Current Paediatrics (2005) **15**, 292–300

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The multidisciplinary management of Duchenne muscular dystrophy

K. Bushby[a,*], J. Bourke[b], R. Bullock[c], M. Eagle[a], M. Gibson[d], J. Quinby[d]

[a]*Institute of Human Genetics, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK*
[b]*Department of Cardiology, Freeman Hospital, Freeman Road, Newcastle upon Tyne, UK*
[c]*Department of Anaesthesia, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, UK*
[d]*Department of Orthopaedics, Freeman Hospital, Freeman Road, Newcastle upon Tyne, UK*

KEYWORDS
Duchenne muscular dystrophy (DMD);
Corticosteroids;
Respiratory failure;
Cardiomyopathy;
Scoliosis

Summary Duchenne muscular dystrophy (DMD) is an X-linked disorder for which there is currently no curative treatment. The natural history is such that affected boys need to use a wheelchair at around 9 years, develop respiratory and cardiac complications and die at a mean age of 19 years. While treatments based on gene modification or replacement are eagerly awaited, advances in medical management of DMD have made a significant difference to the natural history of the condition such that most affected individuals can now be expected to live into adulthood. The key interventions relate to the use of corticosteroids to improve muscle strength and function, surgical management of scoliosis and surveillance for and timely management of respiratory and cardiac complications. The predictable nature of the complications of DMD lends itself to the implementation of a planned programme of surveillance and management, which makes a real difference to survival and quality of life.

Introduction

Once considered a hopeless disease where patients were frequently told there was nothing to be offered, in the last few years there has been the recognition that there are a number of management interventions that can alter the natural history of Duchenne muscular dystrophy (DMD) so that the majority of people with DMD can be expected to live into adult life. The four areas that are key to the proper multidisciplinary management of DMD are the improvement, maintenance and support of muscle strength and function, prevention and management of spinal deformity, the management of respiratory complications and the prevention and treatment of cardiomyopathy. Implicit in this is a requirement for a team approach to management, with involvement of

*Corresponding author. Tel.: +44 191 241 8757; fax: +44 191 241 8799.
E-mail address: kate.bushby@ncl.ac.uk (K. Bushby).

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doi:10.1016/j.cupe.2005.04.001

physiotherapy, orthopaedics, the respiratory team and cardiology. Other important input may be from genetics, dietetics and psychology, as well as occupational and wheelchair therapy with an overriding co-ordinating role for the muscle clinic physician. The aim of the medical management of DMD should be to minimise the impact of the predictable complications of the disease on the affected person and his family, in order to allow the attainment of as good as possible quality of life.

Genetics and diagnosis

DMD is an X-linked disorder affecting around 1 in 3500 male live births. Around 8–10% of female carriers have some manifestations of the disease, although these are usually minor and cases presenting with muscle weakness as severe as that seen in boys are very uncommon. There are commonly early signs of delayed and abnormal motor development in affected boys, so that around 50% are not walking independently at the age of 18 months. Affected children never run properly, have difficulty climbing stairs and only around 10% manage to jump with both feet together. The classical sign of proximal muscle weakness—the Gowers manoeuvre—is always present, with boys needing to turn onto their front and rise to standing from the floor using a broad-based stance, usually with the support of their hands on their thighs. Other common features of the disease are muscle hypertrophy, usually of the calves but also of other muscle groups and, frequently, global developmental delay with delayed speech. There is a high incidence of new mutations in the dystrophin gene so that two-thirds of cases presenting do not have a family history of disease, which often results in a delay in diagnosis. The mean age of diagnosis of cases without a family history remains over four and a half years of age. Molecular confirmation of the diagnosis is imperative for clinical practise and genetic counselling of other family members.

Practice Points

Diagnosis of DMD:

- *Clinical examination*: must include seeing the child try to run, jump, climb stairs and get up from the floor. The signs of proximal muscle weakness will be detected much more easily in the corridor than the consulting room.
- *Serum creatine kinase* (*CK*): Massive elevation of the serum CK (at least 10–20 × normal and often much more) is non-specific but always present. The finding of a high CK level should prompt urgent specialist referral for confirmation of the diagnosis.
- *Genetic testing*: a deletion of the dystrophin gene[1] will be found in around 70% of cases, a duplication in around 6% and the remaining cases will have a point mutation. Readily available genetic tests for DMD are not always exhaustive and a negative result on initial testing does not exclude the disease. It is very important to understand the tests offered by a particular laboratory and their limitations—further specialist input may be necessary.
- *Muscle biopsy*: dystrophin analysis on a muscle biopsy specimen will always be abnormal and offers a further route to confirm the diagnosis. However, dystrophin analysis will still need to be followed by molecular genetic testing in order to be able to offer genetic counselling to other family members.
- An integral part of the diagnostic process is determining the carrier status of the mother. Even if the condition has arisen as a result of a new mutation, there is an average 10% risk of recurrence due to germline mosaicism.
- *Support:* around the time of diagnosis it is useful to provide contact with a named member of support staff and imperative to offer details of parent/patient support groups such as the national muscular dystrophy charities and the Parent Project.

The natural history of DMD

Observation of the untreated natural history of DMD shows a predictable clinical course, although somewhat variable in severity from boy to boy. Muscle weakness is progressive and causes loss of independent ambulation at a mean age of 9 years and, by definition, by the age of 13 (there are milder conditions related to DMD that are also caused by dystrophin mutations—if boys manage to walk beyond the age of 13 but lose the ability to walk by 16 this is known as intermediate muscular dystrophy while those maintaining ambulation beyond the age of 16 have Becker muscular

dystrophy). In most boys, progressive loss of muscle power beyond the loss of ambulation results in scoliosis and respiratory impairment and involvement of cardiac muscle results in cardiomyopathy. The mean age at death in untreated DMD is 19 years, with roughly 90% of these deaths attributable to respiratory and 10% to cardiac causes. It is a clear testimony to the improvements in clinical care that in many centres the mean age at death in DMD is now in the late twenties or beyond.

Muscle strength and function

Use of glucocorticosteroids (prednisone/prednisolone and deflazacort) are the gold standard treatment for muscle weakness in ambulant children with DMD.[2–4] Randomised controlled trials provide evidence for an increase in strength in children treated with daily steroids and with intermittent or alternate day dosing schedules. Long-term cohort studies of children on daily deflazacort and prednisolone show a striking improvement in function (ambulation prolonged to the mid teens) and a concomitant reduction in complications such as scoliosis. There is a marked improvement in respiratory function as measured by forced vital capacity (FVC) and some evidence of improvement in cardiac function as well. The most commonly reported side effects of steroid treatment in DMD are weight gain, behavioural problems and, in the longer term, reduction in bone mineral density. Use of these drugs requires careful follow up and attention to the prophylaxis and treatment of side effects (see Practice Points, below).

Practice Points

The use of corticosteroids in DMD:

- *Timing*: experience suggests that the best improvement in performance will be seen with the introduction of medication at or before the point at which the physical performance of the child plateaus (as assessed by sequential functional testing); i.e. well before the loss of ambulation.
- *Regimes*: the most common daily dosage regimes are 0.75 mg/kg/day prednisone/prednisolone and 0.9 mg/kg/day deflazacort. They are likely to be equally effective, but have slightly different side-effect profiles. Deflazacort may produce less weight gain but has a higher risk of asymptomatic cataracts. Other regimes suggested to reduce the incidence of steroid-associated side-effects include alternate day dosing, lower dose daily regimes and intermittent regimes (e.g. 10 days on/10 days off). It is important to note that none of these regimes have been tested against the daily dosing schedules so that their relative efficacy in the long term is not known.
- *Tests before starting steroids*: immunity to chicken pox (and in high risk populations, tuberculosis) should be ensured ahead of starting steroids.
- *Efficacy:* monitoring for efficacy should include tests of muscle function and strength, FVC and parent and child perception of the value of the treatment.
- *Side effects*: monitoring and prophylaxis of the predictable side-effects of steroid use should go hand in hand (http://www.enmc.org/workshops/reports.cfm?p=157). For example, monitoring for weight gain should be accompanied by dietary advice and support, behavioural changes should be supported by psychological input, advice on bone health (see below) should be provided alongside monitoring of fracture frequency, boys should avoid concomitant treatment with non-steroidal anti-inflammatory agents and use antacids as required etc.
- *How long to continue steroid treatment*: continuation of steroids beyond the loss of ambulation is common practise in some centres for the possible protective effect on respiratory and cardiac function. There is, as yet, no evidence for any beneficial effect of starting steroids after the loss of ambulation in steroid naïve patients.
- *Patient information resources*: are available from the European Neuro Muscular centre (ENMC) (http://www.enmc.org/workshops/reports.cfm?p=157) as well as via the muscular dystrophy charities.

Physiotherapy input is also essential for the maintenance of muscle function in DMD.[5] All children with DMD should have access to physiotherapy services from diagnosis. Initially the priority is the maintenance of symmetry as development of asymmetric contractures at the Achilles tendons and hips can predispose to pelvic obliquity and subsequent scoliosis. Passive stretching and the use of ankle-foot-orthoses (AFOs) worn at night are the mainstay of treatment in the ambulant stage to delay development of contractures, together with

encouragement to be active and take part in sports and other activities such as hydrotherapy and inclusion in an appropriate physical education regime at school. In the ambulant child daytime AFOs are not recommended as they may impede walking ability. Knee-ankle-foot-orthoses (KAFOs, also known as long leg callipers) may be considered to prolong the ability to walk and stand around the time ambulation is lost but as a plantigrade position at the foot is required surgical lengthening of the Achilles tendons may be necessary and should be planned to coincide with KAFO provision cooperatively between the surgeon, family and physiotherapist. It is not usually advisable in children who are freely and independently ambulant as it may precipitate loss of ambulation in children with poor quadriceps function. The use of long leg callipers rarely allows the achievement of independent ambulation and some children are reluctant to use them. However, it seems that their use is of benefit as children who walk or even stand beyond the age of 13 years are less likely to require spinal surgery and contracture development is delayed.

Prolongation of ambulation should not be an aim beyond all others. The ability to take part in activities is crucial and manual wheelchairs should be provided early as they are useful for the conservation of energy where walking long distances is tiring. Tilt in space/reclining electric wheelchairs provide functional variations in posture and should be provided when walking is becoming difficult. Special seating and a head rest should be introduced early before there are detrimental postural adaptations.

Non-ambulant children should be provided with sitting AFOs and passive or active assisted exercise should be continued for comfort, aesthetics and contracture prevention. Triple arthrodesis may be required in children who develop severe deformity of the ankle and foot so that shoes can be worn comfortably and pressure sores from severe contractures avoided.

Prevention and management of spinal deformity

Ninety percent of boys with DMD are likely to develop a clinically significant scoliosis. Monitoring for the development of scoliosis should begin before the loss of ambulation and prophylaxis includes physiotherapy and the provision of proper seating to prevent pelvic asymmetry and provide postural support. Once a scoliosis is detected clinically, referral for full assessment and discussion of the options for surgery is indicated. It is clear from the literature that scoliosis surgery in DMD is effective in correcting scoliosis, preventing further deformity and in promoting better seating posture and comfort. There is probably not a significant effect on respiratory function, which continues to decline because of the intrinsic weakness of the respiratory musculature. In experienced centres with appropriate multidisciplinary backup, mortality and morbidity rates of spinal surgery are low. Success rates are likely to be highest and complication rates lowest if surgery is performed when the spine is still mobile at a Cobb angle of 20–40° and at this stage also there is the added advantage that boys are usually relatively fit for surgery from the point of view of respiratory and cardiac function.[6] Fixation to the pelvis is always indicated if there is a pelvic obliquity at the time of surgery but otherwise may be avoided. Spinal bracing provides comfort and postural security in children who are unable to have spinal surgery because of rapidly progressive cardiomyopathy but will not prevent the ultimate progression of the scoliosis.

Practice Points

The role of physiotherapy and orthopaedic intervention in DMD:

- *Aims of physiotherapy*: to encourage activity and develop and promote function.
- *Splinting*: in ambulant children night splints should be provided when there is loss of dorsiflexion at the ankle. Daytime AFOs are not recommended before loss of ambulation.
- *Exercise*: resisted exercises should not be prescribed as there is no evidence that they are useful but there are concerns that they may accelerate muscle damage. Active exercise particularly in the hydrotherapy pool is recommended. Children taking steroids may acquire additional motor skills such as riding a bike and this encourages independent play and interaction with peers.
- *In non-ambulant children*: sitting AFOs are essential as painful contractures will develop that also impact negatively on posture. Some children will require triple arthrodesis but AFOs are still needed after surgery.
- *KAFOs* can be considered to delay contracture development and prolong ambulation. Standing frames or swivel walkers can delay

contracture development in non-ambulant children.
- *Wheelchairs*: should be supplied to improve mobility and independence. Tilt-in-space electric wheelchairs with supportive seating should be supplied early to avoid postural contractures and poor sitting posture.

Respiratory management in DMD

The respiratory problems in DMD tend to be very predictable and correlate with overall muscle strength so that children who lose ambulation early are likely to require ventilation sooner than those who walk longer. Essentially respiratory function in ambulant boys is normal and problems relating to respiratory impairment are not usually seen until after the loss of independent ambulation. FVC peaks in affected boys shortly after they need to use a wheelchair full time and at this stage measures to prevent and treat chest infections promptly should be set in place in partnership with the primary healthcare team and physiotherapists (see Practice Points, below). Progressive fall in FVC predicts the development of respiratory failure, which progresses from nocturnal to daytime hypercapnia and the development of symptoms. These may initially be subtle, such as weight loss, reduction in energy levels and poor performance at school. Sleep disturbance may manifest as an increased requirement for turning overnight. Chest infections may become more frequent and difficult to treat. Once hypercapnia becomes established and is not treated, then symptoms progress to include headaches and more general malaise and there is a high risk of death from respiratory failure during intercurrent infection. There are now several studies showing that respiratory failure in DMD responds well to the initiation of non-invasive intermittent positive pressure ventilation with resolution of symptoms and good quality of life, improvement in physiological parameters and increased survival.[7–9] Discussion of the use of ventilation as a treatment for this complication of DMD is ideally raised early as part of the multidisciplinary management of the condition and treatment instituted electively with full and informed discussion with the patient and his carers. The mean age at institution of elective ventilation is around 17 years. It is, however, on occasion necessary to institute ventilation as an emergency during acute deterioration during infection that may require admission to an Intensive Care Unit. Weaning from invasive ventilation can be protracted but the outcome and quality of life is good in the long term.

The provision of safe assisted ventilation requires considerable technical back-up and should be done as part of an organised home ventilation programme. Long-term follow up in several countries now shows that nocturnal ventilation (either non-invasive or by tracheostomy depending on local

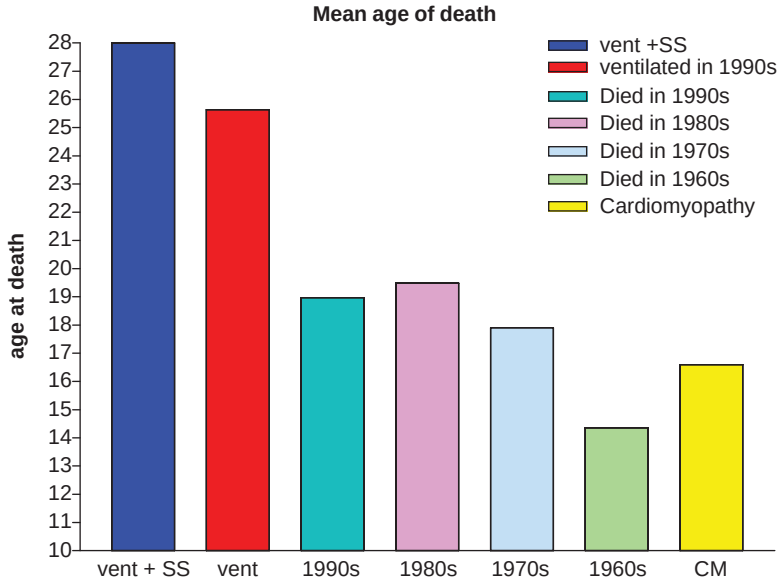

Figure 1 The change in life expectancy in DMD for boys dying in the decades since the 1960s. The yellow column represents the boys dying from an early and prominent cardiomyopathy, the red column the boys who were ventilated in the 1990s and the dark blue column the boys who had both spinal surgery and subsequently were ventilated.

experience) is very effective as a treatment for respiratory failure in DMD and that often nocturnal use alone provides very good stabilisation for many years. Patients commonly notice that the frequency of chest infections falls with ventilator use and that infections that do occur may be effectively managed with the ventilator to assist coughing. Over a period of years patients may develop a need to use the ventilator for increasing periods during the day and at that point a portable ventilator may need to be provided that can be transported on the wheelchair. With the use of ventilation as the major variable, the mean age of death in the Newcastle centre has risen from 19 years to at least 25 years (Fig. 1).[8] Extrapolating from the experience in other countries where ventilation has been used systematically for longer, survival into the fourth decade and beyond should become the norm.

Practice Points

Respiratory management in DMD[7]:

- *Surveillance*: serial measurement of forced vital capacity (FVC: absolute values and as predicted for height or arm span) provides an easy way to document the progression of respiratory muscle weakness. Once FVC drops to 1.25 l or $<40\%$ predicted value, then serial measurement of overnight oxymetry allows the recognition of the development of nocturnal respiratory failure. This can be done easily at home through the use of small postable machines. Symptoms should also be sought at every clinic attendance.
- *Prophylaxis of chest infections*: once a patient's FVC begins to drop, they are susceptible to chest infections and should be offered flu and pneumonococcal vaccination.
- *Management of chest infections*: antibiotics should be provided promptly. Chest physiotherapy such as postural drainage and assisted coughing should be taught when coughing is ineffective and may need to be supplemented with cough aids such as the in/exsufflator.
- *Management of nocturnal hypoventilation*: symptomatic nocturnal hypoventilation is an indication for elective non-invasive nocturnal ventilation.

Cardiovascular management of DMD

Cardiomyopathy is an almost universal complication of DMD but, without screening, it progresses asymptomatically until, when all cardiac reserve has been eroded, symptoms and signs of heart failure emerge. The particularly late cardiac presentation is probably explained by the impact of the muscle weakness on the ability of affected individuals to be physically active. By then, left ventricle ejection fraction is typically only 10–15% and death can be anticipated within a year despite therapy. Although the heart has been considered the primary cause of death in only 10% of DMD patients, from older longitudinal cohort studies, this percentage is expected to rise now as life-expectancy has increased for DMD patients.[10]

The first evidence of ventricular systolic dysfunction on echocardiography is usually found in the postero-basal segments of the left ventricle. This may be because these segments are exposed to greatest repetitive mechanical strain. Without treatment, this area of abnormality extends to involve the whole ventricle in a progressive, dilating cardiomyopathy. It is estimated that 20–30% of DMD boys have left ventricular impairment on echocardiography by age 10 years and, using more sophisticated imaging modalities—such as tissue Doppler, magnetic resonance, metabolic imaging—abnormalities are evident in an even larger proportion of DMD patients in their teens.

Combination therapy with angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocking drugs, loop-diuretics, spironolactone and the addition of non-selective beta-adrenergic blocking drugs at a later stage is established to control symptoms in patients with cardiac failure of diverse aetiologies. The same regimes are also deployed to prevent progressive deterioration of heart function and to improve prognosis in patients with asymptomatic left ventricular dysfunction. Although there are few reports of the use of these drugs or their effects on the course of cardiac dystrophinopathy, initial indications of benefit are consistent and encouraging.

Based on trial evidence of the use of these therapies in dilated cardiomyopathy and pending further results, it seems logical to offer ACE-inhibitor and beta-blocker therapy routinely now to patients with evidence of left ventricular dysfunction in the context of DMD. This can be justified taking account of the progressive course of cardiac involvement, left untreated, and the established safety profile of these agents (Fig. 2). There is one paper suggesting that use of ACE

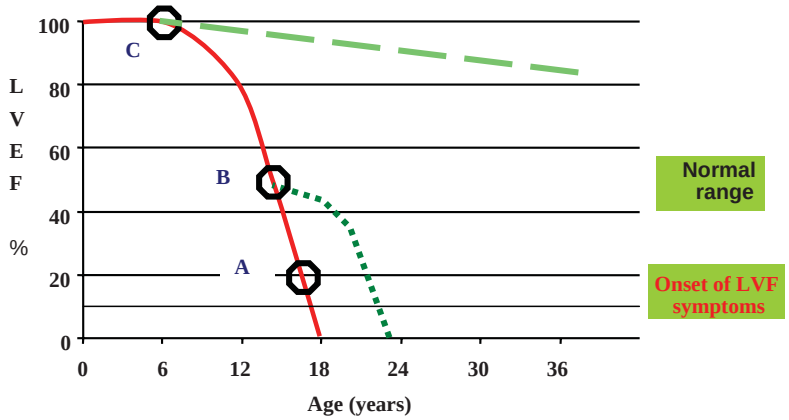

Figure 2 Intervening in cardiac dystrophinopathy: theoretical benefits of ACE-inhibitor and beta-blocker therapy in relation to timing of their introduction. BB, beta-adreno-receptor blocker; LVF, symptoms of left ventricular failure; red line, natural history of progressive left ventricular dysfunction in DMD culminating in cardiac failure; A, temporary symptom relief only if therapy delayed until onset of cardiac failure; B, prognostic impact of introducing therapy in face of progressive left ventricular dysfunction; C, possibility of more fundamental benefit with earlier intervention.

inhibition before cardiac abnormalities are detectable may be protective in the long term.[11]

Practice Points

Management of cardiac involvement in DMD[10]:

- *Surveillance:* cardiac investigation (echocardiogram and ECG) is indicated at diagnosis, every 2 years thereafter to age 10 and then annually, or more often, if abnormalities detected. Cardiac investigation should be done at any age prior to general anaesthesia.
- *Treatment:* ACE-inhibition and beta blocker should be initiated in the presence of progressive abnormalities, with the addition of diuretics etc with onset of heart failure.

Other issues

Bone health

Boys with DMD have low bone mineral density even before loss of independent ambulation.[12–14] This may relate to their relative immobility even at early stages of the disease. Long bone fractures are relatively common and should be treated with early mobilisation wherever possible to avoid a fracture precipitating loss of independent ambulation. The use of long-term corticosteroid treatment reduces bone mineral density further and this effect is especially apparent in the vertebrae. Vertebral fractures in steroid-treated boys can be treated with intravenous bisphosphonates under the guidance of an expert in bone metabolism. At the present time there is insufficient evidence to recommend the use of prophylactic oral bisphosphonates so prophylaxis relies on advice about calcium and vitamin D intake through diet and sunshine with supplementation if necessary to reach an intake of 1000 mg/day of calcium and 400 units of vitamin D.

Nutrition and gastrointestinal issues

The relationship between DMD and weight is not simple. Some boys with DMD tend to be relatively thin despite a good appetite and stay thin all their lives. For other boys, there is a significant weight gain as mobility becomes more difficult and in this group excessive weight gain can be a factor in precipitating loss of mobility. As respiratory failure develops, loss of appetite is a frequent symptom and may be accompanied by weight loss. In later stages of the disease there can be difficulty swallowing and where this leads to aspiration and/or undernutrition, discussion of feeding by tube or percutaneous endoscopic gastrostomy (PEG) is indicated. The use of steroid treatment in DMD adds an extra level of complexity to diet issues and detailed nutritional support should be provided to give advice on weight control, sodium restriction and calcium and vitamin D intake.

Symptomatic involvement of smooth muscle in the disease process is not universal, but constipation is a relatively common problem in older boys,

which may respond to a combination of senna and docusate.

Anaesthetic issues

Anaesthetic techniques must be tailored to minimise intra and post-operative respiratory and cardiovascular depression and may require invasive monitoring and access to intensive care. Depolarising muscle relaxants should be avoided because of the risk of hyperkalaemia.[15] With increasing respiratory and cardiac compromise anaesthetic risks increase but at all ages thorough preoperative assessment is indicated. Current opinion would suggest that stable cardiac function on treatment might not be an absolute contraindication to elective surgery, but that rapid deterioration of cardiac function would be. For patients with declining respiratory function, it may be necessary to familiarise the family with the use of non-invasive ventilation ahead of surgery. Caution is also needed for procedures under sedation in older boys, for example during endoscopy.

Learning and behaviour

There is a well-documented association between DMD and learning difficulties. Many studies have shown that although IQ is normally distributed it is shifted down by two standard deviations compared to the non-DMD population. Learning difficulties are however non-progressive and boys do make steady progress in learning, especially if they have access to special help to address the specific learning difficulties in language that are especially common. There appears to be an association with autism. It is also clear that behavioural difficulties can be an issue in DMD and that these may be exacerbated by steroid treatment.

Access to wheelchair services and other adaptive technology

Quality of life in DMD is enhanced by high quality and timely supply of assistive aids and adaptations and quality of life for the whole family is severely compromised by bureaucratic delays in the provision of essential services. Appropriate adaptations to housing, electric beds and wheelchairs, access to the internet and computers are essential for independent and functional life, but it is clear that with appropriate support adults with DMD can maintain an excellent quality of life.[16]

Conclusions

There have been several areas where management in DMD has improved and, in fact, the combined effects of all of these interventions have yet to be fully appreciated. A nihilistic approach to DMD is no longer tenable. All families should have the opportunity to access the developments in management that have come about in recent years. It is also a time of great optimism in DMD research, with further specific treatment options approaching the point of clinical trials. These include gene replacement techniques, methods to alter the effect of the mutation by antisense oligonucleotide treatment or aminoglycoside therapy and therapies based on the inhibition of myostatin or muscle proteases. It is no longer appropriate to look on DMD as a condition that is inevitably fatal in childhood as the majority can now be expected to reach adulthood. This profound change in life expectancy has implications for all areas of management from the time of diagnosis onwards and also importantly for education and social support.

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