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Duchenne Muscular Disease

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ABSTRACT

Duchenne muscular dystrophy(DMD) one of the most severe forms of inherited muscular dystrophies. It is the most common hereditary neuromuscular disease and does not exhibit a predilection for any race or ethnic group. Mutations in the dystrophin gene lead to progressive muscle fiber degeneration and weakness. This weakness may present initially with difficulty in ambulation but progressively advances to such an extent that affected patients are unable to carry out activities of daily living and become wheelchair bound. Cardiac and orthopaedic complications are common, and death usually occurs in the twenties due to respiratory muscle weakness or cardiomyopathy. Current therapy is centred on treatment with glucocorticoids and physiotherapy to prevent orthopaedic complications. [1] Duchenne muscular dystrophy (DMD), an allelic X-linked progressive muscle-wasting disease, is one of the most common single-gene disorders in the developed world. Despite knowledge of the underlying genetic causation and resultant pathophysiology from lack of dystrophin protein at the muscle sarcolemma, clinical intervention is currently restricted to symptom management. In recent years, however, unprecedented advances in strategies devised to correct the primary defect through gene- and cell-based therapeutics hold particular promise for treating dystrophic muscle. Conventional gene replacement and endogenous modification strategies have greatly benefited from continued improvements in encapsidation capacity, transduction efficiency, and systemic delivery. In particular, RNA-based modifying approaches such as exon skipping enable expression of a shorter but functional dystrophin protein and rapid progress toward clinical application. Emerging combined gene- and cell-therapy strategies also illustrate particular promise in enabling ex vivo genetic correction and autologous transplantation to circumvent a number of immune challenges. These approaches are complemented by a vast array of pharmacological approaches, in particular the successful identification of molecules that enable functional replacement or ameliorate secondary DMD pathology. Animal models have been instrumental in providing proof of principle for many of these strategies, leading to several recent trials that have investigated their efficacy in DMD patients. Although none has reached the point of clinical use, rapid improvements in experimental technology and design draw this goal ever closer. Here, we review therapeutic approaches to DMD, with particular emphasis on recent progress in strategic development, preclinical evaluation and establishment of clinical efficacy. Further, we discuss the numerous challenges faced and synergistic approaches being devised to combat dystrophic pathology effectively.

Keywords: dystrophy, animal models, pharmacological, exon skipping, gene therapy, utrophin. [2]

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INTRODUCTION

The disease was first described by the Neapolitan physician Giovanni Semmola in 1834 and Gaetano Conte in 1836.[3],[4],[5] However, DMD is named after the French neurologist Guillaume-Benjamin-Amand Duchenne (1806–1875), who in the 1861 edition of his book Paraplegie hypertrophique de l'enfance de cause cerebrale, described and detailed the case of a boy who had this condition. A year later, he presented photos of his patient in his Album de photographies pathologiques. In 1868, he gave an account of 13 other affected children. Duchenne was the first to do a biopsy to obtain tissue from a living patient for microscopic examination. [6], [7]

Alfredo Ferrari (born January 1932 in Modena), nicknamed Alfredino or Dino, was the son of Enzo Ferrari. He designed the 1.5 L DOHC V6 engine for F2 at the end of 1955. Dino never saw the engine; he died 30 June 1956 in Modena at the age of 24, before his namesake automobiles Fiat Dino and Dino (automobile) were produced.

Rapper Darius Weems had the disease and used his notoriety to raise awareness and funds for treatment. [8] He died at the age of 27. His brother also suffered from the disease until his death at age 19. Darius Goes West is a documentary that depicts his journey of growth and acceptance of having the disease. A book entitled The Revised Fundamentals of Caregiving, was released in 2012, written by Jonathan Evison. Netflix produced a film, titled The Fundamentals of Caring, in 2016 based on the novel. Both media depict a young man suffering from the disease. Duchenne and Becker muscular dystrophies together affect 1 in 3,500 to 5,000 new born males worldwide. Between 400 and 600 boys in the United States are born with these conditions each year. [9]

Duchenne muscular dystrophy (DMD) is the most common fatal genetic disease diagnosed in childhood. The disease almost always affect boys, and they tend to be diagnosed before the age of 5. Duchenne muscular dystrophy is classified as a rare disease. There are around 2,500 patients in the UK and an estimated 300,000 sufferers worldwide. Children born with Duchenne muscular dystrophy have a fault, known as a mutation, on their dystrophin gene, the longest gene in the body. The fault means that they cannot produce dystrophin, a protein that is vital for muscle strength and function. This lack of dystrophin results in a progressive deterioration of muscle strength and function. [10]

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in India, like most other parts of the world. Affected individuals suffer long years of increasing disability and their parents go through psychological trauma and face hardships of managing a physically challenged child on day to day basis. The information on the molecular pathology and genetics has been

available for over two decades and genetic counselling and prevention can be offered to families at risk. However, issues of illiteracy, social and religious beliefs and the strong Indian desire to have a normal male child pose difficulties in achieving this objective. In the past few years, Polymerase chain reaction (PCR) -based genetic studies have become available in many parts of the country and support groups of parents and medical personnel have begun the efforts to diagnose and rehabilitate the sufferers. This review will discuss the available genetic information and the social and rehabilitative aspects of DMD/ Becker's muscular dystrophy (BMD) in India. [11]

TYPES

Becker muscular dystrophy:

Becker muscular dystrophy is similar to Duchenne muscular dystrophy, but it's less severe. This type of muscular dystrophy also more commonly affects boys. Muscle weakness occurs mostly in your arms and legs, with symptoms appearing between age 11 and 25. Other symptoms of Becker muscular dystrophy include:

- walking on your toes
- frequent falls
- muscle cramps
- trouble getting up from the floor

Many with this disease don't need a wheelchair until they're in their mid-30s or older, and a small percentage of people with this disease never require one. Most people with Becker muscular dystrophy live until middle age or later. [12]

Congenital muscular dystrophy

Congenital muscular dystrophies are often apparent between birth and age 2. This is when parents begin to notice that their child's motor functions and muscle control aren't developing as they should. Symptoms vary and may include:

- muscle weakness
- poor motor control
- inability to sit or stand without support
- scoliosis
- foot deformities
- trouble swallowing
- respiratory problems
- vision problems

- speech problems
- intellectual impairment

While symptoms vary from mild to severe, the majority of people with congenital muscular dystrophy are unable to sit or stand without help. The lifespan of someone with this type also varies, depending on the symptoms. Some people with congenital muscular dystrophy die in infancy while others live until adulthood. [12]

Myotonic dystrophy:

Myotonic dystrophy is also called Steinert's disease or dystrophia myotonica. This form of muscular dystrophy causes myotonia, which is an inability to relax your muscles after they contract. Myotonia is exclusive to this type of muscular dystrophy.

Myotonic dystrophy can affect your:

- facial muscles
- central nervous system
- adrenal glands
- heart
- thyroid
- eyes
- gastrointestinal tract

Symptoms most often appear first in your face and neck. They include:

- drooping muscles in your face, producing a thin, haggard look
- difficulty lifting your neck due to weak neck muscles
- difficulty swallowing
- droopy eyelids, or ptosis
- early baldness in the front area of your scalp
- poor vision, including cataracts
- weight loss
- increased sweating

This dystrophy type may also cause impotence and testicular atrophy in males. In women, it may cause irregular periods and infertility.

Myotonic dystrophy diagnoses are most common in adults in their 20s and 30s. While its symptoms can affect your quality of life, most of the symptoms are not life-threatening. People with myotonic dystrophy often live a long life. [12]

Facioscapulohumeral (FSHD)

Facioscapulohumeral muscular dystrophy (FSHD) is also known as Landouzy-Dejerine disease. This type of muscular dystrophy affects the muscles in your face, shoulders, and upper arms. FSHD may cause:

- difficulty chewing or swallowing
- slanted shoulders
- a crooked appearance of the mouth
- a wing-like appearance of the shoulder blades

A smaller number of people with FSHD may develop hearing and respiratory problems. FSHD tends to progress slowly. Symptoms usually appear during your teenage years, but they sometimes don't appear until your 40s. Most people with this condition live a full life span. [12]

Limb-girdle muscular dystrophy:

Limb-girdle muscular dystrophy causes weakening of the muscles and a loss of muscle bulk. This type of muscular dystrophy usually begins in your shoulders and hips, but it may also occur in your legs and neck. You may find it hard to get up out of a chair, walk up and down stairs, and carry heavy items if you have limb-girdle muscular dystrophy. You may also stumble and fall more easily.

Limb-girdle muscular dystrophy affects both males and females. Most people with this form of muscular dystrophy are disabled by age 20. However, many have a normal life expectancy. [12]

Oculopharyngeal muscular dystrophy (OPMD):

Oculopharyngeal muscular dystrophy causes weakness in your facial, neck, and shoulder muscles. Other symptoms include:

- drooping eyelids
- trouble swallowing
- voice changes
- vision problems
- heart problems
- difficulty walking

OPMD occurs in both men and women. Individuals usually receive diagnoses in their 40s or 50s. [12]

Distal muscular dystrophy:

Distal muscular dystrophy is also called distal myopathy. It affects the muscles in your:

- forearms
- hands
- calves
- feet

It may also affect your respiratory system and heart muscles. The symptoms tend to progress slowly and include a loss of fine motor skills and difficulty walking. Most people, both male and female, are diagnosed with distal muscular dystrophy between the ages of 40 and 60. [12]

Emery-Dreifuss muscular dystrophy:

Emery-Dreifuss muscular dystrophy tends to affect more boys than girls. This type of muscular dystrophy usually begins in childhood. The symptoms include:

- weakness in your upper arm and lower leg muscles
- breathing problems
- heart problems
- shortening of the muscles in your spine, neck, ankles, knees, and elbows

Most individuals with Emery-Dreifuss muscular dystrophy die in mid-adulthood from heart or lung failure. [12]

How is muscular dystrophy diagnosed?

A number of different tests can help your doctor diagnose a muscular dystrophy. Your doctor can:

- test your blood for the enzymes released by damaged muscles
- test your blood for the genetic markers of muscular dystrophy
- perform an electromyography test on your muscle's electrical activity using an electrode needle that enters your muscle
- perform a muscle biopsy to test a sample of your muscle for muscular dystrophy [12]

How is muscular dystrophy treated?

There's currently no cure for muscular dystrophy, but treatments can help manage your symptoms and slow the progression of the disease. Treatments depend on your symptoms.

Treatment options include:

- corticosteroid drugs, which help strengthen your muscles and slow muscle deterioration
- assisted ventilation if respiratory muscles are affected
- medication for heart problems
- surgery to help correct the shortening of your muscles
- surgery to repair cataracts

- surgery to treat scoliosis
- surgery to treat cardiac problems

Therapy has proven to be effective. You can strengthen your muscles and maintain your range of motion using physical therapy. Occupational therapy can help you:

- become more independent
- improve your coping skills
- improve your social skills
- gain access to community services [12]

SIGN AND SYMPTOMS

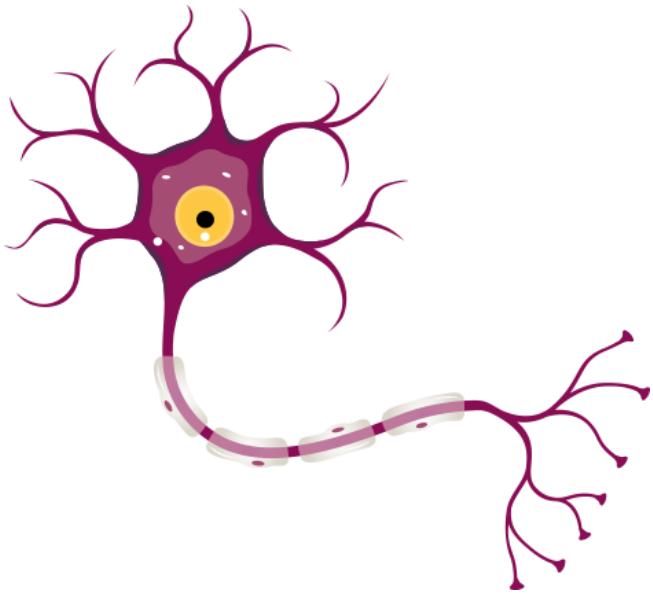
The symptoms of DMD generally start to appear between ages 2 and 6. Many children with DMD develop normally during infancy and early childhood. DMD symptoms may include:

- difficulty walking
- a loss of ability to walk
- enlarged calves
- learning disabilities, which occurs in about one-third of affected individuals
- a lack of motor skills development
- fatigue
- rapidly worsening weakness in the legs, pelvis, arms, and neck [13]

The first signs and symptoms of Duchenne are often noticed around the age of 2 or 3. Children with Duchenne may be slower to sit, stand or walk. Most are unable to run and jump properly due to weakness in the core muscles of the body.

Duchenne's effect on the brain:

Children with Duchenne are more likely to have conditions affecting the brain, such as mental health, learning, or seizure disorders. The key protein for muscle function that is missing in Duchenne, dystrophin, is also believed to have a role in brain development.



Neuron

- In children with Duchenne, the lack of dystrophin is believed to affect the ability of certain brain cells, called neurons, to connect properly and share information
- This can lead to challenges with important brain functions such as attention, memory, learning, speech, and intellectual ability

A higher risk of ADHD, ASD and OCD

- Children with Duchenne are more likely to have such conditions as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disorders such as dyslexia, and obsessive-compulsive disorder (OCD)

- In addition, abnormal electrical activity in the brain makes children with Duchenne more prone to developing epilepsy (seizures). [13]

To learn more about important considerations for parents, visit Parent Project Muscular Dystrophy's Care for Duchenne resource.

Children with Duchenne muscular dystrophy (DMD) are often late walkers.

In toddlers, parents may notice enlarged calf muscles (see image at right). This enlargement is known as pseudo hypertrophy, or "false enlargement," because the muscle tissue is abnormal and may contain scar tissue.

A pre-schooler with DMD may seem clumsy and fall often. Parents also may note that children have trouble climbing stairs, getting up from the floor or running.

By school age, children may walk on their toes or the balls of their feet with a slightly waddling gait, and fall frequently. To try to keep their balance, they may stick out their bellies and pull back their shoulders. Children also have difficulty raising their arms. [14]

Many children with DMD begin using a wheelchair sometime between ages 7 and 12. Transition to a wheelchair usually is a gradual process; at first, the chair may be required only to conserve the child's energy when covering long distances. (Children often experience renewed independence once they fully transition to a power wheelchair.)

In the teen years, activities involving the arms, legs or trunk may require assistance or mechanical support. [15]

Pain and sensation

The muscle deterioration in Duchenne MD isn’t usually painful in itself. Some people report muscle cramps at times; these usually can be treated with over-the-counter pain relievers.

Because muscular dystrophy doesn’t affect nerves directly, touch and other senses are normal, as is control over the smooth, or involuntary, muscles of the bladder and bowel, and sexual functions.

The heart

Lack of dystrophin can weaken the muscle layer in the heart (myocardium), resulting in a condition called cardiomyopathy. Over time, sometimes as early as the teen years, the damage done by DMD to the heart can become life-threatening. The heart should be monitored closely, usually by a paediatric cardiologist. See Medical Management for more on cardiomyopathy in DMD.

Respiratory function

Beginning at about 10 years of age, the diaphragm and other muscles that operate the lungs may weaken, making the lungs less effective at moving air in and out. Although the child may not

complain of shortness of breath, problems that indicate poor respiratory function include headaches, mental dullness, difficulty concentrating or staying awake, and nightmares.

Weakened respiratory muscles make it difficult to cough, leading to increased risk of serious respiratory infection. A simple cold can quickly progress to pneumonia. It's important to get flu shots, and when infections occur, to get prompt treatment. See Medical Management for more on respiratory care in DMD.

Learning

About a third of boys with DMD have some degree of learning disability, although few have serious mental retardation. Doctors believe that dystrophin abnormalities in the brain may have subtle effects on cognition and behaviour. Learning problems in DMD occur in three general areas: attention focusing, verbal learning and memory, and emotional interaction.

Children suspected of having a learning disability can be evaluated by a developmental or paediatric neuropsychologist through the school system's special education department or with a referral from the MDA clinic.

If a learning disability is diagnosed, educational and psychological interventions can begin right away. The specialist may prescribe exercises and techniques that can help improve these areas, and the school also can provide special help with learning. See Medical Management for more about learning disabilities in DMD. [15]]

CAUSES

Duchenne is caused by a genetic mutation that prevents the body from producing dystrophin, a protein that muscles need to work properly. Without dystrophin, muscle cells become damaged and weaken. Over time, children with Duchenne will develop problems walking and breathing, and eventually the muscles that help them breathe and the heart will stop working. Duchenne is an irreversible, progressive disease. There is currently no cure for Duchenne.

Duchenne by the numbers

One of more than 30 forms of muscular dystrophy

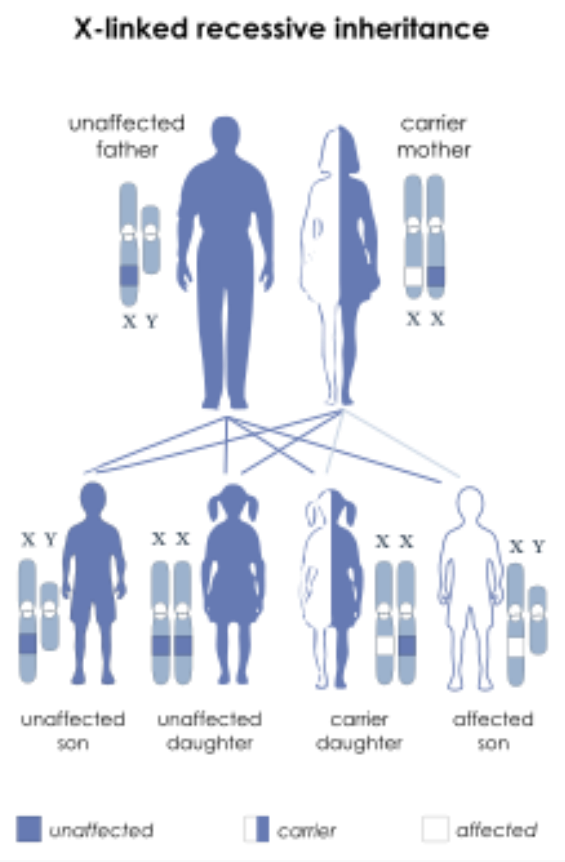
Occurs in 1 in 3,500 to 5,000 males born worldwide

Average age of diagnosis

Time from initial symptoms to diagnosis is 2.5 years

More than 90% in wheelchairs by age 15

- One of the most serious genetic diseases in children worldwide [16]



- DMD is inherited in a X-linked recessive manner
- DMD is caused by a mutation of the dystrophin gene at locus Xp21, located on the short arm of the X chromosome. [18]Dystrophin is responsible for connecting the cytoskeleton of each muscle fiber to the underlying basal lamina (extracellular matrix), through a protein complex containing many subunits. The absence of dystrophin permits excess calcium to penetrate the sarcolemma (the cell membrane).[19] Alterations in calcium and signalling pathways cause water to enter into the mitochondria, which then burst.
- In skeletal muscle dystrophy, mitochondrial dysfunction gives rise to an amplification of stress-induced cytosolic calcium signals and an amplification of stress-induced reactive-oxygen species production. In a complex cascading process that involves several pathways and is not clearly understood, increased oxidative stress within the cell damages the sarcolemma and eventually results in the death of the cell. Muscle fibers undergo necrosis and are ultimately replaced with adipose and connective tissue.
- DMD is inherited in an X-linked recessive pattern. Females typically are carriers of the genetic trait while males are affected. A female carrier will be unaware she carries a mutation until she has an affected son. The son of a carrier mother has a 50% chance of inheriting the defective gene from his mother. The daughter of a carrier mother has a 50%

chance of being a carrier and a 50% chance of having two normal copies of the gene. In all cases, an unaffected father either passes a normal Y to his son or a normal X to his daughter. Female carriers of an X-linked recessive condition, such as DMD, can show symptoms depending on their pattern of X-inactivation. DMD has an incidence of one in 3,600 male infants. [17] Mutations within the dystrophin gene can either be inherited or occur spontaneously during germline transmission.

- DMD can occur in females who have an affected father and a carrier mother, albeit this rarely occurs. The daughter of a carrier mother and an affected father will have a 50% chance of being a carrier as they will always inherit the affected X-chromosome from their father or will have a 50% chance of also inheriting the affected X-chromosome from their mother and thus will be affected. [20]
- Disruption of the blood-brain barrier has been seen to be a noted feature in the development of DMD. [21]

MODE OF TRANSMISSION

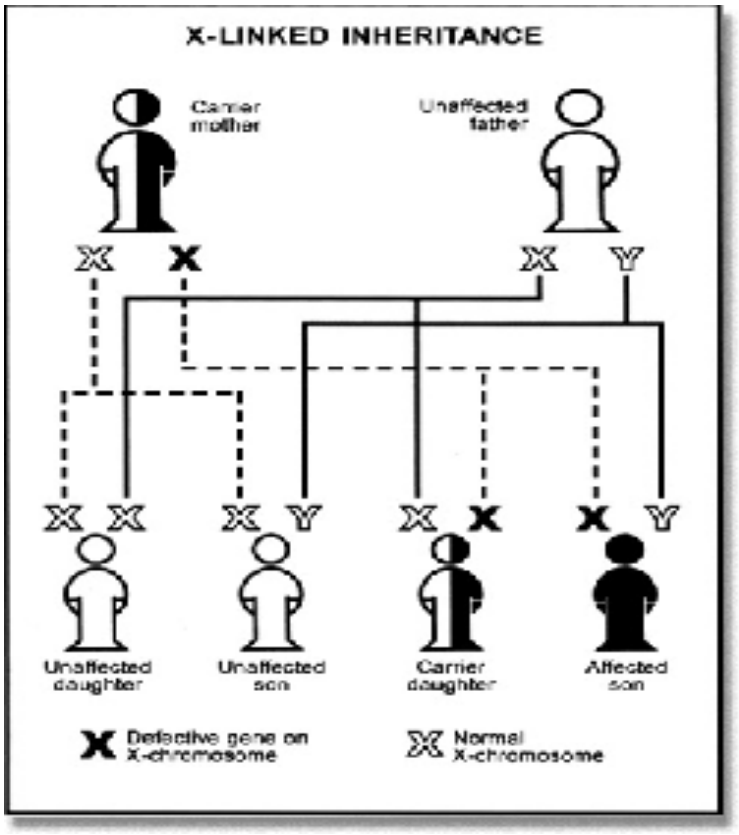
Like the other muscular dystrophies, DMD is inherited – it is a genetic condition. Unlike most of the other dystrophies, it is transmitted by an altered gene on the X chromosome in an "X-linked" (or "sex-linked") recessive pattern of inheritance. When a disorder is transmitted in this way, only males are affected.

X-Linked Recessive Inheritance

To repeat, the gene for DMD is located on the X chromosome. Since the defective gene is recessive, a female with the DMD gene on one of her two X chromosomes will not develop muscular dystrophy. The normal gene on her second X chromosome masks the effects of the defective gene. Such a woman is called a "carrier". Male offspring, however, have only one X chromosome, and there are no equivalent genes on the Y chromosome. Consequently, in males the X-chromosome genes have no "partners". Therefore, a male with the DMD gene on his X chromosome will be affected with the condition because he has no normal gene to counteract the effect of the abnormal one.

Each time a DMD carrier mother has a child, there are four possible outcomes, each with an equal probability of happening. Thus, the chance of producing an affected son is one in four, or 25 %. If we breakdown the risk further according to the sex of the child, it follows that there is a 50% chance that each son will be affected. All daughters will be unaffected, but each has a 50% chance of being a carrier like her mother.

It is important to point out that unaffected sons of carrier mothers do not have the DMD gene, and therefore, cannot transmit DMD to their offspring. The same is true for those daughters of carriers who have not inherited the DMD gene. If circumstances should allow a male affected with DMD to reproduce, and if his wife was not a carrier of DMD, then all of his sons would be unaffected and free of the gene but all of his daughters would be carriers.



The Luck of the Draw

The odds in the transmission of DMD work in exactly the same way they do when you pick a playing card from a full deck. Let us consider that red cards represent males and black cards represent females. Then, let us assume that hearts represents a male with DMD, diamonds are unaffected males, clubs are a carrier female, and spades a female non-carrier. Now, we thoroughly shuffle the deck and draw a card. Because there are equal numbers of cards in each suit, the chance of drawing a heart is one in four. However, if you pick a red card (a boy), the chance of its being a heart is 50%, because there are only two red suits. If you pick a black card (a girl), there is a 50% chance that it will be a club (a carrier).

Keep in mind that "chance has no memory" -if the card is replaced and the deck is reshuffled after each draw, the probability of picking a particular suit is unchanged. Thus, in a serious of four draws, you may pick four spades, or you may pick no spades. The fact that you picked spades in

the first three times does not alter the one-in-four probability of picking a spade on the fourth draw. In other words, the probabilities remain with the same for each child born in a family. If the first is affected with DMD, there is no guarantee that the next three will be unaffected.

Carriers and New Mutations

The mother of a boy with DMD may not be a carrier. The DMD gene she transmits may have becomes defective as the result of a spontaneous change in the particular egg cell that joined with a sperm cell to develop into a child. Such a change in a gene is known as a new mutation and is a possibility to be considered when DMD occurs in families where there is no previous family history of the disease. Mutations are accidents of nature for which it usually is not possible to pinpoint a specific cause.

It is not certain what proportion of DMD cases results from new mutations, but estimates run as high as one-third. In cases where a boy is affected with DMD due to a new mutation, the risk to future offspring is very small. A new mutation is a rare event, unlikely to happen again in the same family.

It must be emphasized, however, that absence of a family history does not mean that a case of DMD has resulted from a new mutation. It may be that the mutation has been in the family for a number of generations and has not shown up before, just by chance. Or, the mutation may have occurred in a family member only one or two generations earlier. In any event, the mother of a child who is the only family member with DMD may or may not be a carrier. It is a major goal of genetic evaluation to determine whether or not she is. [22]

Prevention

Because Duchenne muscular dystrophy is a genetic disorder, it cannot be prevented. If you have a family history of Duchenne muscular dystrophy, genetic screening may be helpful for an early diagnosis and early treatment. These genetic tests can be performed on adults, children, and even fetuses in the womb. Once Duchenne muscular dystrophy is diagnosed, treatment may help reduce symptoms and slow the progression of the disease. [23]

Diagnosis

A child's doctor may suspect Duchenne muscular dystrophy (DMD) in young boys who have the signs and symptoms of DMD, including progressive muscle weakness. Family history is also important. Blood tests can be used to check for increased levels of certain special proteins called muscle enzymes in the blood which can leak from damaged muscles. Most commonly, the blood level of the enzyme creatine phosphokinase (CPK or CK) is checked, but a doctor may also check the blood levels of transaminases such as aspartate transaminase and alanine transaminase. Finding

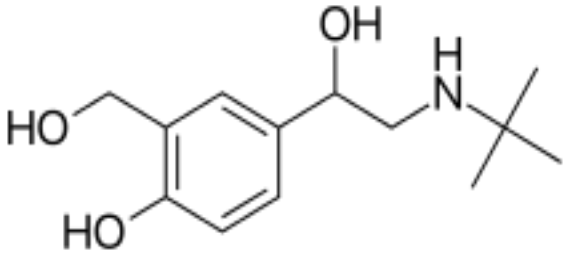
a change in the DMD gene that can cause DMD through genetic testing confirms the diagnosis of DMD. Testing for DMD may include: [23], [24]

- Blood test which measures the levels of serum creatine phosphokinase (CK or CPK). Very high CK levels indicate muscle damage is causing the muscle weakness, rather than nerve damage.
- Molecular genetic testing (usually blood cells are used) to see whether there is a change or mutation in the DMD gene that can cause DMD or one of the related dystrophinopathies.
- Electromyography can be used to distinguish conditions that only impact the muscles (myotonic) from those that involve that brain and muscles (neurogenic).
- Muscle biopsy is rarely used to diagnose DMD due to the decreased cost and higher accuracy of genetic testing.

Testing Resources

- The Genetic Testing Registry (GTR) provides information about the genetic tests for this condition. The intended audience for the GTR is health care providers and researchers. Patients and consumers with specific questions about a genetic test should contact a health care provider or a genetics professional.

Treatment



Salbutamol(albuterol) — a $\beta_2$agonist

Treatment is generally aimed at controlling the onset of symptoms to maximize the quality of life which can be measured using specific questionnaires, [25] and include:

- Corticosteroids such as prednisolone and deflazacort lead to short-term improvements in muscle strength and function up to 2 years. [26] Corticosteroids have also been reported to help prolong walking, though the evidence for this is not robust. [27]
- Randomized controls trials have shown that β_2 agonists increase muscle strength, but do not modify disease progression. Follow-up time for most RCTs on β_2 agonists is only around 12 months, hence results cannot be extrapolated beyond that time frame

- Mild, nonjuring physical activity such as swimming is encouraged. Inactivity (such as bed rest) can worsen the muscle disease.
- Physical therapy is helpful to maintain muscle strength, flexibility, and function.
- Orthopaedic appliances (such as braces and wheelchairs) may improve mobility and the ability for self-care. Form-fitting removable leg braces that hold the ankle in place during sleep can defer the onset of contractures.
- Appropriate respiratory support as the disease progresses is important.
- Cardiac problems may require a pacemaker. [28]

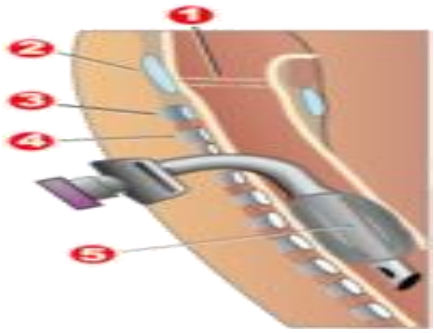
Comprehensive multidisciplinary care standards/guidelines for DMD have been developed by the Centres for Disease Control and Prevention, and were published in two parts in The Lancet Neurology in 2010. [29]

Physical therapy [edit]

Physical therapists are concerned with enabling patients to reach their maximum physical potential. Their aim is to:

- minimize the development of contractures and deformity by developing a programme of stretches and exercises where appropriate
- anticipate and minimize other secondary complications of a physical nature by recommending bracing and durable medical equipment
- monitor respiratory function and advise on techniques to assist with breathing exercises and methods of clearing secretions

Respiration assistance [edit]



Tracheotomy

Modern "volume ventilators/respirators," which deliver an adjustable volume (amount) of air to the person with each breath, are valuable in the treatment of people with muscular dystrophy-related respiratory problems. The ventilator may require an invasive endotracheal or tracheotomy tube through which air is directly delivered, but for some people, non-invasive delivery through a face

mask or mouthpiece is sufficient. Positive airway pressure machines, particularly bi-level ones, are sometimes used in this latter way. The respiratory equipment may easily fit on a ventilator tray on the bottom or back of a power wheelchair with an external battery for portability.

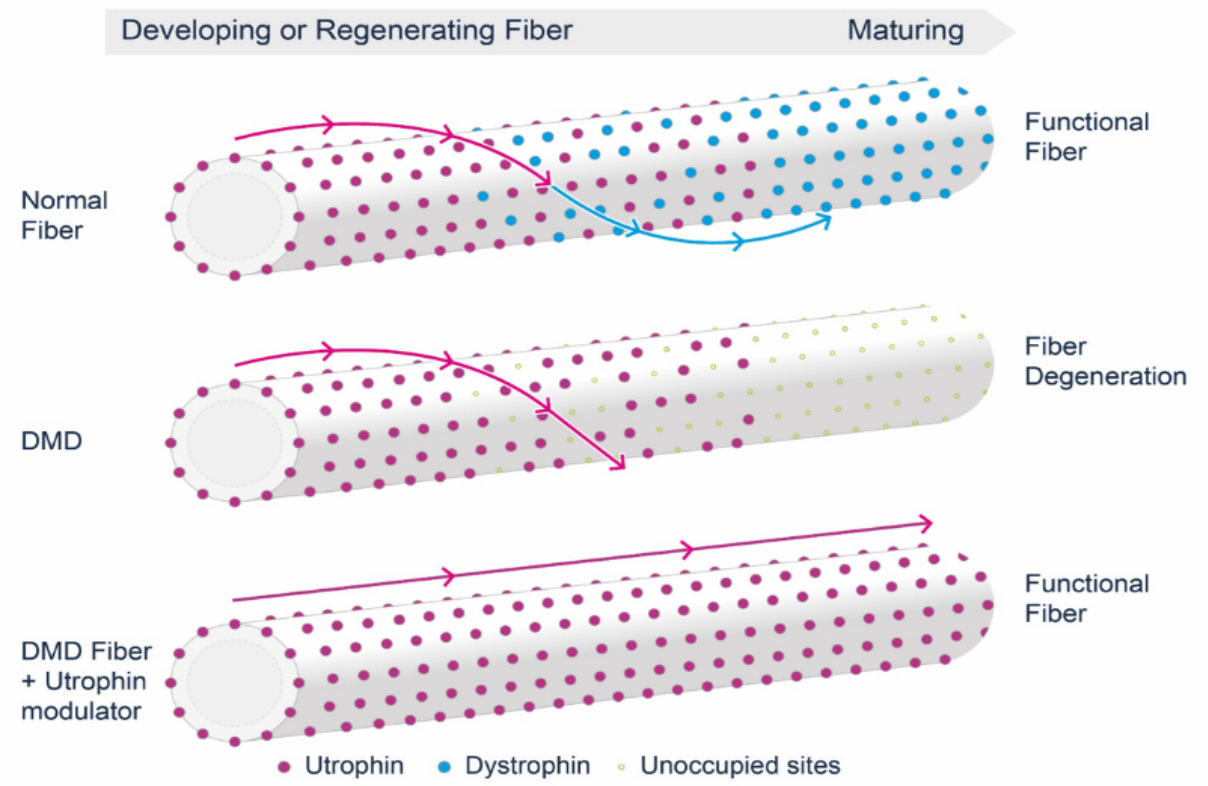
Ventilator treatment may start in the mid- to late teens when the respiratory muscles can begin to collapse. If the vital capacity has dropped below 40% of normal, a volume ventilator/respirator may be used during sleeping hours, a time when the person is most likely to be under ventilating (hypo ventilating). Hypoventilation during sleep is determined by a thorough history of sleep disorder with an oximetry study and a capillary blood gas (see pulmonary function testing).

A cough assist device can help with excess mucus in lungs by hyperinflation of the lungs with positive air pressure, then negative pressure to get the mucus up. If the vital capacity continues to decline to less than 30 percent of normal, a volume ventilator/respirator may also be needed during the day for more assistance. The person gradually will increase the amount of time using the ventilator/respirator during the day as needed. However, there are also people with the disease in their 20s who have no need for a ventilator.

Summit Therapeutics focuses on the development of treatments that can help patients suffering from diseases that currently lack options. The biotech has reported Phase II results for its drug for the genetic disease, Duchenne muscular dystrophy (DMD). Summit's candidate, ezutromid, significantly reduced muscle inflammation, which should, in turn, reduce damage to muscle fibers.

DMD, a progressive muscle wasting disease, affects around 50,000 boys and young men in the developed world. The disease is caused by mutations in the gene that encodes dystrophin, a protein required for keeping muscles healthy and functioning correctly. Muscle weakness begins in the hips, pelvis, thighs, and shoulders, then spreads to the arms and legs, and eventually reaches the heart and muscles around the lungs. With no cure for the disease available, patients with the disease often die before the age of 30.

Summit believes that the modulation of another protein, utrophin, could offer a treatment for DMD. Utrophin is functionally and structurally similar to dystrophin and its presence improved muscle performance in preclinical studies. Summit's drug, ezutromid, is a utrophin modulator that replaces missing dystrophin to maintain muscle fibers. The drug has received Orphan Drug, Fast Track, and Rare Paediatric Disease designations from the FDA.



Summit's utrophin modulator maintains utrophin production to compensate for the absence of dystrophin in DMD patients.

The results of the Phase II study indicate that, after 24 weeks, ezutromid was able to statistically significantly reduce muscle inflammation. H Lee Sweeney, Director of the Myology Institute at the University of Florida, commented: "These data could be an early indication that these patients are experiencing a decrease in disease severity and highlight ezutromid's potential as a disease-modifying treatment."

Summit's approach comes up against some very different approaches to the treatment of DMD. uniQure's Gilberta arrival on the market may have been seen as a failure by many but it opened the doors for gene therapies to correct errors in the genome. Sarepta, which paid $40M (€33M) upfront and agreed to up to $500M (€407M) in milestones to secure European rights to ezutromid, teamed up with Noble Généthon to develop a gene therapy for the disease.

Meanwhile, DMD is one of the most popular targets for the most popular therapeutic targets for CRISPR/Cas9 technology. This is because most of the disease-causing mutations are grouped together in hotspots', meaning these could be targeted to allow the production of a functional dystrophin protein in around 60% of DMD patients. CRISPR Therapeutics signalled its intent to use the gene editing tool to fight DMD by striking a deal with an agenesis Biotechnologies, which efficiently produces muscle stem cells. [30]

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