Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a progressive muscle disease that affects approximately 1 out of every 3600 baby boys born. It is the most common of the muscular dystrophy disorders and is caused by an absence of a protein called dystrophin. Closely related to DMD is Becker muscular dystrophy (BMD) which is caused by a decreased or abnormal quality of the same dystrophin protein. Though similar in presentation, BMD has a much milder degree of severity and slower clinical course because there is some functional dystrophin produced. Duchenne muscular dystrophy is named after the French neurologist Guillaume Benjamin Amand Duchenne (1806–1875), who described and detailed the case of a boy who had this condition in a book published in 1861.

Features of DMD

The symptoms usually appear before age 6 and may appear as early as infancy. Typically, the first noticeable symptom is delay of motor milestones, including sitting and standing independently. The mean age for walking in boys with Duchenne muscular dystrophy is 18 months. There is progressive muscle weakness of the legs and pelvic muscles, which is associated with a loss of muscle mass (wasting). This muscle weakness causes a waddling gait and difficulty climbing stairs. Getting up off the floor is difficult and boys tend to use their arms to support the torso when doing this (called the Gower Maneuver). Muscle weakness also occurs in the arms, neck, and other areas, but not as severely or as early as in the lower half of the body. Calf muscles initially enlarge and the enlarged muscle tissue is eventually replaced with fat and connective tissue. Muscle contractures (permanent shortenings) occur in the legs, making the muscles unusable.

There is a steady decline in muscle strength between the ages of 6 and 11 years. By age 10, braces may be required for walking, and by age 12, most boys require a wheelchair. Bones are also affected and may not develop normally. Muscular weakness and skeletal abnormalities such as scoliosis (curvature of the spine) frequently contribute to breathing disorders.

Cardiomyopathy (enlarged heart) occurs in almost all cases, beginning in the early teens in some, and in all after the age of 18 years. Intellectual impairment or learning difficulties may occur, but this is not inevitable and does not worsen as the disorder progresses.

With treatment advances over the years, young men with Duchenne are able to live longer and more fulfilling lives, are able to complete their education and obtain employment. Several treatments have now been approved with more in clinical trial phase.
Dystrophin protein is needed for healthy muscle cell function. A genetic fault in the code for this protein means that there is little or no protein manufactured and the muscle cells are easily damaged. This damage builds up over time and leads to the muscle weakness experienced in DMD.

**What causes DMD?**

DMD, the largest known human gene, provides instructions for making a protein called dystrophin. It is defects in the code (DNA) that tells the body how to make this protein that causes DMD. This protein is located primarily in muscles used for movement (skeletal muscles) and in heart (cardiac) muscle. Small amounts of dystrophin are present in nerve cells in the brain.

In skeletal and cardiac muscles, dystrophin is part of a group of proteins (a protein complex) that work together to strengthen muscle fibers and protect them from injury as muscles contract and relax. The dystrophin complex acts as an anchor, connecting each muscle cell’s structural framework (cytoskeleton) with the lattice of...
proteins and other molecules outside the cell (extracellular matrix). The dystrophin complex may also play a role in cell signaling by interacting with proteins that send and receive chemical signals. Little is known about the function of dystrophin in nerve cells. Research suggests that the protein is important for the normal structure and function of synapses, which are specialized connections between nerve cells where cell-to-cell communication occurs. Skeletal and cardiac muscle cells without enough functional dystrophin become damaged as the muscles repeatedly contract and relax with use. The damaged cells weaken and die over time, causing the characteristic muscle weakness and heart problems seen in Duchenne and Becker muscular dystrophy.

What are the Genetics of DMD?

The sex chromosomes X and Y determine if a baby will be a boy or a girl. DMD is caused by a defect in the dystrophin gene on the X chromosome. One functioning copy is enough to prevent DMD. Girls receive an X from mum and an X from dad and are described as XX. Boys receive a Y from dad and an X from mum and are described as XY. As boys have only one X chromosome if they inherit an X chromosome with the nonfunctioning dystrophin gene then they will have DMD.

The mother is described as a carrier and with one functioning dystrophin gene is usually unaffected. A carrier mother has a 25% chance in each pregnancy of having an affected male child and a 25% chance in each pregnancy of having a carrier daughter.

Approximately 1 in 3 boys with DMD will be the only person in their family to have the condition. This is because the error in the gene has occurred randomly for the first time in the cells that made them. This is called a de novo mutation (new and not inherited).

Genetic counseling is available to families who have had a diagnosis of DMD. This service provides information, helps families understand inheritance patterns and what this means in their family. They can also explain reproductive options available enabling people to make more informed family-planning decisions. Carrier testing of female family members can be arranged if desired when there is a known genetic mutation detected.
Manifesting Carriers of DMD

It is a commonly held belief that carriers merely pass on a condition and are unaffected but approximately 10% of female carriers show symptoms of DMD. Although the disorder in affected girls is usually much milder than in boys, and may include or even exclusively affect cognitive and/or cardiac function, a few girls do have DMD similar in severity to boys.

‘Manifesting’ DMD occurs because there are two X chromosomes in each girl’s cells. This is a double up of the genetic information on the X chromosome so each cell ‘turns one off’. When the X chromosome that has the functioning dystrophin gene on it is turned off then that cell has no dystrophin protein and will be as affected as males with DMD. The number and type of cells which contain the functioning dystrophin gene determines the level of severity in a manifesting carrier.

Diagnosis of DMD

DMD should be suspected in all cases when the following signs are present due to the potential lack of a family history. Most commonly it will be the observation of abnormal muscle function in a male child, occasionally the detection of an increase in serum creatine kinase tested for unrelated indications or after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells). The diagnosis of DMD should thus be considered before liver biopsy in any male child with increased transaminases. Also the presence of Gowers’ sign in a male child should trigger the diagnostic investigation of DMD, especially if the child also has a waddling gait. Toe walking might be present but is not additionally helpful in deciding whether to suspect DMD.

When there is a positive family history of DMD, there should be a low threshold for testing creatine kinase, although this will be influenced by the age of the child. In a child less than 5 years of age, suspicion of DMD probably cannot be excluded completely by a normal muscle examination. However, with increasing age, a normal muscle examination makes the chance of a child having DMD less and less likely. A boy older than 10 years of age with normal muscle function is highly unlikely to have DMD.
**Confirmation of a Diagnosis**

Currently diagnosis of DMD can be confirmed via genetic testing of a blood sample. There are several errors that affect the functioning of the dystrophin gene and once detected this confirms the diagnosis. Sometimes the error is unable to be located. This does not necessarily mean that the boy does not have DMD just that the specific genetic error is hard to determine.

When DMD is suspected but a genetic test is inconclusive a muscle biopsy is required. A muscle biopsy can provide information on the amount and molecular size of dystrophin, as long as the protein is present. Or the measuring of total and partial absence of dystrophin can help to distinguish DMD from other conditions caused by errors in dystrophin production.

**Management of DMD**

The management of Duchenne muscular dystrophy (DMD) has seen dramatic change over the past two decades. Improvements in clinical monitoring of disease progression, management of cardiac and pulmonary complications, and nutritional intervention have all led to decreases in other conditions commonly associated with DMD, and, as a consequence, quality of life and life expectancy of individuals with DMD have both continued to improve.

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**Creatine Phosphokinase (CPK or PK) Testing**

Creatine phosphokinase (CPK) is an enzyme found mainly in the heart, brain, and skeletal muscle. Enzymes are complex proteins that cause a specific chemical change in all parts of the body. For example, they can help break down the foods we eat so the body can use them. Blood clotting is another example of enzymes at work. This is a simple blood test. Remember to tell your doctor about any medications you are taking. Drugs that can increase CPK measurements include amphotericin B, certain anesthetics, statins, fibrates, dexamethasone, alcohol, and cocaine.

When a muscle is damaged, CPK leaks into the bloodstream. Determining which specific form of CPK is high helps doctors determine which tissue has been damaged. This test is used by doctors, in conjunction with other factors present, to detect muscular dystrophies including DMD, dermatomyositis, polymyositis and to help determine DMD carrier status. Factors that may affect test results include cardiac catheterization, intramuscular injections, trauma to muscles, recent surgery, and heavy exercise.
Children with DMD should be under the care of a paediatric neurologist who can refer to other medical disciplines as required. Clinical assessments need to be performed regularly to monitor function.

**NEUROMUSCULAR MANAGEMENT** - maintaining strength and function. Steroids (also called glucocorticoids or corticosteroids) are the only drugs known to slow the decline in muscle strength and motor function in DMD. The goal of steroid use is to help maintain independent walking for longer to allow enhanced participation and to later minimise breathing, heart and orthopaedic problems. They can also reduce the risk of scoliosis (curvature of the spine). Prevention and management of steroid side effects needs to be proactive and anticipatory. Interventions should be put in place EARLY in an effort to prevent problems and to make sure they do not become severe. Side effects associated with steroid use vary.

No recommendations can be made at this time about other supplements or other drugs that are sometimes used in DMD treatment, including co-enzyme Q10, carnitine, amino acids (glutamine, arginine), anti-inflammatories/antioxidants (fish oil, vitamin E, green tea extract, pentoxifylline), and others including herbal or botanical extracts. The experts concluded that there was not enough evidence in the published literature.

**REHABILITATION MANAGEMENT** - will be delivered by physiotherapists and occupational therapists, but other people may also need to help, including rehabilitation specialists, orthotists, providers of wheelchairs and other seating. Orthopaedic surgeons may also be involved. Management of muscle extensibility and joint contractures is a key part of rehabilitation management. The goal of stretching is to preserve function and maintain comfort. The program of stretching will be monitored by the physiotherapist but needs to become part of the family’s daily routine. There are many factors in DMD that contribute to the tendency for joints to get tight or “contracted”. These include the muscle becoming less elastic due to limited use and positioning or because the muscles around a joint are out of balance (one stronger than another). Maintaining good range of movement and symmetry at different joints is important. This helps to maintain the best possible function, prevent the development of fixed deformities, and prevent pressure problems with the skin.
Steroid Use Facts to Remember
1. Steroids are the only medicines known to help slow down muscle weakness.
2. Always tell doctors and other healthcare providers that your son is taking steroids. It is especially important if he is having surgery or has an infection or injury because steroids can suppress the immune system.
3. Your son should never stop taking steroids suddenly.
4. Your son should have regular visits with a doctor who is skilled in managing steroids. The doctor will explain possible side effects and tell you if your son is at risk of developing them.

Psychosocial facts to remember
1. The psychosocial health of your son and your family is important.
2. Your son may have a higher chance of having psychosocial difficulties.
3. You and your family are at risk of some problems such as depression.
4. The best way to manage psychosocial problems is to identify them early and start treatments.
5. Correct use of language may be a problem, as may continuing difficulties at school. These behaviors are often seen in DMD and can be helped with proper assessment and input.
6. Learning problems in DMD are not progressive and most boys catch up when they receive good help.

ORTHOPAEDIC MANAGEMENT - help with bone and joint problems. People with DMD who are not treated with corticosteroids have a 90% chance of developing progressive scoliosis (a sideways curvature of the spine that gets worse as time goes on). Daily steroid treatment has been shown to reduce the risk of scoliosis or at least delay its onset. Proactive management of the risk of scoliosis requires:

Surveillance
• Spinal care should include monitoring for scoliosis. This is done by clinical observation throughout the ambulatory phase and with a spinal X-ray only if scoliosis is observed. In the non-ambulatory phase, clinical assessment for scoliosis is essential at each clinic visit.
• Spinal radiography (X-ray) should be done as a baseline assessment around the time of becoming wheelchair-dependent. Special X rays getting two views of the full spine are needed. Follow up X-rays should be done at least once per year if there is a problem. Gaps of greater than one year between X-rays have the risk of missing a
worsening of scoliosis. After growth has stopped X-rays are only needed if there is any change clinically.

**Prophylaxis (preventive measures)**

- Attention to posture at all times: prevention of asymmetrical contractures in boys who are still walking, proper seating system in the wheelchair giving support of spinal and pelvic symmetry and spinal extension. Spinal bracing is not appropriate to try and delay surgery but may be used if surgery cannot be done or is not the chosen option.

**Treatment**

- Surgery with posterior spinal fusion is indicated when the degree of the curve (known as the Cobb angle) is greater than 20° in boys who have not yet stopped growing and who are not taking steroids. The aim of surgery is to preserve the best possible posture for comfort and function. When boys are taking steroids, there is less risk of deterioration and the decision to proceed to surgery can be left until the Cobb angle is greater than 40°.
- It is important to discuss what type of operation is needed with your surgeon and express any concerns you may have.

**Bone health management**

- Bone health is important in both the ambulatory and non-ambulatory phases of DMD. Boys with DMD at all ages have weak bones, especially if they are taking steroids. They have a lower bone mineral density and are at increased risk of fractures (broken bones) compared to the general population.

**PULMONARY MANAGEMENT** - looking after the breathing muscles. Usually boys do not have trouble breathing or coughing while they are still walking. Because the breathing muscles become affected, as boys with DMD get older they are at risk of chest infections, often due to an ineffective cough. Later on they develop problems with their breathing when sleeping. When they are older, they may require help with breathing during the day as well. As this is a staged progression of problems, a planned and proactive approach to respiratory care is possible based around appropriate surveillance, prophylaxis and interventions. The team must include a doctor and therapist with skill in looking after the delivery of non-invasive ventilation and associated techniques for increasing the amount of air that can enter the lungs (lung volume recruitment), and manual and mechanically assisted cough.
CARDIAC MANAGEMENT - looking after the heart. The aim of cardiac management in DMD is early detection and treatment of the deterioration of heart muscle function (usually cardiomyopathy - involvement of heart muscle, or rhythm problems leading, for example, to palpitations) that commonly accompanies the overall progression of the disease. As this often happens silently (that is without the development of significant symptoms) it needs to be looked out for so it can be treated promptly. The key factors to consider in cardiac management are surveillance and proactive management. You need to be sure that there is a cardiologist involved with the care team.

Nutrition facts to remember
1. Your son’s height and weight should be checked at every visit to the doctor. 2. It is important for your son to have a well-balanced diet, especially one that includes the right amount of calcium and vitamin D. 3. Nutritionists and dieticians are important members of your son’s healthcare team, who can check your son’s diet and help him eat better. 4. Your son should be evaluated if he has signs of swallowing problems. 5. Getting a gastrostomy tube is another option after trying other ways to maintain your son’s weight.

GASTROINTESTINAL MANAGEMENT - nutrition, swallowing and other gastrointestinal issues. Access to the following experts may be needed at different stages: a dietician or nutritionist, a swallowing/speech and language therapist, and a gastroenterologist.

PSYCHOSOCIAL MANAGEMENT - help with behaviour and learning. People with DMD may have an increased risk of psychosocial difficulties, such as problems with behaviour and learning, and medical care is not complete without support for psychosocial wellbeing. Difficulties in social functioning may be due to specific challenges in particular skills, such as getting on with others, judging social situations, and perspectives, while the consequences of DMD (such as physical limitations) may result in social isolation, social withdrawal, and reduced access to social activities. For many parents, the stress caused by the psychosocial problems of the child and difficulties in getting them recognised and properly treated exceeds the stress associated with the physical aspects of the disease.
IN AN EMERGENCY

If you find yourselves needing to go to the hospital in an emergency situation, there are a range of factors that should be taken into account. The diagnosis of DMD, current medication, presence of any respiratory and cardiac complications and the people who are your key medical input should be made clear to the admitting unit. As many health professionals are not aware of the potential management strategies available for DMD, the current life expectancy and expected good quality of life should also be explained.

Research into DMD

There are several strategies for different treatments at the moment. Currently they are going through clinical trials and may or may not become available as a drug for use.

**Atlaturen**, a compound that is under consideration by US FDA, induces ribosomes to not stop at the error in part of the DNA of boys with a specific mutation in the dystrophin gene. This enables the cells to make dystrophin protein and is called exon skipping.

**Eteplirsen** is a splice switching oligonucleotide which changes different DMD mutations, which normally make the DNA unable to be understood, into shorter but functional dystrophin proteins like ones seen in Becker muscular dystrophy.

**Sildenafil** is a drug currently approved for treatment of erectile dysfunction. A study conducted in 10 boys with DMD has found that blood flow to exercising muscles is deficient and that treatment with either tadalafil (Cialis) or sildenafil (Viagra) normalizes this blood flow, at least in the short term (after one dose of either drug). It has not been confirmed if this effect will continue with repeated doses nor if restoring normal blood flow regulation will preserve dystrophic skeletal muscle and slow disease progression. This treatment is continuing to phase 3 clinical trials.

**Resveratrol** is a compound found in foods like grapes and red wine, and it has recently gained popularity due to its anti-inflammatory and oxidative metabolic enhancing properties. In skeletal muscle, resveratrol can reduce inflammation, and improve muscle function in a variety of disease models and encourages cells to produce more utrophin. Utrophin is a protein about 7% shorter than dystrophin, but has a similar structure and function. It is present in the fetus and is replaced by dystrophin at birth.
Cardiac facts to remember
1. Your son’s heart should be checked regularly starting from the time he is diagnosed.
2. In DMD the heart may be already damaged before symptoms appear.
3. This means that your son may need to start heart medication even if he does not have symptoms of heart problems.
4. It is good to pick up silent problems so that they can be treated promptly.
5. Keep a copy of your son’s latest heart tests to show any other doctor who may see your son.

IN AN EMERGENCY REMEMBER
1. You are very likely to know more about DMD than the doctors in Accident and Emergency.
2. Advise the doctor or healthcare staff if your son is taking steroids.
3. If your son has a broken bone, insist that they speak with your doctor or physiotherapist.
4. If you can, bring copies of your son’s most recent test results, such as FVC and LVEF.
5. If your son’s oxygen level drops, the doctor must be very careful about giving him oxygen or sedating medication.
6. If you do not have an emergency card please contact the MDA on 0800 800 337 or info@mda.org.nz to request one.

Resources available
Please go to the MDA website www.mda.org.nz for more information on supports available to you and DVDs and booklets specific to DMD that are currently available. Or contact the Information and Resources Manager on 0800 800 337 or info@mda.org.nz.

The MDA Fieldworkers are available for support. They have in-depth knowledge of a range of neuromuscular conditions, and will have a better understanding of your needs and challenges. Have a chat over the phone or they can come to you for a kanohi ki te kanohi/face-to-face visit. They may have some real practical suggestions that have worked for others to offer as well. This service is offered free of charge to MDA members and is funded through donations and grants. Contact your local MDA Branch to be put in contact with your fieldworker.
Information sourced from
http://www.clinicalnutritionsupplements.com/article/S0261-5614%2812%2900126-4/fulltext
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