Review of Duchenne Muscular Dystrophy (DMD) for the Pediatricians in the Community

Sumit Verma, MD, Yaacov Anziska, MD, and Joan Cracco, MD

Introduction

Duchenne muscular dystrophy (DMD), an inherited X-linked recessive disorder, is characterized by progressive symmetric muscle weakness and gait disturbance, with onset in early childhood. DMD is the most common muscular dystrophy in children, and incidence ranges from 1 in 3600 to 4700 live male births. Early diagnosis (screening, confirmation, and genetic counseling), treatment, and long-term follow-up of affected individuals in routine pediatric practice can be challenging and are the focus of this review.

Natural History and Clinical Features

Infant boys with DMD are often asymptomatic. Although the clinical manifestations may be present by the end of the first year, first symptoms are usually noted during the toddler and preschool years (2-5 years). In spite of increased awareness, there is an average delay of 2.5 years from the onset of symptoms, and mean age of definitive diagnosis is 5 years. Affected children usually present with gait problems (waddling, toe walking, and lordotic posture), calf hypertrophy, positive Gower’s sign (difficulty arising from the floor, spreading their legs, and using their hands to climb up their thighs to help them to an upright position), and difficulty climbing stairs. Pediatricians should be aware of the importance of having preschoolers get up from a sitting position on the floor, walk, and run so as to detect early signs of muscle weakness. Motor status may appear to plateau between 3 and 6 years; deterioration begins between 6 to 8 years. Affected children lose the ability to climb stairs and rise from the floor and also develop Achilles tendon contractures. They may be able to self-propel for some time and maintain posture, but lordosis and scoliosis become obvious. Between ages 9 and 12 years, the majority of DMD patients become wheelchair bound (Figure 1). Upper-limb function is preserved until a later period. Decreased pulmonary function as a result of respiratory muscle weakness and chest deformity (kyphoscoliosis), along with respiratory infections, predisposes to respiratory failure. Cardiomyopathy and arrhythmia result in cardiac failure. Cardiorespiratory complications appear during the second decade and eventually lead to death.

Screening With Creatine Kinase (CK)

CK is a good screening test for muscle disease in clinical practice because levels rise in conditions with active muscle fiber necrosis and injury. In DMD patients, CK levels are usually very elevated and are between 5000 and 150,000 IU/L (normal is less than 200 IU/L). Reversible causes of elevated CK include drugs, trauma, crush injury, recent bacterial/viral infections, and hypothyroidism. However, the CK elevation in these circumstances rarely approaches that of DMD. Newborn screening using CK levels is not done routinely, and such screening has been restricted to research settings because of limited data on the impact of early diagnosis and initiation of (steroid) therapy in DMD.

Disease Confirmation and Genetic Counseling

Those with DMD are deficient in dystrophin, an important muscle structural protein. The gene that codes for dystrophin is large, with 79 exons. Approximately one-third of new cases in children are the result of new mutations. Dystrophin gene mutation testing should be done in all suspected cases. Large deletions or duplications on

1State University of New York (SUNY) Downstate Medical Center, Brooklyn, New York, NY, USA

Corresponding Author:
Yaacov Anziska, Department of Neurology, 450 Clarkson Avenue, Box 1213, Brooklyn, NY 11203
Email: Yaacov.Anziska@downstate.edu
Xp21 locus account for 72% of the mutations among all cases; another 20% are point mutations (amino acid substitution, premature stop mutation, splice mutation), and 7% are small insertions or deletions; entire gene deletions are very rare.\(^9\),\(^10\) Disruption or preservation of the reading frame by deletion mutations accounts for the phenotype severity. The mRNA formed by joining the ends of exons has to be in phase to maintain the correct translational open reading frame for the ribosome. Deletions that shift the translational reading frame (frameshift deletion) result in severely truncated dystrophin molecules. In-frame deletions lead to production of semi-functional protein, which can persist in small quantities, and this results in Becker Muscular Dystrophy (BMD), a milder, later onset muscular dystrophy.\(^11\) EMG has no role in the diagnosis of DMD. Muscle biopsy can be considered in suspected children with negative family history and inconclusive or nonavailable genetic testing.\(^12\) In DMD, dystrophin is absent in the muscle on immunostaining. Clinically asymptomatic siblings and the mother of the index case should be tested for disease and carrier state. Most carrier females are asymptomatic; however, up to 20% of carrier females may develop some degree of muscle weakness or cardiomyopathy.\(^13\) A carrier mother has a 50% risk of having a boy with DMD and a 50% risk of her daughters being carriers. In sporadic cases, with no known family history and negative DNA deletion testing in the mother, germ line mosaicism cannot be excluded. These families have a 7% to 10% recurrence risk. Before planning the next pregnancy, mothers with a carrier state or sporadic germline mutations with previously affected male babies must have genetic counseling and prenatal testing (Southern blot or polymerase chain reaction with chorionic villus sampling or amniocentesis).\(^14\)

**Differential Diagnosis**

The majority of childhood and adult onset inherited muscular disorders involve defects in the dystrophin axis (Figure 2). The axis comprises an actin–dystrophin–dystroglycan–sarcoglycan–laminin complex that connects
the sarcolemma and extracellular basal lamina and provides the mechanical stabilization of the sarcolemma during contraction and relaxation of muscle fibers. Common differential diagnosis for DMD include BMD, limb girdle muscular dystrophies (subtypes 2D, 2E, 2C, 2F, 1C and 2B), Emery-Dreifuss disease, congenital muscular dystrophies with and without brain involvement, congenital myopathies, motor neuron disease (spinal muscular atrophy, type III), dermatomyositis, and acid maltase deficiency (Table 1). Most neuromuscular diseases occurring at similar ages as DMD do not have the striking increase in CK levels. In BMD, CK levels are generally lower but at times may approach those of DMD. CK levels may also be significantly elevated in the autosomal recessive sarcoglyconopathies. Therefore, patients presenting with DMD but having normal dystrophin levels should be evaluated for sarcoglycans on the muscle biopsy. Pediatricians should also consider DMD in children with persistently elevated liver enzymes (aspartate aminotransferase/alanine aminotransferase) with negative workup for liver disease. Dystrophinopathies should be considered in children with unexplained dilated cardiomyopathy. In summary, diagnosis of muscular dystrophy can be made by taking a complete history and pedigree, determining CK levels, and carrying out a thorough neuromuscular exam.

**Treatment of DMD:**

**Role of Glucocorticoids**

Glucocorticoids are the first line therapy in the treatment of DMD. Steroids decrease inflammation, prevent fibrosis, improve muscle regeneration, improve mitochondrial function, decrease oxidative radicals, and stop abnormal signaling of pathways and apoptosis. The 2 most commonly used corticosteroids are prednisone and deflazocort. Oral prednisone 0.75 mg/kg/d (max 80 mg/d) improved muscle strength and function for 6 months to 2 years as shown in Cochrane meta-analysis. Daily scheduling is more effective than alternate-day or intermittent dosing. In those with intolerable side effects, the glucocorticoid dose should be decreased by 25% each month. The minimum effective dose is 0.3 mg/kg/d for prednisone. Deflazocort 0.9 mg/kg/d is another alternative with fewer side effects (less weight gain and behavior problems) but has limited availability. Age of initiation for corticosteroids is debatable. Many experts advocate beginning between 2 and 5 years, when gait difficulty develops. Bone density measurement and up-to-date immunization is a prerequisite for steroid initiation. Children on corticosteroids need calcium and vitamin D supplementation. Vertebral fractures are a well-known complication associated with steroid use and should be aggressively treated with bisphosphonate therapy. Glucocorticoids should be continued even in nonambulatory patients to prevent scoliosis and heart and lung failure. Parents should be informed about the side effects and limitations of steroid therapy and made aware that this form of therapy is not curative.

**Novel Therapies for DMD**

Emerging treatment options for DMD include gene repair or replacement. These therapies include the use of recombinant adeno-associated viral vectors (rAAVs) for dystrophin gene delivery. Studies in dystrophin double-knock-out mice have shown that rAAV/microdystrophin can be used to deliver dystrophin genes in adult dystrophic mice. It is safe and effective for up to 2 years with improvement in phenotype and 5-fold extension in life span in these mice. Encouraging early data of rAAV/microdystrophin delivery in dog models has been reported. Another treatment modality is causing exon skipping (avoiding deletions that disrupt the codon reading frame) with antisense oligonucleotides. This approach has shown promising results in both mice and dog models of DMD and is currently under investigation in humans. A recent Phase 2b trial with overreading of premature stop codons in dystrophin transcription did not achieve clinical significance (PTC Therapeutics). Other treatment strategies include upregulation of compensatory proteins like utrophin, α-dystrobrevin, and α7 integrin. Blocking the downstream effects of muscle degeneration by the use of creatine, CoQ10, MYO-029, IGF (insulin-like growth factor), glutamine, arginine-like drugs, TNF (tumor necrosis factor)-α antagonists, and antifibrotics have been tried without benefit.

**Comorbid Conditions and Their Long-Term Management**

DMD is a multisystem disease. Pediatricians caring for these children need to coordinate with specialists in the field of neurology, cardiology, pulmonology, orthopedics, physical medicine, and rehabilitation. At each pediatric office visit, weight, height, and blood pressure (BP) should be checked and plotted on age- and sex-appropriate anthropometric and BP percentile charts. Intellectual impairment with average intelligence quotient < -1 standard deviation below the mean is common. Verbal ability is more affected than performance skills. A team approach with parents, school teachers, child psychologists, and speech and occupational therapists can
Table 1. Differential Diagnoses of Childhood-Onset Inherited Neuromuscular Disorders

<table>
<thead>
<tr>
<th>Dystrophin Axis Level Affected</th>
<th>Name of Disorder</th>
<th>Gene Location/Pattern of Inheritance</th>
<th>Clinical Features</th>
<th>CK Levels/Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystrophinopathies</td>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>Xp21/XR</td>
<td>Onset 2 to 5 years, calf hypertrophy, cognitive dysfunction, wheelchair bound by 10 to 20 years; cardiorespiratory failure with death in second to third decade</td>
<td>CK level markedly elevated (10-20×), absent dystrophin in muscle on immunostaining</td>
</tr>
<tr>
<td></td>
<td>Becker muscular dystrophy (BMD)</td>
<td>Xp21/XR</td>
<td>Variable age of onset, benign course, wheelchair bound by end of second decade</td>
<td>CK moderately elevated (5×), reduced dystrophin on muscle biopsy immunostaining</td>
</tr>
<tr>
<td>Sarcoglycanopathies</td>
<td>Limb girdle muscular dystrophy</td>
<td>Autosomal recessive: 2C—13q12, 2D—17q21, 2E—4q12, 2F—5q33</td>
<td>Weakness first in hip and proximal leg muscles, progressing onto shoulder and proximal arm weakness. No cognitive impairment, rare cardiac disease</td>
<td>Very high CK (&gt;10× normal), absent sarcoglycan on staining of muscle biopsy, degeneration and regeneration of muscle fibers, increased endomysial connective tissue</td>
</tr>
<tr>
<td></td>
<td>Caveolin LGMD1C</td>
<td>Autosomal dominant, mutations in caveolin-3</td>
<td>Paravertebral rigidity; tendon and joint contractures, including neck; conduction defects and bradycardia; humeroperoneal weakness</td>
<td>Absent caveolin-3 on Western blot, muscle biopsy degenerating and regenerating fibers</td>
</tr>
<tr>
<td></td>
<td>Laminin Emery-Dreifuss disease</td>
<td>Emerin xq28, x-linked: laminin A/C 1q21.2, autosomal dominant or recessive</td>
<td>Loss of emerin or laminin staining on muscle biopsy, mildly elevated CK, EKG-junctional escape rhythm, absent P waves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extracellular matrix defect: congenital muscular dystrophies (CMDs) without brain involvement</td>
<td>Merosin-positive CMD</td>
<td>Moderate severity, neonatal onset, hypotonia, weakness, arthrogryposis, 90% ambulate by 4 years</td>
<td>CK level modestly elevated, immunostaining for dystrophin helps differentiate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Merosin-negative CMD</td>
<td>Severe weakness, hypotonia, may have arthrogryposis, respiratory failure common</td>
<td>MRI: extensive high-signal-intensity white matter</td>
</tr>
<tr>
<td></td>
<td>Dystroglyconopathies: CMD with brain involvement</td>
<td>Fukuyama-type CMD</td>
<td>Moderate severity (progressive) polymicrogyria, lissencephaly, neuronal heterotopia, seizures</td>
<td>CK levels, EMG, and muscle biopsy finding similar to CMD without brain involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Walker-Warburg CMD</td>
<td>Moderate severity polymicrogyria, lissencephaly, neuronal heterotopia, seizures</td>
<td>CK levels, EMG, and muscle biopsy finding similar to CMD without brain involvement</td>
</tr>
</tbody>
</table>

(continued)
Table 1. (continued)

<table>
<thead>
<tr>
<th>Dystrophin Axis Level Affected</th>
<th>Name of Disorder</th>
<th>Gene Location/Pattern of Inheritance</th>
<th>Clinical Features</th>
<th>CK Levels/Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle–eye–brain disease</td>
<td>Links to 1p34-p32</td>
<td>Developmental delay, neuronal heterotopia, hypomyelination, optic nerve hypoplasia</td>
<td>Ocular dysplasia, pyramidal tract dysplasia</td>
<td></td>
</tr>
<tr>
<td>Congenital myopathy</td>
<td>X-linked,Xq28,AD 11q22</td>
<td>Potos, joint contractures, micogynathia</td>
<td>Centrally placed large nuclei, immunochemical increased signal of myofibers against desmin</td>
<td></td>
</tr>
<tr>
<td>Myotubular myopathy</td>
<td>NEB,ACTA1: autosomal dominant or recessive</td>
<td>Muscle wasting, rarely cardiomyopathy</td>
<td>Thread-like inclusions on Gomori trichrome staining</td>
<td></td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>SMN1 mutation, phenotype depends on number of SMN2 genes</td>
<td>Varies based on severity of disease, ranges from death at 1 month from respiratory weakness to living &gt;18 years</td>
<td>Grouped muscle fiber atrophy, mainly type I fibers</td>
<td></td>
</tr>
<tr>
<td>Spinal muscular atrophy (SMA)</td>
<td>SMN1 mutation, phenotype depends on number of SMN2 genes</td>
<td>Proximal muscle weakness, heliotrope rash on upper eyelids, Gottron's papules</td>
<td>Vasculitis on biopsy, perifascicular, CK elevated</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>AR (chromosome 17)</td>
<td>Proximal muscle weakness, childhood onset &lt;5 years with calf hypertrophy in some cases</td>
<td>CK not elevated, EMG is characteristic</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: AR = autosomal recessive.

address this problem. To monitor decline in ejection fraction and the onset of dilated cardiomyopathy, a baseline echocardiogram should be performed at diagnosis or by age 6; it should be repeated every 2 years up to the age of 10 and annually thereafter.²⁸ ACE (angiotensin-converting enzyme) inhibitors are the first line therapy in DMD patients with cardiac failure to aid in cardiac remodeling. β-Blockers and diuretics are also used. Pulmonary involvement from respiratory muscle weakness and chest wall deformity (kyphoscoliosis) needs close monitoring.²⁹ Annual forced vital capacity (FVC) measurement at an age when the child can cooperate is essential. During office visits, pulse oximetry and peak flow should be documented. In the late nonambulatory stage, end-tidal CO₂ can be measured with a capnograph. Pulmonary insufficiency (FVC < 30% predicted, SpO₂ < 95%, end-tidal CO₂ > 45 mm Hg) warrants volume recruitment and deep lung inflation (FVC < 40% predicted) with noninvasive ventilation, including CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure). This may begin with nighttime ventilation, with full-time ventilation if hypoventilation persists. Tracheostomy is required if noninvasive ventilation cannot be done successfully or 3 extubation failures are recorded. A cough assist device may be useful to prevent respiratory infections, which should be treated aggressively. Orthopedic evaluation of the spine and X rays every 6 months between 10 and 16 years are advised. Although scoliosis incidence has decreased with the use of glucocorticoids, spine stabilization surgery may be useful for curvature as little as 15° to 20° to prolong ambulation. A physical medicine and rehabilitation specialist must be involved early in care to emphasize exercise and contracture prevention. Stretching and positioning exercises at the hip, knee, and ankle should be performed daily at home or at school. Aquatic therapy may also be helpful. Use of night ankle bracing has been shown to prevent Achilles contractures. Children on oral steroids also need screening for mood disorder and reflux disease. Diet and swallowing evaluation is
helpful for those with rapid weight gain or weight loss from swallowing difficulty. Gastrointestinal hypo motility secondary to smooth muscle involvement can be seen as acute gastric distension, vomiting, abdominal pain, and distension. The current management approach has dramatically improved life expectancy, and patients may now survive into their late 20s and 30s.30

Summary
DMD is a life-limiting disorder. Pediatricians can play a vital role in screening, diagnosis, and management of the affected children. Observing young children walk and squat during well-child examination, CK level testing in suspicious cases, and referral to muscular dystrophy clinics, if available, can help decrease the delay in diagnosis of DMD. Pediatricians can play an important role in coordinating treatment and follow-up of affected patients with a multidisciplinary team. Pediatricians can also be a great resource in encouraging genetic testing and counseling, prenatal diagnosis, and newborn screening for affected families.

Author's Note
SV conceived the idea and wrote the manuscript; YA and JC reviewed the article and would act as guarantors.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The author(s) received no financial support for the research and/or authorship of this article.

References


