Duchenne Muscular Dystrophy
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Duchenne Muscular Dystrophy

W. Douglas Biggar, MD*

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Dr Biggar did not disclose any financial relationships relevant to this article.

Objectives
After completing this article, readers should be able to:

1. Describe the pathogenesis of Duchenne muscular dystrophy (DMD).
2. Describe the natural history and late complications of DMD.
3. List the laboratory investigations available to diagnose muscle disorders.
4. Discuss the management for DMD.

Case History
MD was born following a normal pregnancy and delivery. His parents were nonconsanguineous, and the family history was unremarkable. He had a 6-year-old brother who was well. MD walked when he was 18 months old, 6 months later than his brother. He was a toe-walker and had large calves. He never ran as well as his brother, and he could not hop on one foot. By 4 years of age, he had difficulty climbing stairs at home and the ladder at the neighborhood playground. His pelvic girdle muscles were weak, he walked with a rocking, side-to-side, waddling gait (Trendelenburg), and he developed lumbar lordosis. He fell more frequently for no apparent reason. His parents became concerned and sought medical advice.

Laboratory testing revealed a serum creatine kinase value 50 times greater than normal. On genetic testing, Duchenne muscular dystrophy (DMD) was diagnosed. His weakness progressed. To get up after falling, he would have to use his hands to climb up his legs to stand.

In the first grade, his academic performance was judged to be delayed. His teachers noticed that his concentration was poor; he had difficulty staying on task. He scored higher on his verbal intelligence quotient than on his performance intelligence quotient. He also was teased by other children at recess. His parents elected to have him repeat the first grade. He required an educational assistant for classroom activities. He also displayed some obsessive-compulsive behaviors.

When he was 10 years old, walking became more difficult, and he required a wheelchair for ambulation. His weight gain became excessive as he lost ambulation. He could, however, dress and feed himself. He developed a scoliosis of 35 degrees and required surgery to stabilize his spine when he was 14 years old. By age 16 years, he could not feed, toilet, or dress himself. Not surprisingly, he was clinically depressed.

The boy's sleep pattern became disturbed, and at age 17 years, he developed symptoms of nighttime hypoventilation. These symptoms included a restless sleep pattern that required him to be turned in bed every hour, gave him morning headaches, reduced his school performance, and caused him to fall asleep in school during the afternoon. His cough became weaker, and he had difficulty clearing respiratory secretions. He required three hospitalizations for pneumonia. At 19 years of age, he developed a severe pneumonia, declined a tracheostomy, and died. At autopsy, a severe dilation of the left ventricle of his heart was discovered.

Pathogenesis
DMD is caused by a mutation of the X-linked gene that encodes for the protein dystrophin. Dystrophin is a large, 427-kDa protein that bridges the inner surface of the muscle sarcolemma to the protein F-actin. The gene, also very large, is located on the short arm of the X chromosome. Most genetic mutations involve deletions; less often, point mutations and duplications are seen. Without dystrophin, the glycoprotein structure of the muscle sarcolemma is less stable. Membrane instability leads to muscle damage, with the initiation of an inflammatory cascade contributing further to muscle damage, necrosis, and

*Professor of Paediatrics, University of Toronto, Bloorview Macmillan Children's Centre, Toronto, Ontario, Canada
fibrosis. Proximal muscles are involved first. Skeletal and cardiac muscle are affected primarily.

**Clinical Features**

The term muscular dystrophy refers to those inherited disorders of skeletal muscle that have no central or peripheral nervous system involvement. Classification of the muscular dystrophies has been difficult. Most, but not all, are associated with progressive muscle weakness, some of the mild dystrophies may be relatively static, and children who have congenital muscular dystrophy (CMD) may show periods of improvement.

The CMDs are a subset of the muscular dystrophies that usually are diagnosed when a child presents with early-onset muscle weakness, delayed development, and contractures. Currently, there are two classifications of CMD: syndromic when other organs (brain, eye) are involved and nonsyndromic when only muscles are involved. The other large group of muscular dystrophies includes the limb girdle muscular dystrophies.

A muscle biopsy may not always be diagnostic. However, with the newer techniques for genetic analysis, including polymerase chain reaction testing, computer-assisted laser densitometry, and immunohistochemical probes, understanding of the muscular dystrophies is growing. Current classifications probably will change over time as new genetic and clinical information is catalogued. For the present, however, the primary criteria for disease classification include phenotype, muscle pathology, and genetic analysis. The most common type of muscular dystrophy is DMD.

DMD is an X-linked recessive disorder affecting primarily skeletal and cardiac muscle. The incidence is 1 in 3,300 liveborn males. Boys who have DMD exhibit a progressive and predictable loss of muscle function. The muscles are affected at birth, but clinical symptoms of proximal muscle weakness usually manifest between 3 and 5 years of age. The boys may walk later than their siblings, but most are walking by 18 months of age. Toe-walking is common. Running, jumping, and hopping are awkward and difficult, if not impossible. Muscle weakness often is apparent when the boys are observed playing with their siblings or other children.

As the pelvic muscles weaken further, affected boys develop a lumbar lordosis and a Trendelenburg gait. They fall more often and have difficulty rising. To raise themselves up, they get into a knee-elbow position, extend their elbows and knees, bring their hands and feet as close together as possible, and place one hand at a time on their knees. They then place their hands on their thighs and move proximally in alternating steps (“climbing up their legs”) to become erect. This is known as the Gower maneuver (Figure).

Boys who have DMD are at increased risk for certain cognitive concerns. Dystrophin is present in the brain, but its function is unknown. Their motor and language development may be delayed. Many affected boys tend to be creative and artistic. Parents may report that their son is easily frustrated, easily distracted, has a poor attention span, and is immature. These boys may be afraid of new situations and have some features of obsessive-compulsive behavior. Unlike their muscle weakness, which is progressive, their cognitive skills do not deteriorate over time. They frequently require extra help for academic work.

Muscle weakness continues, with the legs affected earlier than the arms. The boys begin to use wheelchairs full time between 8 and 12 years of age, most by 10 years. Approximately 3 to 4 years after losing ambulation, 90%
of the boys develop a spinal curvature of greater than 20 degrees. Surgery is required to stabilize the spine. Joint contractures develop initially in the lower extremities, with the feet assuming the typical equinovarus position. Upper extremity function declines in the mid-teens, and the boys lose the ability to feed and care for themselves. This impairment frequently occurs after spinal surgery. Pulmonary function begins to deteriorate between 9 and 11 years of age. The forced vital capacity declines by 5% to 10% per year, their cough becomes weaker, and the ability to clear respiratory tract secretions is impaired. Pneumonia is common. Nocturnal assisted ventilation frequently is required in their mid-to-late teens. Improved pulmonary care and aggressive treatment of pulmonary infections have improved life expectancy.

Electrocardiographic and echocardiographic changes are present in more than 50% of boys who have DMD. They usually are free of cardiac symptoms (fatigue and reduced exercise tolerance) because they use a wheelchair full time and do not exercise vigorously. Some boys experience tachycardia and are aware of their hearts beating. They usually die in their late-teens to mid-twenties—75% from respiratory causes and approximately 25% from severe left ventricular failure.

Laboratory Tests
Laboratory investigations of muscle are performed primarily via four methods: biochemical analysis, electromyography, DNA analysis, and histologic examination. Several muscle enzymes are released from the sarcoplasm when muscle fibers are damaged. Creatine kinase (CK) is measured most commonly. Isoenzymes of CK are found in different tissues, including the brain, but not in hepatocytes. The normal serum concentration of CK varies with age, sex, and physical activity. After significant and prolonged physical activity, the serum concentration of CK may be elevated 5 to 10 times that of normal. Other causes of an elevated serum CK value include trauma, inflammatory muscle disorders from a variety of causes (bacterial, viral, and immunologic), idiopathic myositis, rheumatoid arthritis, spinal muscular atrophy, and muscular dystrophies. The most spectacular elevation of serum CK (50 to 100 times normal) occurs in DMD. It is elevated at birth before there is clinical evidence of muscle weakness.

Other muscle enzymes whose concentrations are elevated in the blood include aspartate aminotransferase, alanine aminotransferase, and lactic dehydrogenase, which also are found in hepatocytes. When concentrations of these enzymes are elevated in serum, they may be misinterpreted as having a hepatic origin and indicating abnormal liver function. An elevated gamma-glutamyl transferase value helps to differentiate a hepatic source from a muscle source because it is not found in muscle. CK is the most useful marker of muscle disease.

Electromyography is the recording of muscle electrical activity by an electrode, both surface and needle. With needle electrodes, electrical activity is measured on insertion, at rest, and during muscle contraction. At rest, healthy muscle usually is electrically silent. Spontaneous activity, as would be seen with muscle fasciculations and fibrillations, usually reflects neurogenic causes or myopathic disorders such as congenital myotonia. Electromyographic changes in DMD are nonspecific and of little use in establishing the diagnosis.

The molecular techniques for complementing the diagnosis of muscular disorders have advanced significantly in the past few years. Approximately two thirds of boys who have DMD have gene deletions; an additional 5% to 10% have a duplication within the DMD gene. If a mutation is not detected by direct analysis, a linkage analysis might be required to assess the carrier risk. These advances have reduced the number of boys requiring a muscle biopsy for diagnosis and have greatly facilitated carrier detection for genetic counseling. The remaining 10% to 20% of boys require a muscle biopsy to confirm the clinical and biochemical suspicion of DMD. Mothers of isolated cases of DMD/Becker muscular dystrophy (BMD) where there is no family history have a recurrence risk of approximately 10% due to a germline mosaicism. BMD is a milder allelic form of DMD.

A muscle biopsy is a very useful diagnostic tool but less so if the CK concentration and electromyography results are normal. The biopsy can be either a needle biopsy or an open biopsy. Histopathology and histochemistry are the two techniques used most commonly. Electron microscopy is most useful in diagnosing mitochondrial disorders of muscle, and findings may be normal early in
the course of disease or when the muscle changes are not present in all muscles. Sampling errors also can occur late in the course of disease when the typical histopathologic changes no longer are seen.

The histologic changes in DMD depend somewhat on the muscle selected and the age of the boy. When the boys are very young, the histologic changes are minimal and include some focal areas of inflammation and muscle degeneration or regeneration. With time, muscle fibers are replaced with fibrous and fatty tissue along with inflammatory cells. Dystrophin, as assessed by immunohistochemical staining, is absent or nearly absent.

**Management**

**Rehabilitation**

Management must be multidisciplinary to accommodate the patient’s complex and changing needs over time. Initially, around the time of diagnosis, genetic counseling and psychosocial support for the boy and family members are important. Referral usually is made to a pediatric rehabilitation program for ongoing management. Early rehabilitation goals focus on promoting mobility and maintaining good ankle positioning through physical therapy and orthotic devices. Moderate activities such as swimming and biking are encouraged. Excessively strenuous activities and fatigue should be avoided.

Obesity is common and can have a major impact on such areas as quality of life, life expectancy, and burden of care. Some boys who are thin and weigh less than the 10th percentile may require extra calories, but excessive weight gain often becomes apparent for many boys between 7 and 10 years of age. This frequently is the time when physical activity is declining and replaced with boredom, increased television viewing, and playing of electronic games. Inappropriate food intake also is common. Nutritional management is most important and frequently requires alterations in the eating habits of all family members.

Some centers advocate the use of surgical tendon lengthening to prolong ambulation. Night splints for the feet and ankles may provide an effective passive stretch to maintain a good range of motion at the ankles and reduce the tendency to toe-walk. Some centers advocate the use of long leg braces or calipers to prolong ambulation. However, some feel that these are heavy and cumbersome and do not really facilitate a functional gait. Some boys say that they are afraid of falling when they are standing in the long leg braces.

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**Corticosteroids**

Despite recent advances in our understanding of the molecular and genetic aspects of DMD, very few treatments exist. Corticosteroids delay the very predictable and relentless progression of muscle weakness; their mechanism of action is unknown. Two corticosteroids, prednisone and deflazacort, seem to be equally effective and the most effective when administered daily. Prednisone can delay the progression of muscle weakness, but it often is associated with significant adverse effects. Weight gain can be particularly problematic.

Deflazacort is an oxazolone derivative of prednisone. It can preserve muscle function as well as prednisone but often without the tendency for excessive weight gain encountered in most boys treated with daily prednisone. We have used a regime of daily deflazacort for more than a decade. The long-term benefits are significant and include improved ambulation, preservation of pulmonary and cardiac function, a significant reduction in the incidence of scoliosis, and maintenance of arm function required for feeding and self-care. There may be adverse effects, but they usually are acceptable. The boys’ appetites may increase, requiring strict dietary control. Their height may be reduced, but that could be considered a benefit because less work is required of the short person for activities such as walking and climbing stairs. Fifty percent of the boys develop asymptomatic posterior subcapsular cataracts that do not impair their vision and do not require treatment.

Boys who have DMD develop osteopenia of immobility and have an increased risk for developing fractures. In our experience, many boys who have DMD and have been treated with deflazacort have reduced bone mineral density but not a significantly greater incidence of long bone fractures. We recommend daily vitamin D and calcium supplementation. When fractures do occur, the period of immobilization should be as short as possible. When possible, this can be achieved by surgical stabilization rather than casting and 4 to 6 weeks of immobilization. We have not seen hypertension, glucosuria, or an increased susceptibility to infection or gastric ulcers in affected boys. We normally continue the steroids after the boys stop ambulating.

Longer-term studies are needed to determine the duration of deflazacort benefits. Our findings to date indicate that deflazacort has had a significant impact on the natural history of this progressive and fatal muscle disease, improved the quality of life for the boys and their families, and reduced the burden of care in the second decade.
School Issues
Many boys who have DMD have significant learning issues. Their schools must accommodate both physical and learning needs. The family, the school, and the rehabilitation team need to communicate with each other and work together. Some suggestions for the school environment include seating the child near the door and allowing “free” bathroom privileges. The desk may need to accommodate a wheelchair. Learning to read should not be pushed if the child is not ready. He may have difficulty understanding complex, multi-stepped tasks, and his frustration may interfere with learning. Computer skills should be encouraged early. Enjoyable activities should be found for the child and emphasized. These children may need assistance with classroom and bathroom activities. The teacher should be encouraged to learn about DMD and approaches that might facilitate and strengthen school experiences.

As independent ambulation becomes more compromised, rehabilitation issues shift to mobility equipment and accessibility for the home and school. The rehabilitation team now expands to include expertise from cardiology, pulmonology, orthopedics, gastroenterology, and nutrition colleagues. Transportation needs to be accommodated. The occupational therapist assumes a more active role for many issues, including accessibility, activities of daily living, communication and writing aids, and feeding and swallowing. Spinal alignment requires close monitoring, along with a medical focus on pulmonary and cardiac function.

The entire family needs support as major decisions are being contemplated, major costs are incurred, and major changes are occurring. Psychosocial support for family members is very important. Support groups and reliable muscular dystrophy-oriented Web sites can provide information about management, research, and education. Two such sites are www.parentprojectmd.org and www.mdausa.org.

Future Treatments
Although only corticosteroids offer any therapeutic benefit today, the future holds real promise. Much can be learned from dystrophin-deficient animal models, including the mouse, dog, and cat. With specific exon deletions being identified in the DMD gene, opportunities for gene repair or gene “patching” are being pursued. For boys whose genetic defect is not a deletion but a stop codon, attempts to “jump this point mutation” and create some read-through of the dystrophin gene are being pursued with compounds that include the aminoglycoside gentamicin and PTC 124.

Another therapeutic approach rests with gene transfer rather than gene repair. Genetic material can be transferred several ways. These include giving the isolated DNA, usually packaged in some type of transport “vehicle,” such as an adenovirus or adeno-associated virus, to the host. Other sources of genetic material include myoblasts and stem cells. Although important progress is being made in gene transfer, clinical trials are still in the future.

Finally, pharmaceuticals (in addition to corticosteroids) directed at the various facets of the pathologic cascade (eg, inflammation, fibrosis, membrane damage) leading to muscle death may offer some relief or attenuation of this progressive and fatal disease of skeletal and cardiac muscle.

Suggested Reading
## PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. For children who have DMD, the absence of dystrophin primarily affects normal physiology within the:
   - A. Anterior horn cell.
   - B. Muscle cell membrane.
   - C. Muscle cell mitochondria.
   - D. Muscle-nerve junction.
   - E. Peripheral nerve.

2. An 11-year-old boy who has DMD is now using an electric wheelchair as his primary method of mobility. Over the next 5 years, the likelihood of him developing a significant spinal curvature is closest to:
   - A. 10%.
   - B. 30%.
   - C. 50%.
   - D. 70%.
   - E. 90%.

3. Many laboratory approaches have been described to diagnose DMD. The most systematic order for this assessment is:
   - A. Molecular testing, muscle biopsy, muscle enzyme.
   - B. Molecular testing, muscle enzyme, muscle biopsy.
   - C. Muscle biopsy, muscle enzyme, molecular testing.
   - D. Muscle enzyme, molecular testing, muscle biopsy.
   - E. Muscle enzyme, muscle biopsy, molecular testing.

4. Corticosteroids represent one of the few treatments for DMD, although their mechanism of action is unknown. Adverse effects of this intervention include the risk of increased:
   - A. Intraocular pressure.
   - B. Linear growth.
   - C. Osteopenia.
   - D. Scoliosis.
   - E. Susceptibility to infection.

5. For mothers of children who have DMD in whom molecular testing results are negative and there is no family history of similar disorders, the recurrence risk is approximately:
   - A. 0%.
   - B. 10%.
   - C. 25%.
   - D. 50%.
   - E. 100%.
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