Current Concepts in Muscle Disease

American Association of Neuromuscular & Electrodiagnostic Medicine

Anthony A. Amato, MD
Timothy M. Miller, MD, PhD
Mark B. Bromberg, MD, PhD
Gregory T. Carter, MD

2005 AANEM Course E
AANEM 52nd Annual Scientific Meeting
Monterey, California
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Dr. Amato is currently the chief of the Division of Neuromuscular Disease, director of the Clinical Neurophysiology Laboratory, and vice-chairman of the Department of Neurology at Brigham and Women's Hospital in Boston. He is an associate professor of neurology at Harvard Medical School. Dr. Amato is a graduate of the University of Cincinnati College of Medicine. He completed his neurology residency at Wilford Hall Medical Center in San Antonio, Texas, and completed his neuromuscular disease fellowship at the Ohio State University. In addition to co-editing the textbook *Electrodiagnostic Medicine*, Dr. Amato has authored numerous publications in the field of neuromuscular disease and electrodiagnostic medicine. He has been involved in clinical research trials involving patients with amyotrophic lateral sclerosis, peripheral neuropathies, neuromuscular junction disorders, and myopathies.

Timothy M. Miller, MD, PhD

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Dr. Miller earned his medical degree and doctorate from Washington University in Saint Louis, Missouri. He then went on to perform an internship in internal medicine at the University of California, San Francisco, as well as a neurology residency and a neuromuscular fellowship there. He is currently a clinical instructor and research fellow at the University of California, San Diego. Dr. Miller is a member of the American Academy of Neurology and the American Association of Neuromuscular & Electrodagnostic Medicine. He has won several awards, including the Golseth Young Investigator Award and the Needleman Award for Pharmacology Research.

Mark B. Bromberg, MD, PhD

Professor and Vice-chairman
Department of Neurology
University of Utah
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Dr. Bromberg began his academic career in basic science research. He received a doctorate in neurophysiology from the Department of Physiology at the University of Vermont and conducted research in the somatosensory and motor systems. Dr. Bromberg attended medical school at the University of Michigan and also completed his neurology training and neuromuscular/EMG fellowship there. He was on the faculty at the University of Michigan until 1994, when he joined the University of Utah, where he is currently a professor and vice-chairman in the Department of Neurology. Dr. Bromberg is Director of the Neuromuscular Program and EMG laboratory, and the Muscular Dystrophy Association clinics. His research interests are in quantitative EMG, including motor unit number estimation (MUNE) and algorithms for automated motor unit analysis, and in clinical aspects of amyotrophic lateral sclerosis.

Gregory T. Carter, MD

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Dr. Carter is Clinical Professor of Rehabilitation Medicine at the University of Washington, where he co-directs Muscular Dystrophy Association (MDA) clinics and attends in the electrodiagnostic lab. He also serves as regional medical director of rehabilitation services for the Providence Health System in Southwest Washington. His clinical research is investigating the relationships between pain, physical disability, and quality of life in neuromuscular disease (NMD). His pre-clinical research involves studying the role of electromyography and muscle magnetic resonance imaging as in vivo measurement tools to follow physiological changes in humans with NMD and transgenic mouse models of muscular dystrophy. He has over 100 peer-reviewed publications in these areas. In 1994 he won the Best Research Paper Published by a Physiatrist Award from the American Academy of Physical Medicine and Rehabilitation. In 1998 he received the Excellence in Research Writing Award from the Association of Academic Physiatrists. In 2002, he received the Excellence in Clinical Care Award from the MDA.

Authors had nothing to disclose.

Course Chair: Rahman Pourmand, MD

*The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.*
CURRENT CONCEPTS IN MUSCLE DISEASE

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OBJECTIVES
As the neuromuscular field continues to advance, the EDX physician not only needs to know the yield of EDX in the evaluation of myopathies, but also needs to understand these diseases as a whole. After attending this course, participants will (1) learn new updates on channelopathies, periodic paralysis, and congenital myotonia with brief clinical presentations and their diagnosis, (2) understand the new classification and diagnosis of inflammatory myopathies as well as the controversies surrounding this topic, (3) learn about iatrogenic myopathies and how the EDX physician can help the referring physician, and (4) know the latest discoveries of new congenital myopathies and muscular dystrophies.

PREREQUISITE
This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX physicians at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

ACCREDITATION STATEMENT
The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME CREDIT
The AANEM designates attendance at this course for a maximum of 3.25 hours in category 1 credit towards the AMA Physician's Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PMR category 1 credit. CME for this course is available 9/05 - 9/08.

Please be aware that some of the medical devices or pharmaceuticals discussed in this handout may not be cleared by the FDA or cleared by the FDA for the specific use described by the authors and are “off-label” (i.e., a use not described on the product’s label). “Off-label” devices or pharmaceuticals may be used if, in the judgement of the treating physician, such use is medically indicated to treat a patient’s condition. Information regarding the FDA clearance status of a particular device or pharmaceutical may be obtained by reading the product’s package labeling, by contacting a sales representative or legal counsel of the manufacturer of the device or pharmaceutical, or by contacting the FDA at 1-800-638-2041.
### 2004-2005 AANEM COURSE COMMITTEE

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<td>Thomas Hyatt Brannagan, III, MD</td>
<td>New York, New York</td>
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<td>Timothy J. Doherty, MD, PhD, FRCPC</td>
<td>London, Ontario, Canada</td>
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<td>Kimberly S. Kenton, MD</td>
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<td>New York, New York</td>
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<td>Bronx, New York</td>
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<td>Knoxville, Tennessee</td>
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<td>Bryan Tsao, MD</td>
<td>Shaker Heights, Ohio</td>
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### 2004-2005 AANEM PRESIDENT

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<tr>
<td>Gary Goldberg, MD</td>
<td>Pittsburgh, Pennsylvania</td>
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INTRODUCTION

Dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) are the three major categories of idiopathic inflammatory myopathy. These inflammatory myopathies are clinically, histologically, and pathogenically distinct (Table 1). Dermatomyositis is not PM with a rash and IBM is not PM with rimmed vacuoles and inclusions. The annual incidence of these disorders is approximately 1 in 100,000. There are a few reports of DM, PM, and IBM occurring in parents and children and in siblings, including identical twins. There may be a genetic predisposition to developing these disorders, possibly secondary to inherited human leukocyte antigens (HLA) haplotypes. However, the inflammatory myopathies are best considered as acquired diseases.

There are hereditary forms of inclusion body myopathy, but with rare exceptions. The muscle biopsies in these cases lack inflammation and the clinical phenotype (i.e., age of onset, pattern of weakness) is different from sporadic IBM. On the other hand, inflammatory infiltrate in skeletal muscle is not specific for the primary autoimmune myositis and can be seen in various forms of muscular dystrophy.

It is important to be able to distinguish the different disorders with inflammation on biopsy from one another because of important differences in prognosis and response to treatment. This entails performing a detailed clinical history and examination, laboratory evaluation, and muscle biopsies. The patient’s pattern of weakness is the most important piece of the puzzle. The phenotype constitutes more than just the pattern of weakness, but also associated clinical features (e.g., cancer, connective tissue disease, interstitial lung disease), laboratory features (creatinine kinase [CK], antinuclear antibodies, myositis-specific antibodies), and histological features on biopsy.

DERMATOMYOSITIS

Clinical Features

Dermatomyositis can present at any age and females are affected more commonly than males. Most childhood cases present between 5 and 14 years of age, but DM can even develop during infancy. Although the pathogenesis of childhood and adult DM are presumably similar, there are important differences in some of the clinical features and associated disorders. Onset of weakness is typically subacute (over several weeks), although it can develop abruptly (over days) or insidiously (over months). The neck flexors, pectoral, and pelvic girdle muscles are the earliest and most severely affected. As a result, patients complain of difficulty lifting their arms over their heads, climbing steps, and arising from chairs. Asymptomatic distal extremity weakness may occasionally be present. Children are more likely to present with an insidious onset of muscle weakness and myalgias which are often preceded by fatigue, low grade fevers, and a rash. Dysphagia, secondary to inflammation of oropharyngeal...
and esophageal muscles, occurs in approximately 30% of DM patients. A minority of patients can have masseter weakness causing chewing difficulties. Involvement of the pharyngeal and the tongue muscles may result in dysarthria or speech delay in children. Sensation is normal and muscle stretch reflexes are preserved until a severe degree of weakness has developed.

Dermatomyositis is easily recognized and diagnosed because of the characteristic rash which may accompany or precede the onset of muscle weakness. The classic skin manifestations include a heliotrope rash (a purplish discoloration of the eyelids) often associated with periorbital edema and papular, erythematous, scaly lesions over the knuckles (Gottron’s papules). In addition, a flat, erythematous, sun-sensitive rash may appear on the face, neck, and anterior chest (V-sign); on the shoulders and upper back (shawl sign); on the hips (holster’s sign); and on the elbows, knees, and malleoli (Gottron’s sign). The nail-beds often have dilated capillary loops and occasionally appear with thrombi or hemorrhage.

Calcifications in the subcutaneous tissues occur in 30-70% of children, while this is an uncommon finding in adults. Cutaneous calcinosis 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 been inadequately treated.

Associated Manifestations

Cardiac

While overt clinical symptoms are uncommon, electrocardiographic abnormalities including conduction defects and arrhythmias occur frequently in childhood and adult DM. Pericarditis, myocarditis, and congestive heart failure can occasionally develop. Echocardiography and radionuclide scintigraphy may demonstrate ventricular and septal wall motion abnormalities and reduced ejection fractions.

Pulmonary

Interstitial lung disease (ILD) complicates at least 10% of adult DM and can also occur in childhood cases. Symptoms of ILD (i.e., dyspnea, non-productive cough) can develop abruptly or insidiously and often precede the development of the characteristic rash and

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TABLE 1  Idiopathic inflammatory myopathies: clinical and laboratory features

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Sex</th>
<th>Age of Onset</th>
<th>Pattern of Weakness</th>
<th>Serum CK</th>
<th>Muscle Biopsy</th>
<th>Response to IS Therapy</th>
<th>Common Associated Conditions</th>
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<tbody>
<tr>
<td>DM</td>
<td>F &gt; M</td>
<td>Childhood and Adult</td>
<td>Proximal &gt; Distal</td>
<td>Normal or increased (up to 50x normal)</td>
<td>Perivascular, perimysial, and endomysial infiltrates; Perivascular / perimysial CD4+ dendritic cells and B Cells; endomysial PCD</td>
<td>Yes</td>
<td>Myocarditis, Interstitial Lung Disease, Malignancy, Vasculitis,</td>
</tr>
<tr>
<td>PM</td>
<td>F &gt; M</td>
<td>Adult</td>
<td>Proximal &gt; Distal</td>
<td>Increased (up to 50x normal)</td>
<td>Perivascular, perimysial , and endomysial infiltrates Endomysial CD8+ T-cells invade non-necrotic fibers expression MHC1 antigen</td>
<td>Yes</td>
<td>Myocarditis, ?Interstitial Lung Disease?, Other Connective Tissue Diseases</td>
</tr>
<tr>
<td>IBM</td>
<td>M &gt; F</td>
<td>Elderly (&gt; 50 yrs)</td>
<td>Proximal = Distal; Predilection For: Finger/Wrist Flexors, Knee Extensors</td>
<td>Normal or Mildly Increased (&lt; 10x normal)</td>
<td>Perivascular, perimysial, and endomysial infiltrates; CD8+ T-cells invade non-necrotic fibers expression MHC1 antigen; Muscle fibers with rimmed vacuoles; Amyloid deposits; Also COX-negative fibers Endomysial macrophages, MDC and PC</td>
<td>None or Minimal</td>
<td>Sensory europathy Paraproteinemia Autoimmune disorders - (Sjögren’s syndrome, sarcoidosis, thrombocytopenia)</td>
</tr>
</tbody>
</table>

C= complement; CK = creatine kinase; DM = dermatomyositis; F = female; IBM = inclusion body myositis; Ig = immunoglobulin; IS= immunosuppressive; M = male; MAC = membrane attack complex; MxA = myxovirus resistance 1 protein; PDC = plasmacytoid dendritic cells; PM = polymyositis; MDC = myeloid dendritic cells; PC = plasma cells

muscle weakness. Chest radiographs reveal a diffuse reticulo-nodular pattern with a predilection for involvement at the lung bases. In the more fulminant abrupt-onset cases, a diffuse alveolar pattern or "ground-glass" appearance is seen. Pulmonary function tests demonstrate restrictive defects and decreased diffusion capacity, while hypoxemia is evident on arterial blood gasses. Antibody directed against t-histidyl transfer ribonucleic acid (RNA) synthetase, so-called anti-Jo-1, are present in at least 50% of ILD cases associated with inflammatory myopathies.72,91,136 Patients with significant oropharyngeal and esophageal weakness can develop aspiration pneumonia.

Gastrointestinal

Inflammation of the skeletal and smooth muscles of the gastrointestinal tract can lead to dysphagia and delayed gastric emptying.113 Vasculitis/vasculopathy of the gastrointestinal tract is a serious complication which is much more common in childhood DM compared to adult DM.113 The vasculitis can result in mucosal ulceration, perforation, and life-threatening hemorrhage.

Joints

Arthralgias with or without arthritis are a frequent presenting feature. Arthritis is typically symmetric and involves both the large and small joints. The arthralgias and myalgias often ease when the limbs are flexed, which unfortunately leads to the development of flexion contractures across the major joints. Flexion contractures at the ankles leading to toe-walking is a common early finding in childhood DM.

Vasculopathy

Besides the skin, muscle, and gastrointestinal system, necrotizing vasculopathy may affect other tissues including the eyes (retina and conjunctiva), kidneys, and lungs.113,139 Rarely, massive muscle necrosis can lead to myoglobinuria and acute renal tubular necrosis.

Malignancy

There is an increased incidence of underlying malignancy in adult DM, ranging from 6-45%.21,23,28,71,132,139 The association with cancer has not been clearly demonstrated in childhood DM. The rare cases of childhood DM associated with malignancies had unusual courses.113 Detection of an underlying neoplasm can precede or occur after the diagnosis of DM; the majority of malignancies are identified within 2 years of the presentation of the myositis. The risk of malignancy is similar in males and females and is greater in patients over the age of 40 years. Some studies have suggested an increased risk of malignancy in patients with cutaneous vasculitis.18 The severity of the inflammatory myopathy does not appear to correlate with the presence or absence of a neoplasm. Treatment of the underlying malignancy sometimes results in improvement of muscle strength.

The search for an underlying malignancy should include a comprehensive history and annual physical examinations with breast and pelvic examinations for women, and testicular and prostate examinations for men. This author obtains a complete blood count (CBC), routine blood chemistries, urinalysis, and stool specimens for occult blood. Chest radiograph, pelvic ultrasound, and mammogram are the only radiographic studies routinely ordered as well as a colonoscopy for anyone over the age of 50 years or those with gastrointestinal symptoms.

Laboratory Features

Blood Work

Necrosis of muscle fibers results in elevations of serum CK, aldolase, myoglobin, lactate dehydrogenase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Serum CK is the most sensitive and specific marker for muscle destruction. Serum CK is elevated in more than 90% of DM patients, and levels can be as high as 50 times the normal value. However, serum CK levels do not correlate with the severity of weakness and can be normal even in markedly weak individuals, particularly in childhood DM. Erythrocyte sedimentation rate (ESR) is usually normal or only mildly elevated and is not a reliable indicator of disease severity.

Antinuclear antibodies (ANA) can be detected in 24-60% of DM patients.71,91,136 These antibodies are much more common in patients with overlap syndromes (discussed later). Myositis-specific antibodies (MSAs) deserve special comment because it has been suggested that they may prove useful in predicting response to therapy and prognosis.76,91,100,118,136 The MSAs are associated with specific human leukocyte antigen (HLA) haplotypes, and each patient can have only one type of MSA. However, the MSAs are demonstrated in only a minority of patients with an inflammatory myopathy and have not been studied prospectively in regards to their predictive value. The pathogenic relationship these antibodies have to inflammatory myopathies is unknown; they may just represent an epiphenomenon.

The MSAs include: (1) the cytoplasmic antibodies directed against translational proteins (i.e., various t-RNA synthetases and the anti-signal recognition particle), and (2) those directed against Mi-2 and Mas antigens.91,100,118,136 The most common of the antisynthetases is the anti-Jo-1 antibodies which
are associated with ILD and arthritis and are demonstrated in up to 20% of patients with inflammatory myopathy.\textsuperscript{72,91,136} The other antisynthetases are much less common and are each found in less than 2-3% of inflammatory myopathy patients. The presence of these anti-Jo-1 antibodies has been associated with only a moderate response to treatment and a poor long-term prognosis.\textsuperscript{76,118} However, it is the associated ILD which is responsible for the less favorable prognosis, not just the presence of the anti-Jo-1 antibodies. There has not been a prospective study demonstrating treatment outcomes of myositis-ILD patients with anti-Jo-1 antibodies compared to similar patients without these antibodies.

Mi-2 antibodies are seen almost exclusively in DM and can be found in 15-20% of DM patients. Mi-2 is a 240 kD nuclear protein of unknown function. The anti-Mi-2 antibodies are associated with an acute onset, a florid rash, a good response to therapy, and a favorable prognosis.\textsuperscript{76,91,118,136} However, it is not known whether DM patients with Mi-2 antibodies respond differently than DM patients without the antibody.

**Electromyography**

The characteristic electromyographic (EMG) features observed in myositis patients are: (1) increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic and complex repetitive discharges, (2) small duration, low amplitude, polyphasic motor unit action potentials (MUAPs), and (3) MUAPs which recruit early but at normal frequencies.\textsuperscript{1,24} Recruitment may be decreased (fast firing MUAPs) in advanced disease due to the loss of muscle fibers of entire motor units. Late in the course of poorly responsive disease, insertional activity may be decreased secondary to fibrosis. In addition, large duration polyphasic MUAPs may also be seen later in the course reflecting chronicity of the disease with muscle fiber splitting and regeneration rather than a superimposed neurogenic process. The amount of spontaneous EMG activity is reflective of ongoing disease activity. Needle EMG can be helpful in determining which muscle to biopsy in patients with only mild weakness. In addition, needle EMG may also be useful in previously responsive myositis patients who become weaker by differentiating an increase in disease activity from weakness secondary to type 2 muscle fiber atrophy from disuse or chronic steroid administration. Isolated type 2 muscle fiber atrophy is not associated with abnormal spontaneous activity seen during needle EMG.

**Muscle Imaging**

Magnetic resonance imaging (MRI) can provide information on the pattern of muscle involvement by looking at the cross-sectional area of axial and limb muscles.\textsuperscript{51,70,79,114,117} Magnetic resonance imaging may demonstrate signal abnormalities in affected muscles secondary to inflammation and edema or replacement by fibrotic tissue. Some have advocated MRI as a guide to determine which muscle to biopsy.\textsuperscript{117} However, this author has found that MRI adds little to a good clinical examination and needle EMG in defining the pattern of muscle involvement and determining which muscle to biopsy.

**Muscle Biopsy**

The pathological process is multifocal and the frequency and severity of histologic abnormalities can vary within the muscle biopsy specimens. The characteristic histologic feature is perifascicular atrophy.\textsuperscript{1,35,47} However, in this author’s experience this is a late histological feature and is seen in less than 50% of cases (particularly less common in adults). The perifascicular area contains small degenerating fibers as well as atrophic and nonatrophic fibers with microvacuolation and disrupted oxidative enzyme staining. Occasionally, wedged-shaped microinfarcts of muscle fascicles are apparent. Scattered necrotic fibers may be present, however, in contrast to PM and IBM, invasion of non-necrotic fibers is not prominent. The inflammatory infiltrate is composed primarily of macrophages, B-cells, and CD4+ cells in the perimysial and perimysial regions.\textsuperscript{6,46} However, recent studies have demonstrated that there are many more CD 4+ cells in the endomysium that previously appreciated and that these are for the most part plasmacytoid dendritic cells and not T-helper cells.\textsuperscript{61}

The earliest demonstratable histologic abnormality in DM is deposition of the C5b-9 or membrane attack complex (MAC) on or around small blood vessels.\textsuperscript{44,83,84} Membrane attack complex precedes inflammation and other structural abnormalities in the muscle on light microscopy and is specific for DM. Other complement components (C3 and C9), IgM, and less often gamma G immunoglobulin are also deposited on or around the walls of intramuscular blood vessels.\textsuperscript{143} The subsequent necrosis of vessels results in a reduction in the capillary density (number of capillaries per area of muscle).\textsuperscript{44} Transforming growth factor b (TGF-b) and its messenger RNA are upregulated in regions of severe ischemia, which probably accounts for the increased fibrosis in these areas.\textsuperscript{33} Electron microscopy (EM) reveals small intramuscular blood vessels (arterioles and capillaries) with endothelial hyperplasia, microvacuoles, and cytoplasmic inclusions; these abnormalities precede other structural abnormalities on EM.\textsuperscript{14,38}

**Pathogenesis**

The immunological studies and other histological features seen with muscle biopsies suggest that DM is a humorally
mediated microangiopathy. This microangiopathy has been postulated to cause ischemic damage and occasionally infarction of muscle fibers. Some authorities suggest that the perifascicular atrophy is the result of hypoperfusion to the watershed region of muscle fascicles. However, many questions remain regarding this hypothesis and the pathogenic basis of DM.\textsuperscript{60,61} It has never been demonstrated that the perifascicular region is indeed the watershed area in muscle fibers or that the perifascicular fibers are more prone to ischemic damage. Of note, perifascicular atrophy is not evident in ischemic muscle damaged from vasculitis. Further, perifascicular atrophy has not been demonstrated in animal models of small vessel ischemia. On the contrary, such models demonstrate a predilection for the involvement of more centrophascicular fibers.

Deoxyribonucleic acid (DNA) microarray studies of biopsied muscle tissue demonstrate an increased expression of genes induced by interferon-\(\alpha/\beta\).\textsuperscript{59,61} Although this is not specific, it is compatible with the hypothesis of a viral infection triggering the autoimmune attack. Interferon-\(\alpha/\beta\) has a well-defined role in antiviral innate immunity, and this has led to additional consideration of a hypothesis of chronic persistent viral infection as a cause of juvenile DM. However, there are other possibilities. In particular, interferon-\(\alpha\) is synthesized by plasmacytoid dendritic cells (PDCs) in response to a serum factor containing immune complexes of antibody, double-stranded DNA, and RNA viruses. These cells, also called natural interferon producing cells for their ability to secrete massive amounts of IFN-\(\alpha\), can be activated to produce IFN-\(\alpha\) by synthetic short palindromic DNA sequences, termed CpG oligodeoxynucleotides. This author and colleagues have recently demonstrated pyruvate dehydrogenase complex (PDC) in the muscle biopsies of of patients with DM. Pyruvate dehydrogenase complex are CD4+ and comprise a large component of the inflammatory cell infiltrate in DM. These CD4+ cells were originally thought to be CD4+ T-helper cells, but it was demonstrated that most are CD3- and thus are PDC and not lymphocytes.\textsuperscript{61} Increased expression of IFN-\(\alpha\) inducible proteins such as myxovirus resistance 1 protein (MxA) has also been demonstrated on blood vessels and muscle fibers (with a predilection for the perifascicular fibers).\textsuperscript{61} Interestingly, one postulated function of MxA is to form tubuloreticular inclusions around RNA viruses. These inclusions have the same morphology as the tubuloreticular inclusions seen with EM in blood vessels in DM. Using immunoelectron microscopy the author and colleagues have demonstrated MxA within inclusions in vessels in DM muscle biopsies. Perhaps dysregulated IFN-\(\alpha\) production is a central driving problem in the pathogenesis of DM.

**Prognosis**

In the absence of malignancy, prognosis is favorable in patients with DM. Poor prognostic features are increased age, associated ILD, cardiac disease, and late or previous inadequate treatment.\textsuperscript{50,71,76,107,139,146} Five-year survival rates of adult DM range from 70-93%. The mortality rate in children is very low.\textsuperscript{113}

**INCLUSION BODY MYOSITIS**

**Clinical Features**

Inclusion body myositis is characterized clinically by the insidious onset of slowly progressive proximal and distal weakness which generally develops after the age of 50 years.\textsuperscript{1,3,35,62,90,126,145} The slow evolution of the disease process probably accounts in part for the delay in diagnosis, averaging approximately 6 years from the onset of symptoms.\textsuperscript{3,90} Males are much more commonly affected than females, in contrast to the female predominance seen in DM and PM. The clinical hallmark of IBM is early weakness and atrophy of the quadriceps, volar forearm muscles (i.e., wrist and finger flexors), and the ankle dorsiflexors.\textsuperscript{3,62,90} Importantly, the manual muscles scores of the finger and wrist flexors are often lower than those of the shoulder abductors and the muscle scores of the knee extensors are often lower than those of the hip flexors in patients with IBM (Tables 2 and 3 and Figures 1 and 2).\textsuperscript{1} The opposite relationship between muscles scores are present in DM and PM.

In addition, muscle involvement in IBM is often asymmetric, in contrast to the symmetrical involvement in DM and PM. The presence of slowly progressive, asymmetric, quadriceps and wrist/finger flexor weakness in a patient over 50 years of age strongly suggests the diagnosis of IBM.\textsuperscript{3}

Dysphagia occurs in up to 40% of patients and can be debilitating requiring cricopharyngeal myotomy.\textsuperscript{37,90,141} Likewise, mild facial weakness can be detected on examination in at least 33% of IBM patients, however, this weakness is clinically insignificant.\textsuperscript{3,90} Extraocular muscles are spared. Although most patients have no sensory symptoms, evidence for a generalized peripheral neuropathy can be detected in up to 30%
of patients on clinical examination and electrophysiological testing. Muscle stretch reflexes are normal or slightly decreased. In particular, the patellar reflexes are lost early.

### Associated Manifestations

Unlike DM and PM, IBM is not associated with myocarditis or ILD; nor is there an increased risk of malignancy. Autoimmune disorders such as systemic lupus erythematosus (SLE), Sjögren's syndrome, scleroderma, thrombocytopenia, and sarcoidosis have been reported in up to 15% of IBM patients. Diabetes mellitus was reported in 20% of patients in one large series.

### Laboratory Features

#### Blood Work

Serum CK is normal or only mildly elevated (less than 10-fold above normal). Autoantibodies are usually absent except for the occasional patients with concurrent connective tissue disease, although some series have reported positive ANAs in approximately 20% of their IBM patients. There is a significant incidence of the HLA DR3 phenotype (*0301/0302) in IBM.

#### Needle Electromyography and Nerve Conduction Studies

Increased spontaneous and insertional activity, small polyphasic MUAPs, and early recruitment are usually evident during the needle EMG examination. In addition, large polyphasic MUAPs can also be demonstrated in one-third of patients. However, large polyphasic MUAPs can also be seen in DM, PM, and other muscle disorders (i.e., muscular dystrophies) and probably reflects chronicity of the disease process rather than a neurogenic etiology. Nevertheless, nerve conduction studies reveal evidence of a mild axonal sensory neuropathy in up to 30% of patients.

#### Muscle Imaging

Radiological studies demonstrate atrophy and signal abnormalities in affected muscle groups.

### Muscle Biopsy

The characteristic light microscopic findings are endomysial inflammation, small groups of atrophic fibers, eosinophilic cytoplasmic inclusions, and muscle fibers with one or more rimmed vacuoles lined with granular material. Amyloid

### Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Initial Diagnosis</th>
<th>PM Response to Therapy</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>22</td>
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<tr>
<td>Age at diagnosis (yr, mean ± SD)</td>
<td>41 ± 14</td>
<td>58 ± 16</td>
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<tr>
<td>Age at onset (yr, mean ± SD)</td>
<td>41 ± 14</td>
<td>55 ± 14</td>
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<td>Duration prior to diagnosis (yr, mean ± SD)</td>
<td>0.07 ± 0.08</td>
<td>3.6 ± 4.5</td>
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<td>Sex (no. male/no. female)</td>
<td>3/6</td>
<td>10/12</td>
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<tr>
<td>Median modified MRC scores (min to max)</td>
<td>5 (4 to 5)</td>
<td>5 (3 to 5)</td>
</tr>
<tr>
<td>Finger flexors</td>
<td>5 (4 to 5)</td>
<td>5 (3 to 5)</td>
</tr>
<tr>
<td>Wrist flexors</td>
<td>5 (4 to 5)</td>
<td>5 (3 to 5)</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>5 (4 to 5)</td>
<td>5 (3 to 5)</td>
</tr>
<tr>
<td>Ankle dorsiflexors</td>
<td>5 (5 to 5)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Knee extensors</td>
<td>5 (4 to 5)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Hip flexors</td>
<td>4 (4 to 5)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Other clinical characteristics (no. present/no. absent)</td>
<td>0/9</td>
<td>7/15</td>
</tr>
<tr>
<td>Asymmetry in strength</td>
<td>0/9</td>
<td>7/15</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>1/8</td>
<td>8/14</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0/9</td>
<td>4/18</td>
</tr>
<tr>
<td>Creatine kinase (IU/liter, mean ± SD)</td>
<td>5,758 ± 6,929</td>
<td>5,097 ± 7,706</td>
</tr>
</tbody>
</table>

*Adjacent values different at the p < 0.05 level.

*Variable in the PM subgroup responding to therapy different from the IBM group at the p < 0.05 level.

DM = dermatomyositis; PM = polymyositis; IBM = inclusion body myositis; SD = standard deviation; MRC = Medical Research Council.
Table 3  Pattern of weakness in the inflammatory myopathies

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Initial Diagnosis</th>
<th>PM Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist flexor and finger flexor MMRC compared with shoulder abductor MMRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than</td>
<td>DM: 0 (11%)</td>
<td>PM: 7 (32%)</td>
</tr>
<tr>
<td>Equal to</td>
<td>DM: 1 (11%)</td>
<td>PM: 4 (18%)</td>
</tr>
<tr>
<td>Greater than</td>
<td>DM: 8 (89%)</td>
<td>PM: 11 (50%)</td>
</tr>
<tr>
<td>Knee extensor MMRC compared with hip flexor MMRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than</td>
<td>DM: 0 (0%)</td>
<td>PM: 5 (23%)</td>
</tr>
<tr>
<td>Equal to</td>
<td>DM: 0 (0%)</td>
<td>PM: 4 (18%)</td>
</tr>
<tr>
<td>Greater than</td>
<td>DM: 9 (100%)</td>
<td>PM: 13 (59%)</td>
</tr>
<tr>
<td>Ankle dorsiflexor MMRC compared with hip flexor MMRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than</td>
<td>DM: 0 (0%)</td>
<td>PM: 1 (4%)</td>
</tr>
<tr>
<td>Equal to</td>
<td>DM: 0 (0%)</td>
<td>PM: 5 (23%)</td>
</tr>
<tr>
<td>Greater than</td>
<td>DM: 9 (100%)</td>
<td>PM: 16 (73%)</td>
</tr>
<tr>
<td>Wrist and finger flexor MMRC less than shoulder abductor MMRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and knee extensor MMRC less than hip flexor MMRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>DM: 0 (0%)</td>
<td>PM: 5 (23%)</td>
</tr>
<tr>
<td>No</td>
<td>DM: 9 (100%)</td>
<td>PM: 17 (73%)</td>
</tr>
</tbody>
</table>

*Data are numbers of patients, with percentages in parentheses.

**Frequencies in adjacent groups different at the $p < 0.05$ level.

***Frequencies of weakness patterns in the PM subgroup responding to therapy different from the IBM group at the $p < 0.05$ level.

DM = dermatomyositis; PM = polymyositis; IBM = inclusion body myositis; MMRC = Modified Medical Research Council scores.

Figure 1  Pattern of weakness in DM, PM, and IBM

DM = dermatomyositis; IBM = inclusion body myositis; PM = polymyositis
deposition is evident on Congo red staining using polarized light or fluorescence techniques. The number of vacuolated and amyloid-positive fibers may increase with time in individual patients. An increased number of ragged red fibers and cytochrome oxidase (COX)-negative fibers are also evident in IBM compared to DM and PM patients and age-matched control subjects. Electron microscopy demonstrates 15-21 nm cytoplasmic and intranuclear tubulofilaments, although a minimum of three vacuolated fibers may need to be scrutinized to confirm their presence. Vacuolated fibers also contain cytoplasmic clusters of 6-10 nm amyloid-like fibrils. Because of sampling error, repeat muscle biopsies may be required to identify the rimmed vacuoles and abnormal tubulofilament or amyloid accumulation in order to histologically confirm the diagnosis of IBM. This sampling error probably accounts for IBM being misdiagnosed as PM or “inflammatory myopathy with COX-negative muscle fibers.”

Similar to PM, the inflammation in IBM is predominantly endomysial and composed of macrophages and CD8+ cytotoxic/suppressor T-lymphocytes which invade non-necrotic fibers. Major histocompatibility complex class 1 antigens are expressed on necrotic and non-necrotic muscle fibers. Investigations of the T-cell receptor repertoire demonstrate an oligoclonal pattern of gene rearrangement, although there is heterogeneity in the CDR3 domain. These findings suggest that the T-cell response is not directed against a muscle-specific antigen, although the response could be triggered by a superantigen. Recently, others have found persistent clonal restriction of T-cell receptors in infiltrating lymphocytes on repeated muscle biopsies in some patients suggesting that there is a continuous antigen driven attack against the muscle fibers. Gene expression studies in muscle demonstrated up-regulation of immunoglobulin genes. This author and colleagues have found large numbers of endomysial plasma cells sometimes surround muscle fibers.
Myelodendritic cells that in part function to present antigens to both T-cells and B-cells are abundant in the endomysium as well.

Pathogenesis

The pathogenesis of IBM is unknown. Whether IBM is a primary inflammatory myopathy like DM and PM, or a myopathy in which the inflammatory response plays a secondary role is the subject of intense research. The histological and immunological studies previously described provides evidence that IBM may be an autoimmune disorder mediated by cytotoxic T-cells. The autoinvasive T-cells in IBM contain perforin granules. Upon release of these granules, pores form on the muscle membrane, resulting in osmolysis. Pruitt and colleagues reported the frequency of invaded fibers was greater than either necrotic or amyloidogenic fibers suggesting that the inflammatory response plays a more important role than the accumulation of vacuoles or amyloidogenic filaments in the pathogenesis of IBM. Although antibodies have not been demonstrated binding to muscle fibers, it is clear that the humoral wing of the immune system is also upregulated, as evidenced by the plasma cell infiltrate.

The lack of significant clinical response with various immunosuppressive therapies alone or in combination argues against IBM being a primary autoimmune disorder. Eight patients were treated with IBM for 6-24 months with immunosuppressive medications. Their response to treatment was evaluated and their pre- and post-treatment muscle biopsies were analyzed. None of the patients improved in strength or function despite lower serum CK levels and reduced inflammation on the post-treatment muscle biopsies. Interestingly, the amount of vacuolated muscle fibers and fibers with amyloid deposition were increased in the follow-up biopsies suggesting that inflammation may play a secondary role in the pathogenesis of IBM, while the accumulation of vacuoles and amyloid may have a more significant role.

Another line of evidence which suggests that IBM could be a degenerative disorder of muscle rather than an autoimmune inflammatory myopathy is the accumulation of “Alzheimer-characteristic proteins” in vacuolated muscle fibers. Abnormal accumulation of B-amyloid, C- and N-terminal epitopes of B-amyloid precursor protein (B-APP), prion protein (PrPc), apolipoprotein E, α1-antichymotrypsin, ubiquitin, hyper-phosphorylated tau protein and neurofilament heavy chain similar to that observed in the brains of Alzheimer’s patients is evident within IBM vacuolated fibers. Interestingly, a study of 14 IBM patients reported a significant increase in the apolipoprotein E ε4 frequency as observed in Alzheimer patients. However, other studies of IBM patients reported no significant increase in apolipoprotein E ε4 allele frequency. Askanas and colleagues have also described increased acetylcholine receptor, PrPc, and B-APP mRNAs in IBM vacuolated fibers. Thus, increased prion and B-amyloid deposition in these muscle fibers probably result, in-part, from increased transcription of the PrPc and B-APP genes. Muscle fibers transfected in vitro with B-APP cDNA using a recombinant-deficient adenovirus vector results in Congo red positive, vacuolated fibers with tubulofilaments, and abnormal mitochondria typical of that observed in IBM. Interestingly, B-amyloid and prion proteins can induce apoptosis of neurons in vitro. In this regard, regenerating and degenerating muscle fibers express Fas and Fas ligand, a pro-apoptotic complex. However, there is no evidence that apoptosis plays a role in muscle fiber destruction in IBM. Perhaps as in PM, the demonstrated increased co-expression of the anti-apoptotic protein, Bcl-2, in muscle fibers protects against the potential apoptotic effect of Fas/Fas ligand. Although intriguing, the pathogenic relationship of the “Alzheimer-characteristic proteins” in IBM to the pathogenesis of the myopathy is not clear. The accumulation of these proteins in IBM vacuolated muscle fibers may be an epiphenomena rather than the primary pathogenic defect of IBM.

Besides the accumulation of rimmed vacuoles and tubulofilaments, mitochondrial abnormalities as indicated by ragged red fibers and mitochondrial DNA mutations are more frequent in IBM patients than in the other inflammatory myopathies. However, these mitochondrial abnormalities are believed to be secondary changes and not the primary cause of the myopathy. In addition, increased immunoreactivity for nitrotyrosine and both the inducible and nuclear forms of nitric oxide synthase (NOS) have been demonstrated in vacuolated muscle fibers. These findings suggest that nitric oxide-induced oxidative stress may play a role in muscle fiber destruction in IBM. αB-crystatin expression, a member of the heat-shock protein family, is increased in normal as well as abnormal appearing IBM muscle fibers suggesting that there is a pathologic stressor acting upstream from to the development of structural abnormalities including the accumulation of Alzheimer-like proteins, NOS expression, and mitochondrial abnormalities.

A viral etiology has also been speculated in the pathogenesis of IBM. Chronic persistent mumps was previously hypothesized based on immunostaining of inclusions by anti-mumps antibodies. This was subsequently rejected after in-situ hybridization and polymerase chain reaction studies failed to confirm mumps infection. Interestingly, histologic
abnormalities on muscle biopsy similar to IBM have been seen in patients with retroviral infections and post-polio syndrome.

**Prognosis**

Most IBM patients are older and life expectancy does not appear to be significantly altered. Progressing slowly, IBM does not respond well to immunosuppressive medications. Most patients remain ambulatory, although they frequently require or at least benefit from a cane or a wheelchair for long distances. However, some patients become severely incapacitated and require a wheelchair or become bed-ridden within 10-15 years.90

Many patients with steroid-resistant or “refractory” PM eventually are diagnosed with IBM. Importantly, there are patients who clinically resemble IBM, but in whom a definitive diagnosis cannot be confirmed with muscle biopsy.3 These patients are diagnosed with “possible” or “probable” IBM.3,62

**POLYMYOSITIS**

**Background**

What had been described in the literature as “polymyositis” is most likely a heterogenous group of disorders.2,36,140 Despite what one might suspect from reading the literature, PM is the least common of the major idiopathic inflammatory myopathies. There are definitely cases of PM, but it is important to realize that many cases of so-called PM in the literature are in fact IBM, dystrophies with inflammation, and perhaps even DM. The reasons for the erroneous diagnosis are multiple.

**Misdiagnosed Dermatomyositis?**

Most published papers regarding epidemiology and treatment of PM have used Bohan and Peter’s criteria for PM and DM (Table 4).21,22 These criteria were fine in 1975, but as one can see a muscle biopsy is not required for the diagnosis of PM and DM, and the only feature distinguish the PM from DM is the presence of a rash in DM. Further, the biopsy abnormalities as listed are nonspecific (except for perifascicular atrophy—a finding specific for DM, but not seen in PM) and do not help in distinguishing PM from DM or any myopathy with necrosis, including muscular dystrophies. Importantly, the histological criteria do not take into account the advances in histopathology, particularly in regard to immunohistochemistry. It is now appreciated that DM is a humerally mediated microangiopathy, while PM is an HLA-restricted, antigen-specific, cell-mediated immune response directed against muscle fibers.

This author believes there is a clinical spectrum of dermatomyositis with respect to muscle and skin involvement (Figure 3).

Most patients with classic dermatomyositis have a combination of skin and muscle involvement. It is appreciated by many authorities that some patients have the characteristic rash but never develop weakness—so called myopathic dermatomyositis or dermatomyositis sine myositis.48,134 What about the converse? Are there patients with dermatomyositis sine dermatitis? Traditionally, such patients have been diagnosed as having PM based on Bohan and Peter’s criteria. However, if one looks carefully at the muscle biopsies, the features are more similar to DM than PM.

In this regard, some have tried to classify the myositis on the basis of so-called MSAs.91,100,118,136 These studies suggested that antibodies such as anti- signal recognition particle (SRP) were specific for PM or that anti-Jo-1 antibodies could be seen in either PM or DM. However, no details regarding the histopathology was ever mentioned in these early papers and the diagnosis of DM apparently was made only because the characteristic rash was not present or at least not appreciated. In studies that have made the diagnosis of PM or DM based

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**Table 4 Bohan and Peter’s criteria for PM and DM**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>PM Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetrical Weakness of the limb girdle muscles and anteripr neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement.</td>
<td></td>
</tr>
<tr>
<td>2. Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophils, large vesicular sarcolemmal nuclei. Anisoprominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size and an inflammatory exudate, often perivascular.</td>
<td></td>
</tr>
<tr>
<td>3. Elevation in serum skeletal muscle enzymes, particularly the CK and often aldolase AST, ALT, and LDH.</td>
<td></td>
</tr>
<tr>
<td>4. Needle EMG triad of short, small polyphasic motor units, fibrillation potentials, positive sharp waves, insertial irritability, and complex repetitive discharges.</td>
<td></td>
</tr>
</tbody>
</table>

Three out of four of the above features are needed for a diagnosis of PM. The diagnosis of DM is made if the patient also has characteristic rash.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DM = dermatomyositis; EMG = electromyography; LDH = lactate dehydrogenase; PM = polymyositis.
upon currently accepted histological criteria, myositis associated with anti-SRP and anti-Jo-1 antibodies all had histological features of a humorally mediated microangiopathy similar to DM.\textsuperscript{59-61,101,105} No patient has been reported with histopathological abnormalities of PM.

Misdiagnosed Inclusion Body Myositis

Bohan and Peter's criteria do not take into account the existence of IBM. This myopathy was not well-appreciated until the late 1980s and early 1990s, particularly in regard to it being the most common inflammatory myopathy in patients over 50 years of age. Further, although more physicians are aware of IBM now, they still do not realize that because of sampling error, any given biopsy may lack definitive histological criteria for IBM.\textsuperscript{3} Thus, many patients with IBM are erroneously diagnosed as PM.

One group of investigators has tried to define a distinct subgroup of PM on the basis of the presence of COX-negative fibers on muscle biopsy and a modest response to methotrexate in a small number of patients.\textsuperscript{20,88} The clinical features of this subgroup are male predominance, age over 50 years, prominent quadriceps weakness, mildly elevated serum CK levels, and poor response to corticosteroid treatment. As illustrated above, these are the characteristic features of IBM, which are believed to be the most likely diagnosis of this “subgroup” of patients.\textsuperscript{2,62}

Misdiagnosed Muscular Dystrophies

Occasionally, prominent endomysial inflammatory cell infiltrates are evident on biopsies of patients with different forms of muscular dystrophy (i.e., congenital, facioscapulohumeral, limb-girdle, and the dysferlinopathies). Myositis with perinatal onset was first described in Japan.\textsuperscript{81,82,108,112} Subsequently, there have been several reports in the western hemisphere of infantile myositis or congenital inflammatory myopathy.\textsuperscript{123,131,137} The myopathy is characterized by the antenatal or perinatal presentation of hypotonia and generalized weakness and the presence of inflammation on muscle biopsy. Serum CK is usually elevated and needle EMG is myopathic. However, careful review of the clinical features in these reported patients are suggestive of a congenital muscular dystrophy (i.e., Fukayama-type, Walker-Warburg syndrome, or the occidental type) in most. Only one case where the patient had perifascicular atrophy and immunoglobulin and complement deposition on the biopsy characteristic of DM, and the patient improved with steroids was strongly suggestive of a primary myositis.\textsuperscript{123} Most of the reported children did not significantly improve with corticosteroids. In addition, the biopsies had dystrophic features in addition to the inflammatory infiltrates. Finally, there have been several reports of patients with the occidental type of congenital muscular dystrophy with hypomyelination whose muscle biopsy showed prominent inflammation and merosin (alpha-2 laminin) deficiency.\textsuperscript{98,103,116} It is suspected that the majority of infants with inflammation seen on muscle biopsy have a form of congenital muscular dystrophy rather than a primary myositis.

Inflammation on biopsies is not specific for the congenital muscular dystrophies, but is also evident in dystrophinopathies, facioscapulohumeral dystrophy, dysferlinopathy, and other forms of limb-girdle muscular dystrophy.\textsuperscript{74,96,106,124,129} This author has seen many patients with muscular dystrophy misdiagnosed as PM and subjected to long-term complications associated with immunosuppressive therapy. There are clinical features that may help distinguish dystrophy with inflammation from a primary inflammatory myopathy. Scapular winging, prominent facial weakness, and asymmetrical involvement is common in facioscapulohumeral muscular dystrophy (FSHD), but is not in PM. Patients who have severe proximal weakness (i.e., Medical Research Council grade 3 or less) but normal strength distally (wrists and ankles) would be more likely to have a form of a limb girdle muscular dystrophy (LGMD) as opposed to PM. Dysferlinopathies can manifest with a LGMD pattern of weakness, early gastrocnemius weakness and atrophy, tibalis anterior weakness, or any combination of the above and markedly elevated serum CK levels.

Muscle biopsy features can also be helpful in distinguishing a dystrophy from PM. Although endomysial inflammatory cell infiltration and necrotic fibers can be seen in dystrophies, unlike PM there should be no invasion of non-necrotic muscle
fibers by the mononuclear inflammatory cells. Also, deposition of MAC may be seen on the sarcolemma of scattered non-necrotic fibers in FSHD, LGMD, and dysferlinopathies, but not in PM, DM, or IBM.22,135 Further, there is often increased endomysial connective tissue in the dystrophies prior to the muscle end-stage.

Necrotizing Myopathy

The idiopathic necrotizing myopathy are often diagnosed as PM by Bohan and Peter’s criteria.25,45,87,142 Nevertheless, the pathogenic basis appears to be quite distinct from PM and in other reported cases more closely resembles humorally mediated microangiopathy. As in DM, deposition of MAC on small blood vessels and depletion of capillaries can be seen. However, these patients do not have a characteristic rash, biopsy shows no perifascicular atrophy, perivascular inflammation is sparse, and tubuloreticular inclusions in endothelium are not commonly seen on EM. So-called pipestem capillaries may be evident on routine histochemistry and EM.45 Necrotizing myopathy should lead to a search for an underlying connective tissue disease (usually scleroderma or mixed connective tissue disease) and cancer. Muscular dystrophies and toxic myopathies (e.g., statin myopathies) also need to be excluded. However, many cases of necrotizing myopathy are idiopathic.

For the various reasons previously listed, it is impossible to determine from the literature the true incidence of PM, associated laboratory abnormalities, medical conditions (e.g., CTD, ILD, myocarditis, cancer) that may accompany it, and prognosis. Prospective trials using currently histopathological criteria for PM are needed to address this issue.

Clinical Features

Polymyositis generally presents in patients over the age of 20 years and is more prevalent in females.3,21,23,71,97,139 Diagnosis is often delayed compared to DM, because there is no associated rash which serves as a “red-flag” to patients and their physicians. Patients present with neck flexor and symmetric proximal arm and leg weakness, which typically develops over several weeks or months. Distal muscles may also become involved but are not as weak as the more proximal muscles. Muscle pain and tenderness are frequently noted. Dysphagia reportedly occurs in approximately one-third of patients secondary to oropharyngeal and esophageal involvement. Mild facial weakness occasionally may be demonstrated on examination. Sensation is normal and muscle stretch reflexes are usually preserved.

Associated Manifestations

The cardiac and pulmonary complications of PM are reportedly similar to those previously described for DM. Myositis with secondary congestive heart failure or conduction abnormalities occur in up to one-third of patients, but again histopathologic confirmation of true PM is lacking in most of these studies.13,39,58,65,68,71,80,139 Anti-SRP antibodies have been associated with myocarditis and had been noted to be specific for PM.51,100,118,136 However, in studies in which detailed immunohistochemistries were performed, the biopsies were not suggestive of PM but rather resembled DM.101

Also, ILD has been reported to occur in at least 10% of PM patients with at least half having Jo-1 antibodies.41,52,91,100,118,127,136,139 However, as has been noted, these studies did not define PM histologically, and subsequent biopsy specimens from patients with Jo-1 antibodies demonstrated features again more similar to DM than PM.

Polyarthritis has been reported in as many as 45% of PM patients at the time of diagnosis.139 The risk of malignancy with PM is lower than that seen in DM, but it may be slightly higher than expected in the general population.23,28,139 But again, the diagnosis of PM in these studies was not based on histopathology so if there actually is an increased risk of malignancy in PM, it is unclear.

Laboratory Features

Blood Work

Serum CK level is elevated 5 to 50 fold in the majority of PM cases. Serum CK can be useful in monitoring response to therapy, but only in conjunction with the physical examination. The serum CK level does not correlate with the degree of weakness. Erythrocyte sedimentation rate (ESR) is normal in at least half the patients and does not correlate with disease activity or severity.22

Positive ANAs are reportedly present in 16-40% of PM patients.71,91,139 Again the exact relationship of ANAs and CTD in patients with histologically defined PM is unclear.

Electromyography and Muscle Imaging

Electromyography is usually abnormal in PM with increased insertional and spontaneous activity, small polyphasic MUAPs, and early recruitment.1,24 Muscle imaging studies can suggest areas of inflammation in affected muscles.51,117
Muscle Biopsy

The histologic features of PM are distinct from DM. The predominate histologic features in PM are variability in fiber size, scattered necrotic and regenerating fibers, and endomysial inflammation with invasion of non-necrotic muscle fibers. All of the invaded and some of the noninvaded muscle fibers may express major histocompatibility complex class 1 antigen which is not normally present in the sarcolemma of muscle fibers. The endomysial inflammatory cells consist primarily of activated CD8+ (cytotoxic), alpha, beta T-cells, and macrophages. A single case of PM with CD4- CD8- gamma/delta T-cell inflammation has been reported in detail. Investigations of the T-cell receptor (TCR) repertoire of endomysial T-cells in PM demonstrate an oligoclonal pattern of gene rearrangements and a restricted motif in the CD3R region of the TCR suggesting the immune response is antigen-specific. Finally, in contrast to DM, there is no evidence of immune deposits (MAC, complement, or immunoglobulins) on the microvasculature in PM. Gene expression studies in muscle demonstrated upregulation of immunoglobulin genes. It has been demonstrated that large numbers of endomysial plasma cells sometimes surround muscle fibers. Myeloidendritic cells that in part function to present antigens to both T-cells and B-cells are abundant in the endomysium as well.

Pathogenesis

The histologic and immunologic features seen by the muscle biopsy suggest that PM is the result of a HLA-restricted, antigen-specific, cell-mediated immune response directed against muscle fibers. The trigger of this autoimmune attack is not known. A viral etiology has been speculated, but there is no conclusive evidence supporting this theory. Most class 1 molecules on the surface of cells express endogenous self-peptides. Viral antigens and genomes have not been identified in the muscle fibers suggesting that the immune response may be directed against endogenous self-antigens rather than processed viral antigens. Nonetheless, viral infection could indirectly 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. Interestingly, PM can develop as a complication of human immunodeficiency virus (HIV) and human T-lymphocyte virus 1 (HTLV-1) infections. In these cases, the myositis appears to be the result of such indirect triggering of the immune response against muscle fibers.

The cytotoxic T cells appear to induce cell death via the perforin pathway. The autoinvasive T-cells in PM contain perforin granules, which are orientated to the surface of the muscle fibers. When released by exocytosis, these granules induce pore formations on the sarcolemma and result in osmolysis of muscle fibers. Although regenerating and degrading muscle fibers express Fas and Fas ligand (a pro-apoptotic complex), there is no evidence that apoptosis plays a role in muscle fiber destruction. The increased expression of Bel-2, an anti-apoptotic protein may protect against the potential apoptotic effect of Fas/Fas ligand.

Prognosis

The majority of patients with PM respond favorably to immunosuppressive therapies, but usually require lifelong treatment. Some retrospective studies suggest that PM does not respond to immunosuppressive agents as well as DM. However, interpretation of the results of these retrospective series is difficult as the diagnosis of PM was usually made on the basis of Bohan and Peter’s criteria rather than more current criteria based on strict clinical and histological criteria.

OVERLAP SYNDROMES

The overlap syndromes apply to a group of disorders in which DM or PM is associated with another well-defined CTD such as scleroderma, mixed connective tissue disease, Sjögren’s syndrome, systemic lupus erythematosus, and rheumatoid arthritis. Whether or not PM is associated with CTD is not clear as the histology in such patients was not described—just that they did not have an obvious DM rash.

Scleroderma

Proximal muscle weakness is common in scleroderma, however, most of the patients have normal serum CKs and normal needle EMG findings. Muscle biopsies may demonstrate mild variability in fiber size with atrophy of type 2 muscle fibers and perimysial fibrosis. However, active myositis has been reported in 5-17% of patients with scleroderma and can occur in either of its two major forms—progressive systemic sclerosis or calcinosis cutis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia (CREST) syndrome. Scleroderma-myositis patients have increased serum CK levels, and irritable and myopathic EMGs.

Anticentromere antibodies are seen in the majority of patients with CREST syndrome, while anti-Scl-70 antibodies are common in patients with progressive systemic sclerosis. In addition, approximately 25% of North American
patients with scleroderma-myositis have anti-PM-Scl (also called anti-PM-1) antibodies. Anti-PM-Scl is not specific for this disorder, because only 50% of patients with this antibody have the scleroderma-myositis overlap syndrome. In Japan, the scleroderma-myositis syndrome is associated with anti-Ku antibodies, rather than anti-PM-Scl antibodies. In North America, anti-Ku antibodies are not associated with myositis, but can be demonstrated in some patients with systemic lupus erythematosus.

Sjögren’s Syndrome

Sjögren’s syndrome is characterized by dryness of the eyes and mouth (sicca syndrome) and other mucosal membranes. Muscle pain and weakness are common in Sjögren’s syndrome, however, actual myositis is rare. Weakness is usually due to disuse atrophy secondary to arthritis and pain. Nonetheless, there are reports of both DM and PM associated with Sjögren’s syndrome. About 90% of patients have ANAs directed against ribonucleoproteins, specifically SS-A (Ro) and less commonly SS-B (La) antibodies.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organ systems. Weakness is not unusual in SLE, but is most often the result of disuse atrophy. Inflammatory myositis is uncommon in SLE. However, some series have reported that up to 8% of DM and PM patients have SLE.

The majority of patients with SLE have positive ANA titers which are directed against native DNA (highly specific for SLE) and ribonuclear proteins (RNP). The anti-RNP antibodies are present in less than half of SLE patients and include anti-SS-A and anti-SS-B (also present in Sjögren’s syndrome), anti-U1 RNP (also present in mixed connective tissue disease), and anti-Sm (specific for SLE).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) has been reported in up to 13% of patients with DM and PM, although the incidence of inflammatory myopathy in patients with RA is much less. The most common etiology of weakness in RA is type 2 muscle fiber atrophy from chronic steroids or disuse secondary to arthralgias.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) has clinical features of scleroderma, SLE, RA, and myositis. Dermatomyositis is more common than PM, although both have been described in association with MCTD. High titers of anti-U1 RNP antibodies are common in MCTD, these antibodies but can also be detected in SLE.

FOCAL MYOSITIS

Clinical features

Focal myositis is a rare disorder which can develop in infancy to late adult life. It presents as a solitary, painful, and rapidly expanding skeletal muscle mass which often mimics a malignant soft tissue tumor. The legs are the most common site of involvement but it can also affect the upper extremities, abdomen, head, and neck. There are rare cases of focal myositis generalizing to more typical polymyositis. The disorder needs to be distinguished from sarcoidosis, Bechet’s syndrome, muscle infarction secondary to diabetes or vasculitis, and soft tissue tumors. The lesions may resolve spontaneously or with corticosteroid treatment.

Laboratory Features

Serum CK and ESR are usually normal. Magnetic resonance imaging and CT imaging demonstrate edema within the affected muscle groups.

Histopathology

Mononuclear inflammatory cells composed of CD4+ and CD8+ T-lymphocytes and macrophages are present in the endomysium. Necrosis and phagocytosis of necrotic fibers is apparent. Nonspecific myopathic features such as fiber size variability, split fibers, increased centronuclei, and endomysial fibrosis are also described. One report noted that MHC class 1 antigens were not expressed on muscle fibers, in contrast to polymyositis where these antigens are typically abnormally expressed on the fibers.

Pathogenesis

The etiology is unknown. Immunological studies suggest the disorder is distinct from PM and not the result of a cell-mediated attack directed against a muscle specific antigen.

SUMMARY

Dermatomyositis, PM, and IBM are clinically, histologically, and pathogenically distinct categories of idiopathic inflammatory myopathy. Features of DM and PM can overlap with those of other autoimmune connective tissue diseases. Other types of inflammatory myopathy are much less common but are clinically and histologically distinguishable. Dermatomyositis is a humorally-mediated microangiopathy,
while PM is a T-cell mediated disorder directed against muscle fibers. The pathogenesis of IBM is unknown. Dermatomyositis and PM are responsive to immunosuppressive therapy, in contrast to IBM which is generally refractory to therapy. Prospective, double-blind, placebo-controlled trials are necessary to determine prognostic features and the best treatment options for the different disorders.

REFERENCES

45. Emslie-Smith AM, Engel AG. Necrotizing myopathy with pipetem capillaries, microvascular deposition of complement membrane attack complex (MAC), and minimal cellular infiltration. Neurology 1991;41:936-939.


Skeletal Muscle Channelopathies

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INTRODUCTION

Selecting which charged molecule and how much of that charged molecule should be allowed to enter or exit a cell or its subcompartments is a critical task accomplished through numerous ion channels. Proper regulation of ions may be particularly important for nerve and muscle given the demands of electrical excitability. Indeed, dysfunction of these channels (“channelopathy”) has been linked to a wide variety of inherited diseases of the nervous system and muscle, including periodic paralysis, myotonia congenita, episodic ataxia, familial hemiplegic migraine, and episodic ataxia (Table 1). Presumably, sporadic disorders with similar phenotypes may also be related to ion channel function, though this remains less well established. The majority of this manuscript will focus on the genetic syndromes since those are the best characterized.

One strikingly common feature of the diverse group of disorders secondary to mutations in ion channels is the paroxysmal nature of the symptoms. Many patients are normal in between attacks. Although some triggers of attacks such as certain foods or temperature have been well defined by patients, how exactly these trigger symptoms and why the disease is episodic remain a mystery. Many of the channelopathies start in infancy or childhood and worsen in adolescence or young adult life. Some improve in the middle to late adult years. A common set of medications is effective in treating these disorders. Carbonic anhydrase inhibitors improve attack frequency and severity in periodic paralysis, episodic ataxia, and migraine headache.

Disorders secondary to mutations in skeletal muscle ion channels are among the best characterized channelopathies and will be the focus in this manuscript. Recognizing the typical presentation of these disorders avoids the risks and costs of further diagnostic testing and has clear implications for treatment. The skeletal muscle channelopathies include hypokalemic periodic paralysis (HOPP), hyperkalemic periodic paralysis (HYPP), Andersen-Tawil syndrome, paramyotonia congenita (PC), Becker’s myotonia congenita (MC), and Thomsen’s MC. Malignant hyperthermia and congenital myasthenic syndromes may also be linked to dysfunction of muscle ion channels.

MUSCLE PHYSIOLOGY AND ION CHANNELS

Nerve input to skeletal muscle depolarizes the outer muscle membrane, which in turn triggers an action potential that is propagated through the muscle membrane. The action potential begins by an inward sodium current mediated by the rapid opening of voltage-gated sodium channels. Inactivation of sodium channels as well as outward flow of potassium through potassium channels leads to repolarization of the membrane. Repolarization is also dependent on high chloride conductance. Propagation of the action potential through the muscle membrane causes release of the of calcium ions from the sarcoplasmic reticulum. This burst of calcium triggers muscle contraction.

Abnormal sodium channel inactivation in vitro first implicated sodium channels as a possible cause for HYPP. Subsequent
genetic studies and functional analysis proved this hypothesis correct\textsuperscript{5,18,19} and helped establish the group of channelopathy diseases. The specific gene defects associated with the disorders are listed in Table 1. Sodium channel dysfunction is also responsible for PC and a small subset of HOPP. The majority of HOPP is caused by mutations in calcium channels. An inwardly rectifying potassium channel has been linked to Andersen-Tawil syndrome.

Myotonia congenita is caused by mutations in the CLCN1 gene, the major skeletal muscle chloride channel.\textsuperscript{9} These mutations shift the membrane potential to the depolarizing range. The sustained depolarization allows a new premature action potential, which results in skeletal muscle hyperexcitability.\textsuperscript{4,6,7,24,25} On needle electromyography (EMG) this is represented by myotonic runs. Patients with MC experience muscle hyperexcitability as stiffness and weakness.

### CLINICAL PRESENTATIONS

#### Periodic Paralyses

Periodic paralyses are a group of dominantly inherited disorders characterized by episodic weakness of skeletal muscles without effects on the central nervous system or respiratory function.

Patients with inherited periodic paralysis typically present in childhood with episodic weakness. In general, those with HYPP present at an earlier age (infancy) than those with HOPP (pre-teen). Onset of symptoms after age 20 is strikingly unusual for the inherited form of the disease.\textsuperscript{15} The attacks of weakness range from mild to full tetraplegia, lasting from several minutes to 24 hours. The frequency of attacks is highly variable, with some patients only having a few attacks per year, while others experience attacks daily. In general, attacks for HOPP occur infrequently (1 per week or month), but when they do occur, they are severe and the patient is unable to get out of bed for hours to a full day. Attacks in HOPP often occur upon first awakening. For HYPP or PC the attacks of episodic weakness are usually much less prominent than the myotonia. Some HOPP and HYPP patients describe cold as a precipitant. For PC, worsening with cold exposure is a nearly universal phenomenon, often associated with significant weakness as well as increased myotonia. The myotonia in HYPP and PC is “paradoxical” in that it is worsened by activity rather than improved with activity. In MC, the myotonia

<table>
<thead>
<tr>
<th>Skeletal Muscle Channelopathies</th>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paramyotonia congenita</td>
<td>SCN4A</td>
<td>Sodium channel</td>
</tr>
<tr>
<td>Potassium aggravated myotonia</td>
<td>SCN4A</td>
<td>Sodium channel</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis</td>
<td>SCN4A</td>
<td>Sodium channel</td>
</tr>
<tr>
<td>Hypokalemic periodic paralysis</td>
<td>CACNA1S</td>
<td>Calcium channel</td>
</tr>
<tr>
<td>Andersen-Tawil syndrome</td>
<td>KCNJ2</td>
<td>Potassium channel</td>
</tr>
<tr>
<td>Myotonia congenita</td>
<td>CLCN1</td>
<td>Chloride channel</td>
</tr>
<tr>
<td>Congenital myasthenic syndrome</td>
<td>CHRNA</td>
<td>Acetylcholine receptor</td>
</tr>
<tr>
<td></td>
<td>CHRNB</td>
<td>Acetylcholine receptor</td>
</tr>
<tr>
<td></td>
<td>CHRNE</td>
<td>Acetylcholine receptor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Neurological Diseases</th>
<th>Disorder</th>
<th>Gene</th>
<th>Channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinocerebellar ataxia type 6</td>
<td>CACNA1A</td>
<td>Calcium channel</td>
<td></td>
</tr>
<tr>
<td>Familial hemiplegic migraine</td>
<td>CACNA1A, ATP1A2</td>
<td>Calcium channel, Sodium-potassium transporter</td>
<td></td>
</tr>
<tr>
<td>Episodic ataxia with myokymia</td>
<td>KCNA1</td>
<td>Potassium channel</td>
<td></td>
</tr>
<tr>
<td>Episodic ataxia with nystagmus</td>
<td>CACNA1A</td>
<td>Calcium channel</td>
<td></td>
</tr>
<tr>
<td>Hereditary hyperekplexia</td>
<td>GLRA1</td>
<td>Glycine receptor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac Disease</th>
<th>Disorder</th>
<th>Gene</th>
<th>Channel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome</td>
<td>Type 1</td>
<td>KVLQT1</td>
<td>Potassium channel</td>
</tr>
<tr>
<td></td>
<td>Type 2</td>
<td>HERG</td>
<td>Potassium channel</td>
</tr>
<tr>
<td></td>
<td>Type 3</td>
<td>SCN5A</td>
<td>Sodium channel</td>
</tr>
<tr>
<td></td>
<td>Type 4</td>
<td>ANK2</td>
<td>Ankyrin B</td>
</tr>
<tr>
<td></td>
<td>Type 5</td>
<td>mIN</td>
<td>Potassium channel</td>
</tr>
<tr>
<td></td>
<td>Type 7</td>
<td>KCNJ2</td>
<td>Potassium channel</td>
</tr>
</tbody>
</table>

QT = quick time.
improves with continued activity, termed the “warm-up” phenomenon.

Neurological examination between attacks in younger patients with periodic paralysis may be entirely normal, with the exception of myotonia in patients with HYPP or PC. As noted earlier, the myotonia is paradoxical. In older patients with periodic paralysis, a surprising number of patients will have evidence of proximal weakness, which in some is severe.

Laboratory testing has found that potassium does indeed help distinguish HYPP and HOPP especially if potassium is tested during one of the attacks. Hyperkalemic periodic paralysis or PC has normal or slightly elevated potassium. Hypokalemic periodic paralysis patients have low potassium during the attacks. Needle EMG is strikingly different between HYPP and HOPP or PC. Electrical myotonia is common in HYPP and PC and almost never found in HOPP. On muscle biopsy, a vacuolar myopathy is the most common finding.

As will be discussed in more detail, the exercise test shows a decrement in HOPP, HYPP, and PC. In general, HOPP and HYPP do not show an objective cold effect; PC patients do have an objective cold effect. In occasional patients with PC or HYPP, there may be some overlap in the exercise test and objective cold effect. Administration of potassium will provoke attacks in HYPP, although this test is not routinely performed. Similarly driving potassium into cells by giving insulin and glucose simultaneously may provoke an attack in HOPP, although this is also not routinely performed.

Genetic testing for periodic paralysis is performed by some specialized laboratories. The easiest way to find such resources may be by logging on to http://www.genetests.org/. Most laboratories will only test for the common mutations. Typically HOPP shows mutations in the calcium channel gene CACNA1S, most commonly R528H and R1239H, although disease-causing sodium channels and potassium channel mutations are recognized. There are some differences between the various mutations, e.g., HOPP secondary to sodium channels is often less responsive to acetazolamide therapy. Two mutations in the sodium channel SCN4A gene, T704M and M1592V, account for the majority of HYPP. Mutations in the sodium channel are also responsible for PC; residues R1448C and T1313M are the most commonly affected.

Treatment with carbonic anhydrase inhibitors decreased attack severity and frequency in both HYPP and HOPP. The efficacy of dichlorphenamide was demonstrated in one clinical trial. Acetazolamide is also commonly used. During an acute attack for HOPP, replacing potassium often helps restore strength. Education regarding typical triggers in the disease may help prevent attacks, although in the inherited forms of the disease, the triggers are usually well-known to the patients.

Andersen-Tawil Syndrome

Andersen-Tawil syndrome is associated with the triad of cardiac arrhythmias, dysmorphic features, and periodic paralysis. The episodic weakness may be similar to periodic paralysis. There is no myotonia. The distinguishing features are the other manifestations of the disease including dysmorphisms such as clinodactyly, syndactyly, hypertelorism, and low set ears. The dysmorphisms may be subtle and not easily recognized. The part of the disease that causes the most concern is the cardiac abnormalities, which sometimes cause malignant ventricular arrhythmias. It is the cardiac problems with this disorder that strongly argues for checking an electrocardiogram (EKG) in all patients suspected to have periodic paralysis, especially since the dysmorphic features may be very subtle. The EKG findings in Andersen-Tawil syndrome may include prolonged quick time interval (common early sign), bigeminy, and ventricular tachycardia. Some patients require cardioverter defibrillators. Andersen-Tawil syndrome is caused by a mutation in potassium channel KCNJ2.

Potassium-Aggravated Myotonia

Potassium administration “aggravates” or brings on myotonia in patients with potassium-aggravated myotonia. They also experience random, episodic myotonia without any associated weakness. The myotonia is not sensitive to cold and is most prominent about 20 minutes after exercise. Like HYPP and PC, the disorder is linked to sodium channel dysfunction.

Inherited Periodic Paralysis of Uncertain Etiology

There is a group of patients that have some of the features of periodic paralysis, but no demonstrable mutation in sodium, calcium, or potassium ion channels. Some of these patients also have a convincing family history. In general, patients without evidence of ion channel mutations are older at disease onset. In addition, these patients rarely describe diet as a precipitant for an attack, a common trigger for those with mutations. Finally, patients with mutations often show vacuolar myopathy on muscle biopsy. Patients without mutations often have nonspecific, abnormal muscle biopsies. Despite the less typical features, these patients also respond to carbonic anhydrase treatment. All of these patients with less
typical features and especially those without a family history need to have a thorough investigation of secondary (metabolic) causes of periodic paralysis.

Metabolic Periodic Paralysis

The most common metabolic derangement associated with HOPP is thyrotoxicity. At first presumed to only affect Asians, it is now recognized among a large number of ethnic groups. Despite the fact that thyrotoxicosis is more common among women, thyrotoxic periodic paralysis is much more common among men (20:1 ratio). The second to fourth decade is the typical age presentation for thyrotoxic periodic paralysis. The genetic contribution and how the thyrotoxicity triggers the HOPP remains unknown. The attacks in this disorder are commonly provoked by rest after exercise or a large carbohydrate meal, and are associated with signs of hyperthyroidism and a low serum potassium. Returning the patient to a euthymic state treats the disorder. Potassium replacement aids recovery of strength, but should be monitored closely, especially if given intravenously, as rebound hyperkalemia may occur. All patients with suspected periodic paralysis should be checked for thyroid disease.

Chronic potassium wasting, e.g., with diuretics or because of renal tubular acidosis, can also cause periodic paralysis. In patients without a family history of the disease and no evidence of the thyroid disease, especially in older patients, a full search for chronic potassium wasting should be sought.

Myotonia Congenita

Myotonia congenita presents in infancy to childhood. Both forms of MC, Thomsen’s MC, and Becker’s MC present with nearly identical phenotypes. They are distinguished by their mode of inheritance. Thomsen’s MC is dominant while Becker’s MC is recessive. Some physicians have noted that Becker’s MC tends to present somewhat later (age 4-12) than Thomsen’s MC (infancy) and that Becker’s MC patients have more severe symptoms. While the attacks of myotonia are often described as being associated with mild weakness, stiffness (myotonia) is the predominant symptom. The myotonia in MC differs clinically from that found in PC or HYPP. In HYPP or PC, the myotonia worsens with continued activity. In MC, myotonia improves with continued activity and this so called, “warm-up” phenomenon is characteristic. Attacks of myotonia may be provoked by rest after exercise or cold, as with the periodic paralyses. However, triggers for the myotonia are usually a less prominent feature of the disease than with the periodic paralyses. As with periodic paralyses, there are patients with a positive family history and some features of the disease who do not have demonstrable mutations in ion channels. There are often less typical features in these patients and myotonia is less prominent on needle EMG.

On examination, patients often have preserved strength with hypertrophied muscles that seem at odds with their physical limitation. Masseter muscle hypertrophy may produce a characteristic facial appearance. Percussion myotonia may be readily demonstrated. Myotonia improves with repeated movement.

General laboratory findings are normal, except creatine phosphokinase may be slightly elevated. Needle EMG shows prominent, widespread myotonia.

A subset of patients with MC may have a decrement on the exercise test. There is no objective cold effect, although electrical myotonia may increase with cooling. Mutations in chloride channels are responsible for MC. Why the various mutations cause either dominant or recessive disease remains a mystery. In fact, the same mutation may cause recessive (Becker’s) or dominant (Thomsen’s) disease. There are few laboratories performing routine genetic testing for MC. The website http://www.genetests.org/ may be the best resource to find current testing.

Many patients with MC do not need or seek treatment for their myotonia. However, for others the symptoms are disabling. Although there are no approved medications for the treatment of MC, the myotonic symptoms are best treated with mexilitene, an orally absorbed lidocaine derivative that functions as a use-dependent sodium channel blocker. Quinine, procainamide, phenytoin, and carbamazepine have also been used with some success.

SPECIALIZED TESTING

Exercise Test

The exercise test and provocative cold test are two straightforward examinations that can be performed in any electrodiagnostic (EDX) laboratory. A protocol for the exercise test and provocative cold test are provided in Tables 2 and 3. The exercise test, as first described by Phil McManis shows a decrement of the compound muscle action potential (CMAP) when the CMAP is tested over time following 5 minutes of sustained exercise. The test is positive in both HOPP, HYPP, and in PC. A positive test is defined as a greater than 40% drop in CMAP. Both metabolic and familial cases are likely to be positive. The decrease in patients with PC differs qualitatively from HOPP and HYPP. In PC, following exercise, there is a rapid fall in the amplitude followed...
by a slow increase back to baseline over the next 60-90 minutes. In HOPP and HYPP, the amplitude may be mildly low at rest, increase slightly, and then fall by greater than 40% over the next 15-30 minutes. Some cases of MC also show a decrement on the exercise test as well, but this is not consistent. The response to the exercise test is summarized in Figure 1.

**Provocative Cold Test**

Patients with PC often describe weakness and stiffness provoked by cold. This may be a direct effect on the muscles and can be reproduced in the EDX laboratory.16,23 A protocol for the provocative cold test is provided in Table 3 and a positive test is defined as an objective cold effect with a decrease in CMAP amplitude greater than 75%. The most specialized piece of equipment not standard to many EDX laboratories is a basic, long thermometer that can be submerged in water. The “old style” with a column of fluid works best. The CMAP is recorded before and after cooling the hand in a bucket of cool (15˚ C) water. Patients with PC may initially show increased myotonia with mild cooling, but will then show decreased electrical activity during needle EMG and a remarkable decrease in CMAP amplitude. Patients with MC will show an increase in myotonia with cooling, but the CMAP amplitude will not be affected. Typically HOPP and HYPP do not show any changes with cooling. However, some “overlap” cases of HYPP do show an objective cold effect.

**Differential Diagnosis**

Table 4 summarizes the clinical features of MC and Table 5 summarizes the clinical findings in MC. With these tables in mind, often the correct diagnosis can be reached by history/physical and relatively few diagnostic tests. Figure 2 outlines one approach to patients with episodic weakness.

The approach to patients with suspected MC is often less challenging than periodic paralysis. In clinical practice, it may make little difference whether the patient is labeled as having Thomsen’s MC versus Becker’s MC, though some authors have argued that Becker’s is more severe than Thomsen’s. The first important step is to establish that there

<table>
<thead>
<tr>
<th>Table 2 Exercise test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rule out compressive or other lesion affecting nerve to be studied</td>
</tr>
<tr>
<td>2. Record CMAP of EDB, APB, or ADM</td>
</tr>
<tr>
<td>3. Be sure that recording electrode is secured well</td>
</tr>
</tbody>
</table>
| 4. Exercise patient by sustained contraction of muscle for 5 minutes  
Rest breaks of a few seconds are allowed for patient |
| 5. Following exercise, record CMAP every 1 minute for 5 minutes |
| 6. After first 5 minutes, record CMAP every 5 minutes for 30 to 60 minutes |
| 7. Test is positive if CMAP area decreased greater than 40% |
| 8. Note that CMAP may increase slightly in the first few minutes |
| 9. See Figure 1 and text for interpretation |

ADM = adductor digiti minimi; APB = abductor pollicis brevis; CMAP = compound muscle action potential; EDB = extensor digitorum brevis.

<table>
<thead>
<tr>
<th>Table 3 Provocative cold test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rule out compressive or other lesion of nerve to be studied</td>
</tr>
</tbody>
</table>
| 2. Record CMAP from APB, ADM or if needed EDB  
Hand muscles preferable |
| 3. Use indelible marker to mark exactly where the recording electrode is placed  
It is useful to draw a box/circle around the entire electrode |
| 4. Remove electrodes |
| 5. Place patient’s hand (or foot) in a basin with water cooled to approximately 15˚ C  
This should be monitored closely with a thermometer. Much colder than 15˚ C is uncomfortable (and possibly harmful)  
and much warmer than 15˚ C may be produce a false negative result |
| 6. Ask patient to self regulate the temperature by occasionally adding ice to the water |
| 7. Cool hand for 15-30 minutes in the water bucket |
| 8. Dry off hand (foot) |
| 9. Replace electrodes in exact same location as was first recorded |
| 10. Record CMAP |
| 11. The test is positive if the CMAP decreases by >75% after cooling |

ADM = adductor digiti minimi; APB = abductor pollicis brevis; CMAP = compound muscle action potential; EDB = extensor digitorum brevis.
Changes in compound muscle action potential (CMAP) in response to 5 minutes of exercise. The amplitude increases minimally in normal subjects with a return to baseline over 5 minutes. In paramyotonia congenita, there is a precipitous decline in CMAP amplitude with a slow return towards baseline. In periodic paralysis, there is an initial increase in CMAP amplitude followed by a slow decline over 15 to 30 minutes. Lambert-Eaton syndrome shows a low amplitude at rest and a prominent (usually > 200%), nonsustained increase in amplitude following exercise.


Table 4 Clinical features of myotonia congrentia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Infancy to childhood</td>
</tr>
<tr>
<td>Myotonia</td>
<td>Always present and with “warm up”</td>
</tr>
<tr>
<td>Weakness</td>
<td>Mild weakness during attack of myotonia</td>
</tr>
<tr>
<td>Precipitants</td>
<td>Cold, exercise</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Muscle hypertrophy, myotonia</td>
</tr>
</tbody>
</table>

Table 5 Clinical features of the familial periodic paralyses

<table>
<thead>
<tr>
<th>Feature</th>
<th>HOPP</th>
<th>HYPP</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, years</td>
<td>5 to 20</td>
<td>&lt;10</td>
<td>Infancy</td>
</tr>
<tr>
<td>Attacks</td>
<td>Infrequent</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Duration, hours</td>
<td>&gt;24</td>
<td>&lt;24</td>
<td>&lt; 24</td>
</tr>
<tr>
<td>Precipitants</td>
<td>Exercise</td>
<td>Exercise</td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Hunger</td>
<td>Cold</td>
</tr>
<tr>
<td></td>
<td>carbohydrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salt</td>
<td>Potassium-rich foods</td>
<td></td>
</tr>
<tr>
<td>Myotonia</td>
<td>No</td>
<td>Yes</td>
<td>Always</td>
</tr>
<tr>
<td>Weakness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Potassium level</td>
<td>Low</td>
<td>Normal to</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Response to potassium</td>
<td>Relieves</td>
<td>Causes</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>acute</td>
<td>weakness</td>
<td></td>
</tr>
<tr>
<td>Objective cold effect</td>
<td>None</td>
<td>None</td>
<td>Causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weakness</td>
<td></td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>Vacular</td>
<td>Vacular</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>myopathy</td>
<td>myopathy</td>
<td></td>
</tr>
</tbody>
</table>

HOPP = hypokalemic periodic paralysis; HYPP = hyperkalemic periodic paralysis; PC = paramyotonia congenital.

Modified from Miller and colleagues, Neurology 2004;63(9):1647-1655 with permission from Lippincott Williams & Wilkins.

Table 5 is reproduced from Miller and colleagues, Neurology 2004;63(9):1647-1655 with permission from Lippincott Williams & Wilkins.
### Diagnosis of Periodic Paralyses

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered consciousness, rhythmic jerking, cranial nerve symptoms, pre-syncopal symptoms, pain, or numbness?</td>
<td>Consider seizure, syncope, vascular disorders, other</td>
</tr>
<tr>
<td>Fluctuations of fixed weakness, rather than attacks of weakness?</td>
<td>Work-up cause of weakness</td>
</tr>
<tr>
<td>Cramps, myoglobinuria, or onset always during exercise?</td>
<td>Consider Metabolic Myopathy (e.g. McArdle’s Disease)</td>
</tr>
<tr>
<td>Infancy to childhood suggests PC or HyperKPP</td>
<td></td>
</tr>
<tr>
<td>Mid childhood to teens suggest HypoKPP</td>
<td></td>
</tr>
<tr>
<td>&gt;20 years?</td>
<td>Consider metabolic causes such as chronic K⁺ wasting, hyperthyroidism, or medications</td>
</tr>
<tr>
<td>Characteristics of attack?</td>
<td>Attacks frequent, less often severe, &lt; 24 hrs suggests PC or HyperKPP</td>
</tr>
<tr>
<td>Myotonia (clinically or by EMG)?</td>
<td>Yes -- PC or HyperKPP</td>
</tr>
<tr>
<td>No -- HypoKPP</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmias, dysmorphic features, or prolonged QT on EKG?</td>
<td>Consider Andersen-Tawil Syndrome—Work up further with Holter Monitor.</td>
</tr>
<tr>
<td>Check TSH</td>
<td>Hyperthyroidism suggests thyrotoxic hypokalemic periodic paralysis</td>
</tr>
<tr>
<td>Potassium level during an attack?</td>
<td>High—suggests HyperKPP</td>
</tr>
<tr>
<td>Normal—suggests HyperKPP or PC</td>
<td>Low—suggests HypoKPP</td>
</tr>
<tr>
<td>In most patients, order specialized EMG/NCS testing (cooling and exercise tests), especially if potassium level during attack unknown and/or lack of a clear history</td>
<td></td>
</tr>
<tr>
<td>Decreased CMAP or myotonia with cooling?</td>
<td>Paramyotonia Congenita</td>
</tr>
<tr>
<td>Decrement on Exercise Test?</td>
<td>HyperKPP or HypoKPP</td>
</tr>
<tr>
<td>Yes</td>
<td>Reconsider other causes</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Diagnosis of periodic paralysis.

Periodic paralyses can usually be diagnosed by following the above list of questions and examinations, especially if the patient presents during one of the paralytic episodes.

Figure 2 is reproduced from Miller and colleagues. Neurology 2004;63(9):1647-1655 with permission from Lippincott Williams & Wilkins.
is indeed myotonia, both clinically and by needle EMG. The next step is to exclude other myotonic disorders, such as myotonic dystrophy.

CONCLUSION

Current management of patients with periodic paralysis and MC depends on an accurate clinical diagnosis, one in which the EDX consultant often plays an important role. Further studies of ion channel mutations and their functional consequences may lead to a better understanding of skeletal muscle channelopathies and other episodic neurological disorders, as well as guide future therapies.

REFERENCES


INTRODUCTION

Toxic and metabolic myopathies are considered to be rare disorders. Or are they? Their incidence is not known, and given the large number of available drugs, the frequency of polypharmacy and its effect on drug metabolism, and other variables such as genetic differences in metabolism, it is likely that the incidence is much higher than suspected. Since toxic and metabolic myopathies are potentially treatable, it is important to recognize them at an early stage. Some of the challenges in assessing a patient for such a myopathy relate to the many possible variables that could cause the myopathy. For example, there are known toxins, toxins that rarely cause muscle disease, and some that are possible toxins in certain situations. Similarly, there are known metabolic states that cause muscle disease, some that rarely do, and others that appear on lists of metabolic disorders with little firm clinical data. Clinically, the definitions of symptoms supporting toxicity vary among incidence reports, and there are patients who present with clear weakness, some with ill-defined fatigue or muscle pain, and some who have normal strength but an elevated serum creatine kinase (CK) level discovered on a random blood test panel and who are also taking a listed drug. Given these factors, assessment of potential toxins and metabolic states must always be considered in the differential diagnosis of any muscle disorder.

This manuscript will focus on toxins and metabolic states in skeletal muscle (and will exclude primary cardiomyopathies). The list of possible agents will be narrowed to those that could be encountered in the outpatient clinic and inpatient consultation service. It will consider primary causes but not secondary causes such as drugs that induce coma resulting in muscle compression. Primary genetic disorders will not be discussed. Tables 1 and 2 include lists of toxins and metabolic states, respectively, for reference. Toxic myopathies have been tabulated by a mixed list of headings, including those based on muscle biopsy findings (necrotic, inflammatory), on organelle involvement (mitochondrial), on class of drug (lipid-lowering agents), and a variety of other headings. It is difficult to improve upon this disparate scheme. For most, the mechanism of toxicity is unknown, and general descriptions have to suffice.

DEFINITIONS OF MUSCLE DISEASE

The spectrum of symptoms used to support a toxic and metabolic myopathy is broad and influences the interpretation of the literature. Examples of definitions are: “myopathy” as any muscle complaint; “myositis” as symptoms plus an elevated CK; and “rhabdomyositis” when the CK is greater than 10,000 IU/L and the creatinine level is elevated.
VULNERABILITY OF MUSCLE

Skeletal muscle is susceptible to a variety of toxic and metabolic insults. Direct pressure and vascular insufficiency are obvious examples, but will not be considered. Muscle is a complex structure. Macroscopically, muscles are made up of innumerable fibers that run the length of the whole muscle. Microscopically, muscle fiber cytoplasm (sarcoplasm) is contained and separated from extracellular and vascular environments by a bi-lipid membrane (sarcolemma). The membrane is composed of a variety of lipids, including cholesterols. Further, the sarcolemma is not a simple tubular structure, but has an extensive network of invaginations of the membrane into the middle of the fiber (transverse tubules), and the overall square area of the sarcolemma is tremendous. Within the sarcoplasm are the contractile proteins actin and myosin. There is an extensive endoplasmic reticulum that participates in the release of calcium required for contractile function. There is also an important series of proteins that may be vulnerable in toxic and metabolic myopathies. These include proteins that link actin to the basal lamina, and include dystrophin and the sarcoglycan complex, and other protein complexes that are involved in muscle function.

Energy requirements of muscle are high, and muscles at rest consume approximately 35% of total energy, and with vigorous activity a much greater percentage. The internal ionic environment of muscle is tightly regulated, particularly for

Table 1 List of drugs implicated in muscle disease.

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing</td>
<td>Cholesterol-lowering agents</td>
</tr>
<tr>
<td></td>
<td>HMG-CoA reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
</tr>
<tr>
<td></td>
<td>Lovastatin</td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
</tr>
<tr>
<td></td>
<td>Fibric acid derivatives</td>
</tr>
<tr>
<td></td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td></td>
<td>Probucol</td>
</tr>
<tr>
<td></td>
<td>Clofibrate</td>
</tr>
<tr>
<td></td>
<td>Epsion-aminocaproic acid</td>
</tr>
<tr>
<td></td>
<td>Immunophilins</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
</tr>
<tr>
<td>Amphiphilic</td>
<td>Cholorquine</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloropuine</td>
</tr>
<tr>
<td></td>
<td>Aminodaronine</td>
</tr>
<tr>
<td>Antimicrotubular</td>
<td>Colchicine</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
</tr>
<tr>
<td>Drug-induced mitochondrial myopathy</td>
<td>Zidovudine</td>
</tr>
<tr>
<td></td>
<td>Other HIV-related antiretrovirals</td>
</tr>
<tr>
<td>Hypokalimic</td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td>Laxatives</td>
</tr>
<tr>
<td>Impaired protein synthesis</td>
<td>Emedine (Ipecac syrup)</td>
</tr>
<tr>
<td></td>
<td>Unknown mechanism</td>
</tr>
<tr>
<td></td>
<td>Critical illness</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A.

Table 2 List of metabolic abnormalities implicated in muscle disease.

<table>
<thead>
<tr>
<th>Category</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid Diseases</td>
<td>Excess</td>
</tr>
<tr>
<td></td>
<td>Cushing disease</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid drugs</td>
</tr>
<tr>
<td></td>
<td>Deficiency</td>
</tr>
<tr>
<td></td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Thyroid Disease</td>
<td>Excess</td>
</tr>
<tr>
<td></td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td>Thyrotoxic periodic paralysis</td>
</tr>
<tr>
<td></td>
<td>Deficiency</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Acromegaly</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A.
calcium, and its regulation has a major role in the contraction process. Adenosine triphosphate (ATP) is the source of energy for these regulatory processes. Energy is supplied by three metabolic pathways. The first, immediate availability ATP, comes from the combining of phosphocreatine with adenosine diphosphate (ADP). This reaction is rapid but is used up within minutes with intense exercise. The second most available source is anaerobic metabolism from glycogen through its conversion to glucose, and on to pyruvate. The energy from glycogen via anaerobic metabolism is limited for two reasons; (1) glycogen stores in muscle are modest, and can be consumed within 2 hours of active exercise; (2) only a net two ATP molecules are generated from each molecule of glucose. Aerobic metabolism results in a greater yield of ATP. Pyruvic acid, through the tricyclic acid cycle, generates 36 ATP molecules. The third metabolic pathway is the metabolism of triglycerides which can yield up to 129 ATP molecules through the electron transport system.

Another issue is that the enzymes responsible for anaerobic metabolism are located in the sarcoplasm, while those for aerobic metabolism are located in mitochondria. Mitochondria are complex in that there are transport proteins that are necessary for the shuttling of molecules back and forth across the inner and outer membranes. Evidence for the key roles that mitochondrial production of energy play in contraction are the large number of mitochondria in muscle and their location close to contractile proteins. Thus, there are many steps where disturbances of muscle metabolism could lead to muscle dysfunction.

**CLINICAL AND LABORATORY FEATURES**

There are a number of clinical and laboratory symptoms and findings that suggest a toxic or metabolic disorder of muscle. Unfortunately, none are specific, and some toxic or metabolic disorders are largely silent. The symptom list includes muscle pain, soreness, swelling, fatigability, and weakness. The laboratory findings are an elevated serum CK, myoglobinuria, needle electromyography (EMG) abnormalities, and pathologic changes in biopsied muscle tissue. Muscle pain or soreness is not specific, making it challenging to determine whether they represent a metabolic or toxic disorder when symptoms are unaccompanied by true weakness, elevated CK, and EMG abnormalities. Similarly, nonspecific fatigability without other clinical features is challenging, and disorders of the neuromuscular junction (myasthenia gravis and Lambert-Eaton syndrome) must be excluded. Nonspecific symptoms are also part of the chronic fatigue syndrome, which further increases the diagnostic difficulties. Muscle weakness is usually assessed by brief testing in the clinic based on the Medical Research Council (MRC) scale that has a wide range for normal (grade 5), and factors for gender, age, physical build, and degree of conditioning must be included, or mild degrees of weakness can be missed. The time course of symptoms varies from acute (rare) to subacute over several months (most common), to insidious over years (least common).

Among laboratory tests, serum CK is felt to be a good marker for sarcolemmal disruption. However, values vary between genders and among ethnic groups. Serum CK is occasionally high (>10 x upper limb of normal [ULN]) to extraordinarily high (1000+ x ULN) in acute cases, and may be mildly elevated (2 x ULN) in asymptomatic individuals who are implicated because they are taking a listed drug. The significance of incidental mild elevations (approximately 2 x ULN) is not clear. Needle EMG is a sensitive tool for assessing structural (architectural) alterations of muscle fibers. Abnormal spontaneous activity (positive sharp waves and fibrillation potentials) and complex motor unit action potentials (polyphasic and polyturn) with rapid recruitment are findings supporting a myopathic process (Figure 1). However, in less severe cases, and with abnormalities of energy metabolism, such changes do not occur and the EMG may be normal. Muscle biopsy findings are helpful in several ways. It is the most sensitive tool for making a diagnosis of a myopathy because subtle morphologic changes can be detected, and histochemical stains can directly measure enzymatic activity and identify specific abnormalities (Figure 2). However, in cases with mild symptoms, the biopsy may be normal or minimally abnormal with only nonspecific findings.

**DIAGNOSIS**

A diagnostic algorithm is advantageous, but there are few clear nodal points (Figure 3). In general, the history and physical examination determines whether there is weakness and its pattern (proximal for a myopathy, proximal and distal for a neuromyopathy), an electrodiagnostic (EDX) study to determine if there is a defect in neuromuscular junction transmission or altered muscle fiber architecture (necrotic and inflammatory myopathies), and a serum CK level. Assessment for myoglobinuria and renal failure are required in severe cases. A muscle biopsy can define the type of pathology (necrotic, inflammatory, mitochondrial, myosin dissolution). Laboratory studies for underlying metabolic causes and contributing factors (renal and hepatic failure, thyroid dys-
function) are appropriate. Finally, careful consideration for possible interactions of multiple drugs, including ones not specifically listed, should be considered for their effect on drug metabolism.

TREATMENT

Treatment is relatively straightforward for most toxic myopathies—removal of the toxic drug and treatment of the metabolic abnormalities. Associated metabolic consequences, such as rhabdomyolysis and renal failure, must be appropriately managed. Muscle has a high capacity to regenerate, and recovery of strength will take time.

RISK FACTORS FOR TOXIC AND METABOLIC MYOPATHIES

The overall incidence of muscle toxicity from prescription drugs is low. This has been assessed for cholesterol-lowering agents with myalgias reported in 2-7%, weakness or elevated CK in 0.1-1%, and severe myopathy in 0.08%. There are associated factors that may increase the risk in subpopulations of patients, and many risk factors are interrelated (Table 3). For example with lipid-lowering agents, advanced age is associated with other diseases that may raise lipid levels and lead to a greater need for such agents. Further, there may be needs for additional medications to treat concurrent age-related diseases, resulting in polypharmacy. Multiple drugs also increase the chances of affecting the cytochrome P-450 (CYP) enzyme system, the major detoxification pathway for many drugs. Advanced age and other diseases may reduce renal and hepatic function, altering metabolism.

The CYP system is responsible for oxidative metabolism of a large percentage of drugs (Table 4). However, drugs may either induce or inhibit CYP enzymes. Inhibition occurs from other drugs, and also with natural foods (grapefruit juice). Further, there are genetic differences in the CYP system in greater than 1% of the population due of polymorphisms or variant alleles that can increase or reduce drug oxidation.

CHOLESTEROL-LOWERING AGENTS

HMG-CoA Reductase Inhibitors

3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase is the rate-limiting step in the synthesis of cholesterol, and catalyzes the formation of mevalonic acid. There are another dozen enzymatic steps from mevalonic acid to cholesterol. While it was initially thought that drugs inhibit-
ing HMG-CoA reductase could contribute to decreased sarcolemmal cholesterol content leading to destabilization and eventual destruction of the membrane, there are newer data to implicate a more complex pathology involving steps along the way.\(^1\)

Clinical features vary from asymptomatic elevations in serum CK to myalgias to weakness.\(^2\) The drug cervistatin is an example of a drug that produced a much higher incidence of rhabdomyolysis leading to mortality and morbidity in the setting of renal failure, and was subsequently taken off the market. Needle EMG in weak patients shows abnormalities consistent with muscle fiber damage, but is usually normal in

**Table 3** Factors and their effects on drug metabolism that may lead to myotoxicity.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Concomitant diseases</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Increases or decreases P-450 metabolism</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>Reduced metabolism</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Reduced elimination</td>
</tr>
<tr>
<td>P-450 enzyme system</td>
<td>Increased or decreased drug metabolism</td>
</tr>
<tr>
<td>Diet</td>
<td>P-450 inhibition by grapefruit juice</td>
</tr>
</tbody>
</table>

**Table 4** List of common drugs and their effect on the CYP3A family of cytochrome P-450 enzyme system (modified from Wilkinson G.).

<table>
<thead>
<tr>
<th>SUBSTRATES</th>
<th>INHIBITORS</th>
<th>INDUCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers</td>
<td>Calcium-channel blockers</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Diltiazem</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant agents</td>
<td>Axole antifungal agents</td>
<td>Anticonvulsant agents</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Ketoconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Microlide antibiotics</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Clarithromycin</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HIV agents</td>
<td>Anti-HIV agents</td>
<td>Anti-HIV agents</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Delavirdine</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Miscellaneous</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Mifepristone</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HIV** = human immunodeficiency virus

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**Figure 3** Algorithm for evaluation and treatment of toxic and metabolic myopathies.

CK = creatine kinase; EMG = electromyography; TSH = thyroid stimulating hormone.
asymptomatic patients with only elevated CK levels. Muscle biopsy shows fiber necrosis and regeneration, and subsarcolemmal accumulation of autophagic lysosomes in electron micrographic examination. In general, symptoms and signs reverse with removal of the drug.

**FIBRIC ACID DERIVATIVES**

In fibric acid derivatives, the mechanism is not known, but is postulated to destabilize muscle fiber membrane leading to degeneration.\(^\text{24}\) The clinical, needle EMG, and biopsy features vary as they do with HMG-CoA reductase inhibitors.

**IMMUNOPHILINS**

Cyclosporine and tacrolimus are immunosuppressive agents used particularly for organ transplant patients. Cyclosporine may cause myalgias and weakness.\(^\text{7}\) Rhabdomyolysis has been described with concurrent use of cholesterol-lowering agents (including HMG-CoA reductase and fibric acid derivatives). Tacrolimus has also been associated with rhabdomyolysis.\(^\text{10}\) Mechanisms of muscle fiber damage are unknown, but postulated to destabilize the membrane in a similar manner as with cholesterol-lowering agents, thus explaining the increased risk with the combination of drugs.

**PROPOFOL**

Propofol is used in intensive care settings for sedation of ventilated patients and treating status epilepticus. There are reports of rhabdomyolysis and myoglobinuria primarily in children.\(^\text{8}\) Given the intensive care setting, concomitant factors such as acute quadriplegic myopathy must be considered.

**AMIODARONE**

Amiodarone is unique in that it can cause a neuropathy and myopathy (neuromyopathy).\(^\text{5,17}\) Thus there may be distal weakness from the neuropathy and proximal weakness from the myopathy. Accordingly, nerve conduction studies are consistent with an axonal neuropathy, but in cases with acute onset there may be initial demyelinating features similar to those recorded in Guillain-Barré syndrome. Needle EMG will show abnormal spontaneous activity and motor units will likely have a myopathic pattern in proximal muscles and a neuropathic pattern (high amplitude potentials with reduced recruitment) in distal muscles. Serum CK levels are elevated. Muscle biopsy shows autophagic vacuoles. Pathogenesis is attributed to drug interaction with the muscle fiber membrane.

**ANTIMICROTUBULAR MYOPATHIES**

**Colchicine**

Colchicine can cause a neuromyopathy and symptoms develop usually after long-term use. Renal insufficiency is a promoting factor.\(^\text{13}\) Weakness develops slowly, and the neuropathy is mild. Nerve conduction studies show distal slowing and reduced sensory and motor responses. Needle EMG shows a proximal myopathic and distal neuropathic pattern, and may include myotonic discharges.\(^\text{22}\) Serum CK levels vary from mildly to markedly elevated. Muscle pathology shows a vacuolar pattern. Disruption of microtubular transport of lysosomes is felt to be the underlying pathologic process.

**DRUG-INDUCED MITOCHONDRIAL MYOPATHIES**

**Anti-human Immunodeficiency Virus Drugs**

Zidovudine is an antiretroviral drug used for human immunodeficiency virus (HIV) infections, and causes myalgias in 20-50% of patients and proximal weakness with or without an elevation of serum CK in patients at all stages of HIV infection.\(^\text{26}\) The muscle biopsy is significant for ragged red fibers and cytochrome oxidase-negative fibers. Other findings are fiber necrosis, cytoplasmic bodies, nemaline rods, and microvacuolated fibers. A clinical challenge in diagnosing antiretroviral-induced myopathy is that HIV itself can cause an inflammatory myopathy, a necrotizing myopathy without inflammation, and type 2 muscle fiber atrophy from a wasting syndrome. Drug-induced myopathy from anti-retroviral drugs is slowly progressive, and should be differentiated from the acute rhabdomyolysis characterized by myalgias, weakness, and high CK levels (>1500) secondary to antiretroviral drug toxicity. Needle EMG will show similar myopathic patterns for all myopathies in HIV, and thus will be unable to differentiate these diagnoses. Accordingly, a muscle biopsy is important to help determine which or whether there are several superimposed pathologic processes.\(^\text{27}\) The source of pathology is thought to result from a mitochondrial cytopathy, and electron microscopy shows such abnormalities. Azidothymidine acts as a false substitute for viral reverse transcriptase not only for cellular deoxyribonucleic acid (DNA)
polymerase but also for mitochondrial DNA polymerase, which is felt to account for mitochondrial abnormalities on biopsy.

EMATINE

Ematine is extracted from the ipecac root and has been used as an amebicide and emetic. Its greatest potential for toxicity is misuse for weight control in people with eating disorders. Overuse over a few days can cause marked weakness of skeletal and cardiac muscle. Serum CK levels are mildly elevated and the needle EMG is mildly abnormal. Muscle biopsy shows necrosis, moth-eaten fiber perimeter, and partial clearing of oxidative enzymes in a targetoid pattern. Electron microscopy shows degeneration of contractile proteins. Ematine interferes with protein synthesis, although the mechanism for the changes in muscle is not clear.

CRITICAL ILLNESS MYOPATHY

Quadriplegia can occur in the setting of critical illness from a variety of causes, including a myopathy. There are a number of terms used, including acute quadruplegic myopathy, acute illness myopathy, critical illness myopathy, and myopathy associated with myosin destruction. Another factor is an axonal neuropathy that may present as a similar clinical picture of weakness, and critical illness neuropathy may co-exist with critical illness myopathy. Given the complexity of critically ill patients, several factors have emerged, and include use of high-dose intravenous corticosteroids with or without nondepolarizing neuromuscular blocking drugs, although the use of these drugs is not required for the development of critical illness myopathy. Weakness develops over days, and failure to wean from the ventilator is a major clinical issue. Serum CK levels are normal or mildly elevated. Needle EMG may show abnormal spontaneous activity, but assessment of motor units is hampered by the patient's inability to recruit motor units. The electrophysiologic technique of direct muscle stimulation may be helpful in separating critical illness myopathy from neuropathy. In this technique, muscle fibers are directly activated by an intramuscular stimulating needle electrode and compared to the response to stimulation of the nerve. With critical illness neuropathy, the response to direct muscle stimulation should be of good amplitude and that to stimulation of the nerve of low amplitude, while with critical illness myopathy, the response to stimulation of either site should be the same. Muscle biopsy shows atrophy of type 2 fibers as well as loss of ATPase staining in type 1 and 2 fibers. By electron microscopy there is loss of myosin. The mechanism is not known, but calcium-activated proteases may be enhanced and thus contribute to myosin breakdown.

Diverse factors related to sepsis may also contribute to breakdown.

ALCOHOL MYOPATHY

Ethanol can cause a variety of myopathic conditions, including: (1) acute necrotizing myopathy; (2) acute hypokalemic myopathy; (3) chronic myopathy; and (4) asymptomatic myopathy. The acute necrotizing form occurs in the setting of high ethanol consumption usually associated with a binge, and includes marked muscle pain, tenderness to palpation, swelling, marked weakness and elevated CK levels. Muscle pathology shows fiber necrosis. Acute hypokalemic myopathy has similar clinical features to other types of hypokalemic myopathy, and is associated with serum potassium levels between 1.4 and 2.1 meq/L. Biopsy findings in the acute phase show vacuoles. Chronic alcoholic myopathy has an insidious onset and affects primarily leg muscles. Biopsy findings are not specific and include atrophy, necrosis, and regenerating fibers. An asymptomatic alcoholic myopathy loosely designates a condition with elevated serum CK levels. The mechanism of ethanol toxicity is not known, and is complicated because many such patients are malnourished and have vitamin deficiencies.

THYROTOXIC MYOPATHY

The incidence of weakness in patients with thyrotoxicosis is high. Serum CK is normal. Needle EMG shows no abnormal spontaneous activity, but motor unit recruitment may be increased and motor units complex. Muscle biopsy findings are variable, and may include inflammatory changes. There is a small increased association between thyroid disease and myasthenia gravis. Thyroid hormones have many metabolic influences affecting a number of aspects of muscle functions—specific mechanisms causing weakness are not clearly known.

THYROTOXIC PERIODIC PARALYSIS

Episodic weakness that is clinically similar to that of familial hypokalemic periodic paralysis occurs in association with thyrotoxicity, most commonly, but not exclusively, in Asian populations. Attacks are associated with ingestion of carbohydrate-rich meals and weakness may be profound. Serum potassium values range from 1.1 to 3.4 mmol/L, and phosphate values are frequently low. Thyrotoxic periodic paralysis is usually a sporadic condition and resolves with treatment of hypokalemia, and does not recur with treatment of the thyroid disorder.
HYPOTHYROID MYOPATHY

When the symptoms of myopathy are expanded to include fatigability, pain, stiffness, cramps, and weakness the incidence of myopathy can be up to 80%. Serum CK may or may not be elevated.

CORTICOSTEROID MYOPATHY

The incidence of weakness due to the use of corticosteroids is difficult to access, in part because corticosteroids are frequently given for disorders that themselves cause weakness, and the balance of positive and negative effects is usually to improved strength, thus masking a negative drug effect on strength. A reasonable estimate of 10% comes from patients with brain tumors treated with corticosteroids or those with asthma. It appears that fluorinated corticosteroids (dexamethasone) are more likely than prednisone to cause weakness. Weakness is not highly correlated with corticosteroid peak or accumulative dose. Serum CK levels are usually normal, as is the EMG. Muscle biopsy is remarkable primarily for type 2 fiber atrophy. Corticosteroids have a number of roles in muscle metabolism, and when in excess, their effect on protein catabolism is likely a major factor.

GROWTH HORMONE MYOPATHY

Acromegaly is associated with a myopathy in 50% of patients. Weakness is mild and serum CK values are normal or mildly elevated. Myopathic EMG findings were mild. Muscle biopsy findings are type 2 atrophy.

SUMMARY

The challenge in assessing for toxic and metabolic myopathies is not to miss them. This is difficult because of the ill-defined symptoms, the vulnerability of muscle to insults, and the growing frequency of polypharmacy. It is always wise to discontinue a suspicious medication, or to substitute with a different type of medication. Finally, when there are doubts, a muscle biopsy is clinically wise.

REFERENCES


INTRODUCTION

The past decade has seen a tremendous expansion in medicine's understanding of muscle diseases, both hereditary and sporadic. The field of myology has benefited probably more than any other area of medicine from the enormous increase in the understanding of molecular genetics. Along with this, there have also been vast improvements in enzyme histochemistry and electron microscopy (EM), allowing for better definition of structural abnormalities. This has led to the discovery of "new diseases," which are based primarily on better pathophysiological descriptions of old diseases, rather than truly new disorders. Newly named disorders generally reflect the abnormal pathophysiology. Examples include: central and multiminicore diseases, nemaline myopathy, and myotubular myopathy. The congenital myopathies can now be identified by their abnormal aggregation of proteins, giving rise to the concept of "protein aggregate myopathies."

Limb girdle, which now includes desminopathies, alpha-B crystallinopathies, selenoproteinopathy, myotilinopathy, actinopathies, and myosinopathies, has expanded from a group of 5 myopathies to a group over over 10, and it is still growing. The recent identification of mutations in respective genes to the recognition of certain accrued proteins within muscle fibers, and the subsequent analysis of their respective genes has resulted in a wealth of genetic data and in reconsidering classification and nosologic interpretation of certain congenital myopathies. Newer and better techniques to image muscle have also made it easier to assess muscle structure in a noninvasive fashion. This manuscript provides an update on myopathic diseases, including hereditary and sporadic diseases, and emphasizes clinical pearls and latest discoveries.

HEREDITARY MUSCLE DISEASES

Dystrophinopathies

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked disorder caused by an abnormality at the Xp21 gene loci. The gene for DMD and Becker muscular dystrophy (BMD) occupies 2.5 million base pairs of DNA on the X-chromosome and is approximately 10 times larger than the next largest gene identified to date. The gene contains 79 exons of coding sequence. Its primary protein product is called dystrophin, which is found in the plasma membrane of all myogenic cells, certain types of neurons and in small amounts in other cell types. Duchenne muscular dystrophy and BMD are thus referred to as dystrophinopathies. Dystrophin-deficiency at the plasma membrane of muscle fibers disrupts the membrane cytoskeleton and leads to the secondary loss of other components of the muscle cytoskeleton. The primary consequence of the cytoskeleton abnormalities is membrane instability, leading to muscle weakness and degeneration.
to membrane injury from mechanical stresses, transient breaches of the membrane, and membrane leakage. \( ^{68,77} \)

Chronic dystrophic myopathy is characterized by aggressive fibrotic replacement of the muscle and eventual failure of regeneration with muscle fiber death and fiber loss.

The incidence of DMD has been estimated to be around 1:3500 male births. \( ^{29} \) Approximately one-third of isolated cases are due to new mutations, which is considerably higher than observed in other X-linked conditions. This high mutation rate might be due to the large size of the gene.

While the history of hypotonia and delayed motor milestones are often reported in retrospect, the parents are often unaware of any abnormality until the child starts walking. There has been variability reported in the age of onset of DMD. In 74-80% of instances, the onset is noted before the age of 4 years. \( ^{71} \) The vast majority of cases are identified by 5-6 years of age. The most frequent presenting symptoms are abnormal gait, frequent falls, and difficulty climbing stairs. Difficulty negotiating stairs is an early feature as is a tendency to fall due to the child tripping or stumbling on a plantar-flexed ankle or the knee buckling or giving way due to knee extensor weakness. There is progressive difficulty getting up from the floor with presence of a Gowers’ sign. Parents frequently note the toe walking, which is a compensatory adaptation to knee extensor weakness. They also note a lordotic posture of the lumbar spine, which is a compensatory change due to hip extensor weakness.

Duchenne muscular dystrophy is occasionally identified presymptomatically in situations where a creatine kinase (CK) value is obtained with a markedly elevated value or when malignant hyperthermia occurs during general anesthesia for an unrelated surgical indication. Early identification also occurs when the diagnosis is pursued in a male with an affected older sibling.

Pain in the muscles, especially the calves, is a common symptom. Enlargement of muscles, particularly the calves, is commonly seen. Recently, children aged 8-11 years with DMD have been noted to exhibit an unusual clinical examination sign that results from selective hypertrophy and wasting in different muscles in the same region. \( ^{30} \) When viewing these patients from behind with their arms abducted to 90° and elbows flexed to 90°, DMD patients demonstrate a linear or oval depression (due to wasting) of the posterior axillary fold with hypertrophied or preserved muscles on its two borders (i.e., infraspinatus inferomedially and deltoid superolaterally) as if there were a valley between the two mounts.

The tongue is also frequently enlarged. An associated wide-arch to the mandible and maxilla with separation of the teeth is frequently seen, presumably secondary to the macroglossia. The earliest weakness is seen in the neck flexors during preschool years. Early in the disease course weakness is generalized, but predominantly proximal. Pelvic girdle weakness predates shoulder girdle weakness by several years. Ankle dorsiflexors are weaker than ankle plantar flexors, ankle inverters are weaker than ankle inverts, knee extensors are weaker than knee flexors, hip extensors are weaker than hip flexors, and hip abductors are weaker than hip adductors. \( ^{4,5} \)

The weakness progresses steadily, but the rate can be variable during the disease course. Quantitative strength testing shows greater than 40-50% loss of strength by 6 years of age. \( ^{50,67,99,105} \) With manual muscle testing, DMD subjects exhibit loss of strength in a fairly linear fashion from ages 5-13 and measurements obtained several years apart will show fairly steady disease progression. However, a variable course is often noted when analyzing individuals over a shorter period of time. \( ^{105,116} \) Investigators have shown a flattening in the rate of strength loss curve at approximately ages 14-15. \( ^{67,105} \) Thus, investigators performing studies involving the natural history of DMD should be cautious about including subjects transitioning to the teenage years because of the flattening of the manual muscle testing strength curve with increasing age. \( ^{67} \) This caution is particularly important in studies of potential therapeutic agents. Quantitative strength measures have been shown to be more sensitive for demonstrating strength loss than manual muscle testing when strength is grades 4-5. \( ^{67} \)

The average age of wheelchair use in an untreated DMD population is 10 years, with a range of 7-13 years. \( ^{14,15,67} \) Timed motor performance is a useful predictor of time when ambulation will be lost without provision of long-leg braces. One large natural history study showed that all DMD subjects who took 9 seconds or longer to ambulate 30 feet lost ambulation within 2 years. \( ^{67} \) All DMD subjects who took 12 seconds or longer to ambulate 30 feet lost ambulation within 1 year. \( ^{67} \) Ambulation past the age of 14 should raise the suspicion of a milder form of muscular dystrophy (MD) such as BMD or limb girdle muscular dystrophy (LGMD). Ambulation beyond 16 years was previously used as exclusionary criteria for DMD. \( ^{13} \) Immobilization for any reason can lead to a marked and often precipitous decline in muscle power and ambulatory ability. A fall with resultant fracture leading to immobilization and loss of ambulatory ability is not an uncommon occurrence.

Significant joint contractures have been found in nearly all DMD children older than age 13. \( ^{67,120,121} \) The most common contractures include ankle plantar flexion and inversion, knee flexion, hip flexion, iliobibial band, elbow flexion, and wrist flexion contractures. \( ^{67} \) Shortening of two joint muscles occurs particularly in the iliobibial band and gastrocnemius. \( ^{67} \) Significant contractures have been shown to be rare in DMD.
before age 9 for all joints. There is no association between muscle imbalance around a specific joint (defined as grade 1 or greater difference in flexor and extensor strength) and the frequency or severity of contractures involving the hip, knee, ankle, wrist, and elbow in DMD.\textsuperscript{67}

The presence of lower extremity contractures in DMD has been shown to be strongly related to onset of wheelchair reliance.\textsuperscript{67,107} Lower extremity contractures were rare while DMD subjects were still upright, but developed soon after they began using a wheelchair for most of the day. The occurrence of elbow flexion contractures also appears to be directly related to prolonged static positioning of the limb, and these contractures develop soon after wheelchair reliance as well. There is a relationship between wheelchair reliance and hip and knee flexion contractures.\textsuperscript{106} Mild contractures of the iliobial bands, hip flexor muscles, and heel cords occur in most DMD patients by 6 years of age.\textsuperscript{45} Limitations of knee, elbow, and wrist extension occurs about 2 years later, however, these early observed contractures were relatively mild.\textsuperscript{45} Given the tremendous replacement of muscle by fibrotic tissue in DMD subjects, it is not surprising that a muscle of less than antigravity extension strength, statically positioned in flexion in a wheelchair, would develop a flexion contracture. The lack of lower extremity weight bearing likely contributes to the rapid acceleration in the severity of these contractures after transition to wheelchair. Ankle plantar flexion contractures are likely not a significant cause of wheelchair reliance, as few subjects exhibit plantar flexion contractures of 15 before their transition to a wheelchair.\textsuperscript{67} Natural history data suggest that weakness is the major cause of loss of ambulation in DMD, rather than contracture formation.\textsuperscript{19,67}

The reported prevalence of scoliosis in DMD varies from 33-100%.\textsuperscript{50,61,67,94} This marked variability is primarily because of retrospective selection for scoliosis, the inclusion or exclusion of functional curves, and dissimilar age groups. The prevalence of scoliosis is strongly related to age. Fifty percent of DMD patients acquire scoliosis between ages 12-15, corresponding to the adolescent growth spurt. At least 90% of older DMD subjects with no specific treatment for scoliosis have clinical spinal deformity. This is consistent with Oda’s report that 15% of older DMD patients show mild nonprogressive curves (usually 10-30\textdegree).\textsuperscript{85} The rate of progression of the primary or single untreated lateral curve is reported to range from 11\textdegree to 42\textdegree per year, depending on the age span studied. Johnson and Yarnell reported an association between the side of curvature, convexity, and hand dominance.\textsuperscript{47} McDonald’s study, on the other hand, showed no correlation between side of primary convexity and handedness.\textsuperscript{67} Oda and colleagues reported that the likelihood of severe progressive spinal deformity could be predicted by the type of curve and early pulmonary function measurements.\textsuperscript{85} Those without significant kyphosis or hyperlordosis and a peak absolute forced vital capacity (FVC) greater than 2000 mL tend not to show severe progressive scoliosis.

No cause-and-effect relationship has been established between the onset of wheelchair reliance and occurrence of scoliosis.\textsuperscript{41,67} Wheelchair reliance and scoliosis are both an age-related phenomenon. The causal relationship between loss of ambulatory status and scoliosis is doubtful, given the substantial time interval between the two variables in most subjects (scoliosis usually develops after 3-4 years in a wheelchair). Both wheelchair reliance and spinal deformity can be significantly related to other factors (e.g., age, adolescent growth spurt, increase in weakness of trunk musculature, and other unidentified factors) and appear to represent coincidental signs of disease progression.

Absolute FVC volumes increase in patients with DMD during the first decade and plateau during the early part of the second decade.\textsuperscript{40,67} A linear decline in percent predicted FVC is apparent between 10-20 years of age in DMD.\textsuperscript{57} Rideau reported that the FVC was predictive of the risk of rapid scoliosis progression.\textsuperscript{95} In the most severe DMD cases, maximal FVC reached a plateau of less than 1200 mL. This was associated with the loss of ability to walk before age 10 and severe progressive scoliosis. Maximum FVCs plateau between 1200 mL and 1700 mL. Spinal deformity was present consistently in these cases but varied in intensity. The least severe DMD cases reached plateaus in FVC of greater than 1700 ml. Similarly, McDonald and colleagues also found that those patients with higher peak FVC (> 2500 mL) had a milder disease progression, losing 4% predicted FVC per year.\textsuperscript{67} The peak predicted FVC less than 1700 mL lost 9.6% predicted FVC per year.\textsuperscript{67} The peak obtained absolute values of FVC that usually occur early in the second decade is an important prognostic indicator for severity of spinal deformity, as well as of the severity of restrictive pulmonary compromise due to muscular weakness.

Reduced maximal static airway pressures (both maximal inspiratory pressure and maximal expiratory pressure) are the earliest indicators of restrictive pulmonary compromise in DMD.\textsuperscript{5,10} Impaired values are usually noted between 5-10 years of age. Vital capacity typically increases concomitant with growth between 5-10 years of age with the percent of predicted FVC remaining relatively stable and close to 100% predicted. Duchenne muscular dystrophy patients typically show a linear decline in percent predicted FVC between 10-20 years of age. An FVC falling below 40% of predicted can contraindicate surgical spinal arthrodesis, irrespective of scoliotic severity, because of increased perioperative morbidity.\textsuperscript{43,94}
Patients who need surgical intervention for scoliosis or other deformities should have surgery before the vital capacity drops below 40% of predicted. Respiratory failure in DMD is insidious in its onset and results from a number of factors, including: (1) respiratory muscle weakness and fatigue; (2) alteration in respiratory system mechanics; and (3) impairment of the central control of respiration. Noninvasive forms of both positive and negative pressure ventilatory support are increasingly being offered to DMD patients.

The dystrophin protein is present in both the myocardium and the cardiac Purkinje fibers. Abnormalities of the heart may be detected by clinical examination, electrocardiogram (ECG), echocardiography, and Holter monitoring. Cardiac examination is notable for the point of maximal impulse palpable at the left sternal border due to the marked reduction in anteroposterior chest dimension common in DMD. A loud pulmonic component of the second heart sound suggests pulmonary hypertension in patients with restrictive pulmonary compromise. Nearly all patients over the age of 13 demonstrate abnormalities of the ECG. Q-waves in the lateral leads are the first abnormalities to appear, followed by elevated ST-segments and poor R-wave progression, increased R/S ratio, and resting tachycardia and conduction defects. Electrocardiogram abnormalities have been demonstrated to be predictive for death from the cardiomyopathy with the major determinants including: R-wave in lead V1 less than 0.6 mV; R-wave in lead V5 less than 1.1 mV; R-wave in lead V6 less than 1.0 mV; abnormal T-waves in leads II, III, AVF, V5, and V6; cardiac conduction disturbances; premature ventricular contraction; and sinus tachycardia. Sinus tachycardia can be due to low stroke volume from the progressive cardiomyopathy, or in some cases can be sudden in onset and labile, suggesting an autonomic disturbance or direct involvement of the sinus node by the dystrophic process.

Autopsy studies and thallium-201 single proton emission computed tomography imaging show left ventricular anterior wall defects that might explain the lateral Q-waves and the increased R/S ratio in V1 seen on ECG. Localized posterior wall fibrosis is peculiar to DMD and is not seen in other types of MD. Pulmonary hypertension leading to right ventricular enlargement is also known to cause prominent R-waves in V1 and has been demonstrated in patients with DMD.

Ventricular ectopy is a known complication of the cardiomyopathy in DMD which likely explains the observed cases of sudden death. Yanagisawa and colleagues reported an age-related increase in the prevalence of cardiac arrhythmias detected by ambulatory 24-hour ECG recordings. They also noted an association between ventricular arrhythmias and sudden death in DMD. Clinically evident cardiomyopathy is usually first noted after age 10 and is apparent in nearly all patients over age 18. Development of cardiomyopathy is a predictor of poor prognosis. Echocardiography has been used extensively to follow the development of cardiomyopathy and predict prognosis in patients with DMD. The onset of systolic dysfunction noted by echocardiography is associated with a poor prognosis. The myocardial impairment remains clinically silent until late in the course of the disease, possibly caused by the absence of exertional dyspnea, secondary to lack of physical activity. Death has been attributed to congestive heart failure in as many as 40-50% of patients with DMD by some investigators. Regular cardiac evaluations with an ECG, echocardiography, and Holter monitor should be employed in teenagers with preclinical cardiomyopathy.

The dystrophin isoform is present in the brain. The role of dystrophin in the central nervous system (CNS) is not known but it has been theorized to play a role in neuronal metabolic transport across the cell membrane. Previous studies on intellectual function on children with DMD have generally revealed decreased intelligence quotient (IQ) scores when these children are compared with both control and normative groups. A mean score for the DMD population of 1.0-1.5 standard deviations (SD) below population norms has been reported. There has generally been a considerable consistency in the degree of impairment across measures reflecting a rather mild global deficit. Some studies have demonstrated relative deficits in verbal IQ. In a longitudinal assessment of cognitive function, McDonald and colleagues found IQ measure in DMD to be stable over time. On neuropsychological testing, a large proportion of DMD subjects fell within the “mildly impaired” or “impaired” range according to normative data. These findings likely reflect a mild global deficit rather than focal nervous system impairment.

Substantial anthropometric alterations have been described in DMD. Short stature and slow linear growth with onset shortly after birth have been reported. Accurate measurement of linear height is extremely difficult in this population. Arm span measurements can be used as an alternative measure of linear growth; but this measurement can be difficult as elbow flexion contractures of greater than 30° are frequently present in patients older than age 13. Forearm segment length has been proposed as an alternative linear meas-
urement in DMD patients with proximal upper extremity contractures and radius length can be followed for those with wrist and finger contractures.62

Obesity is a substantial problem in DMD, subsequent to the loss of independent ambulation.20,27,108 Weight control during early adolescence facilitates ease of care, in particular ease of transfers during later adolescence.

Longitudinal weight measurements in DMD confirm significant rates of weight loss in subjects ages 17-21.27,64 This is likely caused by relative nutritional compromise during the later stages when boys with DMD have higher protein and energy intake requirements because of hypercatabolic protein metabolism.37 Protein and calorie requirements can often be 160% that predicted for able-bodied populations during the later stages of DMD.112 Restrictive lung disease becomes approximately 90% of deletion-positive cases.65,66 Mutations at the Xp21 locus, which maintain the translational reading frame (in-frame mutations), result in an abnormal but partially dysfunctional dystrophin, whereas in DMD the mutations shift the reading frame (out-of-frame mutations) so that virtually no dystrophin is produced.21 The reading frame interpretation is most accurate for deletions in the center of the gene (exons 40-60) and is least accurate for deletions in the beginning of the gene (exons 1-20).

Becker Muscular Dystrophy

Becker muscular dystrophy is a form of MD with a similar pattern of muscle weakness seen in DMD. It also has X-linked inheritance, but with later onset and a much slower rate of progression than DMD. It was first described by Becker and Kiener in 1955.6,96 The disorder has the same gene location as the DMD gene (Xp21) and is allelic. Using immunoblotting or immunostaining of muscle biopsy specimens, the presence of altered molecular weight or decreased abundance of dystrophin suggests a BMD phenotype.2 Some subjects have 20-80% dystrophin levels of the normal quantity of dystrophin while other subjects may have reduced or increased molecular weight dystrophin.2 Becker muscular dystrophy has a lower incidence than DMD, with prevalence rates for BMD ranging from 12-27 per million and a recent estimated overall prevalence of 24 per million.30,32,66

The demonstration of a deletion in the Xp21 gene with c deoxyribonucleic acid (DNA) probes is useful in the diagnostic evaluation of dystrophin deficient myopathies.21 In the gene deletion test, small blood samples are used as a source of patient DNA, and the dystrophin (DMD, BMD) gene is tested to determine whether it is intact or not. This is performed by polymerase chain reaction (PCR) or Southern blotting, and the methods determine whether all segments of the gene are present. If any segment is missing, the findings indicate the presence of a “deletion mutation.” Not all DMD and BMD patients have deletion mutations. Many have point mutations that cannot be detected by these methods. Since the gene is so large and complex, it is currently not feasible to routinely test for the other types of smaller mutations. Approximately 55% of DMD patients and 70% of BMD patients show deletion mutations of the gene on currently available tests.21 A positive DNA test result (presence of a deletion) is diagnostic of a dystrophinopathy (DMD or BMD). There are no false-positives if the test is performed appropriately.21

Differential diagnosis between DMD and BMD is best performed by family history of clinical phenotype. If the patient is still ambulating at 16-20 years of age and has a deletion mutation, then the correct diagnosis is BMD. Some laboratories will report “the reading frame.” This information can differentiate between a DMD and BMD diagnosis in approximately 90% of deletion-positive cases.65,66 Mutations at the Xp21 locus, which maintain the translational reading frame (in-frame mutations), result in an abnormal but partially dysfunctional dystrophin, whereas in DMD the mutations shift the reading frame (out-of-frame mutations) so that virtually no dystrophin is produced.21 The reading frame interpretation is most accurate for deletions in the center of the gene (exons 40-60) and is least accurate for deletions in the beginning of the gene (exons 1-20).

Absent dystrophin or levels less than 3% of normal generally are considered diagnostic of DMD, however, 5% of such patients have BMD phenotypes. The dystrophin in BMD typically has an abnormally small molecular weight (<427 kDa). A minority of patients have dystrophin of larger than normal molecular weight (>427 kDa), or normal molecular weight. Most BMD patients with larger or smaller molecular weight dystrophin also have decreased quantities of the protein.65,66 All BMD patients with normal molecular weight dystrophin have decreased quantities, usually less than 30% normal. Smaller size dystrophin typically is caused by deletion mutations, and larger size dystrophin by duplication mutations. A further refinement is the use of antibodies specific to the carboxy-terminal (C-terminal) region of dystrophin. Using such antibodies, immuno-histochemistry reveals that the C-terminal region is almost always absent in DMD but invariably present in BMD.2

Studies have shown significant overlap in the observed age of onset between DMD and BMD.66 Determination of the quantity and molecular weight of dystrophin has substantially improved the early differentiation among BMD, “outlier” DMD, and the more common and rapidly progressive DMD phenotype. However, Bushby and colleagues found no clear correlation between abundance of dystrophin and clinical course within the BMD group.13
The series of Bushby and Gardner-Medwin included 67 BMD subjects and supported the presence of two major patterns of progression in BMD—a “typical” slowly progressive course and a more “severe” and rapidly progressive course. All of the “severe” BMD cases showed difficulty climbing stairs by age 20, whereas none of the “typical” BMD cases had difficulty climbing stairs before age 20. Abnormal ECGs were seen in 27% of typical BMD subjects and 88% of subjects with more severe phenotype. Bushby and Gardner-Medwin found BMD subjects to have a mean age of onset of 12 years in the typical group and 7.7 years in the severe group. Some patients with BMD present with major muscle cramps as an isolated symptom.

The most useful clinical criterion to distinguish BMD from DMD is the continued ability of the patient to walk into late teenage years. Those with BMD will typically remain ambulatory beyond 16 years. Some patients become wheelchair reliant in their late teens or 20s, whereas others continue walking into their 40s and 50s, or later. Outlier DMD cases generally stop ambulating between 13-16 years of age.

As in DMD, preclinical cases are often identified by the finding of a grossly elevated CK value. There is also considerable overlap in CK values between DMD and BMD cases at the time of presentation, and CK values cannot be used to differentiate DMD from BMD.

Patients with BMD have a distribution of weakness that is similar to those with DMD. Proximal lower limb muscles are involved earlier in the disease course. Gradual involvement of the pectoral girdle and upper limb musculature occurs 10-20 years from onset of disease. Extensors have been noted to be weaker than flexors. The muscle groups, which are the most severely involved early in the course of disease includes the hip extensors, knee extensors, and neck flexors.

Calf enlargement is a nonspecific finding in BMD, as is the presence of a Gowers’ sign. Over time, the gait becomes similar to other neuromuscular disease conditions with proximal weakness. Patients often ambulate with a lumbar lordosis, forefoot floor contact, decreased stance phase knee flexion, and a modified Trendelenburg or gluteus medius lurch, often described as a waddle.

Early development of contractures does not appear to be a feature of BMD. As with DMD, nonambulatory BMD subjects may develop equinus contractures, knee flexion contractures and hip flexion contractures. Subjects with BMD are more likely to develop flexion contractures subsequent to wheelchair reliance.

Spinal deformity is not nearly as common or severe in BMD as it is in DMD. Spinal instrumentation is rarely required by BMD patients.

Compromised pulmonary function is also much less problematic in BMD. The percent predicted FVC does not appear substantially reduced until the third to fourth decade. The percent predicted maximal inspiratory pressure appears relatively more reduced at younger ages than the percent predicted maximal inspiratory pressure, a finding seen in DMD and other neuromuscular diseases. This might be due to more relative involvement of the intercostals and abdominal musculature, with relative sparing of contractile function in the diaphragm of BMD. Predicted maximal expiratory pressure can be a useful quantitative measure of impairment and perhaps disease progression early in the course of BMD.

The pattern of occasional life-threatening cardiac involvement in otherwise mild and slowly progressive BMD has been reported. A significant percentage of BMD cases develop cardiac abnormalities. The rate of progression of cardiac failure can be more rapid than the progression of skeletal myopathy. In fact, successful cardiac transplantation has been increasingly reported in BMD subjects with cardiac failure. Approximately 75% of BMD patients have been found to exhibit ECG abnormalities. The abnormal findings most commonly reported include abnormal Q-waves, right ventricular hypertrophy, left ventricular hypertrophy, right bundle branch block, and nonspecific T-wave abnormalities. Unlike DMD, resting sinus tachycardia has not been a frequent finding. Echocardiography has shown left ventricular dilation in 37%, whereas 63% have significant systolic function because of global hypokinesia. The cardiac compromise can be disproportionately severe, relative to the degree of restrictive lung disease in some BMD subjects. The evidence for significant myocardial involvement in BMD is sufficient to warrant screening of all of these patients at regular intervals using ECG and echocardiography. The slowly progressive nature of this dystrophic myopathy, which is compatible with many years of functional mobility and longevity, makes these patients suitable candidates for cardiac transplantation if end-stage cardiac failure occurs.

Some cases with BMD present with an isolated cardiomyopathy with no clinical manifestation of skeletal muscle involvement. The diagnosis can be established by demonstration of a deletion in the Xp21 gene or by muscle biopsy. Isolated cases of cardiomyopathy in children, particularly those with family histories indicative of X-linked inheritance, should be screened for BMD with an initial serum CK estimation and molecular genetic studies of the Xp21 gene.
Cognitive testing in BMD subjects has shown large variability in IQ scores and neuropsychological test measures. Mildly reduced intellectual performance has been noted in a subset of BMD patients, however, the degree of impairment is not as severe as noted in DMD.66

Other atypical clinical presentations include a complaint of cramps on exercise in individuals with no muscle weakness.32 Patients with focal wasting of the quadriceps who have previously been diagnosed with quadriceps myopathy have recently been diagnosed with BMD. This is based on molecular genetic testing and/or dystrophin analysis on muscle biopsy.66

**Myotonic Disorders**

**Myotonic Muscular Dystrophy**

Myotonic muscular dystrophy (MMD) is an autosomal dominant multisystem MD with an incidence of 1 per 8000.29,44 The disorder affects skeletal muscle, smooth muscle, myocardium, brain, and ocular structures. Associated findings include frontal pattern baldness and gonadal atrophy (in males), cataracts, and cardiac dysrhythmias. Insulin insensitivity can be present. The gene has been localized to the region of the DM protein kinase gene at 19q13.42,93 Patients demonstrate expansion of an unstable cytosine thymine guanine trinucleotide repeat within the region. Normal individuals generally have less than 37 repeats that are transmitted from generation to generation. Myotonic muscular dystrophy patients may have 50 to several thousand CTG repeats with remarkable instability. The age of onset is inversely correlated by the repeat links.42 Mild, late onset MMD usually is associated with 50-150 repeats, classic adolescent or young adult onset MMD shows 100-1000 repeats and congenital MMD patients show greater than 1000 repeats.21,42,93 The expanded CTG repeat further expands as it is transmitted to successive generations, providing a molecular basis for “genetic anticipation.” Both maternal-to-child and paternal-to-child transmission occurs. However, it can be more severe if transmitted from the mother with repeat size in offspring exceeding 1000 CTG repeats or more. Affected fathers seldom transmit alleles larger than 1000 copies to offspring due to a lack of sperm containing such alleles, presumably due to the poor motility of sperm containing alleles of that size, although this has not been proven.

Several characteristic facial features of MMD may be seen on inspection. The adult with long-standing MMD often has characteristic facial features. The long thin face with temporal and masseter wasting is drawn and has been described by some as lugubrious or “hatchet face.” Adults of both sexes often exhibit frontal balding.

Myotonia is a state of delayed relaxation or sustained contraction of skeletal muscle that is easily identified in children with MMD. Grip myotonia can be demonstrated by delayed opening of the hand with difficulty extending the fingers following tight grip. Percussion myotonia can be elicited by striking the thenar eminence with a reflex hammer, producing adduction and flexion of the thumb with slow return. Needle electromyography (EMG) shows myotonic discharges, which are spontaneous waxing and waning spikes that produce a characteristic “dive bomber” sound.53

Myotonic muscular dystrophy is one of the few dystrophic myopathies with greater distal weakness than proximal weakness.52 Although neck flexors, shoulder girdle musculature, and pelvic girdle musculature can become significantly involved over decades, the weakness is initially most predominant in the ankle dorsiflexors, ankle everters and inverters, and hand muscles.44 Significant muscle wasting can occur over time. In MMD patients with infantile onset, a congenital clubfoot or talipes equinovarus frequently occurs. In adult onset MMD, contractures at the wrist, ankle, and elbows are relatively uncommon and mild.44,45 Patients with congenital onset MMD may develop spinal deformity requiring surgical spinal arthrodesis.41

Abnormalities on ECG and echocardiography are demonstrated in approximately 70-75% of patients with MMD.44,59,75 Prolongation of the pulse rate-interval, abnormal axis, and infranodal conduction abnormalities are all suggestive of conduction system disease which might explain the occurrence of sudden death which occurs in less than 5% of MMD patients.59 Ventricular tachycardia can also contribute to the syncope and sudden death associated with MMD. Some patients have required implantation of cardiac pacemakers. Q-waves have been reported on screening ECGs in MMD patients and this abnormality might reflect myocardial fibrosis.54,59 Any MMD patient with dyspnea, chest pain, syncope, or other cardiac symptoms should receive thorough cardiac evaluation.

Subjects with MMD have a very high incidence of restrictive lung disease.44,117 Involvement of respiratory muscles is a major cause of respiratory distress and mortality in affected infants with MMD. Swallowing difficulties that produce aspiration of material into the trachea and bronchial tree, along with weakened respiratory muscles and a weak cough have been reported as factors that may result in pulmonary complications in MMD patients. Care should be taken during general anesthesia in MMD due to risk of cardiac arrhythmias and malignant hyperthermia.

Constipation is a fairly common complaint in congenital MMD, owing to smooth muscle involvement. Myotonic
muscular dystrophy patients should also be screened for diabetes mellitus as there is an increased incidence of insulin insensitivity.

Those with congenital MMD usually show significantly reduced IQ, often in the mentally retarded range. In adult onset MMD, there is evidence for a generally lower intelligence of a mild degree (full-scale IQs have been reported to be in the 86-92 range). However, there is a wide range of IQ values found in this population with many subjects scoring in the above-average range. Cognitive functioning also appears to be directly related to the size of the CTG expansion at the MMD gene locus.

There is a newly discovered form of MMD, known as type II MMD (MMD2 or DM2). It has also been referred to as proximal myotonic myopathy. MMD2 is now known to be caused by a mutation on chromosome 3 and is thought to be clinically less severe than either typical MMD or congenital MMD, and may be associated with insulin insensitivity, diabetes, and low testosterone levels in males.

Myotonia Congenita

Myotonia congenita (MC) (Thomsen’s disease) is inherited as an autosomal dominant condition. It is a condition in which the patient has myotonia but not weakness. Symptoms may be present from birth, but usually develop later. The myotonia can manifest as difficulty in releasing objects or difficulty walking or climbing stairs. Prolonged rest or inactivity exacerbates the myotonia. Myotonia may be aggravated by cold. Patients may demonstrate grip myotonia or lid lag following upward gaze or squint, and diplopia following sustained conjugate movement of the eyes in one direction. The other common feature of MC is muscle hypertrophy. Patients can have a “Herculean” appearance.

A recessive form of MC (Becker form) also exists with later onset, more marked myotonia, more striking hypertrophy of muscles and associated weakness of muscles. The dominant form seems more prone to aggravation of the myotonia by cold.

The diagnosis is essentially made clinically with confirmation of classical myotonic discharges on electrodiagnostic examination. Muscle biopsy is essentially normal, apart from hypertrophy of fibers and an absence of type II-B fibers.

Paramyotonia Congenita

Paramyotonia congenita (PC) is an autosomal dominant myotonic condition characterized by generalized hypertrophy, mild involvement of proximal muscles, and more severe involvement of hands and muscles of the face. Myotonic episodes usually subside within a matter of hours but are significantly aggravated by cold temperatures. This is usually not a severe disease and these patients have a good overall prognosis and normal life expectancy.

Schwartz-Jampel Syndrome

Schwartz-Jampel syndrome is an autosomal recessive disorder with myotonia, dwarfism, diffuse bone disease, narrow palpebral fissures, blepharospasm, micrognathia, and flattened faces. Limitation of joint movement can be present along with skeletal abnormalities, including short neck and kyphosis. Muscles are typically hypertrophic and clinically stiff. The symptoms are not progressive and the overall prognosis is good.

Electrodiagnostic studies show continuous electrical activity with electrical silence being difficult to obtain. There is relatively little waxing and waning in either amplitude or frequency of complex repetitive discharges. Abnormal sodium channel kinetics in the sarcolemma of muscle has been demonstrated. Some therapeutic benefit has been reported with procainamide HCL and carbamezapine.

Limb Girdle Muscular Dystrophies

Advances in molecular biology have shown that LGMD is a heterogeneous group of dystrophic myopathies, usually with a childhood or adolescent onset (although there are late onset forms), no sex linkage, and a distribution and pattern of weakness similar to DMD but with a much slower rate of progression. There are at least 15 different subtypes of LGMD, most of which have been linked to abnormalities of the dystrophin-associated glycoproteins (DAG), especially alpha sarcoglycan (adhalin), a 50kD DAG and gamma sarcoglycan. The 50 DAG protein has been linked to the 17q12-q21.33 locus and children with this have been referred to as severe, childhood-onset, autosomal recessive muscular dystrophy (SCARMD), which is also classified as LGMD 2D. Other families with SCARMD have been linked to chromosome 13q12 and individuals with LGMD 2C may show a primary deficiency of gamma sarcoglycan and a secondary deficiency of alpha sarcoglycan. Limb girdle muscular dystrophy 2E patients (chromosome 4q12) show a primary deficiency in beta sarcoglycan and LGMD 2F patients (chromosome 5q33-q34) show a primary deficiency of delta sarcoglycan. Most of the primary sarcoglycan abnormalities lead to secondary deficiencies of alpha sarcoglycan. All the DAGs are reduced in DMD patients because the C-terminal portion of dystrophin binds to the dystrophin-associated proteins and maintains their integrity. A less severe autosomal recessive dystrophic myopathy (LGMD 2A) has
been linked to chromosome 15q1-q21.1, the gene for the protein Calpain III. Diagnosis of SCARMD or LGMD subtypes is confirmed by muscle biopsy.59

Dystrophin analysis is generally normal in subjects with LGMD.21 Of the seven recessive loci identified to date, four are sarcoglycan genes.21,65 These four proteins make up the sarcoglycan complex, which is believed to interact directly with the 43kD DAG and with dystrophin.21,86 Dystrophin-associated glycoproteins probably provide connections between the extracellular matrix (the protein merosin) and the intracellular membrane cytoskeleton (attached to dystrophin).21,61,65,86 An abnormality of the dystrophin-glycoprotein complex, resulting from primary deficiencies of one or more of the dystrophin-associated glycoproteins results in a disruption in the linkage between the intracellular sarcolemmal cytoskeleton and the extracellular matrix. Disruption of the membrane cytoskeleton is common to the pathophysiology of most MDs, the dystrophinopathies.

Patients with SCARMD can exhibit calf hypertrophy and a Gowers’ sign. Loss of ambulation generally occurs between 10-20 years but occasionally after 20 years of age. In one series, several differences between DMD and SCARMD were noted.69 In contrast to DMD, the limb extensors were not weaker than limb flexors. In particular, ankle dorsiflexors were similar in strength to ankle plantar flexors, knee extensors showed similar strength compared with knee flexors and hip extensors and hip flexors showed similar strength values. The severity and rate of progression often varies between and within the families of SCARMD patients. Contractures appear to be much less prevalent and severe in SCARMD compared with DMD. The prevalence of joint contractures in SCARMD subjects was found to be similar to that observed in BMD subjects in one series.45

Spinal deformity appears to be less problematic in SCARMD than DMD. Less than 50% of SCARMD subjects were found to have curves of mild-to-moderate severity, ranging from 5-30°.67 The prevalence and severity of spinal deformity in SCARMD appears to be similar to that observed in BMD.

Restrictive pulmonary insufficiency occurs in SCARMD but is not as severe as that seen in DMD. The prevalence of severe restrictive lung disease in SCARMD is similar to that observed in BMD.7,69

Few studies have systematically evaluated the cardiac manifestations of SCARMD and other limb girdle dystrophies. In one series, the prevalence of abnormal ECG findings in SCARMD was 62%.69 Electrocardiogram abnormalities include evidence of infranodal conduction defects, evidence of left ventricular hypertrophy, increased R/S ratio in V1, and abnormal Q-waves. Intellectual function in SCARMD has generally been found to be normal.69

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive dystrophic myopathy with predominant involvement of facial and shoulder girdle musculature. The condition is autosomal dominant with linkage to the chromosome 4q35 locus.118,119,124 Prevalence has been difficult to ascertain because of undiagnosed mild cases, but has been estimated at 10-20 per million.29,51

Facial weakness is an important clinical feature of FSHD. The initial weakness affects the facial muscles, especially the orbicularis oculi, zygomaticus, and orbicularis oris. These patients often have difficulty with eye closure, but not ptosis. Subjects with FSHD often have an expressionless appearance and exhibit difficulty whistling, pursing the lips, drinking through a straw, or smiling. Even in the early stages, forced closure of the eyelids can be easily overcome by the examiner. Masseter, temporalis, extraocular, and pharyngeal muscles characteristically are spared in FSHD.

Patients with FSHD show characteristic patterns of muscle atrophy and scapular displacement. Involvement of the latissimus dorsi, trapezius, rhomboids, and serratus anterior results in a characteristic appearance of the shoulders, with the scapula positioned more laterally and superiorly, giving the shoulders a forward-sloped appearance. The upper border of the scapula rises into the trapezius, falsely giving it a hypertrophied appearance. From the posterior view, the medial border of the scapula may exhibit profound posterior and lateral winging. The involvement of shoulder girdle musculature in FSHD can be quite asymmetric.

The typical onset is in adolescence or early adult life. Initially, patients show predominant involvement of facial and shoulder girdle musculature. Scapular stabilizers, shoulder abductors, and shoulder external rotators may be significantly affected, but at times the deltoids are surprisingly spared if tested with the scapulae stabilized. Both the biceps and triceps may be more affected than the deltoids. Over time, ankle dorsiflexion weakness often becomes significant in addition to pelvic girdle weakness. Late in the disease course, patients can show marked wrist extension weakness. Some authors have found asymmetric weakness in the dominant upper extremity.46,51

A sensory neural hearing deficit was originally observed in Coates syndrome (early onset FSHD). These individuals have a myopathy that presents in infancy. The disease pro-
Spinal deformity is common with 80% of FSHD subjects exhibiting hyperlordosis, alone or in combination with scoliosis. Rarely, severe and progressive hyperlordosis is associated with FSHD. The patient with severe hyperlordosis might utilize their lordotic posturing to compensate for hip extensor weakness. Scoliosis alone accounts for only 20% of spinal deformity in FSHD and patients with scoliosis typically have mild and nonprogressive curves.

Mild restrictive lung disease has been reported in nearly one-half of FSHD patients. Expiratory musculature appears to be more affected than inspiratory muscles in FSHD. A recent Dutch study identified 10 FSHD patients on nocturnal ventilatory support at home, representing approximately 1% of the Dutch FSHD population. Severe muscle disease, wheelchair dependency, and kyphoscoliosis appeared to be risk factors for respiratory failure.

The presence of cardiac abnormalities in FSHD is still debated. While diverse ECG abnormalities have been noted, one study showed no abnormalities on ECG, chest radiography, Holter monitoring, and echocardiography. Nuclear scanning with thallium-201 has demonstrated diffuse defects consistent with diffuse fibrosis. Abnormalities in systolic time intervals on echocardiography and elevations in atrial natriuretic peptide are consistent with subclinical cardiomyopathy. Cardiac complications in FSHD are rare and patients in general have normal longevity. There is usually no associated intellectual involvement in this dystrophic myopathy.

Changes seen with muscle biopsy are relatively slight, with the most consistent finding being the presence of isolated small atrophic fibers. Other fibers may be hypertrophied. Serum CK levels are normal in the majority of patients. Molecular genetic testing for the FSHD gene is now available for diagnostic confirmation.

**Emery-Dreifuss Muscular Dystrophy**

Emery-Dreifuss muscular dystrophy (EDMD) is an X-linked recessive progressive dystrophic myopathy with a gene locus identified at Xq28. The muscle protein that is deficient in EDMD has been termed as “Emerin.” The condition usually presents in adolescence or early adult life, and many clinical features can be seen in early childhood. Patients can present with a selective scapulohumeral peroneal distribution weakness with striking wasting of the biceps, accentuated by sparing of the deltoids and forearm muscles. However, this is clinically differentiated from FSHD by the lack of facial involvement. Ankle dorsiflexors often are weaker than ankle plantar flexors. Significant atrophy usually is present in the upper arms and legs due to focal wasting of the calf muscles and biceps.

An associated cardiomyopathy usually presents with arrhythmia and may lead to sudden death in early adult life. The cardiomyopathy can progress to four-chamber dilated cardiomyopathy with complete heart block and ventricular arrhythmias. Atrial arrhythmia usually appears prior to complete heart block. Reported features include first degree heart block, followed by Wenckebach phenomenon and then complete atrial ventricular dissociation and atrial fibrillation or flutter with progressive slowing of the rate. Syncope or near-syncope commonly occurs later in the second decade or early in the third decade. Evidence of cardiac arrhythmia, sometimes only present at night, might be detected on 24-hour Holter monitoring. The provision of a cardiac pacemaker to the patient with arrhythmia may be life-saving and can considerably improve life expectancy.

Some patients with EDMD may show evidence of nocturnal hypoventilation as a result of restrictive expansion of the chest in association with the rigid spine, and partly due to involvement of the diaphragm.

Creatine kinase can be moderately elevated, with a value between 2 and 5 times the upper limit of normal. Needle EMG usually shows a myopathic pattern. Muscle biopsy
shows a myopathic process with variation in fiber size, clusters of atrophic fibers, mild proliferation of connective tissue, and some focal necrosis of fibers.

A clinical hallmark of EDMD is the early presence of contractures of the elbow flexors with limitation of full elbow extension. Heel cord tightness might be present early in the disorder, concomitant with ankle dorsiflexion and toe walking. Unlike DMD, the toe walking in EDMD usually is secondary to ankle dorsiflexion weakness and not a compensatory strategy to stabilize the knee due to proximal limb weakness. Tightness of the cervical and lumbar spinal extensor muscles, resulting in limitation of neck and trunk flexion, with the inability to flex the chin to the sternum and to touch the toes, also has been reported in EDMD.

A dominantly inherited disorder with a similar phenotype has been reported, but the gene locus is unknown. Some reported cases of “rigid spine syndrome,” a form of congenital MD (CMD), may be EDMD cases in view of the marked predominance of males with this disorder and the associated contractures reported at the elbows and ankles.

**Congenital Muscular Dystrophy**

The term “congenital muscular dystrophy” has been widely used for a group of infants presenting with hypotonia, muscle weakness at birth or within the first few months of life, congenital contractures, and a dystrophic pattern on muscle biopsy. The dystrophic changes noted on biopsy separate this group of disorders from the congenital myopathies. The condition tends to remain relatively static. However, some subjects show slow progression, whereas others gain developmental milestones and achieve the ability to walk.

There are several syndromes of CMD with CNS abnormality. Fukuyama CMD is associated with mental retardation, structural brain malformations evident on magnetic resonance imaging (MRI) imaging and a dystrophic myopathy. The dystrophic changes noted on biopsy separate this group of disorders from the congenital myopathies. The condition tends to remain relatively static. However, some subjects show slow progression, whereas others gain developmental milestones and achieve the ability to walk.

Muscle-eye-brain disease describes a syndrome comprising CMD, mental retardation, and ocular abnormality. Infants present with congenital hypotonia, muscle weakness, elevated CK, myopathic EMG, and a dystrophic changes on muscle biopsy. Ophthalmologic findings include severe visual impairment with uncontrolled eye movements associated with severe myopia. Patients often deteriorate around 5 years of age with progressive occurrence of spasticity. Computerized tomography scans have shown ventricular dilatation in low density of the white matter. Walker-Warburg syndrome is described as CMD with mental retardation and consistent CNS abnormalities on imaging (type II lissencephaly, abnormally thick cortex, decreased interdigitation between white matter and cortex and cerebellar malformation). Ocular abnormalities and cleft lip or palate may also be present.

Cases with more pure CMD without CNS involvement have been identified. The main clinical features are muscle weakness and hypotonia, congenital contractures, histological changes of a dystrophic nature—often with extensive connective tissue or adipose proliferation—but no substantial evidence of necrosis or regeneration, normal to moderately elevated CK, normal intellect, and brain imaging which may be either normal or show changes in the white matter on CT or MRI imaging. One form results from merosin deficiency, an extracellular protein important for maintenance of sarcolemmal membrane stability in the muscle fiber. The loci for merosin deficient CMD has been linked to chromosome 6q. A further subtype of congenital muscular dystrophy without CNS involvement and normal merosin has been reported, but the genetic locus has not been established.

Patients with CMD often exhibit early contractures, including equinovarus deformities, knee flexion contractures, hip flexion contractures, and tightness of the wrist flexors and long finger flexors. The contractures can become more severe over time with prolonged static positioning and lack of adequate ROM and splinting/positioning.

**THE CONGENITAL MYOPATHIES**

The term congenital myopathy is used to describe a group of heterogeneous disorders usually presenting with infantile hypotonia due to genetic defects causing primary myopathies with the absence of any structural abnormality of the CNS or peripheral nerves. The specific diagnosis of each entity is made on the basis of specific histological and electron microscopic changes found on muscle biopsy. While patients can be hypotonic during early infancy, they later develop muscle weakness that is generally nonprogressive and static. The weakness is predominantly proximal, symmetric, and in a limb girdle distribution.

The serum CK values are frequently normal and the needle EMG findings may be normal or may show mild, nonspecific changes, usually of a myopathic nature (small amplitude polyphonic potentials). The only congenital myopathy consistently associated with needle EMG abnormalities is
myotubular (centronuclear) myopathy. In this disorder, the needle EMG shows myopathic motor unit action potentials with frequent complex repetitive discharges and diffuse fibrillation potentials. These myopathies can be considered primarily structural in nature. Patients do not actively lose muscle fibers.

Central Core Myopathy

This is an autosomal dominant disorder with autosomal dominant gene locus at 19q13.1, the same gene locus as the malignant hyperthermia gene. Indeed, these patients have a high incidence of malignant hyperthermia with inhalation anesthetic agents. Muscle fiber histology shows amorphous-looking central areas within the muscle that may be devoid of enzyme activity. Electron microscopy shows the virtual absence of mitochondria and sarcoplasmic reticulum in the core region, and a marked reduction in the interfibrillary space and an irregular zig-zag pattern (streaming) of the Z-lines. There is a predominance of high oxidative, low glycolytic type I fibers and a relative paucity of type II fibers, resulting in a relative deficiency of glycolytic enzymes.

Patients generally demonstrate mild and relatively nonprogressive muscle weakness, either proximal or generalized, presenting in either early infancy or later. Mild facial weakness can be seen. Patients often achieve gross motor milestones rather late, such as walking, and have difficulty climbing stairs. They may show a Gowers’ sign. The disorder typically remains fairly static over the years. A frequent occurrence of congenital dislocation of the hip is observed.

Central core myopathy and familial malignant hyperthermia appear to be allelic as the ryanodine receptor chain implicated in malignant hyperthermia has the same locus.

Nemaline Myopathy

Nemaline myopathy, also referred to as rod body myopathy, represents a varied group of disorders with different modes of inheritance, but the most typical form is autosomal recessive. While the rods can be easily overlooked using routine hematoxylin-eosin staining, they can readily be demonstrated with the Gomori trichrome stain. The rods are readily demonstrated with an EM. They are thought to be abnormal depositions of Z-band material of a protein nature and possibly alpha-actinin.

A severe form of the disease may present in the neonatal period with very severe weakness, respiratory insufficiency, and often a fatal outcome. Most cases present with a mild, nonprogressive myopathy with hypotonia and proximal weakness. In more severe cases, swallowing difficulty can be present in the neonatal period. Skeletal abnormalities, such as kyphoscoliosis, pigeon chest, pes cavus feet, high arched palate, and an unusually long face has been noted. Cardiomyopathy has been described in both severe neonatal and milder forms of the disease.

Autosomal dominant inheritance has been described in a few instances with the gene localized to chromosome 1, q21-q23. The locus of the more common autosomal recessive forms have not yet been located.

Myotubular Myopathy (Centronuclear Myopathy)

Patients with non-X-linked myotubular myopathy have muscle biopsies showing a striking resemblance to the myotubes of fetal muscle. Patients typically present with early hypotonia, delay in motor milestones, generalized weakness of both proximal and distal musculature. They also present with ptosis with weakness of the external ocular muscles as well as weakness of the axial musculature. Nocturnal hypoventilation has been described. The gene locus has not been identified to date, but most known non-X-linked forms appear to show autosomal dominant inheritance.

Severe X-linked (Congenital) Myotubular Myopathy

Cases with neonatal onset and severe respiratory insufficiency have been identified with an X-linked recessive mode of inheritance. The gene for this disorder has been located to Xq28. Muscle biopsy shows characteristic fetal-appearing myotubes.

Patients present with severe generalized hypotonia, associated muscle weakness, swallowing difficulty, and respiratory insufficiency. They often become ventilator-dependent at birth. If they are able to be weaned from the ventilator, subsequent death due to pulmonary complications is not uncommon. Aspiration pneumonias are common. Additional clinical features include congenital contractures, facial weakness, and weakness of the external ocular muscles. Needle EMG shows many fibrillations and positive sharp waves.

Minicore Disease (Multi-Core Disease)

Minicore disease is a relatively rare congenital myopathy with muscle biopsies showing multiple small randomly distributed areas in the muscle with focal decrease in mitochondrial oxidative enzyme activity and focal myofibrillar degenerative change. Characteristic changes are present on EM. There is a predominance of type I fiber involvement.

Clinically, patients present with hypotonia, delays in gross motor development and nonprogressive symmetric weakness of the trunk and proximal limb musculature. There may be mild facial weakness and there is also associated diaphragmat-
ic weakness, placing patients at risk for nocturnal hypoventilation. Subtle ultrastructural changes allow this condition to be distinguished from central core disease. Inheritance is autosomal recessive, but the gene location is not yet known.

**Congenital Fiber-Type Disproportion**

Congenital fiber-type disproportion represents a heterogeneous group of conditions most likely with varied genetic defects. The condition was initially delineated by Brooke on the basis of the muscle biopsy picture demonstrating type I fibers which are smaller than type II fibers by a margin of more than 12% of the diameter of the type II fibers.\(^{26,79}\) Congenital MD, MMD, and severe spinal muscular atrophy all may show small type I fibers and should be excluded. The diagnosis of congenital fiber-type disproportion should be made only in the presence of normal-sized or enlarged type II fibers and not in cases where both type I and type II fibers are small. There may also be abnormalities on ischemic exercise testing.\(^{83}\)

Patients typically present with infantile hypotonia and delay in gross motor milestones. The severity has been noted to be quite variable, but it is generally nonprogressive. There is generally short stature and low weight. Patients may exhibit a long narrow face, high-arched palate, and deformities of the feet. Kyphoscoliosis has been reported. Lenard and Goebel documented a case with fairly severe weakness and associated respiratory deficit, necessitating tracheostomy.\(^ {57}\) The mode of inheritance for congenital fiber-type disproportion is varied with both autosomal recessive and autosomal dominant patterns of inheritance reported. Genetic loci have not been identified to date.

**SUMMARY**

The past few decades have seen an explosion of new discoveries regarding the underlying molecular genetic causes and subsequent pathophysiological deficits in many major myopathic disorders. Hopefully this increased understanding of these disorders will turn in to a functional treatment modality such as gene transfer. This is a real possibility in the next 25 years, but such a great achievement will take the cooperative efforts of the international scientific community working together. It is this author’s sincerest hope that this scientific goal will soon become a reality.

**REFERENCES**


