

Delay in diagnosis of Duchenne muscular dystrophy may reduce benefit from new corticosteroid protocol

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About one-third of boys with Duchenne muscular dystrophy (DMD) have associated learning difficulties, particularly speech and language delay, and this may be the initial presenting complaint. Attention is often focused on behaviour and learning difficulties, and the progressive muscle weakness may not be noticed until the condition is advanced.

Now that corticosteroids have been established as the gold standard of care, delay in the diagnosis of DMD has become far more relevant because any delay may limit the benefit that can be gained from steroid therapy, since muscle strength that has been lost cannot be regained.

We present 3 cases of boys with unexplained learning difficulty in whom the diagnosis could have been made far earlier if a creatine kinase test had been done at presentation.

Duchenne muscular dystrophy (DMD) affects 1:3 500 live male births.¹ It is an X-linked recessive disorder of the dystrophin gene at Xp21 resulting in absence of dystrophin in muscle fibres. This condition causes progressive muscle weakness with loss of ambulation and early death due to progressive respiratory impairment and cardiomyopathy. One-third of cases are due to new mutations in the dystrophin gene,² so the typical pattern of X-linked family inheritance may be absent. Delay in motor development is common, with at least half not walking until the age of 18 months.³ Others may present as toe-walkers. Later, typical muscle weakness and a positive Gowers sign develop. However, about one-third of boys with DMD have associated learning difficulties, particularly speech and language delay, and this may be the initial presenting complaint. Attention may then be focused on behaviour and learning difficulties, and the progressive muscle weakness may not be noticed until the condition is advanced. A number of publications in recent years have described delayed diagnosis in DMD and have emphasised the importance of screening all young boys with learning difficulties using a creatine kinase (CK) test.^{4,5} Unfortunately, delay in diagnosis continues to occur. This has often led to difficulties for families, particularly where a second affected boy is born before the first is diagnosed. However, now that corticosteroids have been established as the gold standard of care,⁶ delay in diagnosis has become far more relevant because steroids can significantly delay the progression of the disorder, and late diagnosis means that affected boys may have reduced benefit from corticosteroid treatment. We present 3 cases of boys with unexplained learning difficulty in whom the diagnosis could have been made earlier if a CK test had been done at presentation.

Case 1

A 6-year-old boy was referred by his GP because of lapses in concentration. There had been concerns regarding his development since he started to walk at 18 months of age. At that time he was referred to a child development centre and was found to have global developmental delay and behavioural problems. His parents later noticed that he had an abnormal gait. He had never been able to run or jump, and recently he struggled to get up off the floor. He was attending a special school for children with learning difficulties and had regular contact with physiotherapists and occupational therapists. There was no family history of muscular dystrophy. The history did not suggest a seizure disorder.

Examination revealed calf hypertrophy, increased lumbar lordosis and a waddling gait. He had a positive Gowers manoeuvre timed at 7 seconds. Formal muscle strength testing confirmed proximal weakness involving the hip and shoulder girdle. He had mild contractures of the Achilles tendons.

A general anaesthetic for grommet insertion had been planned for 3 weeks after his first clinic appointment, and the choice of anaesthetic was changed based on the likely diagnosis of DMD in order to reduce the danger of a malignant hyperthermia-type reaction.

Investigations confirmed the diagnosis of DMD with a serum CK level of 16 000 IU/l (upper limit of normal 190 IU/l). A muscle biopsy taken from the vastus lateralis confirmed a dystrophic process with absent dystrophin staining for all 3 dystrophin epitopes. DNA studies confirmed a duplication in the dystrophin gene (Xp21) involving exons 16 and 17.

Case 2

A 7½-year-old boy with motor difficulties was referred to the muscle clinic. He had sat without support at 9 months of age and crawled soon afterwards. He had global developmental delay and did not walk independently until 20 months of age. He did not speak in sentences until 3½ years, and was over 4 years of age before toilet training could be commenced. On starting school, it was noticed that he had significant behavioural problems. He was seen regularly by multiple child health professionals. He had never been able to jump or hop and had never been able to run. He had always walked with a wide-based gait and had recently started to toe-walk. There was no family history of muscular dystrophy.

On examination, he had a positive Gowers manoeuvre timed at 7 seconds, pseudohypertrophy of his calf muscles, increased lumbar lordosis and a Trendelenburg gait. He was found to have proximal shoulder and pelvic girdle muscle weakness, and he had contractures of the Achilles tendons.

Investigations confirmed an elevated serum CK level of 16 000 IU/l. Muscle biopsy of the left vastus lateralis confirmed the diagnosis of DMD with complete absence of dystrophin staining. DNA studies demonstrated a duplication in the Xp21 gene at exon 54.

Case 3

A boy was referred at 6 years 8 months with motor problems. He had walked at just under 2 years of age and had always had difficulties with stairs and with running. He had speech and language delay and was receiving speech therapy, and had been referred to a specialist language unit. He had also been assessed for additional educational support because of learning and concentration problems. There was no relevant family history.

At presentation he had proximal shoulder and pelvic girdle weakness with a waddling gait, increased lumbar lordosis and a positive Gowers manoeuvre. His calves were hypertrophied and firm and his Achilles tendons were tight.

Investigations confirmed the diagnosis of DMD with a CK level of more than 10 000 IU/l. Muscle biopsy showed an absence of dystrophin, and DNA studies revealed a duplication in the dystrophin gene at exons 8 to 12.

Within 9 months of presentation he was struggling to get up from the floor, with a Gowers' time of 13 seconds, and he lost independent ambulation at 8 years 11 months.

Discussion

The natural history of DMD is that all boys become wheelchair-dependent between the ages of 6 and 12 years, with a mean age of 9.5 years.⁷ This is followed by progressive decline of respiratory function, and death follows in the early 20s.⁸ The main aim of early management is to delay this progression and preserve ambulation for as long as possible. Long-term survival has been significantly improved with the use of non-invasive nocturnal ventilation.⁹ Since the 1970s there have been a number of randomised controlled trials of steroid treatment in DMD. Evidence from certain studies demonstrates at least short-term benefit with preservation of functional scores for up to 2 years.⁸ Recently, long-term open studies have suggested that steroids preserve respiratory and

cardiac function at least until the age of 18 years.¹⁰ A European Neuromuscular Centre (ENMC) Workshop has recommended that corticosteroid treatment be offered as the gold standard of care in DMD.⁶ The UK Duchenne Steroid Group consensus guideline recommends that prednisolone be used at a dose of 0.75 mg/kg per day given daily or intermittently (10 days on, 10 days off). Current recommendations are that steroids should be started when there is a plateau of gross motor development, usually around the age of 5 - 7 years. Delay in diagnosis may limit the benefit that can be gained from steroid therapy because muscle strength that has been lost cannot be regained.

The benefit of steroids is not the only advantage to early diagnosis. Other clear advantages include genetic counselling, which allows informed decisions to be made about family planning. Early diagnosis also helps the family to adjust to the prognosis and plan for housing adaptations and education. Both Duchenne and Becker muscular dystrophy run the risk of an anaesthetic reaction similar to malignant hyperthermia, and this can be avoided if the diagnosis is known.¹¹

DMD has a wide phenotypic variability and the initial presenting complaint can be misleading. In all 3 of the cases we have described, attention was focused on learning difficulties, and the loss of muscle function was not noticed until it was advanced. In these patients the optimum time to start steroids had passed. However if a serum CK level is measured in all boys presenting with unexplained learning difficulties or global developmental delay, then the detrimental consequences of late diagnosis can be avoided, and the benefits of early diagnosis can be fully utilised.

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