Update on the management of Duchenne muscular dystrophy

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Adnan Y Manzur, Maria Kinali, Francesco Muntoni

Dubowitz Neuromuscular Centre, Department of Paediatric Neurology, Great Ormond Street Hospital for Children, Institute of Child Health, London, UK.

Disclosures

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Correspondence to:

Dr Adnan Y Manzur
Consultant Paediatric Neurologist
Great Ormond Street Hospital for Children NHS Trust
Great Ormond Street,
London WC1N 3JH
Email: manzua@gosh.nhs.uk
Summary

Duchenne Muscular Dystrophy (DMD) is familiar to paediatricians as the most common childhood muscular dystrophy, leading to severe disability and early death in late teenage years, if untreated. Improvement in general care, glucocorticoid corticosteroid treatment, non-invasive ventilatory support, cardiomyopathy and scoliosis management have significantly changed the course of the DMD in treated individuals, so that survival into adulthood is now a realistic possibility for most DMD patients. This has important implications for the medical and social sectors to provide transition to adult medical services, suitable employment, and social care. Multidisciplinary team working for optimal management of the DMD-specific multisystem complications is essential, and collaboration in disease specific national clinical networks is recommended. Several curative therapeutic strategies including cell and gene therapy in DMD are being pursued, but these are still at an experimental stage.

Key words: Duchenne muscular dystrophy, management, therapy, North Star clinical network.

Introduction

Duchenne Muscular Dystrophy (DMD) affects 1 in every 3,500 live male births. Paediatricians are familiar with the course of untreated DMD: common presentation is with abnormal gait, calf hypertrophy and difficulty in rising from the floor between 2 to 5 years of age. Progression of muscle weakness and leg contractures leads to loss of walking and complete wheelchair dependence, at a mean age of 9.5 years, and the ensuing early teenage years are marked by development of progressive scoliosis. The leading cause of death is respiratory insufficiency in the late teens or early twenties, though a minority demise because of cardiac complications such as dilated cardiomyopathy. Feeding difficulties and weight loss are common in the late stages of the disease.

No curative treatment for DMD is yet known, but advances in management over the last two decades have altered the natural history of DMD, so that most of these individuals can now be anticipated to survive into adulthood. The multisystem complications of DMD necessitate a multidisciplinary team approach for optimal surveillance and management (table 1). This review describes the advances in management and outlines the challenges to paediatric practice to achieve early diagnosis, the best possible outcome, quality of life and transition to adulthood.
Table 1. The multidisciplinary team for management of DMD. The predictable evolution of disease course and multisystem complications in DMD allows a plan for input from various disciplines at the appropriate time.

<table>
<thead>
<tr>
<th>Core team. Continuous follow up through childhood</th>
<th>Complication dependent follow up</th>
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<tbody>
<tr>
<td><strong>Doctors</strong></td>
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<td>Paediatrician</td>
<td>Geneticist</td>
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<td>Neurologist</td>
<td>Muscle histopathologist</td>
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<td>GP</td>
<td>Orthopaedic surgeon</td>
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<td>Pulmonologist / intensivist</td>
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<td>Wheel chair specialists</td>
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<td>Psychologist</td>
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<td><strong>Other associated professionals</strong></td>
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<td>Hospital / community nurse</td>
<td>Family care officer</td>
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<td></td>
<td>Social services worker</td>
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**Genetics and Pathophysiology**

A brief review of the molecular genetic basis of DMD is necessary to understand the approach to diagnosis and limitations of the various diagnostic techniques. DMD is caused by mutations in the Dystrophin gene on the X chromosome at Xp21. The dystrophin locus contains 85 exons and encodes for a large but low abundance protein, named dystrophin. Dystrophin is a rod shaped molecule, which localises at the cytoplasmic side of the sarcolemma: one end binds to the dystrophin associated glycoprotein complex at the sarcolemma while the other end binds to the cytoskeletal actin. Dystrophin is postulated to be essential for force transduction by providing an indirect link between the contractile apparatus in the muscle fibre with the extracellular matrix. The mutations in the dystrophin gene which result in DMD cause disruption of the reading frame, resulting in a severe reduction or complete absence of dystrophin in the skeletal and cardiac muscle, which in turn leads to mechanically induced sarcolemmal damage, loss of intracytoplasmic calcium homeostasis, and muscle fibre degeneration. Several dystrophin isoforms are also expressed in brain and their
deficiency in this tissue is responsible for the mental retardation which complicates the course of DMD in approximately 1/3 of cases.

Approximately 65% of patients with DMD have intragenic out-of-frame (gross rearrangements) deletions and approximately another 10% have duplications of one or more exons of the dystrophin gene. The remaining patients have point mutations or other smaller gene rearrangements (pure intronic deletions, insertions of repetitive sequences, splice site mutations). As a general rule out-of-frame dystrophin gene mutations lead to a severe reduction or absence of dystrophin in the muscle resulting in DMD phenotype, whereas in-frame mutations lead to the expression of abnormal but partly functional truncated dystrophin protein, resulting in the milder Becker muscular dystrophy (BMD). The frame shift hypothesis holds true for over 90% of cases and is commonly used both for diagnosis and for differentiating between DMD and BMD. There are important exceptions to the frame shift rule; in-frame mutations in the gene coding for the crucial actin-binding domain of dystrophin protein may cause the Duchenne severity phenotype, whereas some out of frame mutations are associated with BMD.²

The X linked recessive inheritance of DMD is well recognized, but there is a high incidence of new mutations and two-thirds of the cases do not have a positive family history at presentation.

**Diagnosis**

Delay in diagnosis of cases without a family history, to over four and half years of age, continues to be a problem.³ The principal reasons for missing the diagnosis on parents initial contact with the health professionals, is the failure to see the child “running” and rising from the floor (thereby missing the valuable clues of waddling gait and Gowers’ manoeuvre). In addition it is often not appreciated that that global developmental delay is a frequent early presentation of DMD.⁴ Table 2 lists the various presentations of DMD.

**Table 2. The various presentations of DMD**

**Motor Presentations**
- Walking delayed beyond 18 months
- Frequent falls
- Foot posture abnormalities / deformities
- Toe walking
- Waddling gait
- Difficulty running / rising from the floor
Non-motor Presentations*

- Global developmental delay
- Severe learning difficulties / “Autism”
- Failure to thrive
- “Liver disease” – Elevated ALT, AST discovered incidentally during investigation of intercurrent or other illness
- Myoglobinuria, rhabdomyolytic hyperkalemic, malignant hyperthermia-like reaction to suxamethonium, halothane or other halogenated inhaled anaesthetics during anaesthesia

* Motor difficulties are present when specifically looked for, but are often missed because the clinical presentation is dominated by other issues.

Serum Creatine Kinase (CK) is massively elevated (10-100 x normal since birth) and should be the first investigation when DMD is suspected. A high CK should prompt urgent specialist referral for confirmation. A normal CK at presentation excludes the diagnosis. CK levels fall with disease progression reflecting muscle wasting and reduced physical activity. CK therefore is not a reliable screening test in late presenters who are already constant wheelchair users. Electromyography (EMG) has no role in the investigation of DMD and should not be requested.

The last decade has seen important advances in molecular genetic testing to identify Dystrophin gene mutations. As most DMD patients carry deletions in two mutational hot spots of the gene, the screening of only 19 exons, following amplification of genomic DNA, could identify mutations in over 65% of cases with DMD. An important limitation of the technique is not only the inability to identify rarer mutations but also the breakpoint of several common deletions. More recently other testing, such as multiplex ligation dependent probe amplification method, or more recently a combinatorial strategy using the fluorescent multiplex quantitative PCR followed by conformation sensitive capillary electrophoresis (CSCE) of the same PCR products on a multi-capillary genetic analyser, have increased the efficiency of mutation detection close to 100%. These techniques have the additional advantage of being able to unequivocally detect mutations in carrier females, allowing a precise genetic counselling of affected families. Molecular genetic documentation of a dystrophin mutation confirms dystrophinopathy (dystrophin gene related muscular dystrophy); determination of the endpoints of the mutation establish the in/out-of-frame status, and may allow assignment of the severity with regards to Duchenne or Becker phenotype, but exceptions to the frame shift hypothesis have been described. Establishing the precise diagnosis of DMD is therefore best achieved by a combination of clinical observation of the patient’s strength and functional abilities,
ascertainment of dystrophin levels on muscle biopsy and knowledge of the gene mutation. Dystrophin protein assay on muscle biopsy in DMD shows severe reduction or complete absence and allows the most robust diagnosis. Muscle sample can be obtained by a needle biopsy under oral sedation. It is our unit policy at the Dubowitz Neuromuscular Centre to offer a muscle biopsy (in addition to molecular genetic testing) as the first and confirmatory test to boys with suspected DMD, unless there is positive family history in a sibling, or the presentation is late (after 7 years of age) when the disease course is clearly in the Duchenne severity range.

**Female carriers of DMD:** The advances in molecular genetics now allow precise evaluation of carrier status of the relevant females in the family. In addition to accurate counselling and antenatal diagnosis, determination of carrier status is important as carriers have a 10% life time risk of developing cardiomyopathy, and this allows institution of appropriate surveillance and treatment protocols.

**Physiotherapy and orthoses**
Physiotherapy to promote walking and prevent joint deformities, remains important and detailed recommendations are available. Rehabilitation in knee ankle foot orthoses (KAFOs) is offered to DMD boys at the end of independent ambulation, and is effective in prolonging walking for an average of 18 months to two years. The technique entails custom-built KAFOs, and used to require surgical release of the tendon Achilles, to reduce ankle contracture, to allow fitting of KAFOs, and is generally well tolerated. We have recently shown that serial casting of the ankles can be offered instead of the surgical release of the Achilles tendons in many cases.

**Glucocorticoid corticosteroids**
To date, glucocorticoid corticosteroids have been the most effective medication in DMD, and a Cochrane systematic review of the glucocorticoids in DMD is available. Randomised controlled trials (RCT) have shown that treatment with prednisone can stabilise of strength and function for 6 months to 2 years. Prednisone has been the most widely used medication and the starting dose of 0.75mg/kg/day. Non-randomised studies with prednisone or deflazacort, have documented prolongation of walking ability, preservation of respiratory function and reduction in the incidence of scoliosis and cardiomyopathy in Duchenne boys who tolerated long-term daily dose corticosteroids.
Predictably, the daily glucocorticosteroid therapy has significant side effects, notably, in the short-term weight gain can be a bothersome side effect and dietetic input from initiation of steroid therapy helps prevent/ameliorate this side effect. Vertebral fractures are a significant side effect in approximately a third of the long-term treated patients. The Dubowitz intermittent regime was recommended to reduce the adverse effects associated with the daily steroid regimes; a six month RCT of Prednisone 0.75 mg/kg/day for the 1st 10 days of every month, demonstrated slowing of functional deterioration, and international RCT to compare daily dose prednisone and deflazacort with intermittent prednisone regime is planned.

A consensus on the role of corticosteroids in DMD is emerging after careful consideration of pros and cons of long-term steroid treatment, based on expert and evidence based reviews. Corticosteroids should preferably be started in all early ambulant cases (4 - 6 years) and in most of the older ambulant children, unless contraindicated. Treatment needs to be monitored for benefit, adverse effects. The optimal starting dose of prednisolone 0.75 mg/kg/day is often not tolerated in the long term and, over the course of years, careful dose adjustment is required. Regular reviews, in collaboration with specialist centre allows for appropriate monitoring, dosing and adverse effects management. Optimising bone health in corticosteroid treated patients includes dietary advice regarding calcium and vitamin D, and supplementation if plasma Vitamin D levels are low. There is currently no evidence that oral bisphosphonates should be used prophylactically in children receiving steroids; however their acute administration is recommended in the treatment of vertebral fractures, where they are very effective.

In the UK, North Star Clinical Network for Paediatric Neuromuscular Disorders (NSCN) is a Muscular Dystrophy Campaign UK (MDC) sponsored collaboration between 16 specialist centres caring for boys with DMD (http://www.muscular-dystrophy.org/research/northstar/). The clinicians on the NSCN have a consensus on the treatment and standardised assessment protocols for the use of glucocorticosteroids in DMD, and are prospectively collecting data on a web based database to allow audit of clinical practice and refinement of the protocols. It is anticipated that this approach will standardize the steroid related DMD management in the UK regardless of postcode.

**Management of respiratory complications**

The teenage years in DMD are marked by worsening respiratory reserve and sleep hypoventilation, which is a sequel of respiratory muscle weakness, REM sleep, related
hypoxemic dips and obstructive apnoeas. The resulting symptoms may include morning drowsiness, poor appetite, headaches, nausea, fatigue, tiredness, poor concentration at school, failure to thrive, reduced coughing ability or overt respiratory failure in the course of “minor” respiratory infections. In untreated patients who become hypercapnic, the survival is less than a year.

Until recent decades, the onset of symptomatic sleep hypoventilation signified imminent demise, as the only way to prolong life was mechanical ventilation through tracheostomy, and this was limited by the complex ethical issues of invasive ventilation of patients with totally incapacitating and incurable disease. In the recent years, domiciliary non-invasive ventilation (NIV) has proven effective in symptom relief and prolonging survival. The patient's breathing at night is augmented with breaths delivered by a compact, portable ventilator with a snugly fitting facial or nose mask. NIV corrects sleep hypoventilation and affords symptom relief without significant encroachment on living space or restriction of travel. NIV, and if needed, the use of cough assist devices, can extend average survival to mid-twenties and in some cases to the fourth decade. This has led to the opinion that denying NIV to hypercapnic DMD patients is unethical.

Forced vital capacity (FVC) predicts the development of hypercapnia and survival. Regular monitoring for symptoms of sleep hypoventilation, FVC, and overnight sleep studies when the FVC falls below 50% allow for timely initiation of NIV. Gradual initiation of NIV in individuals with nocturnal hypercapnia but daytime normocapnia is a valid approach, as waiting for daytime ventilatory failure exposes patients to minor chest infections and uncontrolled decompensation.

Management of cardiac complications
Dilated cardiomyopathy (DCM) occurs in up to 90% of DMD individuals ≥18 years. The severity of the physical disability of DMD boys in the late teens and later on masks the clinical symptoms of cardiac failure unless these are very florid; traditionally cardiomyopathy was considered responsible for death in up to 20% of DMD individuals; however this proportion is likely to increase over the coming years in individuals in whom NIV prevents respiratory related mortality. The optimal timing of introducing therapy for DCM remains an unresolved issue. Duboc et al. reported that early treatment with perindopril delayed the onset and progression of prominent LV dysfunction, and was associated with lower mortality in DMD. Some cardiologists suggest that treatment is not necessary for a complication that is often asymptomatic for a long time before deteriorating into clear-cut cardiac failure, although this view...
is at odds with the current evidence on related forms of DCM, in which early treatment is clearly superior compared to late therapy. Indeed considering the well-described incidence and clinical course of DCM in DMD, and the recent suggestions from several groups of the positive effect of therapeutic intervention, the most logical approach appears to intervene before a too severe damage has occurred.

While awaiting the results of RCT, the published consensus documents recommend the use of Angiotensin converting enzyme (ACE) inhibitors, beta blockers and diuretics in patients with early cardiomyopathy. It is important to look for and treat co-existing nocturnal hypoventilation, which aggravates cardiac function.

The risk of cardiac involvement in carriers of DMD is approximately 10%, and this may occur in the absence of muscle weakness. Genetic counselling should include informing the carriers of the cardiac risks and plan for surveillance and treatment.

**Scoliosis management**

Scoliosis usually develops after loss of walking, shows rapid progression during pubertal growth spurt and adversely affects respiratory function, feeding, seating and comfort. The reduced incidence and severity of scoliosis in glucocorticosteroid treated boys is likely to be secondary to prolongation of walking and increase in truncal muscle strength.

Progression of the spinal curve is the indication for surgical spinal fusion, and the optimum time for making the decision is when the range of the curve’s Cobb angle is $20^\circ - 40^\circ$. Multidisciplinary team input to make the decision to offer surgery, and pre-operative assessment are essential to ensure that the operation is safe and choosing a time when the FVC is above 30% predicted for height, and the cardiac function, as demonstrated by echocardiogram, is good. Spinal surgery can be performed when the FVC is between 20-30%, but the risks are greater, and this should be undertaken in specialized centres.

Spinal brace (jacket) does not prevent progression of scoliosis, but may be useful in postural management, especially in cases where spinal surgery is contraindicated or is not acceptable to the patient.

**Nutritional aspects**

Nutritional difficulties include initial presentation with failure to thrive, obesity during the late ambulant phase, especially in corticosteroid treated individuals, and severe wasting
in the spinal surgery post-operative period and the late teenage years. Regular weight monitoring and dietary advice to avoid obesity should be available to all DMD patients, especially when treated with daily corticosteroids.

Young adults with DMD may have chewing and swallowing difficulties, prolonged mealtimes, choking on food, and failure to thrive. Appropriate facilities for weighing the wheelchair dependent adolescents should be available in the clinics to allow for regular weight monitoring. Patients with failure to thrive and/or swallowing difficulties benefit by dietetic and speech and language therapist’s assessment for nutritional supplementation; observation of mealtimes and swallowing videofluoroscopy allow further advice about postural management, feeding aids or gastrostomy insertion.

Survival and transition of care
The improvements in general care and the frequent provision of NIV from 1990s, has improved the mean survival of DMD patients in the UK to 27 years, and further prolongation of survival is anticipated as the currently corticosteroid treated cohort matures and accrues the long-term beneficial effects, particularly on respiratory function. This change in natural history of treated DMD means that most of these adolescents are now anticipated to reach adulthood. This underlines the need for development of robust protocols for transition of care to the adult medical teams, and in particular, for the drive to enable improvement in rehabilitation, employment, social participation and social services for the adult with DMD.

“Gene therapy” for DMD
The major advances in understanding of the molecular genetics, and pathogenesis of DMD has raised expectation of a curative treatment with gene therapy. Research in this area has been greatly facilitated by the improved understanding of the disease pathogenesis and the use of two naturally occurring animal models; the dystrophic golden retriever dog (GRMD), which suffers a fatal clinical course akin to the humans and the mdx mouse which has a stop codon in exon 23 resulting in dystrophin deficient muscle fibres but is not overtly weak, and its survival only minimally limited compared to wild type. A detailed discussion of the various genetic strategies aimed at restoration of dystrophin in the affected muscle is beyond the scope of this article, but they are listed with a basic description and current status in table 3.
Of particular interest is the UK Department of health funded “molecular patch therapy” trial, utilizing the exon skipping approach (http://www.muscular-dystrophy.org/research/), which is a good example of collaborative efforts of basic and clinical scientists, parent and patient organisations, the governmental funding bodies and pharmaceutical industry. The strategy behind the “molecular patches” is the modification of dystrophin mRNA splicing using antisense oligonucleotides (AOs). These small RNA like molecules prevent the normal splicing of the gene by masking crucial areas of the messenger RNA during the splicing process, and induce exon skipping. In DMD patients with out of frame deletions (which represent ~ 65% of all boys) the manipulation of exon skipping can result in deletions that maintain the open reading frame, similar to what is found in the milder BMD. The early proof of concept studies on the role of this approach was obtained in cell cultures of the mdx mouse and subsequently demonstrated in DMD cells. Systemic administration of AOs in the mdx mouse also resulted in appreciable induction of exon skipping which resulted in dystrophin expression of functional levels in body-wide skeletal muscles of the mdx mouse, with corresponding improvement in muscle function 41. There are several limitations of AOs. Firstly, different deletions will require different AOs and secondly
the treatment is not permanent but limited to the period in which the AO persist in the
tissue. AO treatment will therefore require repeated administrations for the entire life of
the DMD boys, and whether this will be associated with any toxicity is not known.
AOs nevertheless have a fairly good safety profile from data available on human trials. Two European Consortia are currently testing safety and local efficacy of intramuscularly administered AOs with the view of performing systemic AOs trials in 2008. One group is based in Holland (http://prosensa.eu/news/news_may10_06.pdf), and the other in UK (http://clinicaltrials.gov/ct/gui/show/NCT00159250). The results of these studies are expected in 2007, and this will inform the feasibility of future systemic delivery studies.

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