THE CLINICAL APPROACH TO MUSCLE DISORDERS (2017)

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OVERVIEW

In approaching a patient with weakness, the first task of the clinician is "lesion localization:" to determine by comprehensive clinical evaluation, which one of the four organs of the motor unit – motor neuron, peripheral nerve, neuromuscular junction, and muscle – is the site of the "lesion." Once localized to the muscle, a thorough history often helps clinicians determine whether the disorder of muscle (the myopathy) is inherited or acquired **(Table 1)**. By characterizing the distribution of muscle weakness, the physical examination may then provide additional diagnostic clues that help to identify correctly specific muscle disorders. Finally, the results of laboratory studies help to confirm and refine the diagnosis.

The history provides clinical clues:

In most myopathies, weakness is proximal (affecting movements of the hips, thighs, shoulders, upper arms) and is characterized by difficulty climbing stairs, arising from low chairs, and carrying out tasks above ones' head, such as placing a book on a high shelf or brushing ones' hair. Less commonly, weakness is distal (affecting movements of the feet-toes and hands-fingers) manifested by tripping because of foot drop or difficulty opening jars. Occasionally, weakness affects the cranial muscles so that patients report ocular symptoms (lid drooping or ptosis), difficulty swallowing (dysphagia), and effortful speech (dysarthria).

Associated "negative" symptoms of muscle disease, include fatigue, exercise intolerance, and muscle atrophy. "Positive" symptoms often point in the direction of a specific myopathy: For example, myalgias tend to be associated with toxic or infectious myopathy, with certain forms of inflammatory myopathy (associated with connective tissue disease), and with some myotonic myopathies; cramps suggest metabolic or endocrine myopathies; stiffness or impaired relaxation of muscle points to the possibility of myotonia as seen in the myotonic disorders; episodic tea-colored urine or myoglobinuria is strongly suggestive of a metabolic myopathy; and complaints of muscle enlargement deemed muscle hypertrophy by the clinician is often associated with muscular dystrophy (notably, the dystrophinopathies).

Determining onset, duration, and evolution of muscle disease enhances the effectiveness of the diagnostic process:

For example, weakness presenting at birth suggests some forms of congenital myopathy and infantile myotonic dystrophy; weakness emerging in childhood is typical of most types of muscular dystrophy, congenital myopathy, metabolic and mitochondrial myopathy, and rarely, inflammatory myopathy; and later-onset weakness, coming on in adulthood, is often seen in inflammatory, toxic and endocrine myopathies, and occasionally is a first manifestation of muscular dystrophy, metabolic and mitochondrial myopathies.

In the vast majority of myopathies, weakness, once established, is fairly stable or constant over the course of a 24-hour period, and is relatively uninfluenced by physiological state (for example, active or resting; fasting or post-prandial). There are certain muscle diseases, however, like the periodic paralyses, and the metabolic myopathies, that are characterized by episodic weakness of varying intervals and intensity, and with or without concomitant metabolic derangements such as myoglobinuria.

The tempo of the progression of weakness over time offers a clue to the character of the myopathy:

Acute to subacute progression (that is, weakness evolving over weeks to several months) is typically seen in toxic or inflammatory myopathies (polymyositis, dermatomyositis, immune-mediated necrotizing myopathy). Chronic progression (with weakness developing over many months to years) is typical of most muscular dystrophies and sporadic inclusion body myositis. Nonprogressive or mildly progressive weakness over the course of decades is characteristic of most forms of congenital myopathy, which explains why in some rare instances of mild congenital myopathy, diagnosis is not established until adulthood.

The pattern of inheritance:
Obtaining a detailed family history in any patient with a suspected myopathy is key to unlocking an underlying inherited disorder and identifying its pattern of inheritance. Patients are asked to reflect on certain details of their relatives' medical history such as overall strength, functional capacity, ability to walk and run, whether there was a need for assistive devices or orthoses to walk, need for a wheelchair or scooter, history of cardiac disease, whether the patient's (or proband's) symptoms were shared by males and females or were gender specific. Armed with such information, the clinician may have a heightened index of suspicion for an inherited muscle disease and be in the position to hypothesize the pattern of inheritance (autosomal dominant, autosomal recessive, X-linked, or mitochondrial), and thereby narrow the differential diagnosis and improve the ability to provide genetic counseling.

Clues to the diagnostic process are often found in exploring the patient's medication list, exercise experience, dietary preferences, and motor function in a cool or cold environment. For example, subacute myopathies in adulthood may have a toxic etiology, caused by a cholesterol lowering agent (statin), or by colchicine for gout, or chronic alcohol use. Corticosteroids, prescribed for a wide spectrum of medical disorders may be responsible for a subacute or chronic myopathy. In a susceptible individual with a defect in the glycolytic pathway, short bursts of activity could lead to muscle cramping, weakness and myoglobinuria; and in a patient with a disorder of lipid oxidation, long periods of low intensity exercise could predispose to muscle weakness and myoglobinuria. In individuals with a genetic predisposition to periodic paralysis, a high carbohydrate meal could be the trigger for an attack of severe muscle weakness. Finally, muscle stiffness that worsens with cold exposure may be seen in paramyotonia congenita.

The physical examination provides additional important clues that help in the diagnostic process:
Some myopathies affect tissues other than skeletal muscle per se, either because they are multisystem disorders like myotonic dystrophy, in which case the extra-muscular involvement may be truly multi-organ and multi-system (for example, in myotonic dystrophy, cataracts, arrhythmia, cognitive impairment, glucose intolerance are common) or because they affect cardiac muscle in addition to skeletal muscle, like the dystrophinopathies, Emery-Dreifuss dystrophy, and poly- and dermatomyositis, and may have a serious concomitant cardiomyopathy, with a clinical course punctuated by arrhythmia and congestive heart failure. The diaphragm is a striated muscle which can be involved in certain muscle diseases including dystrophinopathies, myotonic dystrophy, acid maltase deficiency, centronuclear myopathy, nemaline myopathy, and the inflammatory myopathies. Muscle thinning or hypertrophy (for example, enlarged calves) are important clinical signs that might suggest a congenital myopathy or a form of dystophinopathy, respectively. Dysmorphic features may be associated with congenital myopathies. Skin changes, especially a rash over the face and hands, are typical of dermatomyositis. Musculoskeletal contractures indicate of longstanding, usually inherited myopathy (including muscular dystrophy), such as Emery-Dreifuss dystrophy, and Bethlem myopathy. Finally, myopathy in the context of pronounced multi-organ involvement suggests such disorders as sarcoidosis, amyloidosis, endocrinopathies, connective tissue and infectious disorders, myotonic dystrophy and mitochondrial cytopathies.

Distribution of muscle weakness provides a clue to the diagnostic process:
In most myopathic disorders, the proximal and limb-girdle muscles bear the brunt of involvement; but there are important exceptions. For example, distal muscle involvement is quite characteristic of classic myotonic dystrophy type I, and dysferlinopathy; and ocular weakness is often an early manifestation of mitochondrial myopathy and oculopharyngeal dystrophy. The patterns of weakness can help narrow the differential diagnosis; thus, are further characterized by the distribution of predominant weakness as: proximal "limb-girdle", distal, proximal arm/distal leg, distal arm/proximal leg, ptosis with or without ophthalmoplegia, prominent neck extensor, bulbar, and episodic weakness **(Table 2)**.[1]

Laboratory tests often confirm the diagnosis when evaluating a patient with suspected myopathy.

These tests include:
1) Serum creatine kinase (CK) levels are expected to be elevated in myopathic disorders marked by muscle fiber necrosis, and normal in muscle disorders with little injury to the muscle fiber membrane.

2) Electrodiagnostic studies will show fibrillation potentials and positive sharp waves in the context of an aggressive myopathy (like inflammatory, toxic or dystrophic); yet no such potentials in most congenital and endocrine myopathies; early recruitment of short duration, low amplitude, motor unit potentials in weak muscles are seen irrespective of the cause of the myopathy.

3) Myositis Antibody Panel **(Table 3)**: A number of antibodies have been identified in myositis patients that are rarely found in other diseases. The presence of these myositis specific antibodies (MSAs) are not only diagnostic but can be predictive of disease outcome. Other autoantibodies, known as myositis associated antibodies (MAA), have also been identified. These autoantibodies are found in patients with myositis, but they are also present in patients with other autoimmune diseases such as scleroderma and systemic lupus erythematosus. While they are not diagnostic, the presence of these autoantibodies may be helpful in determining treatment and outcomes. Autoantibodies—either MSAs or MAAs—can be found in more than 80% patients with polymyositis or dermatomyositis.[2-4] Recent research has identified anti-cN-1A as a biomarker for sIBM with a sensitivity varying from 33-70% of IBM patients positive for the autoantibody.[5-7] Similarly, autoantibodies to the cholesterol regulating enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) have been identified as a marker for immune-mediated necrotizing myopathy.[8]

4) Muscle Imaging
Magnetic resonance imaging (MRI) has become a helpful method for sampling large volumes of muscle in a noninvasive manner and provides insight into disease activity as well as pattern of muscle involvement. Findings of edema in skeletal muscle on MRI are suggested by increased signal on T2 and STIR sequences or by gadolinium enhancement and can be seen in many of the inflammatory myopathies (indicating active disease with potential for immunotherapeutic response), but can also be seen in some muscular dystrophies. Other findings of muscle atrophy or fatty replacement can be markers of longstanding myopathies and an indicator of poor response to therapies.[9-11]

Additionally, MRI helps identify the pattern of muscle involvement. For example, in IBM patients, a forearm muscle MRI may highlight the preferential involvement of the forearm flexor compartment that correlates to the selective finger flexor weakness seen in sIBM patients (and not in DM or PM).[11-13]

MRI is also a helpful tool for localizing the site for muscle biopsy, to make certain the specimen is taken from an abnormal area.

5) Muscle biopsy analysis by light microscopy usually provides information that helps corroborate the classification into inherited and acquired myopathy and often provides further diagnostic specificity (for example: acquired myopathy that is inflammatory with features of perifascicular atrophy seen in dermatomyositis or rimmed vacuoles seen in inclusion body myositis); and immunohistochemical analysis of sections of frozen muscle tissue for specific muscle proteins when a muscular dystrophy is suspected. In selected cases, when metabolic myopathy is suspected, biochemical analysis of frozen muscle tissue for analysis of the glycolytic or oxidative, or mitochondrial metabolic pathways can be performed.

6) Genetic testing: In cases where muscular dystrophy is suspected but cannot be identified by immunohistochemical studies, molecular genetic testing by DNA analysis of leukocytes can sometimes confirm the diagnosis of a muscular dystrophy by identifying a specific known mutation. Dried blood spot test can be performed to screen for acid alpha-glucosidase deficiency and then confirmed by genetic testing.[14-16] Additionally, the Jain Foundation provides free genetic testing for the limb-girdle muscular dystrophies (LGMD) if the patient qualifies based on an automated algorithm of clinical features raising the suspicion for LGMD.

Table 1: Traditional Classification: Inherited versus Acquired Myopathies	
Inherited Myopathies	**Acquired Myopathies**

○ Dystrophinopathies
○ Limb girdle dystrophies
○ Myotonic dystrophies
○ Facioscapulohumeral dystrophy
○ Emery-Dreifuss dystrophy
○ Oculopharyngeal dystrophy
○ Congenital muscular dystrophy
○ Distal myopathies
○ Congenital myopathies
○ Metabolic myopathies
○ Mitochondrial myopathies
○ Periodic paralysis and channelopathies
	○ Idiopathic inflammatory myopathies
	  ○ Dermatomyositis
	  ○ Polymyositis
	  ○ Immune-mediated necrotizing myopathy
	  ○ Inclusion body myositis
	○ Endocrine myopathies
	○ Critical Illness myopathy
	○ Myopathy associated with sarcoidosis
	○ Toxic and drug-induced myopathies
	○ Electrolyte disturbance-related myopathies
	○ Infectious agent-related myopathies

Table 2: Distribution of Weakness	
Pattern of Weakness	**Differential Diagnoses**
Proximal “Limb Girdle”	○ Most acquired and many hereditary myopathies ○ Limb girdle muscular dystrophies
Distal	○ Distal myopathies
Proximal arm/Distal Leg “Scapuloperoneal Pattern”	○ Facioscapulohumeral dystrophy ○ Acid Maltase Deficiency ○ Central Core Myopathy ○ Emery-Dreifuss Humeroperoneal dystrophy ○ Limb-girdle dystrophy 2A, 2C-F, 2I ○ Nemaline myopathy ○ Scapuloperoneal dystrophy
Distal arm/Proximal Leg	○ Inclusion body myositis ○ Myotonic dystrophy
Ptosis (without Ophthalmoparesis)	○ Congenital myopathies (Nemaline, Central core) ○ Desmin Myofibrillar myopathy ○ Myotonic dystrophy
Ptosis (with Ophthalmoparesis)	○ Centronuclear myopathy ○ Mitochondrial myopathy ○ Multicore myopathy ○ Oculopharyngeal muscular dystrophy ○ Oculopharyngodistal myopathy ○ (Neuromuscular Junction: Myasthenia, Lambert-Eaton, Botulism)
Neck Extensor Weakness	○ Isolated Neck Extensor Myopathy (INEM) ○ Dermatomyositis ○ Polymyositis ○ Inclusion body myositis ○ Carnitine deficiency ○ Facioscapulohumeral dystrophy ○ Myotonic dystrophy ○ Congenital myopathy
Episodic Weakness	○ Metabolic (Glycogenoses, Lipid disorders) ○ Periodic paralysis/Channelopathies ○ Neuromuscular junction diseases

Barohn RJ, Dimachkie MM, Jackson CE. A pattern recognition approach to patients with a suspected myopathy. Neurologic clinics 2014;32:569.

Table 3: Myositis Antibodies		
Myositis-Associated Antibodies		
○ Anti-Ro ○ Anti-PM/Scl ○ Anti-Ku ○ Anti-U1 RNP		
Myositis-Specific Antibodies		
Autoantibody	Immune target	Clinical Association
Anti-Aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, KS, Ha, Zo)	tRNA synthetases	Polymyositis Anti-synthetase syndrome
Anti-Mi-2	NuRD subunit	Dermatomyositis, Mild disease
Anti-TIF1-γ	Transcriptional intermediary factor 1γ	Severe Dermatomyositis, Cancer-associated
Anti-NXP-2	Nuclear matrix protein 2	Severe Dermatomyositis, Cancer-associated
Anti-MDA5	Melanoma differentiation-associated protein 5	Amyopathic Dermatomyositis, Interstitial lung disease, Poor prognosis
Anti-SAE	SUMO-1 activating enzyme	Dermatomyositis, Initially amyopathic dermatomyositis
Anti-SRP	Signal recognition particle	Necrotizing myopathy
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase	Necrotizing myopathy Prior statin use
Anti-cN-1A (NT5c1A)	cN-1A	Inclusion body myositis

Ghirardello A, Borella E, Beggio M, Franceschini F, Fredi M, Doria A. Myositis autoantibodies and clinical phenotypes. Auto- immunity highlights 2014;5:69-75.

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