Duchenne muscular dystrophy

Key facts

- Duchenne muscular dystrophy (DMD) is a disorder characterised by progressive symmetric muscle weakness (proximal>distal) commencing in the thighs and pelvis, then extending to other muscles of the body.
- DMD is the most common form of muscular dystrophy in children.
- The incidence rate of DMD is 10.7 to 27.8 per 100,000 newborn males. In the UK, about 100 boys are born with DMD each year, and there are about 2,500 people living with the condition at any one time.
- DMD is an X-linked recessive disorder caused by genetic variants in the dystrophin gene on the X chromosome. This means that it usually affects boys, though girls can be affected in rare cases.
- DMD should be considered in all boys who have delayed motor milestones and speech delay, especially when they occur in addition to a positive family history compatible with X-linked inheritance.
- Most individuals with DMD can today expect to survive until at least their early 20s, some even longer, and many maintain a good quality of life.
- Complications of DMD include respiratory failure, cardiomyopathy, scoliosis, osteoporosis and learning disability.
- Symptoms are not usually evident until 18 months of age, and many boys are not diagnosed until five years of age. Increasing awareness of the condition should improve early diagnosis.

Clinical features

- The first symptoms of DMD, as identified by parents, typically include:
  - general motor delays;
  - gait problems, including persistent toe-walking and flat-footedness;
  - delay in walking;
  - learning difficulties; and
  - speech problems.
- Other common features of DMD include:
  - speech delay;
  - weakness, falls and difficulty with motor skills;
  - progressive muscle weakness, most commonly in the legs and pelvis, which is associated with a loss of muscle mass, but also less commonly in the arms, neck and other areas;
  - muscle wasting, calf muscle hypertrophy, lordosis and contractures;
  - a positive Gower's sign (though this is not pathognomonic of DMD, as it can be seen in other forms of muscular dystrophy); and
  - wheelchair dependency by early teens.
- Complications of the condition include: permanent and progressive disability, decreased mobility, contractures, scoliosis and skeletal deformities, osteoporosis, obesity, respiratory failure and pneumonia

or other respiratory infections, cardiomyopathy, congestive cardiac failure and arrhythmias.

- Learning disability is seen in almost half of affected boys. DMD is also associated with increased rates of autism spectrum disorder, attention deficit hyperactivity disorder, obsessive compulsive disorder and anxiety.

Diagnosis

- A diagnosis of DMD should be considered with any evidence of delayed motor milestones in a young child with a positive family history of DMD.
- When there is no family history of DMD, a child not walking by 16 to 18 months, the presence of Gower's sign, toe walking, calf hypertrophy, or unexplained increases in transaminases (for example, aspartate transaminase and alanine transaminase) are all indications of the condition.
- Serum concentration of creatine phosphokinase (CK) level is nearly always increased, even amongst newborns. Serum CK peaks by the age of two; it is usually 10 to 20 times the upper limit of normal, and may be higher. These levels then progressively fall at a rate of about 25% per year, eventually reaching the normal range in many cases, as more and more muscle is replaced by fat and fibrosis. A very high CK makes a diagnosis of DMD probable.
- There is a high spontaneous new mutation rate in DMD, which is why a boy with the condition may be born in a family where there is no family history.
- The diagnosis can usually be confirmed by DNA studies; this has replaced the need for a muscle biopsy and electromyogram in most cases.

Genetic basis and genetic testing

- DMD is an X-linked recessive condition, caused by genetic variants of the dystrophin gene, which is located in the short arm of the X chromosome.
- If a male has an altered dystrophin gene on his X chromosome, then he will be affected with DMD.
- If a woman has an altered dystrophin gene on only one of her X chromosomes, then she is said to be a carrier. It is very rare for a female to have DMD. Occasionally, female carriers may have muscle weakness and cramping. These symptoms are typically milder than the severe muscle weakness and atrophy seen in affected males. Female carriers also have an increased risk of developing heart abnormalities, including cardiomyopathy.
- If a female carrier of DMD has a son, there is a 50% (one-in-two) chance that he will have DMD. If a female carrier has a daughter, there is a 50% (one-in-two) chance that she will be a carrier for DMD.
- In cases where the mother is not a carrier, DMD may occur due to a new mutation in the male, or germline mosaicism in the mother.
- Different types of alterations in the dystrophin gene cause Duchenne muscular dystrophy and Becker muscular dystrophy. Becker muscular dystrophy (BMD) is characterised by muscle weakness of later onset, and most individuals remain ambulatory into their 20s. Genetic testing can establish the diagnosis of DMD and BMD in the majority of, but not all, individuals with these conditions.

Genetic testing is widely available in the UK, and is usually provided through specialist clinics or regional genetic centres. It can be used to:

- confirm the diagnosis in someone with possible DMD or BMD (diagnostic testing);
- provide information about the genetic status of female relatives of someone with DMD through carrier testing; and

- offer prenatal and preimplantation genetic diagnosis:
  - » Prenatal diagnosis is usually possible by chorionic villus sampling (CVS) or amniocentesis.
  - » If a couple are considering prenatal diagnosis, referral should be made to the local clinical genetics service prior to a pregnancy. This ensures that appropriate advice and investigations are undertaken, and confirms whether or not prenatal diagnosis is possible.
  - » All couples considering preimplantation genetic diagnosis must be referred to their local clinical genetics service.
  - » Fetal sex determination by non-invasive prenatal diagnosis is now available, potentially reducing the need for invasive procedures by 50%.
  - » It should be discussed with families, but needs to be facilitated by clinical genetics departments or fetal medicine units.

Clinical management

- Receiving optimal care from a multidisciplinary team, with the input of specialists in many different areas, dramatically improves the quality of life and life expectancy of individuals with DMD, and international guidelines have been agreed to this effect.
- Affected individuals and their families should be actively engaged with the process of individualising care. 'The Diagnosis and Management of Duchenne Muscular Dystrophy: A Guide for Families', published in March 2010, is a useful booklet designed to help with this process.
- DMD is a condition where needs change with time. The different areas of care required at each stage of DMD after diagnosis include: neuromuscular, orthopaedic, rehabilitation, pulmonary, cardiac, gastrointestinal and psychosocial management.
- There are a number of therapeutic clinical trials in progress that are aimed at overcoming the effects of certain types of gene alterations, highlighting the importance of genetic testing.

Direction to further reading, guidelines and patient groups

- More information about DMD can be found on the NHS website.
- Action Duchenne has established a national registry for DMD patients here.

Patient support groups include:

- Duchenne UK - Email: info@duchenneuk.org
- Muscular Dystrophy UK - Tel: 0800 652 6352
- Muscle Help Foundation - Tel: 01763 274658
- 'Joining Jack' Facebook group

This information is intended for educational use and was current in May 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Royal Cornwall Hospital NHS Trust's Clinical Genetics department.