

## **Duchenne muscular dystrophy**

### **An overview of Duchenne muscular dystrophy**

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Duchenne muscular dystrophy (DMD) affects approximately 1 in 3,500 live male births [1]. It is caused by a large variety of mutations in the dystrophin gene. Because of these mutations, the body can no longer make dystrophin which is a protein important for stabilisation of the muscle cell during a contraction. Without dystrophin, muscle cells are damaged and slowly replaced by fat and scar tissue.

### **Genetics**

The DMD gene was first described in 1986 [2]. Subsequently, its great extent and complexity has been revealed. As the largest gene in the human genome, the DMD gene spans ~2.5Mb of genomic sequence and contains 79 exons [3]. Due to this very large size, a great many different types of mutational change are possible varying both in location and in type of functional disruption. To date, > 4,700 different mutations in the DMD gene have been documented [4]. These can be grouped into three main categories: deletions, duplications (or triplications), or point mutations (small changes within a single exon). Point mutations are further classified as: nonsense, frame shift, missense or splice site mutations.

### **Clinical signs and symptoms**

Boys with DMD present in early childhood with failure to meet developmental milestones, and soon exhibit delayed walking, increased falls, decreased activity, difficulty climbing stairs or difficult getting up off the floor [5]. Unique identifiers of DMD include a positive “Gower’s sign”, whereby the boy uses his hands to walk himself up his legs; and enlarged calf muscles which is indicative of fibrous infiltration of the muscle. Toe walking may also be present. Diagnosis can be confirmed by genetic analysis with or without elevated serum creatine kinase or a muscle biopsy demonstrating an absence of dystrophin [1]. A family history may or may not be present, as approximately 30% of cases result from spontaneous mutations [6]. The mean age of diagnosis is approximately five years of age [7, 8]. A milder condition, Becker muscular dystrophy (BMD), may be identified in older boys presenting with similar symptoms.

The natural history of DMD is characterised by progressive muscle weakness that usually first manifests in boys ~3 to 7 years old [1]. By 8 years of age, most boys have difficulty climbing stairs and frequently fall while walking. By age 10 to 13 years, young men with DMD lose the ability to walk independently [9-12].

### **Management**

Steroid therapy is now accepted as best practice for the medical management for DMD usually given either as prednisone or deflazacort [1, 13, 14]. Steroids have clear benefits in the maintenance of muscle strength and functional ability [15]. Their precise mode of action is unclear as is the optimal time to commence steroid treatment [14, 16]. The recent practice guidelines suggest steroids should be commenced when a boy reaches a plateau; that is, when there is no longer any progression of motor skills but prior to any decline [1]. This will usually occur between the ages of 4-8 years. The standard initial therapeutic dose is 0.75mg/kg/day for prednisone and 0.9mg/kg/day for deflazacort [14] with preference for a

daily regimen over alternative regimens (alternate day, high dose weekend, or 10 day on/10 day off cycling) [1].

Boys treated with steroids have improved walking ability, less curvature in the spine and better lung function than those not taking steroids [17-20]. However, side effects of treatment such as excessive weight gain, cushingoid features, weak bones, impaired growth, cataracts and behavioural changes, can be of sufficient concern to cause their withdrawal [18, 21, 22]. Steroid therapy can also delay puberty, which in itself has repercussions for bone health and psychosocial wellbeing [22, 23].

Data on the longer term effects of steroid are beginning to emerge. In the United States, steroid use for DMD has increased from 20% in 1991 to 44% in 2005 [24]. Steroid therapy is also changing the natural history of DMD. A recent review demonstrates that long term steroid therapy in boys with DMD prolongs ambulation by 2-5 years, reduces the need for spinal surgery, improves heart and lung function, delays the need for ventilation, and increases survival and quality of life [25].

The goals of multidisciplinary treatment are supportive and work in conjunction with steroid treatment. The multidisciplinary team involves many specialities: neurology, cardiology, respiratory, orthopaedics, gastroenterology, physiotherapy, occupational therapy, psychology, social work, and nutrition and dietetics [1]. With the exception of physiotherapy, boys may only require these specialities intermittently. Daily physiotherapy, on the other hand, aims to maintain mobility, flexibility and independence in boys with DMD and may reduce complications such as the development of contractures and scoliosis [26].

### **Potential therapies**

Many promising advances into treatments for DMD are emerging. Therapeutics can be divided into two categories: pharmaceutical interventions that aim to restore dystrophin expression, or gene therapy whereby a functional copy of the DMD gene is introduced into the muscle fibres. Pharmaceutical therapies appear to be the most promising treatment option to date. Ataluren (PTC124®) is an orally administered drug that promotes ribosomal read-through of nonsense mutations. Exon skipping uses antisense molecules that can skip targeted exons. This treatment option may ameliorate the most severe symptoms, resulting in a milder phenotype. Two different types of antisense molecules can skip exon 51 and both have been investigated in Phase 2 clinical trials: phosphorodiamidate morpholino oligomer (AVI-4658) and 2'-O-methylphosphorothioate (PRO051/GSK2402968) [27, 28]. Until a cure is found, therapeutic and supportive interventions must assist in preventing or delaying complications and preserving quality of life.

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