levels and HIV. In patients with an inflammatory myopathy, serologic determinations for systemic lupus erythematosis, rheumatoid arthritis, and other immunologic markers (eg. 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.(Martin A, Haller RG, Barohn RJ. Metabolic myopathies. Curr Opin Rheumatol 1994;6:552 558.)

Forearm exercise testing can often be an important part of the evaluation of a patient with a suspected metabolic myopathy. The exercise test should be carried out without the blood pressure cuff since ischemic exercise may be hazardous in patients with defects in the glycolytic enzyme pathway. The test is performed by asking the patient to perform isometric contractions using a hand grip dynamometer for 1.5 seconds separated by rest periods of 0.5 sec 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 (phosphoglycerase mutase deficiency). Forearm testing is normal in all disorders of fat metabolism and is also in some glycolytic disorders with fixed muscle weakness such as acid maltase deficiency.

Conclusion

While 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 which must be ordered to confirm the diagnosis. There will always be patients with muscle disease who will not fit neatly into any of these ten 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, while proximal greater than distal weakness is most often seen in a myopathy, patients with acquired demyelinating neuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy) 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 neurologic examination and laboratory evaluation will usually, however, lead the clinician to a timely and accurate diagnosis.

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References

1. Amato, AA.; Russell, JA. Neuromuscular Disorders. New York: McGraw Hill; 2008.
2. Barohn, RJ. Cecil Textbook of Medicine. 23. Goldman & Bennett; 2008. General Approach to Muscle Diseases; p. 2816-2834.
3. Brooke, MH. A Clinician’s View of Neuromuscular Disease. 2. Baltimore: Williams & Wilkins; 1986.
4. Griggs, RC.; Mendell, JR.; Miller, RG. Evaluation and Treatment of Myopathies. Philadelphia: FA Davis; 1995.
5. Medical Research Council. Aids to the Examination of the Peripheral Nervous System. London: Balliere Tindall; 1986.

BOX 1
CLASSIFICATION OF MYOPATHIES

Acquired:	
	Drug-induced myopathies
	Endocrine myopathies
	Inflammatory/immune myopathies
	Myopathies associated with other systemic illness
	Toxic myopathies
Hereditary:	
	Channelopathies
	Congenital myopathies
	Metabolic myopathies
	Mitochondrial myopathies
	Muscular dystrophies
	Myotonias

BOX 2

SYMPTOMS ASSOCIATED WITH MYOPATHIES

"Negative":
Exercise Intolerance
Fatigue
Muscle atrophy
Weakness
"Positive":
Cramps
Contractures
Muscle Hypertrophy
Myalgias
Myoglobinuria
Stiffness

BOX 3

MUSCLE DISEASES ASSOCIATED WITH MYALGIAS

Toxic/drug-induced myopathies (statins and others)
Eosinophilia-myalgia syndrome
Hypothyroid myopathy
Inflammatory myopathies (dermatomyositis, polymyositis)
Myotonic disorders
Mitochondrial myopathies
Tubular aggregate myopathy
Muscular dystrophies, examples:
X-linked myalgia and cramps/Becker's dystrophy variant
Infectious myositis (especially viral)
Myoadenylate deaminase deficiency (controversial)

BOX 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
- Rippling muscle disease

BOX 5

MYOPATHIES ASSOCIATED WITH MUSCLE STIFFNESS

Hypothyroid myopathy
Myotonia congenita
Paramyotonia congenita
Myotonic dystrophy type 1
Proximal myotonic myopathy (myotonic dystrophy type 2)
Hyperkalemic periodic paralysis

BOX 6

CAUSES OF MYOGLOBINURIA

Prolonged, intensive exercise

Drugs and toxin

Metabolic myopathies

- Glycogenoses (myophosphorylase deficiency)
- Lipid disorders (carnitine palmitoyltransferase deficiency)
- Malignant hyperthermia (Central core myopathy, Duchenne MD)

Heat stroke

Some muscular dystrophies (ex. Limb Girdle MD 2C-F (sarcoglycanopathies), 2I (FKRP), dystophenopathies

Neuroleptic malignant syndrome

Severe metabolic disturbances, including prolonged fever

Trauma (crush injuries)

Viral and bacterial infections (rare)

Inflammatory myopathies (rare)

BOX 7
DIAGNOSIS OF MYOPATHY BASED ON AGE OF ONSET

Myopathies Presenting at Birth

- Central core disease
- Centronuclear (myotubular) myopathy
- Congenital fiber-type disproportion
- Congenital muscular dystrophy
- Congenital myotonic dystrophy
- Glycogen storage diseases (acid maltase and phosphorylase deficiencies)
- Lipid storage diseases (carnitine deficiency)
- Nemaline (rod) myopathy

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 – Congenital, Duchenne, Becker, Emery-Dreifuss, Facioscapulohumeral, Limb-girdle

Myopathies Presenting in Adulthood

- Centronuclar myopathy
- Distal myopathies
- 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
- Mitochondrial myopathies
- Muscular dystrophies – Limb-girdle, Facioscapulohumeral, Becker, Emery-Dreifuss
- Myotonic dystrophy
- Nemaline myopathy
- Toxic myopathies – alcohol, corticosteroids, local injections of narcotics, colchicine, chloroquine

BOX 8

DIAGNOSIS OF MYOPATHY BASED ON PATTERN OF INHERITANCE

X-linked

Becker's MD, Duchenne's MD, Emery-Dreifuss MD

Autosomal dominant

Central Core Myopathy, FSH, Limb-Girdle Muscular Dystrophy type 1, Oculopharyngeal MD, Myotonic dystrophy, Paramyotonia congenita, Periodic paralysis, Thomsen's disease

Autosomal recessive

Becker's myotonia, Limb-Girdle Muscular Dystrophy type 2, Metabolic myopathies

Maternal transmission

Mitochondrial myopathies

BOX 9

DRUGS THAT CAN CAUSE TOXIC MYOPATHIES

Inflammatory:

- Cimetidine
- D-penicillamine
- Procainamide
- L-tryptophan
- L-dopa

Rhabdomyolysis and Myoglobinuria:

- Alcohol
- Amphetamine
- Cholesterol lowering drugs
- Cocaine
- Heroin
- Toluene
- ε-aminocaproic acid

Non-inflammatory Necrotizing or Vacuolar:

- Alcohol
- Cholesterol lowering agents
- Chloroquine
- Colchicine
- Cyclosporine and tacrolimus
- Emetine
- ε-aminocaproic acid
- Isoretinoic acid (vitamin A analogue)
- Labetalol
- Vincristine

Myosin Loss

- Non-depolarizing neuromuscular blocking agents
- Steroids

BOX 10

MYOPATHIES ASSOCIATED WITH CARDIAC DISEASE

Arrythmias

- Andersen-Tawil syndrome
- Kearn-Sayre syndrome
- Polymyositis
- Muscular Dystrophies: Myotonic, Limb-girdle1B, 2C-F, 2G, Emery-Dreifuss

Congestive heart failure

- Acid maltase deficiency
- Carnitine deficiency
- Muscular Dystrophies: Duchenne, Becker, Emery-Driefuss, Myotonic, Limb-girdle 1B, 2C-F, 2G
- Nemaline myopathy
- Polymyositis

BOX 11

MYOPATHIES ASSOCIATED WITH RESPIRATORY INSUFFICIENCY

Muscular Dystrophies	**Mitochondrial Myopathies**
Becker	
Duchenne	
Congenital	**Congenital Myopathies**
Emery-Driefuss	Centronuclar
Limb-girdle 2A, 2I	Nemaline
Myotonic	
FSHD	
Metabolic Myopathies	**Inflammatory Myopathies**
Acid maltase deficiency	Polymyositis
Debrancher deficiency	

BOX 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, disconjugate 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, inability to prevent escape from hand grip
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

BOX 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

BOX 14

Distal myopathies

- Late adult onset distal myopathy Type 1 (Welander)
- Late adult onset distal myopathy Type 2 (Markesbery/Udd)
- Early adult onset distal myopathy Type 1 (Nonaka)
- Early adult onset distal myopathy Type 2 (Miyoshi)
- Early adult onset distal myopathy Type 3 (Laing)

Centronuclear myopathy

Debrancher deficiency

Hereditary Inclusion Body Myopathy

Inclusion Body Myositis

Myofibrillar myopathy

Myotonic dystrophy

BOX 15

PATTERN 3: SCAPULOPERONEAL PATTERN OF WEAKNESS

Acid maltase deficiency
Central core myopathy
Emery-Dreifuss humeroperoneal dystrophy
Facioscapulohumeral dystrophy
Limb-girdle dystrophy 2A (calpain), 2C-F (sarcoglycans), 2I (FKRP)
Nemaline myopathy
Scapuloperoneal dystrophy

BOX 16

PATTERN 5: MYOPATHIES WITH PTOSIS OR OPHTHALMOPARESIS

Ptosis Without Ophthalmoparesis
Congenital myopathies
Nemaline myopathy
Central core myopathy
Desmin (myofibrillary) myopathy
Myotonic dystrophy
Ptosis With Ophthalmoparesis
Centronuclear myopathy
Mitochondrial myopathy
Multicore Disease
Oculopharyngeal muscular dystrophy
Oculopharyngodistal myopathy
Neuromuscular junction disease (Myasthenia Gravis, Lambert-Eaton, Botulism)

BOX 17

PATTERN 6: MYOPATHIES WITH PROMINENT NECK EXTENSOR WEAKNESS

Isolated neck extensor myopathy (INEM)
Dermatomyositis
Polymyositis
Inclusion body myositis
Carnitine deficiency
Facioscapulomumeral dystrophy
Myotonic dystrophy
Congenital myopathy
Hyperparathyroidism

BOX 18

PATTERN 8: MYOPATHIES WITH EPISODIC PAIN, WEAKNESS, AND MYOGLOBINURIA/ RHABDOMYOLYSIS

- **Related to exercise**
  - "Couch Potato" syndrome
  - Glycogenoses (McArdle's, etc.)
  - Lipid disorders (CPT deficiency)
- **Not related to exercise**
  - Central non-neuromuscular causes:
    - Neuroleptic malignant syndrome
    - Status epilepticus
  - Drugs/toxins
  - Malignant hyperthermia
  - Polymyositis/Dermatomyositis (rarely)
  - Viral/bacterial infections

BOX 19

PATTERN 9 EPISODIC WEAKNESS: DELAYED OR UNRELATED TO EXERCISE

- Periodic paralysis
  - Ca^{++} channelopathies (hypokalemic)
  - Na^{++} channelopathies (hyperkalemic)
  - Andersen-Tawil syndrome
  - Secondary PP (thyrotoxicosis)
- Other: Neuromuscular junction diseases

BOX 20
CHANNELOPATHIES AND RELATED DISORDERS

DISORDER	CLINICAL FEATURES	PATTERN OF INHERITANCE	CHROMOSOME	GENE
Chloride Channelopathies	Myotonia	Autosomal dominant	7q35	CLC-1
Myotonia Congenita				
Thomsen's disease	Myotonia	Autosomal dominant	7q35	CLC-1
Becker type	Myotonia + weakness	Autosomal recessive		
Sodium Channelopathies	Paramyotonia	Autosomal dominant	17q13.1-13.3	SCNA4A
Paramyotonia Congenita				
Hyperkalemic Periodic Paralysis	Periodic paralysis and myotonia and paramyotonia	Autosomal dominant	17q13.1-13.3	SCNA4A
Potassium-Aggravated Myotonias				
Myotonia fluctuans	Myotonia	Autosomal dominant	17q13.1-13.3	SCNA4A
Myotonia permanens	Myotonia	Autosomal dominant	17q13.1-13.3	SCNA4A
Acetazolamide-responsive	Myotonia	Autosomal dominant	17q13.1-13.3	SCNA4A
Calcium Channelopathies	Periodic paralysis	Autosomal dominant	1a31-32	Dihydropyridate receptor
Hypokalemic periodic paralysis				
Schwartz-Jampel Syndrome (Chondrodystrophic Myotonia)	Myotonia; dysmorphic	Autosomal recessive	1p34.1-36.1	Perlecan
Rippling Muscle Disease	Muscle mounding/stiffness	Autosomal dominant	1q41 3p25	Unknown Caveolin-3
Anderson-Tawil Syndrome	Periodic paralysis, cardiac arrhythmia, dysmorphic	Autosomal dominant	17q23	KCMJ2-Kir 2.1
Brody's Disease	Delayed relaxation, no myotonia	Autosomal recessive	16p12	Calcium-ATPase
Malignant Hyperthermia	Anesthetic induced delayed relaxation	Autosomal dominant	19q13.1	Ryanodine receptor

BOX 21

PATTERN 10 STIFFNESS/DECREASED ABILITY TO RELAX

- Improves with exercise
  - Myotonia – Na^{++} or Cl^{-} channelopathy
- Worsens with exercise/cold sensentivity
  - Paramyotonia – Na^{++} channelopathy
  - Brody's disease
- With fixed weakness
  - Myotonic dystrophy (DM 1)
  - Proximal myotonic myopathy (DM 2)
  - Becker's disease (AR Cl^{-} channelopathy)
- Other:
  - Malignant hyperthermia
  - Neuromyotonia
  - Rippling muscle
  - Stiff-person syndrome

BOX 22
CLINICAL PATTERNS OF MUSCLE DISORDERS

	Weakness						
	P	**D**	**Asy**	**Sy**	**E**	**T**	**Diagnosis**
Pattern 1 Limb girdle*	+			+			Most myopathies – hereditary and acquired (overlap with spinal muscular atrophy)*
Pattern 2* Distal		+		+			Distal myopathies (overlap with neuropathie s)*
Pattern 3 ProximaL arm / distal leg “scapuloperone al”	+ A	+ L	+ (FS	+ (oth			FSH, Emery-Dreifuss, Acid maltase, congenital scapuloperoneal
Pattern 4 Distal arm/proximal leg	+ L	+ A	+				IBM Myotonic dystrophy
Pattern 5 Ptosis/ Ophthalmoplegia	+		+ (M	+ (oth			OPD, MG, myotonic dystrophy, mitochondria
Pattern 6* Neck – extensor	+			+			INEM, MG (overlap with ALS)*
Pattern 7* Bulbar (tongue, pharyngeal)	+			+			MG, LEMS, OPD (overlap with ALS)*
Pattern 8 Episodic weakness/Pain/ rhabdo + trigger	+			+	+	+	McArdle’s, CPT, drugs, toxins
Pattern 9 Episodic weakness Delayed or unrelated to exercise	+			+	+	+	Primary periodic paralysis Channelopathies: Na^{++} Ca^{++} Secondary periodic paralysis
Pattern 10 Stiffness/Inabilty to relax					+	+	Myotonic dystrophy, channelopathies, rippling muscle (other: stiff-person, neuromyotonia)

*Overlap patterns with neuropathy/motor neuron disease

BOX 23

DIFFERENTIAL DIAGNOSIS OF CK ELEVATION

Myopathies	**Neuropathies**
Carrier state (dystrophinopathies)	Charcot-Marie Tooth
Channelopathies	Guillain Barre syndrome
Congenital myopathies	
Drug/toxin-induced	**Others**
Inflammatory myopathies	“Idiopathic hyperCKemia”
Metabolic myopathies	Increased muscle mass
Muscular dystrophies	Hypothyroidism/hypoparathyroidsim
	Medications
Motor neuron diseases	Race
Amyotrophic lateral sclerosis	Sex
Post-polio syndrome	Strenuous exercise
Spinal muscular atrophy	Surgery
	Trauma (EMG studies, IM, or SQ injections)

BOX 24

EFFECT OF RACE AND GENDER ON CK MEASUREMENTS

Group	Constituents	ULN
High	Black males	1,201 IU/L
Intermediate	Nonblack males	504 IU/L
	Black females	621 IU/L
Low	Nonblack females	325 IU/L

Adapted from Silvestri NJ, Wolfe GI. Asymptomatic/pauci-symptomatic creatine kinase elevations (hyperckemia). Muscle Nerve. 2013 Jun;47(6):805-15.

BOX 25

UTILITY OF MUSCLE BIOPSY STAINS AND HISTOCHEMICAL REACTIONS

Histochemical Reactions and Stains	Clinical Utility
ATPase	Distribution of fiber types
Gomori Trichrome	General histology and mitochondrial disease
Hematoxylin and Eosin	General histology
NADH, SDH, cytochrome oxidase	Myofibrillar and mitochondrial abnormalities
Oil Red O	Lipid storage diseases
Periodic acid-Schiff	Glycogen 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

BOX 26

COMMERCIALLY AVAILABLE MOLECULAR GENETIC STUDIES PERFORMED WITH PERIPHERAL BLOOD SAMPLES

Chronic progressive external ophthalmoplegia (POLG, TWINKLE, ANT1, OPA1)
Collagen VI Disorders (COL61, COL62, COL63)
Congenital Musclar Dystrophy (FKRP, FCMD, LAMA2, POMGNT, POMT1, POMT2)
Duchenne's and Becker's Muscular Dystrophy (DMD Sequencing)
Emery-Dreifuss Muscular Dystrophy (EMD, FHL1)
Facioscapulohumeral Muscular Dystrophy (FSHD)
Hypokalemic and Hyperkalemic periodic paralysis (CACNA1S, SCN4A)
Limb Girdle Muscular Dystrophy (CAPN3, CAV3, DYSF, FKRP, LMNA, SGCA, B, D, G, CAPN3, SGCA)
Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke (MELAS)
Myoclonic Epilepsy and Ragged Red Fibers (MERRF)
Myotonic Dystrophy (DM1, DM2)
Myofibrillar Myopathy (CRYAB, DES, FLNC, LDB3, MYOT, BAG3)
Myotubular Myopathy (MTM1 mutations)
Nemaline Myopathy (ACTA1 mutations)
Oculopharyngeal Muscular Dystrophy (OPMD)

KEY POINTS

- The initial key to the diagnosis of myopathies is recognition of a clinical pattern.
- There are six key questions the clinician should consider in arriving at the pattern that fits the patient.
- After arriving at the pattern that fits best, then the clinician can better determine the most appropriate diagnostic tests and management.