223 Muscular Dystrophies
Brenda L Banwell

Historical overview
Descriptions of boy with progressive motor paralysis (now known as “Duchenne muscular dystrophy”) date back to reports by Dr. Charles Bell in 1830.1 Dr. Edward Meryon, in his book Practical and Pathological Researches on the Various Forms of Paralysis published in 1864, described the clinical and pathological findings in eight affected boys from three families. He was the first to recognize the maternal inheritance of this disorder.1 In his report he stated that “fibers were found to be completely destroyed, the sarcolemmal element being diffused, and in many places converted into oil globules and granular matter, whilst the sarcoplemma and tunic of the elementary fiber was broken down and destroyed.”1

Over the next 100 years, genetic and phenotypically distinct forms of muscular dystrophy were recognized. In the late 1970s, genetic studies linked the Duchenne gene to chromosome Xp21, and the cDNA and protein product, dystrophin, were discovered in 1987.2,3 Many other genes encoding structural proteins associated with the sarcoglycan, nuclear membrane proteins, and proteins involved in myofiber metabolism have now been sequenced and mutations ascribed to specific forms of dystrophy. The genes for other dystrophies have yet to be discovered.

This chapter discusses the management of patients with muscular dystrophy and highlights issues pertinent to specific forms of dystrophy. Even with the best current management, the inexorable downhill progression of the dystrophic process cannot be arrested. The recent rapid advances in gene therapy, however, hold promise that the course of these diseases eventually may be mitigated.

Epidemiology
The incidence of several forms of muscular dystrophy is listed in Table 223.1. Some dystrophies show regional variability due to founder effects or the relative frequency of consanguineous marriages. The incidence of milder forms of dystrophy, mild variants of more severe dystrophies, and severe forms of dystrophy that result in death before diagnosis is likely underestimated.

Etiology
The genetically distinct forms of muscular dystrophy that have been recognized result from mutations in genes encoding integral structural proteins of the sarcolemmal membrane (α, β, γ, and δ sarcoglycan, integrin α7) and structural proteins associated with the inner (dystrophin, plectin) or outer (laminin α2, collagen type VI) or specialized regions of the sarcolemma (caveolin 3), with the inner nuclear membrane (emerin, lamin A/C, plectin), with muscle-specific protein kinases (myotonic dystrophy protein kinase), with muscle-specific proteases (calpain), and with proteins whose function remains to be defined (dysferlin). The distribution within muscle of proteins implicated in the various muscular dystrophies is outlined schematically in Figure 223.1. In dystrophinopathies, ultrastructural studies have shown focal loss of the sarcolemma4 and increased calcium in the muscle fiber regions underlying the sarcolemmal defects.5 A similar loss of sarcolemmal integrity likely underlies the pathological changes of the limb-girdle dystrophies associated with sarcoglycan mutations.6 The defects in sarcolemmal-associated proteins likely predisposes the fiber to damage during contraction. How deficiency of proteins not associated with the

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence/prevalence</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>1/3300</td>
<td>5</td>
</tr>
<tr>
<td>Becker muscular dystrophy</td>
<td>1/18 000–1/31 000</td>
<td>5</td>
</tr>
<tr>
<td>Female dystrophinopathy carriers</td>
<td>40/100 000</td>
<td>5</td>
</tr>
<tr>
<td>Manifesting female dystrophinopathy carriers</td>
<td>1/100 000</td>
<td>87</td>
</tr>
<tr>
<td>Emery-Dreifuss muscular dystrophy</td>
<td>1/100 000</td>
<td>5</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>1/8000</td>
<td>53</td>
</tr>
<tr>
<td>Oculopharyngeal muscular dystrophy</td>
<td>1/200 000</td>
<td>70</td>
</tr>
<tr>
<td>Fascioscapulohumeral muscular dystrophy</td>
<td>1/20 000</td>
<td>74</td>
</tr>
<tr>
<td>Muscle-eye-brain disease</td>
<td>1/50 000 (Finland) and isolated cases elsewhere</td>
<td>98</td>
</tr>
<tr>
<td>Fukuyama congenital muscular dystrophy</td>
<td>7–12/100 000 (Japan)</td>
<td>97</td>
</tr>
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Figure 223.1 Representation of various proteins implicated in muscle disease and their distribution within the myofiber. (Only proteins discussed in the chapter are shown.) Collagen type IV and type VI, laminin α2, and α-dystroglycan are components of the basement membrane surrounding muscle; α, β, γ, δ, and ε-sarcoglycan, sarcospan, β-dystroglycan, and α7- and β1-integrins span the sarcolemma, and caveolin 3 exists in specialized regions of the sarcolemma termed “caveolae.” Emerin is located in the inner nuclear membrane, and lamin A/C is a component of the inner nuclear lamina. Proteins localized to the subsarcolemmal region include dystrophin, α- and β-syntrophin, and dystrobrevin. Desmin and plectin are concentrated at the region of the Z-disk and also form important cross-linkages throughout the cytosol. The cellular distribution of dysferlin, calpain 3, and MDPK (myotonic dystrophy protein kinase) have not been fully elucidated; for convenience, these proteins are depicted in the cytosol near the sarcolemmal membrane. In the lower part of the figure, the contractile apparatus of the myofiber, the “sarcomere,” is outlined. As shown, electron-dense bands termed “Z-disks” delineate the sarcomere. Thin filaments emanate from the Z-disk, forming the I band on either side of the Z-disk. The thin filaments are joined together at the Z-disk by the protein α-actinin (not shown). The I band is composed of thin filaments that extend from the Z-disk to intersect with thick filaments of the A band, troponin and tropomyosin (not shown), which form a complex important for contractile regulation, and a large intermediate filament protein, nebulin. The A band is composed of thick filaments interlaced with thin filaments for part of its length and a central region devoid of thin filaments. Thick filaments are composed primarily of myosin as well as C protein, H protein, X protein, AMP deaminase, creatine kinase, M protein, and myomesin (not shown) and are associated along their length with the giant protein titin. The midpoint of the A band is termed the “H band,” which is of lower density owing to the absence of thin filaments in this region. The midpoint of the H band is termed the “M line.”
motor milestones. Later onset dystrophies present with generalized or regional muscle weakness and atrophy and reduced exercise tolerance. Patients may report symptoms of cardiac or respiratory failure (described below). The family history may document relatives who have muscle disease, cardiac disease, sudden death, reactions to anesthesia, recurrent fetal loss, or neonatal deaths. Examination of family members is important, especially in myotonic dystrophy or fascioscapulohumeral dystrophy in which mildly affected persons are often unaware of their disease.

Laboratory investigation of patients, and occasionally also of family members, includes determination of the serum level of creatine kinase (CK), electromyography (EMG) studies, electrocardiography, muscle biopsy, and genetic studies. The serum level of CK is increased in most forms of muscular dystrophy, but it also is increased in other metabolic and acquired muscle diseases. EMG demonstrates myopathic features (short-duration polyphasic motor unit potentials and, often, fibrillation potentials), and differentiates myopathy from neuropathy. Imaging studies, including

<table>
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<tr>
<th>Table 223.2 Autosomal recessive dystrophies</th>
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<tr>
<td>Disease</td>
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</tr>
<tr>
<td>LGMD 2A</td>
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<tr>
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<td>LGMD 2C</td>
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<td>LGMD 2D</td>
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<td>LGMD 2F</td>
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<tr>
<td>LGMD 2G</td>
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<tr>
<td>LGMD 2H</td>
</tr>
<tr>
<td>Distal myopathy with rimmed vacuoles</td>
</tr>
<tr>
<td>Miyoshi myopathy</td>
</tr>
<tr>
<td>Oculopharyngo-distal myopathy</td>
</tr>
<tr>
<td>Hereditary inclusion body myopathy</td>
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<td>Epidermolysis bullosa simplex with muscular dystrophy</td>
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LGMD, limb-girdle muscular dystrophy. Modified from Neuromuscular Disorders107

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<tr>
<th>Table 223.3 Autosomal dominant dystrophies</th>
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</tr>
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<tr>
<td>LGMD 1B</td>
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<tr>
<td>LGMD 1C</td>
</tr>
<tr>
<td>Fascioscapulohumeral dystrophy</td>
</tr>
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<td>Fascioscapulohumeral dystrophy type 2</td>
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<td>Myotonic dystrophy</td>
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<td>Myotonic dystrophy type 2</td>
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<tr>
<td>Bethlem myopathy</td>
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<tr>
<td>Bethlem myopathy</td>
</tr>
<tr>
<td>Emery-Dreifuss autosomal dominant type</td>
</tr>
<tr>
<td>Myofibrillar myopathy*</td>
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<tr>
<td>Tibial muscular dystrophy</td>
</tr>
<tr>
<td>Autosomal dominant distal myopathy</td>
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<td>Welchander distal myopathy</td>
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<td>Familial dilated cardiomyopathy with conduction defect and muscular dystrophy</td>
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LGMD, limb-girdle muscular dystrophy. *Genetically heterogeneous. Modified from Neuromuscular Disorders107
computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography of muscle may be useful. In Duchenne dystrophy, ultrasonographic examination is very sensitive for detecting fibrosis. In other diseases, such as Miyoshi distal dystrophy, CT of the lower limbs shows a characteristic pattern of muscle involvement. For most dystrophies, muscle biopsy is still the cornerstone of diagnosis. Appropriately stained or reacted frozen sections typically show myopathic features—that is, necrotic and regenerating fibers, fiber size variation, fiber splitting, internalized nuclei, and endomysial and perimysial fibrosis—as well as disease-specific features described below. Immunocytochemistry using the currently available antibodies may be diagnostic for dystrophinopathies, sarcoglycanopathies, and the dystrophies caused by deficiency of laminin α2 (merosin), emerin, integrin α7, or plectin. Commercially available genetic studies alone can be used to diagnose myotonic dystrophy or dystrophinopathy.

It is important to exclude an acquired myopathy from genetically determined dystrophy. Inflammatory myopathy, viral or parasitic myositis, toxic myopathy due to exposure to toxins or certain medications, or metabolic myopathy may present with weakness and increased serum levels of CK. The absence of previous neuromuscular complaints, a history of recent illness, onset of illness with exposure to a new medication, and rapid progression suggest an acquired process. Severe muscle pain favors an inflammatory or metabolic disorder. There are exceptions to these generalizations. Muscle pain is a frequent symptom of Becker dystrophy, and the progression of some inflammatory myopathies can be insidious. Moreover, some dystrophies appear to present more acutely either because of concomitant illness or because early symptoms were not recognized.

Management and treatment: general considerations

General health

Avoidance of obesity is extremely important for all patients with muscular dystrophy because excess weight increases the work that muscles must perform for ambulation, compromises seating, exacerbates respiratory insufficiency, and hinders self or assisted transfer. The total caloric requirements vary with lean body mass, decreasing by at least 10% in nonambulatory patients even if the lean body mass remains unchanged. A well-balanced high-fiber diet is essential to prevent constipation, a problem that can be very serious in nonambulatory patients. Patients should consume adequate fluids, both to reduce constipation and to help keep respiratory secretions thin. A urine specific gravity between 1.010 and 1.015 is ideal. Dependent peripheral edema develops in many nonambulatory patients. Edema results in increased weight and decreased mobility, and it predisposes to skin ulcers and infection. Elevating the legs periodically, maximizing mobility, performing range of motion exercises, reducing dietary sodium, and the judicious use of diuretics may be helpful. Any patient in whom edema develops should be examined for signs of cardiomyopathy, respiratory insufficiency,

<table>
<thead>
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<th>Disease</th>
<th>Locus</th>
<th>Gene product</th>
<th>Gene</th>
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<tr>
<td>Duchenne muscular dystrophy</td>
<td>Xp21.2</td>
<td>Dystrophin</td>
<td>DYS</td>
</tr>
<tr>
<td>Becker muscular dystrophy</td>
<td>Xp21.2</td>
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<td>DYS</td>
</tr>
<tr>
<td>Emery-Dreifuss muscular dystrophy</td>
<td>Xq28</td>
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Modified from Neuromuscular Disorders

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<th>Inheritance</th>
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<tr>
<td>AR</td>
<td>CMD with merosin deficiency*</td>
<td>6q2</td>
<td>Laminin-α2 chain</td>
<td>LAMA2</td>
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<tr>
<td>AR</td>
<td>CMD without merosin deficiency</td>
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<tr>
<td>AR</td>
<td>CMD with integrin deficiency</td>
<td>12q13</td>
<td>Integrin-α7</td>
<td>ITGA7</td>
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<tr>
<td>AR</td>
<td>CMD with rigid spine</td>
<td>1p35–36</td>
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<td>AR</td>
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<td>1p31–p33</td>
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<td>AR</td>
<td>Muscle-eye-brain disease</td>
<td>1p32–p34</td>
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<tr>
<td>AR</td>
<td>Walker-Warburg syndrome</td>
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AR, autosomal recessive; CMD, congenital muscular dystrophy.
*Late-onset variants exist.
Modified from Neuromuscular Disorders.
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and cor pulmonale. Certain medications, namely β-blockers, nonsteroidal anti-inflammatory agents, and calcium channel blockers, can also cause dependent edema and should be avoided if possible.

Physical and occupational therapy

The goal of physical therapy is to prolong ambulation and to prevent contractures. Muscle fibrosis and imbalance between flexor and extensor muscles can result in hip, knee, or ankle contractures. Passive range-of-motion exercises, performed after a brief warm-up, for approximately 30 minutes daily delay or even prevent contractures and improve ambulation. Excessive exercise, indicated by muscle pain after exertion, should be avoided because it may increase muscle damage. As disability proceeds, individualized aids may be of enormous benefit. Door handle modifications, handrails in the bathroom, computers, and companion dogs are a few examples.

The overall goal is to increase independence and to allow patients to pursue educational, vocational, and leisure activities. Muscular Dystrophy: The Facts and numerous publications by the Muscular Dystrophy Association of the United States and of Great Britain contain further information.

Orthopedic management

The development of contractures impedes ambulation and function of patients with muscular dystrophy. Flexion contractures of the knees and hips produce hyperlordosis of the lower spine, and Achilles tendon contractures produce toe-walking.

The surgical management of contractures is individualized but may include one or more of the following: release of flexion contractures of the hips, release of the tensor fasciae latae to correct abduction contractures, and tenotomy of the Achilles tendon combined with a posterior tibial-tendon transfer to allow dorsiflexion and eversion rather than excessive plantar flexion and inversion. If performed while the patient is still ambulatory but already showing gait impairment, contracture release may prolong ambulation by 1 to 3 years. However, lengthening already severely weakened muscles may further decrease strength, and intervention to restore walking after a patient has been nonambulatory for more than 3 to 6 months is of no benefit. The orthopedic management of scoliosis is described below in the section on Duchenne dystrophy.

As with any operative procedure, appropriate anesthesia must be used (see below), and cardiac and respiratory function must be investigated and monitored carefully. Early and active physiotherapy is crucial in the postoperative period, and immobilization must be minimized.

Respiratory care

Respiratory compromise in patients with muscular dystrophy may be associated with intercurrent chest infection or may develop as a chronic component of the underlying muscle disease. The following preventive measures: avoidance of smoking or exposure to second-hand smoke, annual influenza vaccination, early and aggressive recognition and treatment of pulmonary infections, avoidance of large evening meals, and avoidance of cough suppressants and nocturnal sedatives. A high protein, low calorie diet sufficient to maintain ideal body weight is recommended because obesity increases the risk of obstructive sleep apnea and further compromises respiratory function.

One of the earliest symptoms of respiratory failure is exertional dyspnea. Baseline pulmonary function studies should be performed on all patients at the time muscular dystrophy is diagnosed and then performed routinely with a frequency dictated by the type of dystrophy and the rate of disease progression. Weakness of the respiratory muscles results in a restrictive ventilatory defect and eventual hypercapnia. Maximal inspiratory (Pmax) and expiratory (Pmax) pressures are often reduced by more than 50%. Subsequently, the patient's vital capacity and forced expiratory volume in 1 second (FEV1) decrease. Reduction of the vital capacity closely reflects the degree of general disability and predicts the need for artificial ventilation. A vital capacity less than 1.5 L, especially in combination with hypercarbia (Paco2 > 45 mm Hg) or hypoxemia (PaO2 < 75 mm Hg), indicates that ventilatory support is needed. As Pmax decreases below 40 cm H2O, cough becomes ineffective, causing mucous plugging and microatelectasis, which will eventually decrease O2 diffusing capacity and lead to hypoxemia. During the period of intercostal and accessory muscle atonia associated with REM sleep, ventilation is supported by movements of the diaphragm muscle. Diaphragmatic weakness, particularly prominent in Duchenne dystrophy, results in orthopnea, and REM-sleep associated hypoventilation.

Paradoxical inward movement of the abdominal muscles during inspiration and more than 20% decrease in vital capacity on lying down from sitting also indicate diaphragmatic weakness. Chest wall deformities caused by shortening or fibrosis of intercostal and accessory muscles or by progressive scoliosis decrease chest wall compliance and further compromise respiratory function.

Many patients with relatively static forms of dystrophy have nocturnal hypoxemia and complain of symptoms related to nocturnal hypoventilation. Poor sleep, frequent nocturnal awakenings, night terrors or nightmares, nocturnal seizures, morning headaches, reduced school performance, and daytime hypersomnolence are symptoms of nocturnal hypoventilation. In these patients, routine daytime pulmonary function tests may fail to detect the degree of respiratory compromise. Polysomnography in combination with oximetry and transcutaneous CO2 measurements are required for adequate assessment. For these patients, long-term nocturnal ventilation at home can dramatically improve the quality of life. Biphasic positive airway pressure (BiPAP) delivered via nasal mask is well tolerated. It rapidly improves nocturnal hypoxemia, restores
Figure 223.2 A general guide for the respiratory management of patients with neuromuscular disease. The suggested pulmonary function variables are similar to those outlined by the Muscular Dystrophy Association in its pamphlet, "Breathe Easy." The importance of general health maintenance and careful inquiry into clinical features of nocturnal hypoventilation are stressed. (a) Basic respiratory management of all patients with marked muscle weakness includes healthy diet with adequate protein, avoidance of obesity, scoliosis screening and management, early recognition and treatment of chest infection (chest physiotherapy, postural drainage, adequate hydration to thin secretions, antibiotics), and annual influenza vaccination. (b) Patients should be encouraged to exert their maximal effort, testing mask or tubing should be properly fitted for the patient, and intercurrent or recent illness should be noted. (c) Symptoms of nocturnal hypoventilation: daytime hypersomnolence, morning headache, poor or declining school/ work performance, excessive fatigue, unexplained weight loss, or failure to gain weight (infant or child). FVC, forced vital capacity; noct. hypovent., nocturnal hypoventilation; PFTs, pulmonary function tests; S+S, symptoms and signs.
normal sleep patterns, eliminates morning headaches, reduces daytime somnolence, and prevents cor pulmonale. Assisted ventilation is discussed further in the section on Duchenne muscular dystrophy.

Cardiovascular management

Involvement of cardiac muscle can be prominent in patients and manifesting carriers of dystrophinopathies and in patients with Emery–Dreifuss muscular dystrophy or myotonic dystrophy. Rarely, heart disease develops in patients with facioscapulohumeral, congenital muscular dystrophy associated with merosin deficiency, or sarcoglycanopathies. Syncope or palpitations should prompt immediate cardiac assessment. Additional studies, including Holter monitoring, His bundle electrocardiograms, or echocardiography, should be performed on symptomatic patients under the guidance of a cardiologist.

Anesthetic issues

Anesthetic complications can occur in patients with muscular dystrophy, particularly in those with dystrophinopathies or myotonic dystrophy. The complications include tachycardia, atrial and ventricular fibrillation, a malignant hyperthermia-like reaction, and, rarely, cardiac arrest. These complications occur even in the absence of overt cardiomyopathy. Postoperatively, a marked increase in the CK level and myoglobinuria may occur in Duchenne patients. Anesthetists should avoid the use of nondepolarizing blocking agents and be alert to the risk of complications in any patient with muscular dystrophy.

Psychological issues

The diagnosis of a progressive neuromuscular disorder has an enormous impact on the psychological well-being of the patient and the patient’s family. Both the patient and the family should be provided with information about local and national support groups and be offered specific counseling as needed. Because the psychological effects of a chronic disease may not be manifested immediately, it is important to periodically ask the patient and family about their emotional well-being. Many parents are reluctant to ask for help because they feel that this reflects a lack of compassion or commitment to their child. It is crucial that parents spend time together as a couple and have time to focus attention on their other children. The incidence of marital discord is greater than 50% and the divorce rate is higher than 25% for couples with a chronically ill child. Many communities have a local Muscular Dystrophy Association chapter that enables parents to derive support from other parents and allows affected children to spend time with other similarly affected children. Summer camp programs provide invaluable independence and recreation for children as well as respite for families. In the case of an affected adult, a few hours each day of in-home nursing services provides relief for the spouse or care-giver.

Whenever a specific dystrophy is diagnosed, the initial discussion should occur when both parents are present. The decision to include the child in the initial discussion depends on the age and cognitive maturity of the child. Open, accurate, and honest discussions with the child over time increase understanding of the disease and encourage discussion of frustrations, fears, and expectations. It is important to encourage independence and to recognize a child’s need for privacy. In late adolescence, these issues become pressing, as the teenager attempts to form peer and sexual relationships, establish educational and vocational goals, and achieve independent living arrangements. Independent living or group home arrangements can be achieved in many cases by careful planning and with home assessment by an occupational therapist.

Gene therapy

Despite reasons for optimism, numerous hurdles remain before gene therapy can be realized for muscular dystrophy. Trials of dystrophin replacement using local intramuscular injections of paternally derived myoblasts failed to result in long-term dystrophin expression in mature muscle fibers and did not improve muscle strength or patient outcome in boys with Duchenne muscular dystrophy.

In a recent review, Karpati proposed five strategies for gene therapy: (1) specifically designed pharmacotherapy, (2) protein replacement (not applicable for structural proteins), (3) upregulation of a functional protein analogue, (4) RNA repair, and (5) somatic gene replacement. Of these strategies, the latter three hold the most promise. Utrophin, a protein encoded on chromosome 6, has 80% sequence homology to dystrophin. In mature muscle, utrophin is localized to the postsynaptic sarclemna of the neuromuscular junction. In fetal muscle, utrophin is also expressed at the extrajunctional sarclemna. In the dystrophin-deficient (mdx) mouse and in muscle from patients with Duchenne muscular dystrophy, utrophin expression resembles the fetal pattern. However, this naturally occurring up-regulation of utrophin is not sufficient to prevent ongoing muscle damage in patients with Duchenne muscular dystrophy. The mdx mouse, a murine model for Duchenne muscular dystrophy, has absence of dystrophin expression in muscle, increased levels of CK, pathological features of mild dystrophy in selected muscles, and mild weakness. In recent studies, mdx mice genetically engineered to overexpress a truncated utrophin minigene or full-length utrophin showed improved mechanical strength, normal or minimally increased serum levels of CK, and little or no dystrophic changes in muscle. A search for methods to up-regulate utrophin expression in humans is under way.

RNA repair involves the use of targeted antisense oligonucleotides designed to bind to mutated RNA regions, change the reading frame, and bypass the original mutation. It is postulated that RNA repair occurs spontaneously in the small number of dystrophin-positive (revertant) fibers found in muscle of
patients with Duchenne muscular dystrophy. Early studies of this technique are also under way.

Somatic gene cell replacement for muscular dystrophy holds great promise, but numerous methodological issues remain to be solved. In general terms, replacement of a defective gene requires the following:

- Knowledge of the target gene and its promoters
- The ability to construct a full-length gene, or a functional “minigene”
- The ability to insert the gene or minigene into a vector
- Creation of a vector large enough to receive the insert, small enough to infect the tissue of interest, and modified enough to prevent vector-related disease or malignancy
- Delivery of the vector (with the inserted gene) to a significant proportion of affected muscles
- Failure of the vector to disrupt other proteins
- Processing of the newly inserted gene by the host cell must lead to continual expression and appropriate cellular localization of the target protein
- The ability of the newly expressed protein to associate with its appropriate binding partners
- Tolerance of the patient’s immune system to both the vector and the newly expressed protein

Several dystrophin minigenes have been engineered successfully into viral vectors, but human trials must await the development of safe and efficient delivery systems.

**Disease-specific management issues**

**Duchenne and Becker muscular dystrophies**

Dystrophin is a large cytoskeletal protein (427 kDa) expressed in many tissues. It is particularly important at the sarcolemma of skeletal muscle, where it forms a complex with a group of membrane-associated glycoproteins. In general, frame-shifting deletions cause a virtual absence of dystrophin expression in muscle and result in the Duchenne muscular dystrophy phenotype, whereas in-frame deletions or missense mutations with attenuated dystrophin expression produce the milder Becker muscular dystrophy phenotype.

**Clinical features** Boys with Duchenne muscular dystrophy present around the age of 3 years with a clumsy gait, frequent falls, and toe walking. The disease progresses such that ambulation is typically lost by age 13 years, and death ensues in the second or third decade. Patients with Becker muscular dystrophy may present similarly but retain the ability to walk past age 13 years, or they may be mildly affected and not present until adulthood. Some patients with Becker muscular dystrophy, and some female carriers of dystrophin mutations, present with an isolated cardiomyopathy.

**Diagnosis** The diagnosis of either Duchenne or Becker muscular dystrophy rests on the history, physical examination, serum level of CK (increased), muscle biopsy findings, and genetic studies. The serum level of CK is elevated 10- to 50-fold at age 3 years and declines by approximately 20% per year thereafter. Because of the enormous size of the dystrophin gene, only certain regions are screened by commercially available molecular DNA studies. Large scale deletions are detected in only 60% to 70% of affected patients. It is important to recognize that a Duchenne or Becker muscular dystrophy phenotype cannot be predicted reliably on the basis of the type of mutation alone. In families in which no mutation is found, linkage analysis looking for markers that cosegregate with the X-chromosome of a patient with Duchenne muscular dystrophy can be performed provided a sufficient number of family members are available. Muscle biopsy studies using antibodies directed against the carboxyl and amino termini and rod domain of dystrophin can be helpful in distinguishing Duchenne from Becker muscular dystrophy and for establishing the diagnosis of a dystrophinopathy in the 30% to 40% of such patients in whom no mutation was found. Most patients with Duchenne muscular dystrophy show absence of dystrophin immunoreactivity in all but a few “revertant” fibers. However, patients with partially preserved dystrophin expression cannot be guaranteed to have a Becker muscular dystrophy phenotype. Western blot analysis of the muscle shows decreased dystrophin content and an abnormal size of the mutated protein. Muscle biopsy specimens may show patchy dystrophin immunoreactivity in manifesting female carriers or in unaffected mothers. Because only 70% of female carriers have increased serum levels of CK, this test alone is not sufficient to exclude carrier status.

**Genetic counseling** Genetic counseling should be provided to parents and siblings of patients with Duchenne or Becker muscular dystrophy. Female carriers have a 50% chance of producing an affected son, and 50% of female offspring will be carriers. Not all cases of dystrophinopathy are familial, because of the high spontaneous mutation rate in the dystrophin gene. The risk in these families for a subsequently affected son is approximately 7%.

Prenatal diagnosis of dystrophin deficiency can be performed on amniocytes or chorionic villus samples. Preimplantation diagnosis performed after a single cell biopsy at the blastomere stage before in vitro fertilization is available for families with known mutations. Needle biopsy specimens from a limb muscle of an at-risk fetus can be analyzed with dystrophin antibodies, but there is a 3% to 5% miscarriage rate with the procedure. Specialized techniques, such as transfection studies of fetal amniocytes or chorionic villus cells using the muscle promoter myoD with analysis of dystrophin expression in transfected cells, are performed at a few research centers. Fetuses with absent dystrophin expression can then be detected.

**Treatment** Despite reasons for optimism about the future of genetic therapies, current treatment for boys
with Duchenne or Becker muscular dystrophy revolves around the prevention or limitation of secondary complications and maximizing the quality of life.

1. Physical therapy: Parents and caregivers need to be taught by an experienced therapist the appropriate techniques to prevent contractures. Range of motion exercises may cause minor discomfort. If pain is elicited, the exercise should be stopped and the child examined for fracture or joint injury. Physical therapy in combination with appropriate surgical intervention may prolong ambulation for 1 to 5 years. Therapy should consist of range of motion exercises, passive stretching, and participation in enjoyable exercises and sports in the early phase (age 2 to 8 years) and continuation of stretching and participation in concentric exercises such as supervised swimming in the intermediate phase (age 8 to 12 years). The use of long-leg orthotics (Dubowitz braces) may prolong the ability to stand by up to 3.9 years. Fitting of these braces may require release of existing ankle and hip contrac-
tures.

2. Scoliosis: The development of scoliosis is invariant in Duchenne muscular dystrophy but is delayed if ambulation is prolonged into adolescence. The scoliotic curve progresses at a rate of 1 to 2 degrees per month after ambulation is lost. Bracing and proper seating (narrow width chair, proper back support) slow the progression of scoliosis, but surgical intervention is eventually required. Surgical intervention is indicated when the spinal curvature reaches 40 degrees or if it is rapidly progressive. Spinal stabilization using the sublaminar wire technique (Luque instrumentation) and spinal arthrodese decreases spinal curvature by approximately 50% and results in substantial improvement in seating, comfort, cosmetic appearance, and quality of life. Respiratory function is not markedly improved with spinal stabilization.

As with any operative procedure, appropriate anesthesia must be administered (see below), and cardiac and respiratory function should be investigated and monitored carefully. Patients with dystrophin deficiency also have platelet dysfunction, despite normal bleeding time, and may require extensive blood replacement during a spinal operation. Early and active physiotherapy are crucial postoperatively, and immobilization must be mini-
mized.

3. Corticosteroids: Ambulation is prolonged in patients with Duchenne muscular dystrophy treated with corticosteroids. The beneficial effects of corticosteroids may be due to increased muscle mass (decreased protein catabolism or increased protein synthesis), sarcolemmal membrane stabilization, or suppression of the immune response directed against degenerating fibers. The best results are achieved with prednisone at a dose of 0.75 mg/kg daily. Improvement in strength testing is noted by 10 days and becomes maximal by 2 months. The subsequent rate of decline in muscle strength is decreased in comparison with that of untreated historical controls, and this effect is sustained for at least 3 years. These benefits must be weighed against the potentially severe side effects of long-term prednisone administration (weight gain, cushingoid appearance, avascular necrosis of the femoral head, osteopenia, hyperglycemia, cataracts, and gastrointestinal distress). Treatment with an equivalent anti-inflammatory dose of deflazacort produces benefits similar to those observed with prednisone. In the initial trial, patients given deflazacort had less weight gain but developed significantly more cataracts than patients given prednisone. Immunosuppression with azathioprine (Imuran) alone or in combination with prednisone was found to be of no value. A 3-month pilot trial using the anabolic steroid oxandrolone (0.1 mg/kg daily) showed statistically significant improvement in muscle strength scores comparable to the results achieved in the corticosteroid trials. No side effects were reported.

4. Respiratory management: Seventy percent of deaths in Duchenne muscular dystrophy are respiratory. Mechanical ventilation of patients with a progressive disability raises numerous ethical, financial, emotional, and practical issues for affected boys and their families. These issues must be discussed openly and, preferably, well before respiratory intervention has to be considered. In Japan, nearly all affected boys offered assisted ventilation chose to pursue this option.

Respiratory assessment requires detailed pulmonary function studies. Baseline studies should be performed shortly after diagnosis and then repeated every 6 to 12 months. After ambulation has been lost, pulmonary function must be monitored more frequently. The first stage of respiratory failure, due to a weak cough, results in accumulated secretions and microatelectasis. Incentive spirometry, used before a marked decline in pulmonary function, may help reduce atelectasis. However, the use of spirometry to improve respiratory muscle strength is of no benefit. Intermittent use of an Emerson In-Exsufflator, a small electrical machine that pushes a fixed volume of air into the lungs and then forcefully withdraws air and mucus, may be helpful in patients with a weak cough, especially during intercurrent pulmonary infections. The second stage of ventilatory failure relates to nocturnal hypoventilation. At this point, the vital capacity is usually less than 30% of predicted and polysomnography demonstrates hypoxemia that is most prominent during REM sleep.

When vital capacity decreases to 10% to 20% of predicted or is less than 1 L, assisted ventilation should be considered. The use of assisted ventilation can prolong life by as much as 10 years. Both negative and positive pressure ventilation systems are available for nocturnal or full-time ventilation. Negative pressure ventilation, initially pioneered as the iron lung and now as the cuirass tank or wrap
5. **Cardiac management:** Essentially all patients with Duchenne muscular dystrophy will show signs of cardiac disease by their 18th birthday. Changes in the electrocardiogram (ECG), including conduction defects and sinus tachyarrhythmias, are present by age 10 years but are of limited value in predicting marked cardiac compromise. Patients should be followed by a cardiologist after 8 years of age and should have echocardiography annually beginning at age 10. Cardiac failure may be helped by treatment with angiotensin-converting enzyme inhibitors. Digoxin may cause severe arrhythmias and must be used with extreme caution.

6. **Gastrointestinal management:** Dystrophin is also expressed in smooth muscle. Many patients with Duchenne muscular dystrophy have impaired gastric motility and can present with severe gastric distention and intestinal pseudo-obstruction. Acute abdominal pain should receive immediate medical attention.

7. **Education:** Although the role of dystrophin in the central nervous system is unknown, a functional role is suggested by the fact that the average intelligence quotient of boys with Duchenne muscular dystrophy is 1 standard deviation below the mean (even in comparison with siblings), and 30% of the boys have significant learning disabilities or are mentally retarded. Educational needs must be assessed and modified if required.

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**Myotonic dystrophy**

“Myotonic dystrophy” is the most common form of muscular dystrophy in adults.

**Genetics** The myotonic dystrophy gene localizes to chromosome 19q13.3. The genetic defect results from a trinucleotide (CTG) expansion in the 3′ non-coding region of the myotonic dystrophy protein kinase (DMPK) gene. The number of (CTG) repeats correlates positively with disease severity. Patients with minimally expanded repeats (CTG)38-40 may be asymptomatic and have normal findings on electromyography. Genetic anticipation, the tendency for disease severity (and number of expanded repeats) to increase in subsequent generations, occurs and is especially likely when the mother is the affected parent. DMPK is a transmembrane protein localized to the sarcoplasmic reticulum and appears to be expressed predominantly in type I fibers, at the neuromuscular junction, and in intrafusal fibers of the muscle spindle. The function of DMPK and the mechanism whereby expansion in the non-coding region of the protein results in disease are not understood. Recent studies have shown a reduction in expression of DMPK in muscle specimens from affected patients, suggesting a dominant negative effect of the trinucleotide expansion at the RNA level. Alternatively, the expanded region may disrupt function of a contiguous gene, such as the myotonic dystrophy-associated homeobox gene (DMAHP).

**Clinical features**

Myotonic dystrophy is a multisystem disorder of variable severity, and many mildly affected patients are unaware of their diagnosis. Affected patients have weakness of facial (ptosis, long myopathic facies), jaw (temporomandibular dislocations), distal limb, and, to a lesser degree, proximal muscles of the shoulder and pelvic girdle. Limb weakness is usually mild and progresses slowly. Weakness of ankle dorsiflexion as well as more proximal weakness necessitates use of a cane or wheelchair by more severely affected patients. “Action myotonia” is often described by patients as difficulty in releasing their grip or in initiating voluntary movements. “Percussion myotonia” is best demonstrated in the tongue, hand, or finger extensor muscles by firmly tapping the muscle with a reflex hammer.

Cardiac manifestations, including conduction block and tachyarrhythmias due to degeneration of the cardiac conducting system, can occur in otherwise mildly affected patients. More than 90% of patients with myotonic dystrophy show gradually progressive ECG abnormalities, which may require His-bundle pacing as well as routine ECG recordings for diagnosis. Sudden death is well documented.

The diaphragm is often involved, resulting in nocturnal respiratory compromise and manifesting as daytime hypersomnolence. Although weakness of respiratory and facial muscles and craniofacial abnor-
malities, including micrognathia, predispose to respiratory compromise, an additional defect in central respiratory drive has also been suggested. The involvement of smooth muscle causes disturbed swallowing, constipation, weakness of the anal sphincter (especially notable in affected children and often mistaken for abuse), and delayed gallbladder emptying, with an increased incidence of gallstones.

Cataracts develop in most patients with myotonic dystrophy, and retinal degeneration also can occur. Examination with a slit lamp to look for multicolored subcapsular cataracts and a detailed retinal examination should be performed annually.

Endocrine manifestations include testicular atrophy, reduced fertility, hyperglycemia with increased insulin resistance (true diabetes is rare), and early-onset frontal balding.

The combination of effects on the uterine smooth muscle and the endocrine system results in a high incidence of pregnancy complications, including fetal loss, hydramnios, prolonged labor, retained placenta, postpartum hemorrhage, and an increased risk of premature delivery.

A more severe form of myotonic dystrophy occurs in congenitally affected neonates. Affected infants have severe bifacial weakness with a “tented mouth,” poor feeding, diffuse hypotonia, thin ribs, elevated diaphragms, and respiratory failure often requiring artificial ventilation. Some infants also have arthrogryposis and hydrocephalus. Neonatal mortality is high. In one study, all infants who required ventilation for more than 4 weeks eventually succumbed, even if they were weaned successfully from ventilation for more than 4 weeks eventually succumbed, even if they were weaned successfully from ventilatory support. In less severely affected infants, motor development is delayed but ambulation eventually is achieved. Cognition is significantly impaired in at least two-thirds of affected children, and few are of normal intelligence.

**Diagnosis** Serum CK levels are normal or minimally increased. Muscle biopsy findings include increased central nuclei, ringed fibers, type I fiber atrophy, sarcoplasmic masses, and a variable degree of fibrosis.

EMG studies show electrical myotonia consisting of discharges that wax and wane in frequency and amplitude as well as positive sharp waves, fibrillation potentials, and myopathic motor units. EMG studies rarely show myotonia until late childhood. The presence of myotonia early in life suggests the diagnosis of a nondystrophic myotonic disorder. Because many mildly affected women are unaware of their condition until the birth of an affected child, EMG should be performed on all mothers of severely hypotonic neonates.

**Management**

1. **Myotonia:** Unlike other myotonic disorders, the myotonia of myotonic dystrophy is rarely disabling. In the few patients with marked myotonia, phenytoin (100 mg 3 times daily) may be of benefit. Women must be warned about the risk of teratogenicity, and phenytoin therapy should be stopped before conception. Medications such as tocainide, procainamide, and quinidine used to treat other myotonic disorders may exacerbate cardiac arrhythmias and should be avoided.

2. **Anesthesia:** A malignant hyperthermia-like reaction, postulated to be due to abnormal calcium influx from the extracellular space, may occur with depolarizing muscle relaxants and neostigmine. It is critical that anesthesiologists be aware of the diagnosis of myotonic dystrophy preoperatively. A medic alert bracelet is advised.

3. **Cardiac:** Signs of progressive conduction defects or symptoms of syncope or palpitations should prompt immediate cardiac assessment and Holter monitoring. Pacemaker insertion may be required.

4. **Respiratory:** Hypersomnia may be improved but not entirely reversed by nocturnal assisted ventilation. In these patients, methylphenidate may enhance alertness. Respiratory muscle training can improve respiratory strength. Opiates, barbiturates, and benzodiazepines can cause marked respiratory depression and should be prescribed with caution. Nocturnal sedatives should be avoided.

Patients with an autosomal dominant disorder that shares many of the features of myotonic dystrophy but without an expanded trinucleotide repeat on chromosome 19 have been reported. The disorder is genetically and clinically heterogeneous. The terms “proximal myotonic dystrophy” and “myotonic dystrophy type 2” have been applied and some kindreds have been linked to chromosome 3q.

**Oculopharyngeal muscular dystrophy**

**Genetics** Genetic studies show an expanded (GCG) repeat from (GCG)8–13 in the amino terminus of the poly(A) binding protein 2 gene (PABP2) located on chromosome 14q11. Inheritance in these families follows an autosomal dominant pattern. Two percent of the normal population harbor a single copy of an alternative (GCG)4 allele, which when combined with an expanded (GCG)8–13 allele produces a particularly severe phenotype. Patients homozygous for the (GCG)4 allele are mildly symptomatic, and these kindreds show an autosomal recessive pattern of inheritance. Although the function of the PABP2 gene has yet to be elucidated, it is postulated that expansions of the polyalanine tract may cause aggregation and possibly defective degradation of the poly(A) binding protein. These abnormal aggregates may correspond to the filamentous 7- to 10-nm nuclear inclusions that are the pathological signature of the disease.

**Clinical features** Oculopharyngeal muscular dystrophy presents in the 5th to 6th decade of life with progressive dysphagia, ptosis, and proximal muscle weakness. When ptosis is severe, the patient tilts the head back and contracts the frontalis muscle in order to see. The serum levels of CK usually are normal, and EMG studies show a myopathic
pattern. Increased serum levels of IgA and IgG were reported in French-Canadian pedigrees, but this could have been related to intercurrent pulmonary infections due to chronic aspiration. Muscle biopsy specimens show atrophic fibers, rimmed vacuoles (especially in atrophic fibers), scattered ragged red fibers, and degenerating fibers. Intranuclear inclusions consisting of 7 to 10-nm filaments are demonstrated by electron microscopy.

In the presence of a strong family history of late-onset ptosis and dysphagia, the diagnosis of oculopharyngeal muscular dystrophy is straightforward. Mitochondrial myopathy and myasthenia gravis are the main differential diagnoses. Short stature, deafness, central nervous system involvement, increased serum levels of lactate, pigmented retinopathy and night blindness, onset before age 20 years, and a maternal pattern of inheritance suggest a mitochondrial disorder. The presence of circulating acetylcholine receptor antibodies, a decremental response to repetitive stimulation during EMG, and a history of fatigueable weakness point to a myasthenic disorder.

**Treatment**

1. **Dysphagia:** Patients with oculopharyngeal muscular dystrophy have dysfunction of the striated muscle of the upper one-third of the esophagus (cricopharyngeal achalasia). The failure of the cricopharyngeal muscles to contract properly results in pooling of secretions and food in the hypopharynx and predisposes to aspiration. Severe difficulty with swallowing leads to reduced oral intake and subsequent malnutrition. Patients who require more than 7 seconds to drink 80 mL of ice water are likely to have significant achalasia, and formal swallowing studies should be performed.

2. **Ptosis:** Ptosis, defined as a palpebral fissure width of less than 8 mm, may be improved with the use of lid crutches or may be corrected with blepharo-plasty.

**Fascioscapulohumeral muscular dystrophy**

**Genetics** Fascioscapulohumeral muscular dystrophy is an autosomal dominant disorder, with 10% of cases due to spontaneous mutations. The most severely affected patients are more likely to have spontaneous mutations or to have inherited the disorder from their mother. The genetic locus for this condition is at the telomeric region 4q35 and is associated with deletion of an integral number of tandemly arrayed 35- to 300-kb repeats. This likely exerts an adverse effect on upstream genes (position effect variegation), but the genes whose functions are altered have not been discovered.

There is a direct correlation between the number of deleted repeats and the severity of disease.

**Clinical features** Fascioscapulohumeral muscular dystrophy is characterized by weakness of the facial, upper limb, and shoulder girdle muscles, with later involvement of lower extremity muscles in about 20% of cases. Weakness of the anterior tibial muscles produces a footdrop gait, which can become disabling for some patients. Weakness of the shoulder girdle results in scapular instability, marked limitation in arm abduction, and the characteristic “scapular winging.” Hearing loss and retinal venous anomalies are common but may be subclinical. The risk of Coats disease (retinal telangiectasias, exudate, and retinal detachment) is increased.

A more severe congenital variant presents with one or more of the following: severe facial diplegia, marked sensorineural hearing loss, Coats disease, and weakness that may progress to wheelchair dependence in the second decade of life.

**Diagnosis** Pathological changes in muscle are variable and reflect the regional and asymmetrical distribution of the disease. A biopsy specimen from a mildly to moderately affected muscle shows increased fiber size variation, increased central nuclei, occasional necrotic fibers, fibers with a lobulated distribution of oxidative enzymes, and increased endomysial and perimysial connective tissue. In some cases, small perivascular, endomysial, or perimysial collections of mononuclear cells are also present. Approximately 60% to 80% of patients with fascioscapulohumeral muscular dystrophy have a modest increase in the serum level of CK, and EMG demonstrates a myopathic pattern.

**Treatment** Many patients with fascioscapulohumeral muscular dystrophy are affected only mildly and require no specific treatment.

1. **Scapular arthrodesis:** For patients with severe limitation of arm abduction, scapular arthrodesis can be considered. Scapular arthrodesis involves the use of an iliac crest bone graft and wiring to fix the scapula to the thoracic rib cage. The procedure offers long-lasting improvement in shoulder movement, but it is associated with the risk of perioperative pneumothorax and pulmonary atelectasis.

2. **Medications:** Treatment with corticosteroids does not increase a patient’s strength. A pilot trial of the β-agonist albuterol showed a 12% improvement in muscle strength over 3 months.

3. **Ophthalmology:** Visual loss due to Coats disease may be prevented by early diagnosis and therapeutic photocoagulation of abnormal vessels.

4. **Audiology:** The sensorineural hearing loss in congenitally affected patients may be improved with hearing aids. Early recognition and intervention are important for language development.

**Emery–Dreifuss muscular dystrophy**

**Genetics** Two phenotypically similar diseases are termed “X-linked” and “autosomal dominant” Emery–Dreifuss muscular dystrophy. The X-linked form is due to mutations in the nuclear membrane-associated protein emerin. The gene for the autosomal dominant form encodes the nuclear
lamina-associated protein lamin A/C\textsuperscript{65} and appears to be an allelic disorder to the autosomal dominant limb girdle dystrophy associated with cardiac involvement (LGMD 1B).\textsuperscript{66} How mutations in these genes result in muscular dystrophy is not understood.

Clinical features Both forms of Emery–Dreifuss muscular dystrophy are characterized by the early onset of elbow, neck, and Achilles tendon contractures, slowly progressive wasting and weakness of the proximal muscles, and potentially lethal cardiac conduction block and cardiomyopathy.\textsuperscript{65}

Diagnosis The serum level of CK is moderately increased, and EMG shows myopathic features with rare fasciculations.\textsuperscript{87} Muscle biopsy studies demonstrate myopathic features and angulated atrophic type I fibers.\textsuperscript{67} In the X-linked form of the disease, immunostains for the nuclear lamina-associated protein emerin show reduced or absence of nuclear membrane staining. Emerin is also expressed in skin, and the diagnosis of an affected male or a carrier female can be made by immunostaining skin biopsy specimens.\textsuperscript{68}

Treatment Treatment in Emery–Dreifuss muscular dystrophy is aimed at preventing the cardiac complications of the disease. Up to 40% of the patients die suddenly, most without preceding cardiac symptoms.\textsuperscript{89} Thus, early diagnosis of the disease is essential. All patients should be monitored closely by a cardiologist. Timely insertion of a cardiac pacemaker is lifesaving.\textsuperscript{87}

Congenital muscular dystrophy Genetics Congenital muscular dystrophies are degenerative disorders of muscle with in utero or early infantile onset. “Merosin-deficient congenital muscular dystrophy” is associated with mutations in the LAMA\textsubscript{2} gene encoding the laminin \(a2\) chain (merosin), a component of the basement membrane surrounding muscle.\textsuperscript{90}–\textsuperscript{92} Congenital muscular dystrophy with preserved laminin \(a2\) expression and without severe structural abnormalities of the central nervous system is likely a genetically heterogeneous disorder.\textsuperscript{95} A small number of these patients have been reported to have mutations in the integrin \(a7\) gene.\textsuperscript{96}

Prenatal diagnosis of merosin-deficient congenital muscular dystrophy can be performed on trophoblast tissue obtained from chorionic villus sampling.\textsuperscript{94} This test is reliable only in families with a complete absence of laminin \(a2\) (merosin). Confirmatory linkage analysis should also be performed.\textsuperscript{94}

Three forms of congenital muscular dystrophy are associated with severe central nervous system anomalies.\textsuperscript{95} “Fukuyama congenital muscular dystrophy” is the second commonest form of muscular dystrophy in Japan,\textsuperscript{96} but it is not restricted to the Asian population. It is an autosomal recessive disorder due to mutations in the protein fukutin encoded on chromosome 9q31.\textsuperscript{97} The function of fukutin, a secreted protein, is unknown.\textsuperscript{97} “Muscle–eye–brain disease” has been reported predominantly in Finland and is linked to chromosome 1p32–p34.\textsuperscript{98} The third and most severe form is Walker–Warburg syndrome. The locus for this disorder has not been mapped.\textsuperscript{99}

Clinical features Neonates have marked hypotonia, weakness, increased serum levels of CK, and delayed motor development. Many also have or develop contractures and have marked respiratory and feeding difficulties.\textsuperscript{99,100} Patients with merosin-deficient congenital muscular dystrophy have severe nonprogressive weakness; they are able to sit by age 3 years but have poor head control and most remain wheelchair-dependent. Rarely, patients with partial merosin deficiency present with a limb–girdle distribution of weakness,\textsuperscript{101} which may manifest in adulthood.\textsuperscript{102} Cognition is usually normal in congenital or late-onset cases, despite MRI scans that demonstrate abnormally high T2 signal in the white matter.\textsuperscript{95} However, a seizure disorder develops in up to 30% of patients.\textsuperscript{103} Merosin is also expressed in Schwann cells, and merosin-deficient patients have a mild demyelinating peripheral neuropathy.\textsuperscript{91} Rarely, there is cardiac involvement.\textsuperscript{75}

Congenital muscular dystrophy associated with normal cognition, normal findings on neuroimaging, and preserved merosin expression is termed “merosin-positive,” or “pure,” congenital muscular dystrophy. These children usually are affected less severely than those with merosin-negative congenital muscular dystrophy, and ambulation may eventually be achieved.\textsuperscript{91}

Fukuyama congenital muscular dystrophy, muscle–eye–brain disease, and Walker–Warburg syndrome are associated with severe central nervous system malformations (one or more of the following: lissencephaly, polymicrogyria, polycystic hydromyelic cavities, cerebellar and midline structures, and abnormal white matter) and ocular manifestations (retinal detachment, severe myopia, macrocornea).\textsuperscript{95,99,100,105} Patients with Fukuyama congenital muscular dystrophy are weak and few attain ambulation. Most are mentally retarded, with IQ scores between 20 and 90, and 20% have epilepsy.\textsuperscript{101} Ocular abnormalities may be present, but most patients have some functional vision.\textsuperscript{102} Survival is into the second decade of life.\textsuperscript{91}

Muscle–eye–brain disease is associated with facial dysmorphism (prominent forehead, narrow temporal areas) and severe central nervous system and ocular malformations. Patients may survive into late adulthood but are severely retarded.\textsuperscript{98}

Patients with Walker–Warburg syndrome typically die within the first 6 months of life, have brain and ocular malformations, and are clinically blind.\textsuperscript{99}

Diagnosis Muscle biopsy findings in all the forms of congenital muscular dystrophy show prominent fiber size variation and fibrosis. Necrotic fibers are rare and help to differentiate congenital muscular dystrophy from Duchenne dystrophy.\textsuperscript{106} Antibodies directed
against the laminin α2 chain are attenuated or absent in muscle and skin in merosin-deficient patients; thus, biopsy of either tissue may be useful. It is important to note that some merosin-deficient patients have attenuated reactivity only with antibodies directed against the 300-kDa fragment that contains the N terminal region of the laminin α2 chain and preserved reactivity with antibodies directed against the 80-kDa isoform that contains the C terminal end of the molecule. Thus, both antibodies should be used if merosin deficiency is suspected.

**Treatment** Management of children with congenital muscular dystrophy centers on prevention of contractures and scoliosis and requires close monitoring of respiratory function. Seizures should be treated with conventional anticonvulsant agents.

**Summary**

This chapter highlights specific issues in the management of the more common forms of muscular dystrophy. As the disease loci are mapped, the candidate genes sequenced, and the physiological function and cellular localization of the putative proteins discovered, specific therapies and possibly cures for these debilitating conditions may emerge.

**References**

13. Barthlen GM. Nocturnal respiratory failure as an indication of noninvasive ventilation in the patient with neuromuscular disease [see comments]. Respiration 1997;64 Suppl 1:35–38
46. Griggs RC, Moxley RT, III, Mendell JR, et al. Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and azathioprine (12 months) [see comments]. Neurology 1993;43(3 Pt 1):520–527
61. Rutherford MA, Heckmatt JZ, Dubowitz V. Congenital muscular dystrophy—a family with autosomal dominant myotonic myopathy to chromosome 3q [see comments]. Neuromuscul Disord 1996;6(3):61–68
68. Ricker K. Myotonic dystrophy and proximal myotonic dystrophies.
87. Grimm T, Janka M. Emery–Dreifuss muscular dystro-