SYNDROMES

Duchenne muscular dystrophy

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Introduction

In 1868, Guillaume Duchenne (1806–1875), working in Paris, described a “pseudohypertrophic paralysis ... which deceives and deludes by giving the limbs the appearance of great muscularity”.\textsuperscript{1} Duchenne muscular dystrophy (DMD) is the most common childhood neuromuscular disorder, was the first muscular dystrophy described, is incurable at present and is invariably fatal. The disease involves a progressive degeneration of skeletal muscle without associated abnormality in the central or peripheral nervous system.\textsuperscript{2}

Epidemiology and genetics

DMD has an incidence of 2–3 per 100,000, or 1 in 3500 boys. It is an X-linked recessive disorder, and can therefore present in XO females (Turner’s syndrome). The incidence is reducing due to genetic counselling, but 30% of cases involve spontaneous mutations. The gene involved was first mapped in 1987 and is located on the short arm of the X chromosome (Xp21). It codes for dystrophin, a 400 kDa membrane protein involved in membrane stability. Many different mutations and deletions have been described, causing varying phenotypic severity.

Clinical presentation and diagnosis

Affected boys are normal at birth and early motor milestones may be appropriate (head control, sitting, etc.). Independent ambulation is usually delayed, with tiptoe walking and delayed speech. Steady progression results in a waddling gait with frequent stumbling and tripping, difficulty standing up and problems with stair climbing.

Proximal muscle weakness precedes distal. Early involvement of the gluteal musculature results in Gower’s sign (when rising from the floor, the child “walks” his hands up his thighs due to weakness of hip extension, although widely described as pathognomonic for DMD, this sign can also be present in the early stages of discitis).\textsuperscript{3} Relative sparing of tibialis posterior function causes tiptoe walking and equinovarus deformity (Fig. 1). Another classic feature is calf pseudohypertrophy due to fibro-fatty infiltration, giving a firm rubbery feel on palpation.

By the age of 7, walking becomes increasingly difficult. The knee is hyperextended and the torso tilted back in an attempt to lock out the hip and knee joints. The ability to walk is lost on average at 9 years of age (range 6–12), after which the patient becomes wheelchair bound and may develop severe flexion contractures. Scoliosis affects 90%, with progressive collapse into a C shape, and severe pelvic obliquity leading to loss of sitting balance. Painful hip dislocation may occur. Most die in their early 20s from cardio-respiratory failure.

The lack of dystrophin in the cell membrane leads to the release of creatine kinase (CK) from myocytes, allowing the diagnosis to be made by markedly increased serum CK levels (100 × normal) before symptoms and signs develop. Carrier
females, although asymptomatic, will also have CK levels 75% greater than normal. Electromyography will demon-
strate myopathic signs (short duration action potentials and polyphasic units) and muscle biopsy shows absence of
dystrophin on staining. Genetic testing is available for confirmation in the affected boy, carrier mother or foetus.

The pattern of physical findings should allow a clinical diagnosis to be made from the age of 3 years onwards, but it is often missed at first presentation, leading to the potential for further affected pregnancies in uninformed families. A serum CK estimation should be carried out on any boy with a clumsy or abnormal gait or with an unexplained equinus deformity. The only way reliably to reduce the age of diagnosis would be to introduce a newborn screening programme, but there are no plans for this in the UK.

The less common but milder Becker muscular dystrophy, which involves a different type of mutation in the same gene, causes structurally abnormal dystrophin to be produced. There is a later age of onset and slower progression.

**Treatment**

**General**

Currently, no curative treatment is available for DMD. Affected boys should be kept ambulatory or standing for as
long as possible. Regular stretching and strengthening exercises, night-time splinting, ground-reaction AFOs and a standing frame may all be useful. Corticosteroids (prednisolone and deflazacort) have been shown to delay the loss of muscle strength and function by up to 3 years and delay or prevent the onset of scoliosis, but have serious potential side effects including weight gain and Cushing's syndrome.

Lower limbs

Serial hip radiographs are used to screen for subluxation. Flexion and abduction contractures of the hip may require percutaneous release. Equinovarus foot deformity is treated with tenoachillis lengthening and tibialis posterior transfer which prolongs the ability to walk. Surgical release of soft tissue knee contractures is less effective. Aggressive post-operative rehabilitation is needed to preserve overall function, with an avoidance of prolonged immobilisation.

Spine

The spinal deformity is not amenable to non-surgical control. Early fusion with segmental instrumentation improves the Cobb angle, delays the deterioration in lung function and improves survival (Fig. 2). Timing is crucial, with a narrow window of opportunity after the curve starts to develop, but before respiratory and cardiac function are compromised to the point that the risk of surgery is too great. An FVC less than 30% of the predicted value does not necessarily preclude surgery.

A long thoraco-lumbar fusion is performed. In boys with significant shoulder weakness, any kyphosis should be only partially corrected to avoid the loss of ability to raise the hand to the mouth. Blood loss and overall complications are higher than for idiopathic scoliosis correction. The vital capacity at the age of 10 is a good predictor of the speed of progression and is useful in identifying those that require early surgical intervention.

Gene therapy

Although the gene defect responsible for DMD was identified nearly 20 years ago, the development of effective therapy has been slow. The large size of the dystrophin gene makes transfer difficult by the standard vector systems, necessitating the development of novel approaches. A minigene has been successfully transferred in a mouse model of DMD, with restoration of normal muscle function. Other attempts are being made to target the downstream effects of DMD, such as the implantation of myoblasts into dystrophic muscle to repair a proportion of damaged myofibrils. Together these advances in molecular biology suggest a cure for DMD may be available in the near future.

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References