MUSCULAR DYSTROPHIES
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Muscular Dystrophies are distinguished from other myopathies by two main features: 1) they are hereditary, and 2) they result in progressive muscle weakness and wasting. There has been an explosion of new genetic information about the muscular dystrophies during the last decade. It is hoped that this will eventually translate into more effective treatments.

The five most commonly encountered forms of muscular dystrophy include Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, Myotonic Dystrophy, Facioscapulohumeral Muscular Dystrophy, and Limb-Girdle Muscular Dystrophy.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

This X-linked recessive disease is the most rapidly progressive form of muscular dystrophy. It almost exclusively affects young boys and generally leads to death from respiratory failure by the mid-teens or twenties.

The gene altered in DMD is located on the short arm of the X-chromosome (band Xp21) and recently the gene’s protein product (dubbed “dystrophin”) was identified. Dystrophin is part of a large complex of proteins that attaches to the inner surface of the muscle cell membrane. The precise functional role of dystrophin in normal muscle is currently being studied. Investigations to date suggest dystrophin serves normally to maintain the integrity of the muscle fiber membrane in the face of mechanical stresses produced by repeated contraction and relaxation.

Incidence

A wide range of estimates is available. Recent data indicates an incidence of 30 per 100,000 or 1 in 3,300 male births. One third of all DMD cases represent new mutations.

Clinical Features

The disease is present at birth, but the diagnosis is usually not suspected until the age of 2 or 3 years. The patient walks late, usually after 18 months, and exhibits delayed motor milestones. Very early in the disease, there is weakness of forward head flexion. The walking from ages 3-6 is typically broad-based and waddling with an exaggerated lumbar lordosis. The pelvic girdle and proximal lower extremity muscles are involved early and before the development of upper extremity weakness. Patients have a characteristic way of arising from the ground, called the Gower sign: they roll over to kneel, push down on the ground with arms extended to straighten the legs, then move the hands onto the knees to climb up the thighs. Although all muscles become diffusely weak, the ankle plantar flexor and ankle inversion muscles remain relatively strong throughout the entire illness. While most muscles waste away, there are certain muscles that undergo hypertrophy, especially the calves, quadriceps, gluteals, and
deltoids. Early in the disease this represents a true hypertrophy. Later, however, most of the muscle is replaced by fat and the term “pseudohypertrophy” is used.

By age 10 most patients require long leg braces to ambulate or stand. Almost all patients are wheelchair dependent by age 12. Death, commonly due to respiratory failure, usually occurs around age 20.

Complications in other systems are common and are most prominent once the patient is wheelchair bound:

1. **Respiratory:** Hypoventilation due to muscle weakness and kyphoscoliosis; decreased power of cough; increased risk for general anesthesia.

2. **Orthopedic:** Kyphoscoliosis and contractures may be severe.

3. **Cardiac:** Tachycardia without heart failure; cardiac fibrosis; 90% have abnormal ECG’s typically with deep, narrow Q waves in the inferior and lateral precordial leads and tall right precordial R waves. Most patients with DMD are relatively free of cardiovascular symptoms however.

4. **Central Nervous System:** The average IQ of patients with DMD is about 1 standard deviation below the mean.

**Laboratory Studies**

1. **Creatine Kinase** - At least 10 times above the upper limit of normal, even during the first year of life.

2. **ECG** - See above

3. **Electromyography** - Shows a myopathic pattern

4. **Muscle Biopsy - Histology**
   - Marked variation in fiber size with type 2B fiber deficiency
   - Necrotic muscle fibers
   - Regenerating muscle fibers
   - Increased connective tissue (fibrosis)

5. **Muscle Biopsy - Dystrophin Analysis**
   - Completely absent. This is the only way to make a definitive diagnosis of DMD.

**Genetics**

DMD is an X-linked recessive disorder and therefore affects almost only males. Females who inherit the gene are almost always asymptomatic carriers although “manifesting carriers” are known. Male patients do not live to reproduce, so new mutations must occur for the disease to perpetuate. Once again, it is estimated that one third of all DMD cases represent new mutations.
A female with an affected son plus one other affected male relative, in a pattern consistent with an X-linked recessive inheritance, is considered an obligate carrier and has a carrier risk of 100%. A women with two sons with DMD would also be considered an obligate carrier. Each male offspring of an obligate carrier has a 50% chance of getting the diseased gene. Since 1/3 of all DMD cases arise as new mutations, the mother of an isolated DMD case is, therefore, not necessarily an obligate carrier and should be classified as a possible carrier. Methods to determine the carrier probability of a possible carrier includes:

1. **Pedigree Analysis** - This takes into account a potential carriers position within the pedigree relative to the affected male(s) as well as the presence of any normal male descendants. A carrier probability is generated. In general, a females carrier risk is decreased the more distant her relationship is to the affected male and is also reduced with each normal son she bears.

2. **Creatine Kinase Level (CK)** - A significantly elevated CK is a strong indication that an at-risk female is a carrier, however the false positive rate is around 2.5%. The determination of CK is probably helpful in identifying only around 50% of obligate carriers.

3. **DNA Analysis** - The isolation of the DMD gene has revolutionized the previously inexact approach to DMD carrier testing and this is now the standard method to search for deletions, duplications, or point mutations in potential carriers. DNA analysis can only be performed in families with identifiable mutations. Therefore, DNA analysis should be done on all DMD patients. The exact gene lesion identified by DNA testing in the patient can then be sought in his mother and other potential carriers.

**Pathophysiology**

DMD results from a mutation in the gene for dystrophin at Xp21. Dystrophin provides a structural link between actin and the extracellular matrix and appears to play an important role in maintaining the integrity of the muscle cell membrane. Lack of dystrophin results in instability of the sarcolemma and an excessive influx of calcium, which causes muscle fiber necrosis.

**Treatment**

The lack of precise understanding of the pathophysiology of DMD has severely limited the development of a specific treatment. New advances have been made in the use of braces, spinal stabilization surgery, and in the use of portable ventilators for those patients who elect this approach for their respiratory failure. The treatment of the complications of the disease is, thus, improving with advances in technology. Recent clinical studies suggest that the corticosteroid prednisone may improve function in DMD patients but the result of long term trials (which are in progress) are needed before this treatment can be recommended for all DMD patients. Prednisone treatment has proven effective in stabilizing muscle strength in patients receiving a dose of 0.75 mg/kg/day for up to two years.
BECKER MUSCULAR DYSTROPHY (BMD)

BMD is also an X-linked recessive form of muscular dystrophy with a more benign course than DMD. Although DMD and BMD can be distinguished clinically, recent investigations indicate that the two disorders result from defects of the same gene.

Incidence

BMD is approximately 10 times less frequent than DMD with an incidence of around 3 per 100,000. New mutations account for approximately 10% of BMD cases.

Clinical Features

The pattern of muscle weakness closely resembles that seen in DMD. The pelvic girdle and proximal lower extremities are initially involved, followed by neck flexor weakness. Diffuse weakness follows, as in DMD. The initial weakness in BMD occurs later though, sometime between ages 5 and 15. Disease progression is also much slower in BMD and most patients are still ambulatory past age 16. Over 90% of BMD patients are alive at age 20 and the majority survives into the fourth or fifth decade. Death is usually due to respiratory failure.

Complications in other systems (cardiac and respiratory) can occur, as in DMD. Mental retardation is also seen in BMD but is not as common as in DMD.

Laboratory Studies

1. Creatine Kinase - Usually > 10 times normal
2. ECG - Abnormalities not as specific as with DMD
3. Electromyography - Shows a myopathic pattern
4. Muscle Biopsy - Histology is similar to that seen in DMD but with less connective tissue proliferation. Dystrophin analysis, however, shows a detectable amount of dystrophin, but it is qualitatively altered.

Genetics

BMD results from a defect of the same gene as DMD. Genetic counseling for BMD families is similar to that for DMD except BMD patients may live to reproduce. A daughter of a BMD male is an obligate carrier for the BMD gene.

Carrier detection and prenatal diagnosis can be approached in the same manner as with DMD families.

Pathophysiology

As with DMD, the mechanism for muscle cell death in BMD is unclear. Insight into the process depends on a better understanding of dystrophin's role in muscle. Recent
investigation suggests that there is a normal amount of dystrophin in BMD muscle but the protein is abnormal in size.

**Treatment**

Similar to that for DMD patients

**MYOTONIC DYSTROPHY (MyD)**

MyD is an autosomal dominant disorder that demonstrates extreme clinical variability. The gene for MyD has been localized to chromosome 19 and controls the production of threonine-serine protein kinase. The function of this kinase is not known.

**Incidence**

MyD is the most common form of muscular dystrophy in adults. The estimated incidence of the disease is around 13 per 100,000. The incidence will likely increase in the future due to our newly acquired ability to detect subclinical cases.

**Clinical Features**

A range of disease severity is observed even within families. Not uncommonly, affected individuals are asymptomatic or untroubled by their symptoms. Symptomatic disease onset is generally in the second or third decade. A severe congenital form of the disease may present in the neonatal period (see below).

The pattern of muscle weakness seen in MyD is quite characteristic. The term “hatchet face” has been used to describe the typical facial appearance of MyD patients. This results from weakness of eyelid elevators (ptosis), facial muscle weakness, and weakness and wasting of the temporalis muscles. Tongue, palate, and pharyngeal weakness results in a nasal voice. The sternocleidomastoids are typically quite weak. Variable involvement of limb muscles occurs and as rule distal muscles are more affected than proximal ones. Weakness of the wrist flexors, wrist extensors, and ankle dorsiflexors (the latter may result in foot drop and a tendency to trip) is common. Occasionally the diaphragm and accessory respiratory muscles weaken and this may contribute to respiratory insufficiency.

Myotonia, which manifests itself as an inability to quickly relax a muscle once it is contracted, is most easily demonstrated by having the patient grip the examiners hand and then trying to quickly release. Patients will have problems releasing their grip and although they are often aware of this problem, they usually are not troubled by it. Myotonia can also be detected by percussing the thenar eminence or wrist extensor muscles.

**Congenital MyD** presents at birth or in early childhood. In the vast majority of congenital cases the mother is the affected parent. Affected infants are hypotonic, feed poorly and may have breathing difficulties. Death within the first hours or days of life is not uncommon. If these patients survive the neonatal period, they tend to improve in strength during childhood but go on to develop typical features of adult MyD. In
addition, mental retardation of varying degrees occurs in the majority of congenital cases.

**Non-muscular Manifestations** are very common:

1. **Cardiac conduction abnormalities** - Generally asymptomatic but can progress to complete heart block with a risk of sudden death.

2. **Mental retardation** - Especially common in congenital MyD

3. **Respiratory insufficiency** - Due to a combination of respiratory muscle weakness and central hypoventilation

4. **Cataracts** - Very common

5. **Frontal Balding**

6. **Endocrine Dysfunction** - Insulin resistance is a feature of MyD but the frequency of clinical diabetes mellitus is probably not increased. Testicular atrophy and decreased testosterone levels may be observed in male MyD patients.

**Laboratory Studies**

1. **Creatine Kinase** - Usually normal

2. **Electromyography** - Needle electromyography reveals the electrophysiologic counterpart of clinical myotonia. Myotonic discharges appear as repetitive discharges of single motor units which wax and wane in amplitude and frequency and produce an audio signal likened to the sound of a dive-bomber.

3. **Muscle Biopsy** - Atrophy of Type 1 muscle fiber (slow twitch, high oxidative activity fibers) and muscle fibers with an increased number of central nuclei are seen.

4. **Slit Lamp** - May reveal the characteristic iridescent cataracts of MyD.

5. **ECG** - Possible cardiac conduction defect

**Genetics**

MyD is an autosomal dominant disorder. An affected parent, therefore, has a 50% chance of transmitting the gene to an offspring. A mutation on a gene of the long arm of chromosome 19 results in an expansion of a **trinucleotide repeat** (CTG). MyD tends to increase in severity with successive generations (called **anticipation**). Anticipation is due to a greater number of trinucleotide repeats, particularly in maternally transmitted cases. The disease tends to be more severe, therefore, in children of affected mothers.

**Pathophysiology**

The MyD gene produces a threonine-serine protein kinase (sometimes called myotonin-protein kinase). Kinases modulate ion channel function, which may explain the
abnormal excitation of muscle. The mechanism for the multitude of abnormalities in these patients is still not understood.

Treatment

Treatment is symptomatic. Ankle/foot orthoses (which keep the foot in a neutral position) are helpful for patients with symptomatic foot drop. Phenytoin may be used to treat myotonia, but most patients are not troubled enough by their myotonia to require treatment. Quinine and procainamide, which are also anti-myotonia agents, should be avoided because they have the potential for worsening cardiac conduction. Cardiac pacemakers may be needed for patients with advanced or symptomatic conduction system abnormalities. Cataract extraction is performed for patients where the cataracts impair visual acuity. Hypersomnolence, which can be disabling, may be treated with the stimulants methylphenidate (Ritalin) or pemoline.

FACIOSCAPULOHUMERAL DYSTROPHY (FSH)

FSH is an autosomal dominant disorder. Penetrance of FSH is virtually complete by middle age, although as many as 1/3 of affected individuals may be asymptomatic.

Incidence

About 1 per 100,000 population

Clinical Features

Symptomatic onset is generally towards the end of the first or second decade although some patients are not affected until middle age. Facial weakness is the initial manifestation in most cases. Patients appear expressionless and glum, and become progressively unable to smile, whistle, use a straw, or to completely close their eyes. Weakness of the shoulder girdle is more often the reason for seeking medical attention, however. Weakness of the scapular stabilizers results in pronounced protruding of the shoulder blades and gives rise to difficulty handling heavy objects above the shoulders or performing activities such as chin-ups or push-ups. Interestingly, the deltoids are typically spared. Ankle dorsiflexor weakness results in foot-drop with a tendency to trip.

The severity of the disease can vary greatly even within families. Some individuals may require the use of a wheelchair whereas others who inherit the gene are without symptoms. The muscle weakness is usually slowly progressive but may plateau for years. A particularly severe course may occur when the disease has its onset during the first 2 years of life. Life expectancy is generally not reduced in FSH.

An unusual association of FSH with sensorineural hearing loss or retinal disease has been reported.

Laboratory Studies

1. Creatine Kinase - May be normal or mildly elevated
2. **Electromyography** - Usually indicates a myopathic pattern

3. **Muscle Biopsy** - Increased fiber size variability, scattered necrotic fibers, and occasionally dark angulated fibers. A prominent inflammatory response may be seen, particularly in patients with the severe infantile form of FSH.

**Genetics**

FSH is inherited in a typical autosomal dominant fashion and genetic counseling should follow along lines appropriate for an autosomal dominant disorder (e.g., the offspring of an affected individual has a 50% chance of being affected). The gene for FSH has been localized to chromosome 4. Careful physical examination is the most reliable means of establishing inheritance of the FSH gene.

**Pathophysiology**

The pathogenesis of muscle fiber damage in FSH is not known.

**Treatment**

No specific treatment exists for FSH. Ankle foot orthoses (which maintain the foot in a neutral position) are useful for patients with symptomatic ankle dorsiflexor weakness. Patients with prominent pelvic girdle weakness may require the use of a wheelchair. Surgical fixation of the scapula to the posterior thoracic wall may improve the functional and cosmetic affects of scapular stabilizer weakness but unfortunately the scapula may break loose after the procedure.

**LIMB-GIRDLE DYSTROPHY (LGD)**

This is the most poorly defined of the major dystrophies and most likely comprises more than a single disorder. LGD basically refers to muscular dystrophy patients who do not fit into one of the better-defined groups.

**Clinical Features**

LGD is characterized by progressive weakness of the shoulder and pelvic girdle musculature. Muscles of the neck may also be involved and severe weakness and wasting of the biceps is not infrequently seen. LGD typically has its onset in the second or third decade. The disease tends to progress slowly and may result in wheelchair confinement. Death may occur from cardiopulmonary complications and pneumonia.

**Laboratory Studies**

1. **Creatine Kinase** - Usually 5-10 times normal

2. **Electromyography** - Shows features typical for a myopathic process
3. **Muscle Biopsy** - prominent fiber size variability, split fibers, numerous internal nuclei and other non-specific findings suggestive of a myopathic process. It is critical to analyze dystrophin to distinguish LGD patients from those with DMD or BMD.

**Genetics**

Genetic linkage studies have so far defined an autosomal recessive form linked to chromosome 15q, and an autosomal dominant form linked to chromosomal 5q. It is possible that a cytoskeletal protein related to the dystrophin complex might be abnormal in LGD.

**Pathophysiology**

The pathogenesis of this heterogeneous group of disorders is uncertain.

**Treatment**

No specific treatment exists. The therapeutic approach is along the lines of the symptomatic care given to other muscular dystrophy patients.
INFLAMMATORY MYOPATHIES

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The term “inflammatory myopathy” is used to denote muscle diseases in which inflammatory cells are a conspicuous histopathological feature. For most inflammatory myopathies, although their etiology remains uncertain, clinical, histologic, electromyographic, and serologic criteria now permit definition and clinical classification (Table 1). Three diseases, dermatomyositis, polymyositis, and inclusion body myositis affect muscle much more than other organ systems. On the other hand, collagen-vascular and connective tissue diseases, as well as a large number of infectious diseases, usually do not present as a myopathy because of the conspicuous involvement of other organ systems.

Dermatomyositis, polymyositis, and inclusion body myositis have recently become readily distinguishable by clinical and laboratory diagnosis criteria (Table 2). There is likely to be an entirely different pathogenesis for each. They should no longer be lumped together by terms such as “poly-dermatomyositis”.

DERMATOMYOSITIS

Dermatomyositis represents the most easily recognized of the inflammatory myopathies. Childhood and adult forms of dermatomyositis have overlapping clinical and laboratory features, although there are important differences in prognosis and treatment.

Clinical Features

Skin

The presence of a highly characteristic skin rash distinguishes dermatomyositis. Erythema and scaling and telangiectatic lesions occur over the malar region of the face, usually involving the eyelids, which often have a violaceous (heliotrope) appearance. Similar lesions may be seen in sun exposed areas at the hairline of the neck and "shawl" area (V-sign), the dorsum of the hands, particularly the metacarpophalangeal and interphalangeal joints, the extensor surfaces of the knees and elbows, and the medial and lateral malleoli. Papular, erythematous changes over the knuckles are highly characteristic and are referred to as Gottrens’s papules. Periorbital edema occurs commonly. Necrotizing vasculitis of the skin can occur in severe childhood and adult dermatomyositis.

Evaluation of nailfold capillaries often reveal enlarged and deformed capillary loops surrounded by avascular areas. These changes also occur in progressive systemic sclerosis and in the mixed connective tissue disease.
Muscle Weakness

Myalgias seldom represent the chief complaint of adult patients with dermatomyositis. Children, however, often have some degree of muscle pain and tenderness upon direct questioning. Muscle weakness usually develops subacutely (weeks), especially in childhood, but may develop insidiously (months) or fulminantly (days). The weakness initially affects proximal muscles, including neck flexors, hip flexors and extensor, trunk and shoulder girdle muscles. Weakness may progress to involve distal muscles. Dysphagia occurs in at least one-third of patients. Abnormalities of esophageal motility occur in the upper (skeletal muscle) and lower (smooth muscle) portion of the esophagus and are the result of inflammation and muscle fiber degeneration. Even gastric emptying may be impaired. Weakness only rarely progresses to involve respiratory muscles and ventilatory failure is uncommon. Muscle stretch reflexes are usually preserved and may seem hyperactive considering the degree of muscle weakness.

Other Manifestations

Joint

Arthralgias with and without arthritis are frequent and joint effusions may be seen. Contractures represent a frequent and early complication, especially in childhood dermatomyositis. Even prior to diagnosis, limitation of motion may occur at the elbows, wrists, and shoulders.

Calcifications

Subcutaneous calcifications occur in over 30% of children while this is an uncommon finding in adults. Cutaneous calcnosis tends to develop over pressure points (buttocks, knees, elbows) and present as painful hard nodules. Ulceration of the overlying skin with extrusion of calcific debris can be seen in severe cases or in patients who have received inadequate treatment.

Heart

Cardiac involvement rarely causes overt clinical manifestations but electrocardiographic disturbances, cardiomegaly, dyspnea and congestive heart failure have all been observed. Focal areas of myocardial inflammation may lead to heart failure. Abnormalities of the conduction system, including atrioventricular and bundle branch block, frequent premature ventricular beats, and tachycardia of either ventricular or supraventricular origin can occur. In addition, defects in ventricular and septal wall motion can be detected by echocardiography or radionuclide scintigraphy.

Throat and Gastrointestinal

Dermatomyositis patients with significant pharyngeal and upper esophageal motility impairment may develop aspiration pneumonia. Aspirated materials include not only food substances, but also bacterial-laden oropharyngeal secretions and regurgitated gastric contents. Delayed gastric emptying also occurs. Vasculitis of the G-I tract is
more common in childhood cases and causes mucosal ulceration, perforation, and life threatening hemorrhage.

**Pulmonary**

Interstitial lung disease affects 5-10% of adult patients with dermatomyositis. A fulminant and sometimes fatal form of the disease presents with acute fever, dyspnea and productive cough, and diffuse "ground glass" appearance on chest radiographs. Other patients have an insidious form of interstitial lung disease with dyspnea and a diffuse reticulonodular infiltration on chest film. In some cases interstitial lung disease has few clinical manifestations but may be recognized on chest radiographs and by abnormal pulmonary functions. About 50% of patients with interstitial lung disease have antibodies against t-histidyl transfer RNA synthetase, so called anti-Jo-1 antibodies. Pulmonary artery hypertension can accompany dermatomyositis, although this complication usually occurs in the setting of an overlapping connective disease.

**Vasculitis**

Necrotizing vasculitis affecting several organs, particularly the skin, muscle and gastrointestinal tract leading to visceral perforations has occurred, especially in the childhood form of dermatomyositis. This vasculitis has been referred to as the "systemic angiopathy of childhood". Vasculitis can rarely occur in other tissues including retina, kidneys, and lung.

**Cancer**

Many clinicians believe that patients with dermatomyositis and polymyositis have an increased risk of cancer. The estimates, especially with dermatomyositis, have been reported to be 5 to 11 times greater than the population at large, and even higher for men over age 50. No prospective longitudinal study has addressed these issues. There is no established association with cancer for childhood dermatomyositis.

A reasonable synthesis of existing information favors a small but definite association between dermatomyositis and polymyositis in adults and malignancy. There is a strong clinical impression that the risk may be greater in patients over age 40 with dermatomyositis, but this has not been conclusively confirmed, nor can the cancer type be predicted. No data substantiates that males have an increased risk or that severity correlates with the presence of an underlying neoplasm. Most malignancies occur before or concurrently with the inflammatory myopathy. From a practical standpoint, extensive work-up for cancer does not increase the identification of occult neoplasms and is not cost ineffective. For individual patients, the appropriate evaluation for malignancy includes a thorough physical examination, analysis of stool for occult blood, a chest roentgenogram and mammography.
Laboratory Features

Blood studies

Serum creatine kinase is elevated in over 90% of dermatomyositis cases; levels do not correlate with severity of weakness or rate of progression. The CK may be normal even with marked limb weakness. The erythrocyte sedimentation rate is usually normal.

A broad range of autoantibodies to a variety of nuclear antigens [antinuclear antibodies, ANA] occurs in patients with connective tissue diseases. Most autoantibodies do not help in diagnosis of inflammatory myopathies except that their presence suggests an overlapping collagen vascular disorder or the mixed connective tissue disease. Four autoantibodies, however, may help define subsets or myositis. The most important is the antibody to Jo-1 antigen, which is present in one third of patients with inflammatory myopathies. Jo-1 is a cytoplasmic enzyme (histidyl-transfer RNA synthetase). Of interest, this antibody occurs in a genetically distinct group with HAS-DR3 or HLA-DRw6 haplotypes in the setting of a polymyositis syndrome with interstitial lung disease, arthritis and Raynaud’s phenomenon. Antibodies to PM-1 and Ku antigens occur with increased frequency in the overlap syndrome of polymyositis and progressive systemic sclerosis. The antibody to SS-A (Ro) is associated with Sjögren’s syndrome and may be a marker for predicting myocardial involvement in the inflammatory myopathies.

Electrodiagnostic studies

Electromyographic study during the initial phase of acute dermatomyositis demonstrates increased insertional activity with trains of fibrillations and positive waves accompanied by complex repetitive discharges and myopathic motor units. The amount of spontaneous activity correlates with the degree of disease activity. In more chronic or relapsing dermatomyositis (as well as in other inflammatory myopathies), an increased incidence of long duration, high amplitude polyphasic potentials are encountered. The enlarged motor unit potentials presumably reflect sprouting and reinervation of regenerating muscle fibers and subsequent enlargement of motor unit territory. Moreover, with very advanced disease, and probably as a result of extensive fibrosis in markedly weak muscles, a decreased recruitment pattern may be observed. The finding of reduced recruitment and long duration motor units can be erroneously interpreted as neurogenic, but particularly the presence of long duration motor units may characterize any severe, long-standing muscle disease. Electromyography may also be helpful in distinguishing an increase in disease activity from weakness secondary to type 2 fiber atrophy from disease or from corticosteroid therapy. Isolated atrophy of type 2 fibers does not cause abnormal spontaneous activity on EMG in contrast to active dermatomyositis.

Histologic Studies

Perifascicular muscle fiber atrophy represents a highly specific histologic finding for dermatomyositis, occurring in nearly 75% of cases. The term atrophy, however, is misleading since the small fibers at the periphery of the fascicle are selectively damaged due to microvascular insult. During early stages of injury, damaged muscle fibers exhibit focal myofibrillar and oxidative enzyme loss followed by the appearance of features typical for regeneration, including basophilic cytoplasm and internal nuclei. Loss of the
microvasculature (especially the capillary network) occurs selectively within perifascicular muscle fiber damage. The histologic changes in dermatomyositis are multifocal and vary in severity if different regions of the same muscle biopsy. Fascicles exhibiting very severe damage may show only remnants of very small (atrophic) fibers at the periphery. In fulminant cases wedge-shaped or contiguous areas of muscle fiber necrosis are produced by muscle infarction.

The inflammatory component in dermatomyositis differs from that of a polymyositis and inclusion body myositis. Focal invasion of muscle fibers by inflammatory cells occurs infrequently in dermatomyositis. Instead, collections of inflammatory cells in dermatomyositis occur in the perimysial connective tissue and in a perivascular location. The inflammatory cell infiltration consists of a relatively higher percentage of B cells and CD4+ (T helper) compared to CD8+ (cytotoxic suppressor T cells). In polymyositis and inclusion body myositis the proportion of CD8+ cells is higher. Macrophages represent one-fourth to one-third of the inflammatory cells in both dermatomyositis and polymyositis.

Immune deposits in blood vessels are another characteristic feature in the muscle biopsies of dermatomyositis. The earliest demonstrable histologic abnormality in dermatomyositis is deposition of the C5b-9 complement membrane attack complex (MAC) on small blood vessels. MAC precedes inflammation and other structural abnormalities in muscle on light microscopy and is specific for dermatomyositis. Other components of complement (C3 and C9), IgM, and less often IgG are also deposited within the walls of intramuscular blood vessels. The subsequent necrosis of vessels results in a reduction in the capillary density (number of capillaries per area of muscle). Transforming growth factor beta and its messenger RNA are upregulated in regions of severe ischemia, which probably accounts for the increase in fibrosis in these areas. Electron microscopy (EM) reveals small intramuscular blood vessels (arterioles and capillaries) with endothelial hypoplasia, microvacuoles, and cytoplasmic inclusions. These abnormalities precede the other structural abnormalities on EM. Strong evidence suggests that these immune deposits play an important role in the pathogenesis of the vascular lesion discussed below. Similar immune deposits may be seen in the affected area of the skin at the dermal-epidermal junction.

**Pathogenesis**

Current evidence points to a different pathogenesis of dermatomyositis compared to other inflammatory myopathies. The microvasculature appears to be a primary site of injury and studies indicate a complement-mediated vasculopathy as the primary immunopathogenic event in the evolution of muscle lesions in dermatomyositis. Both immunoglobulin and complement, with activation of C5b-9 complement membrane attack complex, can be demonstrated in the microvasculature as an accompaniment to early muscle fiber damage. In addition, ultrastructural studies show that capillary abnormalities precede other structural changes in muscle. Dermatomyositis is a humorally mediated microangiopathy with an unknown etiology.

Studies characterizing the mononuclear cell infiltrate in dermatomyositis muscle biopsies show several distinguishing features compared to other inflammatory myopathies. There are more B cells infiltrating the biopsy and the invasion of muscle fibers by cytotoxic T cells is an uncommon occurrence in dermatomyositis. In addition, the
inflammatory infiltrate in dermatomyositis shows a more abundant perivascular and perimysial distribution compared to the endomysial cell location characteristic of other inflammatory myopathies.

Factors responsible for initiating vascular damage in dermatomyositis have not been uncovered. The presence of tubular structures resembling virus within capillaries has suggested a viral etiology to some investigators. Other than a single well-documented case of influenza virus-associated childhood dermatomyositis, no conclusive evidence supports a viral pathogenesis. There is preliminary evidence that picornavirus is present in muscle in a small number of cases, but further work is necessary.

**Management**

The therapy and prognosis of childhood dermatomyositis differs from that of adult dermatomyositis. Corticosteroids are effective in virtually 100% of patients with the childhood disease and remission with eventual complete withdrawal of medication can be anticipated. Adults usually respond to corticosteroids but often require other agents and seldom remain in remission if medication is stopped. Oral prednisone is the commonly used drug, but intravenous corticosteroid therapy is sometimes preferred.

Opinions vary as to the appropriate amount and schedule of corticosteroid treatment. Disease tempo and severity are key factors in decision-making. Although there are no double-blind controlled studies, the dramatic change in the natural history of the disease indicates that childhood dermatomyositis responds favorably to corticosteroid treatment in most patients. It is best to avoid the use of cytotoxic agents such as azathioprine, cyclophosphamide and methotrexate in children because of their possible long-term carcinogenic and teratogenic effects. These drugs may be necessary, however, in patients that experience dose-limiting side effects of corticosteroids. Under such circumstances, azathioprine is the best choice of an alternative immunosuppressant drug whether used alone or as a corticosteroid-sparing agent. More recently intravenous infusions of immune globulin have been used as an alternative to corticosteroid therapy, and it has proven to be very effective in both childhood and adult types of dermatomyositis.

Current treatment of childhood dermatomyositis, especially the use of high dose corticosteroids, has changed the natural history of the disease. The severe disabling complications of immobility, muscle atrophy, and contractures, which previously affected as many as half of the patients, have disappeared. In addition, cutaneous calcinosis is less frequent and less severe with aggressive corticosteroid management, although this complication may occur after several months of active disease. Furuncle-like lesions, which on palpation feel indurated or even rock hard, tend to develop over pressure points and extrude caseous or chalky material. These lesions can be painful but improve with surgical or spontaneous discharge. They often leave disfiguring scars. Cutaneous calcinosis may persist and continue to show progression for many years after other signs of disease activity have resolved. A number of agents have been reported to help individual cases including colchicine, diphosphonates, and systemic or local corticosteroids. There is not enough information to recommend one or another of these treatments.
POLYMYSITIS

Polymysitis is not a variant of dermatomyositis without the skin rash. It lacks the diagnostic features on clinical and histologic evaluation described in the previous section. While some of the clinical features of polymysitis and dermatomyositis may be similar, strong evidence indicates a different underlying pathogenesis. The differential diagnosis of polymysitis is long. It is difficult to define specific criteria for the disorder. There is no highly characteristic feature, such as, the skin rash of dermatomyositis. There is no distinctive histopathology such as the perifascicular atrophy seen in the muscle biopsy in dermatomyositis. Using rigid criteria (Table 3) it is possible to define a group of patients that are likely to have polymysitis. Cases without all of these criteria are common. In many such patients a definite diagnosis cannot be made.

Clinical Features

Muscle Weakness

Polymysitis rarely presents before age 20, although childhood and even infantile cases have been reported. Characteristically, muscle weakness develops subacutely or insidiously; rarely the disorder may have a fulminant presentation. Weakness affects proximal limb and neck flexor muscles with variable distal muscle involvement. Absolutely normal distal muscle strength and function should raise suspicion of an alternative muscle disorder, such as, a muscular dystrophy. Dysphagia occurs commonly in polymysitis. As in dermatomyositis, impaired motility can be demonstrated in the pharyngeal muscle as well as in the upper and lower esophagus. Ventilatory failure resulting from muscle weakness is uncommon, but it occurs more often in polymysitis compared to dermatomyositis or inclusion body myositis.

As many as 1/3 of patients with polymysitis have muscle pain. However, muscle pain is rare as a chief complain in polymysitis and prominent myalgia should lead to consideration of other disorders, particularly polymyalgia rheumatica, joint disorders or diffuse fasciitis.

Other Manifestations

The cardiac and pulmonary complications are similar to those of adult dermatomyositis. Cardiac manifestations include inflammatory lesions of the myocardium, congestive heart failure, atrial and ventricular arrhythmias and the sick sinus syndrome. Rarely, the heart manifestations may precede skeletal muscle symptoms. Interstitial lung disease complicates polymysitis with the same frequency as in dermatomyositis. Patients may also have aspiration pneumonia related to dysphagia.

The best available data suggest a small but definite increase in the risk of cancer with polymysitis. Better prospective studies are needed to define this association including the view that cancer more often complicates dermatomyositis than polymysitis.
Laboratory features

Blood Studies

Creatine kinase levels must be elevated to establish an unequivocal diagnosis of polymyositis. A fit to ten-fold or higher increase above normal is expected. Other muscle enzymes, including alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase are often elevated and should not be misinterpreted as a sign of liver involvement. Autoantibodies of value in the diagnosis of polymyositis include JO-1, PM-1 and Mi-2.

Electrodiagnostic Studies

An unequivocal diagnosis of polymyositis cannot be made without abnormal electromyography. The characteristic findings include the presence of small, polyphasic, early recruited motor unit potentials. Fibrillations and positive sharp waves tend to correlate with activity of the disease, and are usually most numerous in paraspinal muscles.

Histologic Studies

Abnormal variability in the size of muscle fibers, scattered necrotic and regenerating fibers, and endomysial inflammation with invasion of non-necrotic muscle fibers are the hallmarks of polymyositis. The endomysial inflammatory cells consist primarily of activated CD8+ (cytotoxic), alpha, beta T-cells and macrophages. Investigations of T-cell receptor (TCR) repertoire of endomysial T-cells in PM demonstrate an oligoclonal pattern of gene rearrangement and a restricted motif in the CD3R region of the TCR suggesting the immune response in antigen-specific. In contrast to dermatomyositis there is no evidence of immune deposits (MAC, complement, or immunoglobulins) on the microvasculature in polymyositis. The degree of inflammation varies; focal collections of inflammatory cells occur in the endomysial connective tissue, especially invading non-necrotic muscle fibers. Perifascicular atrophy does not occur nor are muscle infarcts observed.

Pathogenesis

The histologic and immunologic features observed on muscle biopsy suggest that polymyositis is the result of an antigen-specific, cell-mediated immune response directed against muscle fibers. The trigger for the immune attack is unknown. Viral antigens and genomes have not been identified in the muscle fibers. This suggests the immune response may be directed against endogenous self-antigens rather than processed viral antigens. Nevertheless, viral infection could trigger an autoimmune response secondary to cross-reactivity with specific muscle antigens, altering the expression of self-antigens on muscle fibers, or by the loss of physiologic self-tolerance.

The cytotoxic T-cells appear to induce cell death via the perforin pathway. The autoinvasive T-cells in polymyositis contain perforin granules, which are oriented to the surface of the muscle fibers. When released by exocytosis, these granules induce poor formations on the sarcolemma and result in osmolyis of muscle fibers. Although regenerating and degenerating muscle fibers express Fas and Fas ligand (a pro-
apoptotic complex), there is no evidence that apoptosis plays a role in muscle fiber destruction.

Management

Treatment of polymyositis is the same as dermatomyositis. The goal of converting to an alternate-day prednisone schedule is also important for these patients, in order to reduce steroid side effects. For patients refractory to corticosteroids, or those in whom immunosuppressive agents must be considered, azathioprine in doses outlined for dermatomyositis, is the drug of choice. Methotrexate given weekly is another treatment to consider. Because it can cause interstitial lung disease, methotrexate should be used in patients without this complication of polymyositis.

Pain should not be the major indication for treatment with immunosuppressive drugs. Pain management should be approached through alternative measures, particularly nonsteroidal anti-inflammatory drugs.

INCLUSION BODY MYOSITIS

The term inclusion body myositis (IBM) was coined in 1971 by Unis and Samaha. The disorder resembles polymyositis but the findings of vacuolated muscle fibers and nuclear and cytoplasmic fibrillary inclusions represent distinguishing features. Controversy concerning the specificity of the histopathology of IBM delayed its general acceptance as a distinct disorder. Subsequent reports have unequivocally established this as a well-defined entity separate from dermatomyositis and polymyositis.

Clinical Features

The weakness associated with inclusion body myositis begins and progresses gradually but relentlessly, usually over many months and involves both proximal and distal muscles. The disorder has a male predominance and usually begins after age 50, although no age groups have been entirely excluded. The pattern of muscle weakness on examination helps distinguish inclusion body myositis from other types of inflammatory myopathies. Both proximal and distal muscles are usually affected, and typical findings include a distinctive pattern of weakness and atrophy of the wrist flexors and finger flexors with relative preservation of wrist and finger extensor. In the lower extremities the prominent weakness and atrophy of the quadriceps muscles combined with varying degrees of proximal and distal muscle weakness provides a characteristic picture. Dysphagia occurs in about one-third of inclusion body myositis patients and findings on barium swallow indicate that the major dysfunction is in upper esophageal muscles. Cranial nerve musculature is otherwise spared in most cases. Muscle stretch reflexes are usually normal, although loss of quadriceps reflexes frequently accompanies atrophy and weakness of those muscles.

Heart involvement has not been documented in inclusion body myositis although distinction from other causes of cardiovascular abnormalities in this older group of patients may be difficult.
No documented association with malignancy has been observed but various immune-mediated diseases have been seen in combination with inclusion body myositis including idiopathic thrombocytopenic purpura, interstitial lung disease, diabetes mellitus, systemic lupus erythematosus, and Sjögren’s syndrome

**Laboratory Features**

**Blood studies**

CK may be normal, but is usually two to five-fold elevated although exceptional patients may have levels reaching 10 times normal. Autoantibodies are generally absent in inclusion body myositis. Sedimentation rate is usually normal.

**Electrodiagnostic Studies**

In inclusion body myositis, EMG demonstrates increased insertional activity, often with fibrillations, accompanied by short duration, polyphasic early recruited motor unit potentials. In addition, an increased incidence of long duration potentials commonly occurs and this mixed pattern or short and long duration potentials supports a diagnosis of inclusion body myositis, although it may also occur to other chronic inflammatory myopathies. Nerve conduction studies have revealed evidence of a mild axonal sensory neuropathy in up to 30% of patients.

**Histologic Studies**

The diagnosis of inclusion body myositis clearly rests on muscle biopsy findings. Routine light microscopic histologic sections stained with H&E or modified trichrome demonstrate single or multiple rimmed-vacuoles lined with granular material. These vacuoles tend to occur in small, somewhat angular muscle fibers with an increased reticular pattern. In addition, varying degrees of endomysial inflammation composed of CD8+ T cells and some macrophages occur, especially in relation to non-necrotic muscle fibers. This pattern of inflammation is similar to that of polymyositis. On the other hand, perimysial and perivascular inflammatory infiltration occurs less often in inclusion body myositis than in polymyositis. Small groups of atrophic fibers of mixed histochemical type represent an additional feature commonly observed in inclusion body myositis. The findings raise the possibility of a superimposed neurogenic component. Eosinophilic cytoplasmic or intranuclear inclusions can be seen with careful searching in some cases of inclusion body myositis. An increased number of ragged red fibers and COX negative fibers are also evident in IBM compared to dermatomyositis and polymyositis patients and age-matched controls.

The characteristic light microscopic features of rimmed vacuoles accompanying inflammatory cell infiltrations are usually sufficient for diagnosis. In cases lacking both features, the diagnosis of inclusion body myositis requires electron microscopic demonstration of non-branching filaments. The diameter of the filaments ranges from 10 to 20 nm usually measuring between 15 to 18 nm and varying in length from 1 to 5 nm. Cytoplasmic filaments occur in loose bundles, in parallel or random orientation, most often adjacent to rimmed vacuoles. Filaments also occur within the nucleus, usually surrounded by a thin rim of margined chromatin. The rimmed vacuoles in inclusion
body myositis have myelin figures as well as amorphous debris. Recently the vacuoles have been shown to contain congophilic material with the characteristics of amyloid. These autophagic vacuoles can also be seen in myopathies related to chloroquine, colchicine, vincristine, acid maltase deficiency, hypokalemic periodic paralysis, and oculopharyngeal muscular dystrophy. In these other disorders, autophagic vacuoles have no associated filamentous characteristic of inclusion body myositis. In practice, light microscopy is usually sufficient for a diagnosis of inclusion body myositis, particularly if the clinical features are characteristic. Because of sampling error repeat muscle biopsies may be required to identify the rimmed vacuoles and abnormal tubulofilament or amyloid accumulation to confirm the diagnosis.

**Pathogenesis**

The cause of inclusion body myositis remains unknown. The significance of the filamentous inclusions is a subject of debate. Since the earliest observation of filaments by Chou in 1967, a possible relation to myxovirus has been suggested, including demonstrating antibody reactivity to mumps virus antigens in the area of the rimmed vacuoles. Unfortunately the specificity for mumps antibody has not been confirmed.

The inflammatory infiltrate parallels that seen in polymyositis and is characterized by invasion of non-necrotic muscle fibers by CD8+ cytotoxic/suppressor T cells suggesting an immune-mediated component. Nevertheless, ascribing a primary or secondary role to the inflammation remains difficult. In addition, the inflammatory infiltrate varies significantly between cases, ranging from mild to florid. Histologic and immunologic evidence suggests that IBM is an autoimmune disorder mediated by cytotoxic T-cells. As with polymyositis the autoimmune T-cells in IBM contain perforin granules. Upon release of these granules, pores form on the muscle membrane, resulting in osmolytic. The frequency of finding T-cell invaded fibers is greater than that of finding either necrotic or amyloid containing fibers suggesting that the inflammatory response plays a more important role than the accumulation of vacuoles or amyloid filaments in the pathogenesis of IBM. However, the lack of significant clinical response to immunotherapy argues against IBM being a primary autoimmune disorder.

Recently, a hereditary form of IBM has been demonstrated. Muscle biopsies show typical inclusion bodies in affected families. A multigenerational family supported an autosomal dominant inheritance. In addition, in a sibship affecting 5 of 6 brothers, the muscle disease was associated with a periventricular leukoencephalopathy. These hereditary cases have little if any evidence for inflammation and appear to be a separate disorder, inclusion body myopathy, distinct from sporadic inflammatory IBM. The gene lesion and protein product abnormality have not yet been defined, but there is evidence that amyloid protein is present in the inclusions. This observation raises the possibility that inclusion body myopathy could be a prion-mediated disorder. The availability of histochemical stains for amyloid permits better diagnosis of inclusion body myositis. Ubiquitin (a component of neurofibrillary tangles and senile plaques in Alzheimer's disease) is also present in inclusion body myositis inclusions.
Management

No consistently effective therapy has been found for inclusion body myositis. Intravenous immunoglobulin has been reported to be of slight but significant benefit in one report. Modest transient improvement has been reported with corticosteroids but a sustained response is lacking. Patient numbers have been too small to assess the use of other immunosuppressive drugs alone or in combination with prednisone but trials of azathiprine, cyclophosphamide, nitrogen mustard, cyclosporine and plasma exchange have all been unsuccessful. No beneficial effect was observed following total body irradiation.

References


### TABLE 1

**Inflammatory Myopathies**

**Primary**
- Dermatomyositis
- Polymyositis
- Inclusion body myositis

**Less Common Types**
- Overlap syndromes with progressive systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's
- Mixed connective tissue disease
- Eosinophilia syndromes with myositis
- Giant cell myositis and sarcoidosis
- Graft vs. host disease
- Infection myositis
  - Viral – HIV: Coxsackie
  - Protozoal
  - Parasitic
  - Bacterial
- Toxic myositis – colchicine; penicillamine
### TABLE 2

**Distinguishing Clinical Features of Idiopathic Inflammatory Myopathies**

<table>
<thead>
<tr>
<th></th>
<th>Childhood Dermatomyositis</th>
<th>Adult Dermatomyositis</th>
<th>Polymyositis</th>
<th>Inclusion Body Myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weakness</strong></td>
<td>Proximal&gt;distal</td>
<td>Proximal&gt;distal</td>
<td>Proximal&gt;distal</td>
<td>Proximal and distal</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>Dysphagia</td>
<td>Dysphagia</td>
<td>Predilection for finger/wrist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flexors &amp; knee extensors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dysphagia</td>
</tr>
<tr>
<td><strong>Muscle Pain</strong></td>
<td>&gt;50%</td>
<td>&lt;25%</td>
<td>&lt;10%</td>
<td>No</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Periorbital edema; erythematous rash; calcinosis</td>
<td>Periorbital edema; Erythematous rash</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Joint Involvement</strong></td>
<td>Contractures</td>
<td>Contractures; effusions</td>
<td>Uncommon</td>
<td>None</td>
</tr>
<tr>
<td><strong>Other Systems</strong></td>
<td>Rarely involved Occasional infarcts of bowels, kidney, retina</td>
<td>Arrhythmias, interstitial lung disease</td>
<td>Arrhythmias; heart failure; interstitial lung disease</td>
<td>None</td>
</tr>
<tr>
<td><strong>Risk of Malignancy</strong></td>
<td>Minimal</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
</tr>
</tbody>
</table>
TABLE 2 (CONTINUED)

Distinguishing Clinical Features of Idiopathic Inflammatory Myopathies

<table>
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<tr>
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<th>Adult Dermatomyositis</th>
<th>Polymyositis</th>
<th>Inclusion Body Myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CK</td>
<td>Increased (up to 50x normal)</td>
<td>Increased (up to 50x normal)</td>
<td>Increased (up to 50x normal)</td>
<td>Increased (up to 10x normal)</td>
</tr>
<tr>
<td>Muscle Biopsy</td>
<td>Perimysial and perivascular inflammation; Perifascicular atrophy; MAC-deposition in capillaries</td>
<td>Same as with childhood DM</td>
<td>Endomysial inflammation</td>
<td>Endomysial inflammation; rimmed vacuoles; amyloid deposits; EM shows 15-18 mm tubulofilaments</td>
</tr>
<tr>
<td>Cell Infiltrate</td>
<td>CD4 + T cells; B cells</td>
<td>Same as with childhood DM</td>
<td>CD8 + T cells; macrophages</td>
<td>CD8 + T cells; macrophages</td>
</tr>
<tr>
<td>Common Associated Conditions</td>
<td>Myocarditis; interstitial lung disease; vasculitis; calcinosis</td>
<td>Myocarditis; interstitial lung disease; malignancy; vasculitis; other connective tissue diseases</td>
<td>Myocarditis; interstitial lung disease; other connective tissue diseases</td>
<td>Neuropathy; other autoimmune disease uncommon</td>
</tr>
<tr>
<td>Response to Therapies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Minimal or not at all</td>
</tr>
</tbody>
</table>
TABLE 3

Criteria for Diagnosis of Polymyositis

Clinical: Symmetrical proximal weakness; slight but definite distal weakness is usually present

CK: Elevated (Commonly at least ten-fold)

EMG: Fibrillations, early recruitment and small polyphasic potentials

Biopsy: Endomysial inflammation with focal muscle fiber invasion; muscle fiber necrosis; perivascular mononuclear inflammation

Differential Diagnosis and Criteria for Exclusions

Dermatomyositis: skin rash and biopsy

Inclusion body myositis: severe distal weakness; biopsy

Other collagen vascular diseases: usual criteria

Sarcoidosis: biopsy

Metabolic myopathies: biopsy

Toxic, infectious: history, specific diagnostic study

Endocrine: appropriate hormone studies

Limb girdle muscular dystrophy: family history; biopsy, EMG