1 Duchenne Muscular Dystrophy: A Medical Overview

ALEX HOWARTH

Duchenne muscular dystrophy is the most common and usually most severe form of muscular dystrophy (Kapsa et al., 2003). It is named after Dr Duchenne de Boulogne – a mid-nineteenth-century French physician, who was one of the first people to study and document some of the muscular dystrophies.

Duchenne muscular dystrophy is an X-linked recessive muscle-wasting disorder, involving progressive muscle weakness which normally becomes evident before the age of five years in an affected boy. A defective gene on the X chromosome (at Xp21 site) leads to a deficiency in dystrophin – a rod-shaped cytoskeletal protein which normally maintains the integrity of the muscle cell wall. Where dystrophin is deficient, there is an influx of calcium ions, a breakdown of the calcium calmodulin complex and an excess of free radicals. These changes lead eventually to irreversible destruction of the muscle cells. Dystrophin is also found in the brain and its deficiency is associated with cognitive impairment to a varying degree (Anderson et al., 2002; Leet et al., 2002).

In X-linked recessive inheritance, it is generally the males that are affected because the mutated allele on the X chromosome is not balanced by a normal allele, as it is in the case of females (males have X and Y chromosomes, whereas females have two X chromosomes). In approximately half to two-thirds of all cases of Duchenne muscular dystrophy, the mother carries the defective gene. In these cases, the female relatives of the carrier mother should be offered genetic counselling. The remaining cases arise through spontaneous mutation and, in these instances, female relatives will have the normal population risk of having an affected male child. For the general population, the risk of having an affected child is one in every 3,500–4,000 male births (Lissauer & Claydon, 1997; Nowak & Davies, 2004).

Female carriers are usually healthy, although a small number have a mild degree of weakness themselves and are then known as manifesting carriers. Daughters of affected males will all be carriers, whilst sons will not be affected, since a man passes a Y chromosome to his son. Each son of a female carrier has a 50% risk of being affected, and each daughter a 50% risk of being a carrier.
There are around 1,500 boys with Duchenne muscular dystrophy living in the UK at any one time. About 100 are born with the condition each year. Diagnosis is often made on clinical grounds supported by laboratory tests. The serum creatine phosphokinase is normally grossly elevated (normal values are in the lower hundreds, depending on the particular laboratory, but, in Duchenne muscular dystrophy, this figure will be in the high thousands). At this stage, a blood sample would also be sent to the genetics laboratory to look for a deletion or duplication on the X chromosome. If no deletion or duplication is identified, the next stage would be to proceed to a muscle biopsy. An absence of dystrophin staining on immunocytochemical staining together with the other changes typical of Duchenne muscular dystrophy, such as variation in muscle fibre size, muscle fibre necrosis, regeneration and replacement by fat, would confirm the diagnosis of Duchenne muscular dystrophy.

Once a mutation has been identified in a family, the female relative should be offered genetic counselling. Identification of carrier females requires interpretation of pedigree and specific tests: 70% of carrier females have a raised creatine phosphokinase level. Accurate carrier and prenatal diagnosis can also be made through DNA testing for gene deletion, duplication or point mutation. In the case in which a mutation has been identified in the affected male but not in the mother, there is a chance that the mutation has arisen in the ovaries of the mother. This is called Gonadal Mosaicism. However, tests for this are not available at the present time. In these cases, there is a 5% risk of having a further affected male child. Prenatal diagnosis should therefore be offered to these women.

**CLINICAL FEATURES**

Symptoms usually begin between the second and sixth year of life (Rogers et al., 2001). The average age of diagnosis is 5.5 years, although children are usually referred for a medical opinion when much younger. Involvement begins in the proximal musculature of the pelvic girdle, proceeds to the shoulder girdle and finally affects all muscle groups, including the respiratory and heart muscles. Gower’s Sign, in which the child uses his arms to crawl up his thighs into a standing position from a kneeling position, is diagnostically significant. Other indicators include: delayed walking; a waddling gait; toe-walking; a reluctance to walk; difficulty rising from a sitting or lying position; an inability to hop, skip or jump; frequent falling and stumbling; problems climbing stairs and running; cramp in the legs; and excessive fatigue. Enlargement of the calf, and sometimes of the forearm and thigh, is also characteristic. It is known as *pseudo*-hypertrophy because the enlargement of the muscle is not due to additional muscle fibres, but to replacement of the muscle fibres by fat and fibrous tissue. Progressive atrophy and weakness lead boys to
become wheelchair-dependent, usually at between eight and eleven years of age. Joint contractures at the hip, knee and ankle and spinal deformities (scoliosis, kyphosis and lordosis) are common complications.

Duchenne muscular dystrophy is a life-limiting condition but, with improvement in management in areas such as the introduction of steroids (while the boys are still ambulant), postural management (once they are wheelchair-bound), spinal-fusion surgery, non-invasive ventilation and possibly more intense cardiac surveillance and management, the prognosis is improving. At present, many patients will die as a result of cardiac or respiratory failure (Eagle et al., 2002). Without ventilatory support, the average age of death is around 19 years but, where cardiac and respiratory functions are effectively managed, a survival to the third or fourth decade is not unknown (Brown, 2002; Bushby et al., 2005; Simonds, 2001).

Respiratory management is a subject that needs to be approached with sensitivity. In some cases, discussion of overnight ventilation may lead the family to appreciate fully for the first time that Duchenne muscular dystrophy is a life-limiting condition. Strong emotive reactions to this form of intervention may then ensue – total rejection on the one hand, an exaggerated sense of dependency on the other. In general, medical information may have to be explained several times to allow the families to absorb it fully and make fully informed decisions about future options.

**KEY POINTS**

- Duchenne muscular dystrophy is the most common and usually most severe form of muscular dystrophy. It is a life-limiting condition.
- It is an X-linked recessive muscle-wasting disorder leading to a deficiency in dystrophin – a protein which normally protects the integrity of the muscle cell wall. Dystrophin is also found in the brain and its deficiency is associated with cognitive impairment.
- In X-linked recessive inheritance, it is generally the males that are affected. In approximately half to two-thirds of all cases, the mother carries the defective gene. Spontaneous mutation is responsible for the rest.
- Daughters of affected males will be carriers; each son of a female carrier has a 50% risk of being affected, and each daughter a 50% risk of being a carrier.
- About 1,500 boys are affected with Duchenne muscular dystrophy in the UK at any one time. About 100 are born with the condition every year.
- Diagnosis is often made on clinical grounds supported by laboratory tests. The serum creatine phosphokinase is usually grossly elevated. Duplication or deletion on the X chromosome would then be investigated through blood sampling. Muscle biopsy would be carried out if no deletion or duplication is found. An absence of dystrophin, variation in muscle fibre size, muscle
fibre necrosis, regeneration and replacement by fat would confirm a diagnosis of Duchenne muscular dystrophy.

- Accurate carrier and prenatal diagnosis can be made through DNA testing for gene depletion, duplication or point mutation.
- Symptoms usually begin between the second and sixth years of life. The average age of diagnosis is 5.5 years and wheelchair dependency occurs at between eight and eleven years.
- Involvement begins in proximal musculature of the pelvic girdle, proceeds to the shoulder girdle and finally affects all muscle groups, including the respiratory and heart muscles.
- The Gower’s Sign (a characteristic method of transferring from kneeling to standing) is diagnostically significant. Delayed walking, a waddling gait, problems with stairs and running, leg cramps, excessive fatigue and pseudo-hypertrophy are other indicators.
- Prognosis is improving through developments in respiratory and cardiac management, the introduction of steroids, postural management and spinal-fusion surgery.