

# Clinical Approach to Patients with Muscle Disease

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Weakness is a commonly encountered complaint. Its causes can be divided among problems of the nervous system, neuromuscular junction, skeletal muscle and conditions that alter the function of nerves or muscles, such as anemia or cancer-associated cachexia. Those causes due to diseases of skeletal muscle are termed myopathies.

The first step in approaching the patient with muscle weakness is the history and physical examination. Myopathies typically cause weakness that affects the proximal muscle in a symmetric fashion. However, some patients may report exercise intolerance because of premature fatigue and others seek medical attention because of post-exertional myalgia or cramping. Of course, these three problems can occur singularly or in any combination. The physical examination may reveal weakness of the shoulder- and pelvic-girdle muscles with the remainder of the neurologic examination normal (exceptions maybe inclusion body myositis and myositis associated with anti-SRP antibodies). In some patients the entire physical examination may be normal. Because of the nonspecificity of complaints and lack of helpful physical findings in many patients in these diseases, it is useful to have a detailed understanding of the differential diagnosis of myopathies (Table 1) and have a good understanding of the laboratory tools available in order to make a diagnosis.

## Chemistries

Because electrolytes are critical to physiologic muscle relaxation and contraction, any activity, disease or medication that causes an elevation or a decline in the serum sodium, potassium, calcium, phosphorous or magnesium can cause a myopathic picture.

Elevation of serum enzymes derived from skeletal muscle including creatine kinase (CK),

aldolase, SGOT, SGPT, and LDH helps confirm the presence of a myopathic process. High levels of these enzymes are found in the inflammatory diseases of muscle but are not specific for those diagnoses. CK is a dimer and exists in the serum in three isoforms: MM, MB, and BB. The MM form predominates in skeletal and cardiac muscle. MB composes about 25 percent of the total CK activity in cardiac tissue. MB is a very minor component in skeletal muscle but is present in that tissue in greater amounts in embryonal and regenerating fibers. BB is the major isoenzyme in brain and smooth muscle. It is important to determine the tissue source of CK whenever elevated levels are encountered.

Not all elevated CK values are indications of disease. Racial differences in normal CK levels must be considered in this context. Healthy asymptomatic black males have higher total CK levels than those of whites or Hispanics, with the majority of values judged to be abnormal using the usual laboratory values. Injury to muscle, by blunt or sharp trauma (intramuscular injections, EMG needle insertion, muscle biopsy), is a well-recognized cause of high CK levels. Both isometric and aerobic exercise can also produce elevated CK levels, especially in poorly conditioned individuals. Furthermore, agents such as morphine, diazepam, and barbiturates may elevate the serum CK levels by retarding its elimination from the circulation. Cocaine use can cause sustained elevations even after months of abstinence. Zidovudin (AZT) and lipid-lowering drugs may induce a metabolic myopathy. Elevated CKs in individuals without myopathic symptoms may be carriers of muscular dystrophy, a glycogenosis, or malignant hyperthermia. Recently a group of individuals have been identified with a condition termed "benign hyper-CK-emia". They have persistently elevated values for years with no definable cause.

## Autoantibodies

A number of circulating autoantibodies have been identified in some patients with inflammatory myopathy (Table 2). These have been termed myositis specific autoantibodies.

The prevalence of these is not known and they are commercially measurable only on a limited basis today. It appears, however, that their presence does allow prediction of clinical course and outcome.

## Forearm Ischemic Exercise Testing

This test can be used in the clinic to screen for sertainin glycogenoses and myoadenylate deaminase deficiency. During vigorous ischemic exercise, skeletal muscle functions anaerobically, generating lactate and ammonia. Lactate is the product of the glycolytic metabolism of glycogen and glucose. Ammonia is generated through the conversion of AMP to inosine monophosphate (IMP) by the activity of myoadenylate deaminase. The forearm ischemic exercise test takes advantage of

this. The forearm ischemic exercise test is performed after drawing a venous blood sample for lactate and ammonia, preferably from the nondominant arm at rest and without the use of a tourniquet. Next, a sphygmomanometer is placed around the upper arm of the dominant side and inflated to 20 to 30 mm Hg above systolic pressure. The patient then vigorously exercises that extremity by repeatedly squeezing a ball or other device (1 grip every 2 seconds). The exercise is continued, and the cuff inflated, for a total of 2 minutes (many normal people can exercise only for 90 seconds under these conditions if they give maximal effort). Blood samples for lactate and ammonia are drawn from the dominant arm 2 minutes after the cuff is deflated. The normal response is at least a threefold rise over baseline for each metabolite. In individuals with a glycogenosis, the ammonia level increases normally, but lactate levels remain at baseline. In contrast, in myoadenylate deaminase deficiency, lactate levels increase but ammonia levels do not. A submaximal exercise effort, whether due to pain, weakness, or malingering, can cause a false positive result. Therefore, failure to generate lactate or ammonia after ischemic exercise does not

Table 1. ABBREVIATED DIFFERENTIAL DIAGNOSIS OF MYOPATHY

<p><b>Inflammatory</b>-polymyositis, dermatomyositis, inclusion body myositis, myositis with malignancy, myositis with another collagen-vascular disease</p> <p><b>Neurogenic</b>-anterior horn disease, myasthenia gravis, Eaton–Lambert syndrome, muscular dystrophy</p> <p><b>Toxic or drug-related</b>-alcohol, colchicine, corticosteroids, hydroxychloroquin, cocaine, lipid lowering agents</p> <p><b>Infections</b>-viruses (coxsackie, influenza, , HIV), bacteria (staph, strep), Lyme disease, toxoplasmosis</p> <p><b>Neoplasm</b>-cachexia, Eaton-Lambert, carcinomatosis</p> <p><b>Metabolic</b>-adrenal, thyroid and parathyroid disorders, diabetes, anything that alters electrolytes</p> <p><b>Genetic</b>-glycogenoses, mitochondrial myopathies</p> <p><b>Miscellaneous</b>-fibromyalgia, chronic fatigue syndrome, sarcoidosis</p>
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Table 2. MYOSITIS SPECIFIC AUTOANTIBODIES

<p><b>Anti-synthetase</b>-directed and amino acyl-tRNA synthetase and cause myositis with interstitial lung disease, fever, arthritis, mechanic's hands and Raynaud's</p> <p><b>Anti-SRP</b>-directed at signal recognition particle and associated with acute onset, cardiac involvement, neurologic changes and poorest prognosis</p> <p><b>Anti-Mi-2</b>-directed against helicase and cause dermatomyositis with excellent prognosis</p>
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ensure the diagnosis of the particular enzyme deficiency. Any abnormal result should be confirmed with the appropriate enzyme analysis.

## Electromyography (EMG)

EMG is a valuable technique for determining the classification, distribution, and severity of diseases affecting skeletal muscle and differentiating myopathies from neurogenic and neuro muscular junction diseases. EMG can identify myopathy, but cannot make a specific diagnosis.

## Imaging Studies

Ultrasonography, computed tomography and magnetic resonance imaging may be useful. MRI is perhaps the most useful technique to look for inflammation, fat deposition, denervation and fibrosis in skeletal muscle. T2-weighted image with fat suppression or STIR techniques are required to identify inflamed areas. This technique appears to be an excellent method for identifying a site for muscle biopsy.

## Muscle Biopsy and Histology

The muscle biopsy can be an especially useful in the evaluation of patients with myopathy. Four types of evaluation can be performed on skeletal muscle: histology, histochemistry, electron microscopy, and assays of enzyme activities or other constituents. Nevertheless, only the latter, identification of a specific enzyme deficiency, can make a definitive diagnosis. Muscle biopsy can be performed with a percutaneous needle biopsy or an open surgical technique. Traditionally, an EMG is the most helpful technique used to localize the site for biopsy. MR imaging may also be used in this regard. EMG needles can traumatize the muscle. Since the distribution of most myopathies is symmetric, it is recommended to perform the study on one side of the body and take the biopsy specimen from the identified site on the opposite side when EMG is being used.

H&E and modified Gomori's trichrome stains are used for most histology. A wide variety of stains are used for histochemistry, including adenosine triphosphatase (ATPase), which stains the enzyme of the myofibrils; the reduced form of nicotinamide-adenine dinucleotide (NADH) and succinic

dehydrogenases, both oxidative enzymes in the mitochondria; myophosphorylase, which catalyzes the initiation of glycogenolysis; myoadenylate deaminase, the first enzyme in the purine nucleotide cycle; acid phosphatase and nonspecific esterase, which stain for lysosomes and macrophages; periodic acid-Schiff (PAS) stains for glycogen; and oil red O for lipid. Staining for ATPase and enzymes of other metabolic systems is useful in determining fiber type, size, and distribution.

This combination of histologic and histochemical analysis is generally useful in differentiating myopathic from neuropathic processes. Myopathic changes include rounding and increased random variation of fiber size, internal nuclei, fibrosis, and fatty replacement. Myopathic processes may also cause necrosis associated with phagocytosis. Inflammatory myopathies are associated with fiber atrophy, degeneration, and regeneration plus inflammatory cell infiltrates in both endomysial and perimysial locations. Fiber necrosis, phagocytosis, and regeneration are also typically seen in muscular dystrophy. Neuropathic conditions that cause denervation, such as disorders of the spinal cord and peripheral nerves, produce small, atrophic angular fibers. Target fibers can also result from denervation. Target fibers are seen using the ATPase stain and are generally type 1 cells. Each fiber has a central clear area surrounded by a zone of increased intensity of staining, with normal staining at the periphery. Reinnervation causes fiber type grouping; that is, aggregation of fibers all of the same type.

## Conclusion

Unfortunately, the individual findings that occur in most patients with muscle weakness are too nonspecific to make a diagnosis. Blood tests, EMG, and muscle histology, by themselves, rarely identify the disease. However, if the appropriate tests are performed and the results are correlated with the other findings, a diagnosis can usually be made.

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