Duchenne Muscular Dystrophy

NORD gratefully acknowledges Gyula Acsadi, MD, PhD, Professor of Pediatrics, University of Connecticut, School of Medicine, Chief of Neurology Division, Connecticut Children's Medical Center, for assistance in the preparation of this report.

Synonyms of Duchenne Muscular Dystrophy

- DMD
- dystrophinopathy
- pseudohypertrophic myopathy

General Discussion

Summary Duchenne muscular dystrophy (DMD) is a rare muscle disorder but it is one of the most frequent genetic conditions affecting approximately 1 in 3,500 male births worldwide. It is usually recognized between three and six years of age. DMD is characterized by weakness and wasting (atrophy) of the muscles of the pelvic area followed by the involvement of the shoulder muscles. As the disease progresses, muscle weakness and atrophy spread to affect the trunk and forearms and gradually progress to involve additional muscles of the body. In addition, the calves appear enlarged in most patients. The disease is progressive and most affected individuals require a wheelchair by the teenage years. Serious life-threatening complications may ultimately develop including disease of the heart muscle (cardiomyopathy) and breathing (respiratory) difficulties. DMD is caused by changes (mutations) of the DMD gene on the X chromosome. The gene regulates the production of a protein called dystrophin that is found in association with the inner side of the membrane of skeletal and cardiac muscle cells. Dystrophin is thought to play an important role in maintaining the membrane (sarcolemma) of muscle cells. **Introduction** Muscular dystrophies are characterized by specific abnormalities (e.g. variation of muscle fiber size, muscle fiber necrosis, scar tissue formation and inflammation) in muscle biopsy from the patients. Approximately 30 different genetic conditions make up the muscular dystrophies. DMD is classified as a dystrophinopathy. The dystrophinopathies are a spectrum of muscle diseases, each caused by alterations in the dystrophin gene. The most severe end of the spectrum is known as Duchenne muscular dystrophy lacking completely dystrophin protein. Decreased or truncated dystrophin protein is associated with less severe form is Becker muscular dystrophy. The clinical hallmarks of DMD include weakness and wasting of various voluntary muscles of the body. In most advanced stages of the disease, the heart and gut muscles will be affected.

Signs & Symptoms

DMD usually becomes apparent early during childhood. Affected children develop weakness and wasting (atrophy) of the muscles closest to the trunk (proximal muscles) such as those of the upper legs and pelvic area and upper arms and shoulder area. However, a few other muscles appear disproportionally bulky. As the disease progresses, muscle weakness and atrophy spread to affect the lower legs, forearms, neck and trunk. The rate of progression is quite similar from person to person but individual variation may happen.

In children with DMD, initial findings may include delays in reaching developmental milestones such as sitting or standing without assistance; toe walking; an unusual, waddling manner of walking (gait); difficulty climbing stairs or rising from a sitting position (Gower's sign); and repeated falling. Toddlers and young children may seem awkward and clumsy and may exhibit abnormal enlargement of the calves due to scarring of muscles (pseudohypertrophy). Parents may be falsely encouraged by an apparent improvement between the ages of 3 and 5, but this may be due to natural growth and development. As the disease progresses, additional abnormalities may develop such as progressive curvature of the spine (scoliosis or lordosis), wasting of thigh and pectoral muscles, and abnormal fixation of certain joints (contractures). A contracture occurs when thickening and shortening of tissue such as muscle fibers causes deformity and restricts movement of affected areas, especially the joints. Without physical therapy treatment, leg braces may be needed by age 8-9 to assist affected individuals to walk. By approximately ages 10 to 12, most affected individuals require a wheelchair.

Children with DMD have reduced bone density and an increased risk of developing fractures of certain bones, such as hips and spine. Many affected individuals will display mild to moderate degrees of non-progressive intellectual impairment and learning disabilities.

By the late teens, DMD may also be characterized by additional potentially life-threatening complications including weakness and deterioration of the heart muscle (cardiomyopathy). Cardiomyopathy can result in impairment in the ability of the heart to pump blood, irregular heartbeats (arrhythmias), and heart failure. Another serious complication associated with DMD is weakness and deterioration of muscles in the rib cage. This can result in an increased susceptibility to respiratory infections (e.g., pneumonia), difficulty coughing, and, ultimately, respiratory failure.

Involvement of muscles within the gastrointestinal tract may result in dysmotility, a condition in which the passage of food through the digestive tract usually because of slow and uncoordinated movements of the muscles of the digestive tract. Gastrointestinal dysmotility may result in constipation and diarrhea.

One third of patients with DMD may have various degree of cognitive impairment including learning disability, attention deficit and autistic spectrum disorder.

Causes

DMD is inherited as an X-linked disease. X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and manifest mostly in males. Females that have a defective gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms because females have two X chromosomes and only one carries the defective gene. Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a defective gene he will develop the disease.

Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease and a 25% chance to have an unaffected son.

If a male with an X-linked disorder is able to reproduce, he will pass the defective gene to all of his daughters who will be carriers. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring.

Some females who inherit a single copy of the disease gene for DMD (gene carriers or heterozygotes) may exhibit some of the symptoms associated with the disease such as weakness of certain muscles, especially those of the arms, legs, and back Carrier females who develop symptoms of DMD are also at risk for developing heart abnormalities, which may present as exercise intolerance or shortness of breath. If left untreated, heart abnormalities can cause life-threatening complications in such affected females.

DMD is caused by mutations of the DMD gene located on the short arm (p) of the X chromosome (Xp21.2). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”. Chromosomes are further sub-divided into many bands that are numbered. For example, “chromosome Xp21.2” refers to band 21.2 on the short arm of the X chromosome. The numbered bands specify the location of the thousands of genes that are present on each chromosome.

The *DMD* gene regulates (encodes for) the production of dystrophin, a protein that appears to play an essential role in maintaining the integrity of cell membrane in skeletal (voluntary) and cardiac muscle cells. Dystrophin is found attached to the inner side of the membrane that surrounds muscle fibers. Mutation of the *DMD* gene will result in absence of the dystrophin protein, leading to degeneration of muscle fibers. The body can replace (regenerate) some muscle fibers, but over time more and more muscle fiber is lost. Such degeneration leads to the symptoms and findings associated with DMD. In Becker muscular dystrophy, a related disorder, dystrophin is present, but it is truncated or only present in insufficient levels to properly perform its functions.

Although most boys with DMD inherit the abnormal gene from their mothers, some may develop the diseases as the result of a spontaneous mutation of the dystrophin gene that occurs randomly for unknown reasons (de novo or sporadic cases).

Affected Populations

DMD is the most common childhood onset form of muscular dystrophy and affects males almost exclusively. The prevalence is estimated to be 1 in every 3,500 live male births. Age of onset is usually between 3 and 5 years of age. The muscular dystrophies as a whole are estimated to affect 250,000 individuals in the United States.

Related Disorders

Symptoms of the following disorders can be similar to those of DMD. Comparisons may be useful for a differential diagnosis.

Becker muscular dystrophy is in the category of inherited muscle wasting diseases caused by gene abnormalities (mutations) that result in deficient or abnormal production of the dystrophin

protein (dystrophinopathies). The abnormal gene is the same as for DMD and is located on the X chromosome. Becker muscular dystrophy also follows X-linked inheritance so it mostly affects males, but some female carriers are affected. Becker muscular dystrophy usually begins in the teens or early twenties, but can begin as late as the sixties and symptoms vary greatly between affected individuals. Muscle weakness and deterioration progress slowly but usually results in the need for a wheelchair. Muscles of the heart deteriorate (cardiomyopathy) in some affected individuals more seriously than the skeletal muscles of the body, and this process can become life threatening potentially causing heart failure. Learning disabilities involving visual abilities may be present but rarely. In Becker muscular dystrophy, dystrophin levels are reduced where in DMD they are absent or nearly absent. Consequently, the symptoms of these two disorders are similar, but most cases of Becker muscular dystrophy are less severe. (For more information on this disorder, choose "Becker" as your search term in the Rare Disease Database.)

Emery-Dreifuss muscular dystrophy (EDMD) is a rare, often slowly progressive genetic disorder affecting the muscles of the arms, legs, face, neck, spine and heart. The disorder consists of the clinical triad of weakness and degeneration (atrophy) of certain muscles, joints that are fixed in a flexed or extended position (contractures), and abnormalities affecting the heart (cardiomyopathy) in mainly adults. Major symptoms may include muscle wasting and weakness particularly in arms and lower legs (humeroperoneal regions) and contractures of the elbows, Achilles tendons, and upper back muscles. In some patients, additional abnormalities may be present. In most cases, EDMD is inherited as an X-linked or autosomal dominant trait. In extremely rare cases, autosomal recessive inheritance has been reported. Although EDMD has different modes of inheritance, the symptoms are nearly the same. (For more information on this disorder, choose "Emery Dreifuss" as your search term in the Rare Disease Database.)

Limb-girdle muscular dystrophy (LGMD) is a general term for a group of rare progressive genetic disorders that are characterized by wasting (atrophy) and weakness of the voluntary muscles of the hip and shoulder areas (limb-girdle area). Muscle weakness and atrophy are progressive and may spread to affect other muscles of the body. Approximately 15 different subtypes have been identified based upon abnormal changes (mutations) of certain genes. The age of onset, severity, and progression of symptoms of these subtypes varies greatly even among individuals in the same family. Some individuals may have a mild, slowly progressive form of the disease; other may have a rapidly progressive form that may cause severe disability. The various forms of LGMDs can now be distinguished by genetic and/or protein analysis. The various forms of LGMD may be inherited as an autosomal dominant or recessive trait. Autosomal dominant LGMD is known as *LGMD1* and has five subtypes (*LGMDA-E*). Autosomal recessive LGMD is known as *LGMD2* and has 10 subtypes (*LGMDA-J*). (For more information on this disorder, choose "limb-girdle muscular dystrophy" as your search term in the Rare Disease Database.)

Spinal muscular atrophy (SMA) that is caused by a deletion of the *SMN* gene on chromosome 5 is an inherited progressive neuromuscular disorder characterized by degeneration of groups of nerve cells (lower motor neurons) within the lowest region of the brain (lower brainstem) and certain motor neurons in the spinal cord (anterior horn cells). Motor neurons are nerve cells that transmit nerve impulses from the spinal cord or brain (central nervous system) to muscle or glandular tissue. Typical symptoms are a slowly progressive muscle weakness and muscle wasting (atrophy). Affected individuals have poor muscle tone, muscle weakness on both sides of the body without, or with minimal, involvement of the face muscles, twitching tongue and a

lack of deep tendon reflexes. SMA is divided into subtypes based on age of onset of symptoms and maximum function achieved. (For more information on this disorder, choose “spinal muscular atrophy” as your search term in the Rare Disease Database.)

Diagnosis

A diagnosis of DMD is made based upon a thorough clinical evaluation, a detailed patient history, and a variety of specialized tests including molecular genetic tests. If the genetic tests are not informative, surgical removal and microscopic examination (biopsy) of affected muscle tissue that may reveal characteristic changes to muscle fibers. Specialized blood tests (e.g. creatine kinase) that evaluate the presence and levels of certain proteins in muscle (immunohistochemistry) are also used.

Molecular genetic tests involve the examination of deoxyribonucleic acid (DNA) to identify specific a genetic mutation including deletions, duplications or single point mutations. Samples of blood or muscles cells may be tested. These techniques can also be used to diagnosis DMD before birth (prenatally).

Blood tests may reveal elevated levels of the creatine kinase (CK), an enzyme that is found in abnormally high levels when muscle is damaged. The detection of elevated CK levels (usually in the thousands or ten thousands range) can confirm that muscle is damaged or inflamed, but cannot confirm a diagnosis of DMD.

In some cases, a specialized test can be performed on muscle biopsy samples that can determine the presence and levels of specific proteins within cells. Various techniques such as immunostaining, immunofluorescence or Western blot (immunoblot) can be used. These tests involve the use of certain antibodies that react to certain proteins such as dystrophin. Tissue samples from muscle biopsies are exposed to these antibodies and the results can determine whether a specific muscle protein is present in the cells and in what quantity or what size.

Standard Therapies

Treatment

No curative treatment exists for DMD. Treatments are aimed at the specific symptoms present in each individual. Treatment options should include physical therapy and active and passive exercise to build muscle strength and prevent contractures. Surgery may be recommended in some patients to treat contractures or scoliosis. Braces may be used to prevent the development of contractures. The use of mechanical aids (e.g., canes, braces, and wheelchairs) may become necessary to aid walking (ambulation).

Corticosteroids are used as standard of care to treat individuals with DMD. These drugs slow the progression of muscle weakness in affected individuals and delay the loss of ambulation by 2-3 years. Two common corticosteroid drugs used to treat individuals with DMD are prednisone and deflazacort (which is not available in the United States).

In 2016, Exondys 51 (eteplirsen) injection was FDA approved to treat DMD and is the first drug approved for this condition. Exondys 51 is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13 percent of the population with DMD. Exondys 51 is made by Sarepta Therapeutics.

In 2017, Emflaza (deflazacort) was FDA approved to treat patients age 5 years and older with DMD. Emflaza is marketed by PTC Therapeutics.

Clinical Testing and Work-Up
Children diagnosed with DMD should be monitored regularly for potential heart involvement. In some individuals, severe respiratory distress may necessitate the use of ventilator to assist breathing.

Genetic counseling may be of benefit for affected individuals and their families. Other treatment is symptomatic and supportive.

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

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