Recent developments in the management of Duchenne muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is the most common severe heritable muscle disorder of childhood. Affected boys show first symptoms around the age of 2–5 years with progressive muscle weakness and wasting leading to severe disability and reduced life span due to cardiac and respiratory complications. Although no curative treatment is currently available for this severe and fatal condition recent advances in general, respiratory and cardiac care and judicious use of corticosteroids have changed the natural course of DMD. Careful and timely management of the disease, its complications and psychosocial aspects is mandatory. Such interventions have been shown to improve quality of life and prolong survival, so that most of patients now reach adulthood. New promising treatments have been identified by research studies. Translating these successes into clinical practice to maximize benefit for children and families will benefit from a standardized approach to management.

A multidisciplinary approach is a key element for the care of these patients, where a central role can be played by paediatricians in all aspects of management and coordination of the specialists involved. This review is based on the internationally agreed care recommendations for DMD and aims to provide some guidelines to paediatricians for the management of these patients.

Keywords corticosteroids; Duchenne muscular dystrophy; management; standards of care

Introduction

Duchenne muscular dystrophy (DMD) is the most common and severe childhood muscle condition affecting one in 3500–6000 live male births. It is an X-linked recessive disorder clinically characterized by progressive muscle weakness and wasting, affecting ultimately all body muscles including the respiratory muscles and the heart.

DMD occurs as a result of mutations in the dystrophin gene, the largest gene in the human genome.

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The mutations which result in DMD cause disruption of the reading frame, leading to absence or severe reduction of the protein dystrophin. In-frame mutations lead to the production of a smaller or quantitatively reduced but partially functional dystrophin and results in the milder allelic form of dystrophinopathy, Becker muscular dystrophy (BMD).

Dystrophin is expressed in skeletal and cardiac muscles and in brain; in muscle cells, dystrophin plays an essential role in the maintenance of membrane integrity during muscle fibre contracture. The absence of dystrophin renders muscle cells susceptible to stretch-induced damage and results in progressive muscle fibre degeneration and replacement with fat and connective tissue.

First symptoms are usually noted between 2 and 5 years of age and without treatment, affected boys become wheelchair dependent around the age of ten and die in their twenties due to respiratory and cardiac failures.

The management of these patients includes different steps, starting from early diagnosis, pharmacological treatment and prevention of corticosteroids (CS) side effects, prompt identification and treatment of complications, to psychological and social support. Corticosteroids remain almost the only drug treatment currently available to improve muscle strength for DMD patients. Use of corticosteroids and prompt and adequate management of the cardiac and respiratory complications alter the natural history of DMD, leading to survival into adulthood for most patients. Recently, international agreement has been achieved about care recommendations in DMD, which take into account stages of the disease and the different needs.

Diagnosis

The aim of care around diagnosis is to promptly confirm molecular diagnosis allowing genetic counselling, early plan of appropriate interventions and possibly determine eligibility for ongoing clinical trials. Paediatricians play an essential role in this early process. DMD should be considered in all male children with early clinical signs of muscle weakness, including difficulties with running, hopping, getting up from the floor (Gower's manoeuvre) or climbing stairs, abnormal or tip-toe walking. Presence of calf hypertrophy should enhance the suspicion of DMD. Although recognition of these problems is most common between 2 and 5 years of age, motor and speech development delay can trigger an earlier diagnosis. About one third of DMD boys shows cognitive impairment, and therefore the concomitant presence of learning disability and muscle weakness is highly suspicious of dystrophinopathies. DMD should also be considered suspected in boys with unexplained increase in transaminases, as they can be produced by muscle instead of liver cells. A negative family history does not exclude the diagnosis as de novo mutations occur in approximately one third of the cases.

Massive elevation of the serum CK (more than 1000 and up to 30,000 IU/l), although non-specific, is always present in DMD. Variations can be seen with age, but as rule of thumb, normal CK levels (less than 200 IU/l) exclude the diagnosis. Historically, the route to confirm the diagnosis included a muscle biopsy to prove the absence of dystrophin on muscle fibres followed by genetic testing, however this has been challenged with the advances in molecular genetic testing.

Genetic testing is mandatory even with demonstrated absence of dystrophin on muscle biopsy, as it allows genetic counselling, prenatal diagnosis and consideration for mutation-specific clinical studies and future therapies. In practice many specialized departments rely on genetic testing without an invasive muscle biopsy. Multiplex ligation-dependent probe amplification (MLPA) is the preferable genetic test as covers all exons, detecting deletions and duplications. If neither deletions nor duplications are detected, entire dystrophin gene sequencing should be done to identify point mutations or small deletions/insertions. It is debatable whether a muscle biopsy should be considered before proceeding with this more sophisticated technique and in these cases the diagnostic process might vary from centre to centre depending on the facilities available. Muscle biopsy becomes essential for differential diagnosis, when no mutations in the dystrophin gene are detected.

Despite advances in the techniques available for diagnosis, delay in making the diagnosis is still frequently seen and appears to be due to a combination of delayed referral (presentational delay) and diagnostic delay (failure to check CK levels). Paediatricians have an important role in raising the awareness of DMD to those working in primary care services. An early diagnosis is critical to provide timely access to genetic counselling and allow parents to make informed choices regarding family planning and it is likely to result in better care and access to clinical trials with innovative drugs.

CK blood testing should be considered in primary care for any boy presenting with motor development delay or late speech thus allowing earlier diagnosis of DMD. An acronym (MUSCLE) has been suggested to disseminate awareness of muscle diseases in primary care to improve the diagnosis of DMD (see Box 1). An online module on neuromuscular disorders has been recently published on the Royal College of General Practitioners (RCGP) as part of the RCGP learning environment.

Following the diagnosis, genetic counselling is essential. Genetic counselling should emphasize that germ line mosaicism might occur, with an average 10% risk of recurrence even with negative DNA test in the mother. Psychosocial health of the family and patient is crucial at this stage and the opportunity to contact parent/patient support groups should be offered to prevent social problems and isolation. The key points of diagnosis are summarized in Box 1.

Key points of diagnosis

- Family history
- Clinical signs and symptoms
  - Delayed motor milestones
  - Speech delay
  - Calf muscle hypertrophy
  - Proximal lower limb muscle weakness (falls, tip-toe walking, Gower's)
  - Learning difficulties or autistic spectrum disorders
  - Unexplained increase of transaminases (ALT, AST, LDH)
- Creatine kinase levels
- Genetic analysis of dystrophin gene

Note: Muscle biopsy is not usually required to confirm the diagnosis, although it can be requested in cases where the clinical presentation and the type of mutations are equivocal on the severity of the phenotype. Molecular testing and muscle biopsy should be performed in specialized centres with expertise in neuromuscular pathology and genetics, allowing a correct correlation between clinical phenotype, dystrophin expression and reading frame role.

To diagnose neuromuscular diseases think MUSCLE

M	Motor milestone delay
U	Unusual gait
S	Speech delay
C	CK ASAP
L	Leads to
E	Early diagnosis

Box 1

Treatment, management and follow-up

Clinical appointments and follow-up

DMD is a complex multi-system disorder. Following diagnosis referral to specialized multidisciplinary centres is essential. Such specialized centres can coordinate with the different specialists involved in the patients' care, including muscle specialists, paediatricians, neurologists, cardiologists, respiratory physicians, physiotherapists, orthopaedists, endocrinologists, psychologists and social carers. Patients, especially adults, who attend a specialized clinic are more satisfied with their care than those who do not.

As general rule of thumb, children with DMD should be seen for follow-up visits every 6 months ideally in specialized neuromuscular centres. However, frequency of appointments can vary depending on number of specialists involved, local clinical services, age of the child and stage of the condition, specific or emergency issues. The aim of the assessments is to identify areas of needs and plan preventive interventions to optimize the child's physical, social and intellectual status.

Around diagnosis, closer monitoring is often required to adequately support the family and identify required interventions, including genetic counselling, education, preventive physiotherapy interventions and advices, and considerations about treatment. Other crucial disease stages includes time before entering school, when special educational needs and adaptations due to reduced mobility should be considered, and times around change in function, such as loss of ambulation, development of respiratory and cardiac involvement or feeding difficulties. Planned transition to adult care is crucial as the risk of complications is high at that stage. Data suggest that adult care is provided less systematically than in paediatric age group which is a major cause for concern.

Assessment should not be limited to the neuromuscular features, but should target all different aspects of the condition, including cognitive impairment, psychological and social issues and information for families on the major areas of importance for emergency care (Table 1).