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Myopathic Diseases

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Summary Points

- Skeletal muscles may be involved with inflammation or metabolic abnormalities.
- The clinical effects of muscle involvement include weakness, fatigue, and muscle cramping.
- The diagnosis is made by demonstrating muscle weakness, muscle involvement as indicated by an elevation of the CPK, an abnormality on EMG, and the pathology on muscle biopsy.

Introduction

A large number of diseases and conditions affect skeletal muscle and result in symptoms (1,2). These include objective muscle weakness, premature fatigue, and post-exertional aches, cramps, and pains. It is useful to classify the myopathies within several categories. The history, physical examination, serum chemistries, electrophysiologic studies (EMG), magnetic resonance imaging (MRI), and analysis of muscle tissue, but usually renders a specific diagnosis.

Differential Diagnosis

Idiopathic Inflammatory Myopathies

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by symmetric proximal muscle weakness and elevated serum levels of enzymes derived from skeletal muscle. These include creatine phosphokinase (CPK), aldolase SGOT, SGPT, and LDH. In addition EMG, MRI, and muscle histology show changes indicative of nonsuppurative inflammation (3,4). Today, this group includes the specific diagnoses of polymyositis, dermatomyositis, juvenile dermatomyositis, myositis associated with another connective tissue disease, myositis associated with a malignancy and inclusion body myositis. Patients with an IIM can be further categorized by the presence or absence of a circulating myositis-specific autoantibody (MSA, Table 1).

The IIM are rare diseases with estimates of incidence ranging from 0.5 to 8.4 cases per million. The age at onset has a bimodal distribution, with peaks between 10 and 15 years and again between 45 and 60 years. The age of onset for myositis with another connective tissue disease is

similar to that for the associated condition. Both malignancy-associated myositis and inclusion body myositis are more common after age 50. Women are affected twice as often as men.

Polymyositis in Adults. Weakness of the pelvic and shoulder girdle muscles is the cardinal feature of polymyositis in adults. Weakness of neck flexors can occur, but ocular and facial muscles are spared. Symptoms usually begin insidiously with no precipitating event. Dysphagia may develop secondary to esophageal dysfunction or cricopharyngeal muscles. Pharyngeal muscle weakness may cause dysphonia and difficulty swallowing. Myalgias and arthralgias are not uncommon, but frank synovitis is unusual. Additional findings may include Raynaud's phenomenon or periorbital edema. Velcro-like crackles may be heard on chest auscultation from pulmonary fibrosis. Aspiration pneumonia may complicate the disease course in patients with swallowing difficulties. Cardiac involvement is usually limited to asymptomatic EKG abnormalities, although cardiomyopathy can occur.

In polymyositis, muscle fibers are found to be in varying stages of necrosis and regeneration. The inflammatory cell infiltrate is predominantly focal and endomysial with T lymphocytes, especially CD8+ cytotoxic cells, surrounding and invading initially non-necrotic fibers (5).

Dermatomyositis in Adults. The clinical features of dermatomyositis in adults include all of those described for polymyositis plus cutaneous involvement. Gottron's papules -- symmetric lacey pink or violaceous raised or macular areas found on the dorsal aspect of interphalangeal joints, elbows, patellae, and malleoli -- are considered pathognomonic. Other skin changes include heliotrope discoloration of the eyelids; macular erythema of the posterior shoulders and neck (shawl sign), anterior neck and upper chest (V sign), face, and forehead; and dystrophic cuticles with periungual telangiectasias or abnormal nail fold capillaries. Muscle histology usually differs from that of polymyositis. The inflammatory infiltrate is perivascular in location and is composed of B and CD4+ lymphocytes. Capillary plugging and perifascicular atrophy are also observed (5).

Juvenile Dermatomyositis. The usual IIM in children, termed juvenile dermatomyositis (JDM), has characteristic features. Although the rash, muscles involved and muscle histology are similar, JDM differs from the adult form because of the coexistence of vasculitis, ectopic calcification, joint contractures, and lipodystrophy.

The features of an IIM may dominate the clinical picture in some patients with scleroderma, systemic lupus erythematosus, mixed connective tissue disease, and Sjögren's syndrome. In vasculitic syndromes, however, weakness is more commonly related to arteritis and nerve involvement than to inflammation in muscle.

IIM with an Associated Malignancy. The true incidence of this relationship is not clear, although it may be more common with dermatomyositis (6). Myositis has been found associated with malignancy in all age groups but is quite rare in children. It appears that the sites and types of malignancy that occur are those most expected for the age and gender of the patient. Ovarian cancer may prove the exception because it is over-represented in women with dermatomyositis.

Inclusion Body Myositis (IBM). IBM mainly affects older individuals. Onset is truly insidious with symptoms often having been present for more than 5 years before diagnosis. Clinically and histologically, IBM maybe identical to polymyositis, although differences are clear in more than half the patients. Weakness may be focal, distal, or asymmetric, and it may be accompanied by diminished deep-tendon reflexes. EMG may reveal neurogenic or mixed neurogenic and myopathic changes. Disease progression is usually slow and steady in some, while it seems to plateau in others, leaving them with fixed weakness and atrophy of the involved musculature. The characteristic histologic change in IBM is the presence of intracellular rimmed vacuoles. The

vacuolated fibers are now recognized to contain abnormal deposits of amyloid proteins, similar to those found in the brain in Alzheimer's disease (7).

Fifty percent of patients with an IIM have a circulating autoantibody found almost exclusively in these diseases. Because of this specificity, these have been termed myositis-specific autoantibodies (MSAs). The presence of a particular antibody appears to identify a relatively homogeneous group of patients with regards to clinical features and prognosis (Table 1).

Metabolic Myopathies

Some metabolic myopathies are primary and the result of known biochemical defects that alter the muscle's ability to maintain adequate levels of ATP. These can be attributed to defects in glycogen, lipid, or mitochondrial metabolism. Others are secondary and caused by various endocrine disorders, electrolyte abnormalities, or drug toxicities.

To date, 11 different diseases caused by an underlying defect in glycogen synthesis, glycogenolysis, or glycolysis have been identified (8). These are often referred to as the glycogen storage diseases (GSD), because of the glycogen that accumulates in muscle as a consequence of the defect. McArdle's disease, myophosphorylase deficiency, is the prototypic GSD. It has three potential presentations, together representing the spectrum of GSD symptomatology. Symptoms may begin during childhood with easy fatigue, but significant problems including exercise intolerance with severe muscle cramping, rhabdomyolysis, and myoglobinuria may not develop until adolescence or adulthood. A subset of adults (as old as age 78 years) presents with progressive proximal muscle weakness with no history of cramps or myoglobinuria.

The other more common GSDs are phosphofructokinase deficiency and acid maltase deficiency. Patients with a GSD may be difficult to differentiate from those with an IIM because most GSD patients have elevated CPK levels even when symptom-free, and their EMGs reveal evidence of myopathy. Thus, they fulfill three of the four criteria for polymyositis. Muscle biopsy is needed to differentiate among these conditions and to make the correct diagnoses.

A variety of disorders of fatty acid and mitochondrial metabolism also can cause myopathy. The former are referred to as lipid storage diseases (LSD) and the latter termed mitochondrial myopathies (9). The clinical spectrum of these diseases is quite diverse and includes progressive muscle weakness as well as exercise intolerance with rhabdomyolysis and myoglobinuria.

Knowledge of the specific defect does not allow prediction of the clinical presentation. For example, a deficiency of carnitine -- an essential intermediate necessary for the transport of long-chain fatty acids into mitochondria -- causes lipid deposition in muscle a disease easily confused with polymyositis. These individuals have proximal muscle weakness, elevated CPK levels and myopathic EMG findings. In contrast, a deficiency of carnitine palmitoyltransferase (CPT), the enzyme that catalyzes the transport of the long-chain fatty acid-carnitine complex into mitochondria, cause sporadic attacks of myalgia and myoglobinuria. Serum CPK levels, EMGs, and muscle histology are normal except with attacks. Mitochondrial myopathies may cause each presentation but are more often associated with progressive external ophthalmoplegia, other neurologic findings, or multisystem disease.

Other Causes of Myopathy

Although IIM and metabolic myopathies are relatively rare conditions, the list of disorders that cause myopathic symptoms is extensive (1,2). Neuropathic diseases can generally be differentiated because they cause distal extremity involvement, an asymmetric distribution, and other neurologic abnormalities, such as abnormal deep tendon reflexes or altered sensorium.

Numerous infectious agents can cause myopathy, with viruses the most common. Influenza and Cocksackievirus infections can cause weakness or severe myalgias associated with high CPK levels in children. Weakness is a common finding in patients with AIDS. This may be the result of generalized cachexia, central or peripheral nervous system disease, polymyositis emerging as a consequence of altered immunity, zidovudine (AZT) toxicity or an opportunistic infection with cytomegalovirus, *Mycobacterium avium intracellulare*, *Cryptococcus*, *Trichinella*, or *Toxoplasma*.

Neoplasm must also be considered in the evaluation of patients with myopathic symptoms. Cytokines released from tumor cells or an immune response to the cancer commonly cause fatigue, weakness and other systemic symptoms. Prominent neuromuscular manifestations can also develop as features of paraneoplastic syndromes.

Numerous drugs can cause myopathic changes and do so by a variety of mechanisms. Procainamide and D-penicillamine produce immune-mediated injury. Glucocorticoids causes type 2 muscle fiber atrophy. Alcohol has direct toxicity. Colchicine and hydroxychloroquine induce a vacuolar myopathy. Cocaine, amphetamines, and other illicit drugs induce rhabdomyolysis by producing ischemia, causing convulsions or by inducing coma with compression injury.

All lipid-lowering agents can cause rhabdomyolysis, presumably by altering muscle energetics (10). Any agent that alters levels of potassium (such as a thiazide), sodium, calcium, magnesium, or phosphorous can cause weakness, myalgia or cramps. Zidovudin (AZT) can cause a mitochondrial myopathy (11).

Testing for Muscle Disease

A variety of tests may be necessary to make the diagnosis in patients with myopathic symptoms (1,12). The orderly application of them, however, usually allows one to determine the cause of the condition.

Chemistries

CPK, aldolase, SGOT, SGPT, and LDH are found in skeletal muscle. Elevated serum levels of each of these can occur with a myopathic process, with CPK the most useful to follow. However and elevated CPK is not specific for muscle disease. Trauma -- blunt or sharp -- and physical activity -- aerobic or anaerobic -- may be sufficient to raise serum CPK levels. Racial differences in normal values must be considered because African-American males have higher levels than other groups. Occasionally, elevated CPK levels are observed in asymptomatic individuals. This may indicate a person who is heterozygous for a metabolic myopathy, muscular dystrophy, or malignant hyperthermia; they have very early or "pre-" disease; or benign hyper-CK-emia.

Electromyography (EMG)

EMG is a valuable technique for determining the classification, distribution, and severity of diseases affecting skeletal muscle. Classic EMG changes in IIM include the triad of 1) increased insertional activity, fibrillations, and sharp positive waves; 2) spontaneous, bizarre high-frequency discharges; and 3) polyphasic motor unit potentials of low amplitude and short duration. This triad is characteristic but not diagnostic. The complete triad is seen in approximately 40% of IIM patients. In contrast, 10% to 50% of patients may have completely normal EMGs. In a small number of patients, abnormalities are limited to the paraspinal muscles.

EMG can effectively differentiate between myopathic and neuropathic conditions and can localize the site of a neurologic abnormality to the central nervous system, spinal cord anterior horn cell, peripheral nerves, or neuromuscular junction. In addition, knowledge of the distribution and severity of abnormalities can guide selection of the most appropriate site to biopsy.

Forearm Ischemic Exercise Testing

During vigorous ischemic exercise, normal skeletal muscle functions anaerobically, generating lactate and ammonia. The forearm ischemic exercise test takes advantage of this physiology and has been standardized for use in screening GSD (except acid maltase deficiency). In individuals with a GSD, the ammonia level increases normally, but lactate levels remain at baseline. An abnormal finding using this method would always be confirmed with enzyme analyses because this technique can yield false positive results.

Imaging Techniques

Neither conventional radiography nor radionuclide imaging has proved particularly useful in patients with muscle diseases. However, ultrasonography, computed tomography, and magnetic resonance imaging (MRI) provide useful images. Of these, MRI offers the best imaging of soft tissue and muscle, and is able to identify areas of inflammation, denervation, atrophy, and fatty replacement. Since MRI can detect early or subtle disease changes and show patchy muscle involvement, it may prove superior to EMG in determining the site for muscle biopsy (13).

Muscle Biopsy

Four types of evaluation can be performed on skeletal muscle: histology, histochemistry, electron microscopy, and assays of enzyme activities or other constituents. This combination of histologic and histochemical analysis is generally useful in differentiating myopathic from neuropathic processes. Myopathic changes include rounding and variation of fiber size, internal nuclei, fiber atrophy, degeneration and regeneration, fibrosis, and fatty replacement. Neuropathic conditions that cause denervation produce small, atrophic, angular fibers and target fibers.

Reinnervation causes fiber-type grouping -- aggregation of fibers all of the same type. Hematoxylin and eosin and modified Gornori's trichrome stains are used for most histology. The latter stain is useful in identifying ragged-red fibers, typical findings in many mitochondrial myopathies. A wide variety of stains is used for histochemistry. ATPase stains define fiber type. NADH and succinate dehydrogenases reflect the mitochondria. Periodic acid-Schiff stains are used for glycogen, and oil red for lipid.

Ultrastructural analysis shows characteristic changes in cases of inclusion body myositis, increased numbers of altered morphology of mitochondria in mitochondrial myopathies, and abnormal glycogen or lipid deposition. Enzyme deficiency states may be identified with appropriate histochemical stains but are best diagnosed by subjecting the tissue protein to assays for the specific enzyme activity.

Treatment of Myopathies

The treatment of a myopathic process depends on the diagnosis. However, before initiating any therapy, the patient's muscle strength should be assessed. Without accurate baseline measurements, it is difficult to assess progress in cases in which treatment response is less than desired. In addition, physical therapy is an important component of treatment. It can be used to prevent contracture, to prevent atrophy and to increase endurance.

The treatment of the inflammatory myopathies is largely empiric as controlled clinical trials are severely lacking. Glucocorticoids are the standard first-line medications. Prednisone is usually given in a single dose of 1 mg/kg/day. In severe cases, the daily dose can be divided. In general, the earlier in the disease course that therapy is initiated, the more effective it is.

Clinical improvement may be rapid but more typically is observed over 6 to 12 weeks. As many as 90% of subjects respond to glucocorticoids, with half to three-quarters of those achieving remission. A total lack of response to therapy should bring to mind the possibilities of an

associated malignancy or the diagnosis of inclusion body myositis. Methotrexate and azathioprine, alone or in combination, have been shown to be effective in some patients who have not responded well to prednisone (14).

Other agents such as cyclosporine, cyclophosphamide, chlorambucil an intravenous gamma globulin have also been used in difficult cases (15). Hydroxychloroquine may help the skin in patients with dermatomyositis but does not help the muscle disease.

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