Patient education: Overview of muscular dystrophies (Beyond the Basics)

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MUSCULAR DYSTROPHY OVERVIEW

Muscular dystrophy is an inherited disorder that causes progressive muscle weakness (myopathy) and atrophy (loss of muscle mass) due to defects in one or more genes required for normal muscle function. Some of the genes responsible for these conditions have been identified.

There are a number of different types of muscular dystrophy (table 1). The primary symptom for most types is muscle weakness, although some dystrophies also cause heart disease or reduced mental ability. The diseases are distinguished from one another by the type of symptoms and the nature of the genetic abnormality causing the disorder.

MUSCULAR DYSTROPHY GENETICS

The genetic defect that causes muscular dystrophy is passed from one or both parents to a child by a specific pattern of inheritance that varies from one type of muscular dystrophy to another. A brief explanation of how genes are inherited will assist in explaining how children develop muscular dystrophy.

In the process of reproduction, a male's sperm and female's egg each contribute one sex chromosome. Males have XY sex chromosomes while females have XX sex chromosomes; the male can contribute the X or Y chromosome, while the female must contribute one of their X chromosomes. A male infant results if the male contributes his Y chromosome while a female infant results if he contributes his X chromosome (figure 1).

- Duchenne and Becker muscular dystrophy and one type of Emery-Dreifuss muscular dystrophy (EDMD) are caused by mutations (also called "pathogenic variants") on one of the X chromosomes carried by the female parent. These muscular dystrophies affect 50 percent of male infants of mothers who carry the genetic defect; this is called X-linked recessive inheritance. Females who inherit their mother's defective X chromosome (called carrier females) are usually disease free, although mild symptoms can occur occasionally (figure 2). (See 'Female DMD carriers' below.)

- Myotonic muscular dystrophy, facioscapulohumeral muscular dystrophy (FSHD), some types of congenital muscular dystrophy (CMD), one type of EDMD, and some types of limb-girdle muscular dystrophy (LGMD) can develop if **either** of the parent's chromosomes carries the defect and is passed to the infant; this is called autosomal dominant inheritance.

- Most types of CMD, one rare type of EDMD, and some types of LGMD develop if **both** parents pass a defective chromosome to their infant; this is called autosomal recessive inheritance.

MUSCULAR DYSTROPHY MUSCLE FUNCTION

To understand muscular dystrophy, it helps to understand how the muscles work normally. In a healthy person, electrical signals travel from the brain through the spinal cord and into the nerves that lead to the muscles. From there, the signals are transmitted into the muscles, where they stimulate muscle tissue to contract. Along the way, the nerves must be in good working order, and the muscles must be able to accept the impulses and generate a response.

Problems can occur anywhere along this route. If the brain, spinal cord, or nerves are damaged or diseased, the electrical signal may not be generated or get through. If muscles are inflamed or abnormal, they may not be able to respond properly to a nerve impulse.

Diseases of muscles that cause weakness are called myopathies. With myopathy, nerve impulses usually reach the muscles without any problem, but the muscles are unable to respond in a normal way due to the disease.

Many things can cause myopathy to occur, a few of which include:

- Inflammation of the muscles
- Inherited conditions, particularly muscular dystrophies
- Problems with certain hormones that affect muscle function
- Chemical imbalances in the body
- Drugs and toxic substances
- Infections

MUSCULAR DYSTROPHY TESTS

A number of tools can be used to diagnose muscular dystrophy, including genetic testing, blood tests that identify the signs of muscle damage, electromyography (EMG), muscle biopsy, electrocardiogram (ECG), heart magnetic resonance imaging (MRI), and/or echocardiogram, which is an ultrasound of the heart. Tests are chosen based upon the type of disease that is suspected. This is particularly true of genetic tests, which must be tailored to search for specific abnormalities.

Electromyography — EMG is a test that evaluates the electrical activity of muscles both at rest and during voluntary movement. Abnormalities in this activity can indicate the presence of a muscle or nerve disease.

A small needle is inserted through the skin into a muscle in several locations (usually the arms and legs). The needle is connected to a recording device that displays the muscle's electrical activity at rest and in response to contraction. The electrical activity may also be heard as a static-like noise through a speaker.

The size and pattern of electrical activity recorded from different muscles is analyzed by the physician who supervises the EMG test to determine whether the muscles and nerves are functioning normally.

The test generally takes about 30 minutes. A patient may feel some discomfort as the needle is inserted, and the muscle may feel sore or bruised for several hours and rarely days.

EMG is very useful in determining whether there is weakness due to muscle disease. However, it does not provide a specific diagnosis; genetic testing or muscle biopsy may be more useful if muscle weakness is obvious.

Muscle biopsy — A muscle biopsy is a procedure that removes one or more small piece(s) of muscle from either an arm or leg. Muscle biopsies can sometimes provide a specific diagnosis.

However, muscle biopsies are done less frequently than previously because of the increased availability of genetic testing.

The biopsy may be done by making a small incision and removing a piece of muscle or by using a thick needle (called a punch biopsy), which removes a small cylindrical piece of muscle. The type of biopsy used will depend upon the physician's preference and need to examine the muscle directly before biopsy. A needle biopsy can be done in an office or clinic setting, usually with local anesthesia (medication is injected to numb the area).

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is caused by a defect in the DMD gene located on the X chromosome. This gene is responsible for producing a protein called dystrophin, which normally functions to protect muscle fibers. Without dystrophin, muscles are broken down by enzymes, which cause degeneration and ultimately weakness of muscles.

Affected males — DMD is primarily seen in boys and occurs in about 1 of 3500 to 5000 newborn males; it affects girls at a much lower rate. It occurs in all ethnic groups.

Female DMD carriers — Most female carriers of the abnormal dystrophin gene have few or no symptoms of their disease. Muscle weakness develops in 2.5 to 20 percent of females. Symptoms may present early in life and become progressive (worsen) in certain situations.

Women who have no symptoms but who have a family history of muscular dystrophy and want to become pregnant can consider specialized testing. This can help to determine if the woman is a carrier of the defective gene. However, testing is not always accurate in identifying female carriers. As an example, some female carriers may have the defective X chromosome only in a fraction of their eggs and not in their blood or other somatic cells; this is known as germline mosaicism. Thus, a blood-based genetic test will be negative even though the woman is a carrier of the gene mutation. Any woman with a family history of muscular dystrophy should consider genetic counseling to discuss the probability of having an affected child, even if her blood DNA carrier testing is negative.

If genetic testing confirms that the woman is a carrier, she may have the option of something called preimplantation genetic diagnosis. This involves going through in vitro fertilization (IVF) and testing an embryo for the defective gene before implanting it to try to achieve pregnancy.

Symptoms — Symptoms of DMD usually appear in children between age two and three years. Children usually need to use a wheelchair by age 12 to 13 years. These ages represent the

average for all patients with DMD; individual patients may develop symptoms earlier or later in life.

Weakness starts near the trunk and spreads to the extremities, affecting the legs before the arms. A child may have difficulty running, jumping, and walking up steps, and may use their hands to push upright from squatting or lying down (this is called Gower sign).

DMD may also cause heart problems, including enlargement of the heart tissue (dilated cardiomyopathy) and irregular heartbeat. Abnormal curvature of the spine (scoliosis) combined with muscle weakness can lead to problems with lung function. Fractures involving the arms and legs are frequent, usually caused by falling. In many cases, affected children have some degree of cognitive impairment, although some children have average or above-average intelligence.

Preventing and treating complications of DMD — Early identification of children who are affected by DMD is important to prevent complications and prolong life. Recommendations for managing and preventing problems in these children include:

- Pneumococcal vaccine (given once) to help prevent pneumonia, and annual influenza vaccine for children six months of age and older. (See "Patient education: Vaccines for infants and children age 0 to 6 years (Beyond the Basics)".)

- Screening (usually by echocardiography or cardiac magnetic resonance imaging [MRI]) and early treatment for cardiomyopathy, starting at the time of diagnosis or at around age six years. Female carriers may be screened beginning in the teens.

- Lung treatment while sleeping (nocturnal noninvasive ventilation) or respiratory assistance during periods of lung infection is recommended. Lung function testing should begin around age 9 or 10 years, before the child requires a wheelchair, and should be repeated several times per year when lung function worsens or the child requires a wheelchair.

- Bone density should be maintained to reduce the risk of fractures by ensuring that the child has a diet rich in calcium and vitamin D. Parents should monitor their child's weight to avoid excessive weight gain and obesity; a nutritionist can assist with food planning. Vitamin D levels should be checked periodically.

- Physical therapy can help to maintain muscle function and prevent joint stiffening (contractures). During the early stages of the disease, gentle exercise (for example, swimming and other exercises done in a pool) can help keep muscles active.

- Leg braces can assist with standing and walking. X-rays of the spine may be taken periodically to monitor for scoliosis once the child can no longer walk independently.

- Surgery can help correct joint contractures, especially at the ankle. Lengthening and transferring tendons can return the joint to its normal position and prolong walking with, and sometimes even without, braces.

- Scoliosis, or curvature of the spine, is a common complication of DMD. When severe, it can cause breathing problems, so that surgical treatment may be necessary. Spinal fusion operations have been very effective in correcting deformities and maintaining an upright sitting position in a wheelchair. In less severe cases, braces may be effective.

Treatment of DMD

Glucocorticoids — Glucocorticoids (prednisone or deflazacort) are the primary treatment for DMD and are generally offered to boys who are over the age of five years. Glucocorticoids have been proven to significantly increase strength, muscle function, and lung function. In addition, glucocorticoids decrease the progression of scoliosis.

Regular visits with a health care provider are needed to monitor the benefits and potential side effects of glucocorticoid treatment. Side effects can include weight gain, swelling in the face (known as Cushingoid facies), decrease in height, osteoporosis, long bone and vertebral bone fractures, acne, excessive hair growth, gastrointestinal symptoms, and behavioral changes. The dose can be adjusted if excessive weight gain occurs.

Genetic therapies — A number of genetic therapies for DMD can be used in certain situations for people with particular types of genetic defects that cause DMD. All of these genetic therapies are designed to increase the production of dystrophin, which is the protein that is deficient in DMD. However, despite increasing dystrophin production in muscle, it is not certain whether these genetic treatments improve motor function or lead to clinical benefit in people with DMD.

Several of the genetic treatments are known as "exon skipping" drugs. These include eteplirsen, golodirsen, viltolarsen, and casimersen. These drugs are designed to treat people who have a DMD gene deletion that prevents assembly of the dystrophin protein. They work by skipping over a specific part of the genetic code called an exon, which allows the muscle cell to assemble a shorter but functional dystrophin protein. The dystrophin gene has 79 exons in total, and exons 44 to 55 are a "hot spot" where deletions are more likely to occur:

- **Eteplirsen** – Eteplirsen (brand name: ExonDys 51) can be used to treat a minority of patients — approximately 13 percent — with DMD. The drug works by skipping over exon 51 in the DMD gene.

- **Golodirsen** – Golodirsen (brand name: Vyondys 53) is an exon skipping drug that can be used to treat approximately 8 percent of people with DMD. The drug works by skipping over exon 53 in the DMD gene.

- **Viltolarsen** – Viltolarsen (brand name: Viltepso) is also designed to skip exon 53, and can be used to treat approximately 8 percent of patients with DMD.

- **Casimersen** – Casimersen (brand name: Amondys 45) is designed to skip exon 45 of the DMD gene and can be used in approximately 8 percent of patients with DMD.

Other genetic therapies for DMD work in different ways:

- **Ataluren** – Ataluren (brand name: Translarna), which is licensed in the European Union and United Kingdom, is an oral drug that can be used to treat approximately 13 percent with DMD who have a nonsense (stop) mutation; this mutation stops production of dystrophin. Ataluren works by bypassing the nonsense mutation, which allows production of a functioning dystrophin protein. Where licensed, ataluren is an option to treat patients age two years and older with DMD caused by nonsense mutations. Ataluren is not approved for treating DMD in the United States.

- **Delandistrogene moxeparvovec** – Delandistrogene moxeparvovec (brand name: Elevidys) is a shortened version of the *DMD* (dystrophin) gene, known as micro-dystrophin. It is designed to deliver the micro-dystrophin to the muscle cells using a viral vector. It is given as a single intravenous (IV) infusion. It is approved in the United States for the treatment of ambulatory boys (those who can still walk independently) with DMD four through five years of age who have a proven mutation in the *DMD* gene. It is contraindicated for patients with a deletion in exon 8 or exon 9 of the *DMD* gene.

Prognosis — In early studies, most patients with DMD died in their late teens or twenties as a result of respiratory infections or cardiomyopathy. However, later studies have reported survival to age 35 years. Thus, survival appears to be improving with advances in respiratory care and cardiac care. Again, these ages represent the average for all patients with DMD; individual patients may have complications earlier or later in life. (See 'Life with muscular dystrophy' below.)

BECKER MUSCULAR DYSTROPHY

The pattern of inheritance of Becker muscular dystrophy (BMD) is the same as Duchenne muscular dystrophy (DMD), with the abnormal gene carried by the mother. It also occurs mainly in boys. BMD is also caused by problems with the dystrophin gene, although people with BMD often have partial production of dystrophin.

Female BMD carriers — Female carriers of the abnormal dystrophin gene that causes BMD are similar to those that carry the DMD gene. (See 'Female DMD carriers' above.)

Symptoms — Compared with DMD, the age of onset for children with BMD is usually later, and symptoms are usually milder. Children can usually walk until they are approximately 16 years old or older, with some patients continuing to walk as adults. Cognitive impairment is less common than with DMD. Similarly, heart problems are not common; when they occur, they can be more severe in patients with BMD than in those with DMD.

Management of BMD — Management of patients with BMD is similar to that of DMD. (See 'Preventing and treating complications of DMD' above.)

Treatment of BMD — Prednisone may be used for treatment of BMD, although little is known about its effect on the symptoms and disease progression. (See 'Treatment of DMD' above.)

Prognosis — On average, patients with BMD usually survive into their mid-40s. The most common cause of death is heart failure from cardiomyopathy.

BMD/DMD OUTLIERS

Some patients are found to have the genetic abnormalities of the dystrophin gene, but, clinically, have symptoms between those of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD). These so-called "outliers" may be thought of as having mild DMD or severe BMD. They usually start requiring a wheelchair between the ages of 12 and 16 years.

MYOTONIC DYSTROPHY

Myotonic dystrophy is the most common adult-onset muscular dystrophy. It can affect both boys and girls. There are two genetic types of myotonic dystrophy, type 1 and type 2. Symptoms typically appear during adolescence or adulthood. However, in some forms of type 1 myotonic dystrophy, the symptoms affect newborns or appear during infancy or early childhood.

Myotonic dystrophy affects multiple body systems, causing muscle loss and weakness, especially in the facial muscles, arms, and legs. In addition, myotonic dystrophy can cause heart problems (like heart block), cataracts, problems with glands, and abnormal intellectual functioning. In some cases, there are joint problems or difficulty swallowing. Excessive daytime sleepiness is found in about one-third of patients with myotonic dystrophy.

Myotonia, or delayed muscle relaxation after contraction, is also seen, but this problem typically does not require treatment. Genetic testing, pulmonary function tests, swallowing studies, and heart tests are often used in the evaluation of myotonic dystrophy. People with myotonic dystrophy are treated as symptoms develop. Leg braces are often used as weakness in the legs and feet worsen.

Life expectancy appears to be reduced for people with myotonic dystrophy. Respiratory and cardiac diseases are the most common causes of death, but cardiac death can be prevented with the implantation of a pacemaker or with other interventions.

LIMB-GIRDLE MUSCULAR DYSTROPHIES

Limb-girdle muscular dystrophies (LGMDs) are a group of disorders that have a number of inheritance patterns. The term refers to dystrophies that affect the shoulder girdle (or area surrounding the shoulder), the pelvic girdle (the area surrounding the hips), or both. Low back pain may be a prominent symptom. The muscles of the face are typically spared.

The age of onset varies from early childhood to adulthood. The course is usually slowly progressive, but some people have significant disability during childhood. Cognitive (brain) functioning is usually normal. However, cardiac involvement does occur in certain forms of LGMDs. The diagnosis is usually made by genetic testing.

Treatment of LGMDs focuses on the prevention of contractures. Stretching exercises are often recommended after diagnosis and are useful to prevent disabling symptoms.

EMERY-DREIFUSS MUSCULAR DYSTROPHY

Emery-Dreifuss muscular dystrophy (EDMD), also known as humeroperoneal muscular dystrophy, can be caused by a number of inheritance patterns. It can affect both boys and girls.

Symptoms of muscle weakness and loss typically begin in the arms between 10 and 20 years of age. Leg muscle weakness follows and, in some cases, mild facial weakness is also seen. The

disease tends to progress slowly. Contractures of the elbows and neck are sometimes the first sign of disease. Involvement of the heart is also common and can lead to serious problems with the regulation of heartbeat.

EDMD is usually diagnosed based upon signs and symptoms, family history, and genetic testing. Treatment is focused on preventing death from heart disease. A pacemaker can be lifesaving in patients with arrhythmia (see "Patient education: Pacemakers (Beyond the Basics)"). Physical therapy is useful in preventing contractures.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHD) can affect boys and girls. It usually progresses slowly but is extremely variable in its severity and age of onset. It is usually inherited in an autosomal dominant pattern, which means that a parent with the disease has a 50 percent chance of passing it to their child.

In the infant form, symptoms appear within the first few years of life. Most children with the infantile form require a wheelchair by the age of 9 or 10 years. There is profound facial weakness, with an inability to close the eyes in sleep, to smile, or to show other facial expressions. The weakness rapidly progresses to include the shoulder and hips. There may be marked weakness of the wrist or ankle. Children with early-onset FSHD may have epilepsy, reduced mental ability, and severe hearing loss.

In the classic form, symptoms usually begin between 20 and 30 years of age. Progression is slow, and the lifespan is near normal. The facial muscles are involved initially, with inability to close the eyes tightly, smile, or whistle. There may be a pouting appearance to the face. The facial weakness can be mild and may remain mild for many years. The muscles of the shoulders and upper arms are usually involved.

In some of cases, the disease progresses rapidly in middle age, leading to significant disability. There may be problems with vision or hearing. The heart's rhythm can be affected in some patients.

CONGENITAL MUSCULAR DYSTROPHY

Congenital muscular dystrophy (CMD) refers to a group of muscular dystrophies with onset in the first two years after birth. There are several types, including a classic form and other distinct

genetic forms including Ullrich CMD and Bethlem myopathy, Fukuyama type (seen primarily in Japan), Walker-Warburg syndrome, and muscle-eye-brain disease.

Symptoms of CMD are usually seen at birth and include lack of muscle strength ("floppy baby"), multiple joint contractures (arthrogryposis), and sometimes eye and brain abnormalities. No definitive treatment is available for CMD.

LIFE WITH MUSCULAR DYSTROPHY

Many children and adults with muscular dystrophy can lead active lives. However, the diagnosis of muscular dystrophy can be overwhelming for a parent and a child. Support and education from health care providers, and community organizations can help a family to provide their child with the best possible care. Organizations such as the Muscular Dystrophy Association and others have a large network of support services and information available. A week-long summer camp is available in many locations throughout the United States.

Parents and caregivers are often unsure about how to discuss muscular dystrophy with their child. Because it is a slowly progressing disease in most cases, parents are not obligated to discuss their child's long-term prognosis until the child is mature enough to understand the implications of their diagnosis. Most children have an understanding of death by the age of seven years, but even before this point, children want and deserve to know basic information about their disease and treatments that may be needed. In the terminal stages of illness, adolescents and young adults may want to participate in the decision-making processes about end-of-life care, resuscitation options, and the location of their care.

WHERE TO GET MORE INFORMATION

Your health care provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed on our website (www.uptodate.com/patients). Related topics for patients, as well as selected articles written for health care professionals, are also available. Some of the most relevant are listed below.

Patient level information — UpToDate offers two types of patient education materials.

The Basics — The Basics patient education pieces answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a

general overview and who prefer short, easy-to-read materials.

Patient education: Muscular dystrophy (The Basics)

Beyond the Basics — Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are best for patients who want in-depth information and are comfortable with some medical jargon.

Patient education: Vaccines for infants and children age 0 to 6 years (Beyond the Basics)
Patient education: Pacemakers (Beyond the Basics)

Professional level information — Professional level articles are designed to keep doctors and other health professionals up-to-date on the latest medical findings. These articles are thorough, long, and complex, and they contain multiple references to the research on which they are based. Professional level articles are best for people who are comfortable with a lot of medical terminology and who want to read the same materials their doctors are reading.

Duchenne and Becker muscular dystrophy: Clinical features and diagnosis
Emery-Dreifuss muscular dystrophy
Oculopharyngeal, distal, and congenital muscular dystrophies
Limb-girdle muscular dystrophy
Myotonic dystrophy: Etiology, clinical features, and diagnosis
Duchenne and Becker muscular dystrophy: Management and prognosis
Preimplantation genetic testing

The following organizations also provide reliable health information.

- National Library of Medicine

  (https://medlineplus.gov/musculardystrophy.html)

- National Institute of Neurological Disorders and Stroke

  (www.ninds.nih.gov/Disorders/All-Disorders/Muscular-Dystrophy-Information-Page)

- Muscular Dystrophy Association

  (https://mda.org/)

- Gene Reviews (discusses genetic testing)

  (https://www.ncbi.nlm.nih.gov/books/NBK1119/)

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