

Duchenne muscular dystrophy

BACKGROUND Duchenne muscular dystrophy is one of the most severe muscle diseases to affect children. In the last twenty years, treatments have been established that have significantly improved patients' quality of life and life expectancy. The purpose of this article is to outline the main features of the disease and its treatment, and to examine possible future treatment options.

METHOD The article is based on a literature search in PubMed, current international guidelines and our own clinical experience.

RESULTS Close monitoring by an interdisciplinary rehabilitation team forms the basis of treatment. Treatment with glucocorticoids can slow disease progression and improve motor function in the short term. The treatment may cause side effects, which must be monitored and which may require intervention. A not insignificant proportion of patients have cognitive and neuropsychiatric problems that must be addressed. Active intervention in response to signs of respiratory or cardiac failure is important. More causal treatment of Duchenne muscular dystrophy is under testing and offers cautious hope for future patients.

INTERPRETATION With improved treatment and increased life expectancy come new challenges for patients with Duchenne muscular dystrophy and their families, as well as new demands on the support services. This patient group requires close and comprehensive follow-up, also in the transition from child to adult.

Duchenne muscular dystrophy is the most common muscle disease to affect children, and one of the most severe. The disease is progressive, hereditary and almost exclusively affects boys (1). At the beginning of the 1990s, average life expectancy for this patient population was barely twenty years (1, 2). However, over the last twenty years, treatment and management have changed significantly such that children who are diagnosed today can hope to survive and, given the circumstances, have a good quality of life until they are 30–40 years old (1, 3).

In this article we present an overview of the disease, with emphasis on recent therapeutic advances as well as the challenges that arise with increasing life expectancy.

Method

The article is based on a literature search in PubMed. We used the keywords «Duchenne» and «muscular dystrophy» in combination with a wide range of keywords relevant to the particular topic in each paragraph. In addition, we examined consensus statements (1, 4–9) and the relevant parts of the associated source material. The search was completed on 18 June 2013.

After a discretionary assessment of content and relevance, a total of 71 articles were examined, and 31 of these were selected to form the basis of this article. The references are supplemented by our own clinical experience with children and adolescents with Duchenne muscular dystrophy in Norway.

Genetic basis and diagnostics

Duchenne muscular dystrophy is inherited in an X-linked recessive pattern and is caused by a mutation in the *DMD* gene, localised to chromosome Xp21 (10). To date, more than 4,700 different mutations have been identified in this very large gene. In about one third of patients, the mutation is not present in the mother (11).

The mutations lead to a deficiency in the production of dystrophin (12), which is a structural protein of muscle cells. As a general rule, it appears that any mutation that disrupts the reading frame for translation of mRNA into protein will result in a major loss or total absence of functional dystrophin and the severe phenotype Duchenne muscular dystrophy, while any mutation that does not affect the reading frame will give rise to a partially functional gene product and a milder phenotype (Becker muscular dystrophy) (11). The term «dystrophinopathy» includes both phenotypes, and there is no clear distinction between them.

Duchenne muscular dystrophy is estimated to affect one in 3,500–6,000 newborn boys. Female carriers are usually asymptomatic, but some show mild symptoms of muscle disease, and about 10% may develop isolated cardiomyopathy (13). Mothers of boys with Duchenne muscular dystrophy and their female first-degree relatives should always be offered genetic counselling. Amniocentesis is available for pregnant female carriers.

In most cases, a diagnosis can be made based on a combination of typical clinical

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MAIN MESSAGE

Over the last 20 years there have been significant improvements in quality of life and life expectancy for patients with Duchenne muscular dystrophy.

New research offers cautious hope for cause-specific therapy in the future.

Prolonged survival creates new needs and challenges for patients, carers and the support services.

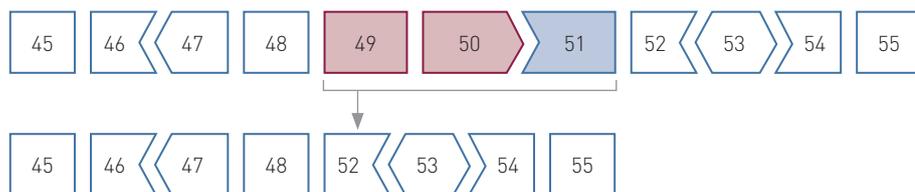


Figure 1. Schematic representation of the principle behind exon skipping. The patient has a deletion of exons 49–50. By blocking exon 51, the mRNA from exon 48 to exon 52 can be spliced together such that the reading frame is restored, and a partially functional gene product (dystrophin) can be produced.

signs, five-digit creatine kinase levels and genetic analysis. The clinical course of Duchenne muscular dystrophy is outlined in Table 1. It is important to emphasise that there are large individual differences in how quickly the disease progresses. Muscle biopsy can, in cases of doubt, still provide important additional information about the degree of dystrophin deficiency, but is no longer an obligatory part of the diagnostic process (1).

Pharmacotherapy

There is no curative treatment for Duchenne muscular dystrophy. However, there is now good evidence that treatment with glucocorticoids improves muscle strength and motor function in the short term (14). Glucocorticoids also appear to reduce the risk of developing scoliosis that necessitates treatment (15) and to delay the development of respiratory and possibly cardiac complications (1, 15, 16). Treatment with prednisolone or deflazacort is now recommended, beginning no later than the point at which the patient's motor development stops and before his functioning starts to deteriorate (1). The current guidelines have arisen

partly from empirical consensus, and there is still much that remains unclear with regard to optimal dose and the long-term effects of glucocorticoid therapy (1, 14).

Long-term glucocorticoid therapy is associated with side effects including weight gain, endocrine disturbances, osteoporosis and behavioural difficulties (14, 17). However, some of these, such as problems with weight and reduced bone density, are also seen in boys with Duchenne muscular dystrophy who have not been treated with steroids. It can therefore be challenging to assess the relative significance of disease progression, treatment efficacy and side effects in individual cases.

There is intense ongoing research into a causal treatment for Duchenne muscular dystrophy. Two methods in particular are undergoing clinical evaluation in international multicentre studies (18, 19): The drug Ataluren (PTC124) makes ribosomes ignore premature stop codons (nonsense mutations) (20), which occur in 10–15% of patients. This should thus enable larger amounts of functional dystrophin to be produced.

The second method, exon skipping, influ-

ences reading of the genetic code at the pre-mRNA level, such that a disrupted genetic reading frame is restored (Figure 1). The aim is to transform a Duchenne scenario into a Becker scenario, in which the reading frame is intact and more functional protein is produced (21). This method uses antisense oligonucleotides that must be «tailored» to the distinct mutations. In some cases, skipping one exon, such as exon 51, can restore the reading frame for several mutations (18).

Neither of these methods could be considered gene therapy in the traditional sense, but they are attempts to achieve a better functioning gene product and thus a milder phenotype. There are high hopes for these methods, but there is still a long way to go before they potentially become established treatments. Research is also ongoing into various forms of gene and stem cell therapy, but this work is at a far more preliminary stage (18, 22).

Additional treatment and care

The main features of the recommended management of Duchenne muscular dystrophy are outlined in Table 2 (23, 24). The following sections will elaborate upon certain key areas.

Physical therapy

Regular physical therapy throughout childhood is very important. The goal is to maintain muscle strength and function and to prevent contractures for as long as possible.

Any immobilisation in connection with surgery, illness and injury while the patient is ambulatory should be kept as short as possible so as not to cause permanent loss of ambulation. Experience suggests that preserving ambulatory and later standing ability for as long as possible helps to delay the development of contractures, scoliosis and respiratory failure.

Respiration

The muscles of the chest wall and abdomen are gradually affected, particularly after loss of ambulation. Inactivity, slumped posture, overweight and scoliosis contribute further to chronic hypoventilation and a reduced ability to cough. Pulmonary function tests should be performed regularly from the time of diagnosis, with increased frequency and scope from the late ambulatory phase (5, 6).

Ventilatory support for patients with Duchenne muscular dystrophy has been shown to relieve symptoms of hypercapnia, extend life expectancy and improve quality of life, and reduce the need for emergency hospital admissions (2, 6, 7). This treatment is no longer controversial. Experience suggests that non-invasive ventilatory support can be used by most patients. In some individuals, a tracheostomy will be required.

Table 1. Typical clinical course of untreated Duchenne muscular dystrophy. Note that there are large individual differences in how quickly the disease progresses.

Age	Clinical signs of muscle wasting
Up to 2 years	Often slightly delayed motor milestones, possibly including walking (close to two years of age)
From 3–4 years	Difficulties with jumping, running, moving over uneven terrain and climbing stairs Reduced physical endurance compared with other children Uses his arms to 'climb up his own legs' to move from a lying to a standing position (Gower's sign) Pseudohypertrophy of calf musculature
From 5–8 years	Plateaued motor development Striking movement patterns: increased lumbar lordosis, increased arm swing, wide waddling gait, toe walking
Before 13 years	Loss of independent ambulation
After loss of ambulation	Gradual weakening of musculature in torso, arms and hands Development of neuromuscular scoliosis Increasingly weak respiratory musculature Development of cardiomyopathy and/or arrhythmia Deterioration of speech and swallowing

Ventilatory support should be discussed with the patient and their family in good time before any need arises, to avoid acute respiratory failure and to ensure compliance and involvement in decision making.

Cardiac complications

The most common forms of heart disease in Duchenne muscular dystrophy are dilated cardiomyopathy and/or arrhythmia. Remodelling of cardiac muscle tissue with areas characterised by atrophy, hypertrophy and myocardial fibrosis has been documented (8). Autonomic dysregulation with reduced heart rate variability has been described, but the significance of this is unclear (8, 25). With significantly more effective ventilatory support now available, progressive cardiomyopathy is becoming a relatively more common cause of death in these patients (5, 8). There is evidence that glucocorticoid treatment postpones the development of cardiomyopathy (16), yet this treatment can also lead to overweight and hypertension, which can place greater demands on cardiac function and complicate heart disease.

Patients have low levels of physical activity and often do not display the typical signs and symptoms of heart disease. They should therefore be monitored with regular echocardiography, ECG examinations and possibly Holter monitoring from diagnosis. There is evidence to suggest that pharmacotherapy should be considered in the event of pathological findings, even if the patient does not have symptoms (5, 8). ACE inhibitors are the consensus-based first choice, supplemented by beta-blockers and diuretics as required (5). Treatment should be managed by a paediatric cardiologist in combination with optimisation of ventilation, nutrition and weight.

Women with known carrier status should be monitored with ECG and echocardiography at least every five years (8).

Anaesthesia, surgery and acute illness

There should be a low threshold for use of antibiotics in respiratory tract infections. Oxygen therapy should be used with caution, as this can seemingly improve hypoxia but mask underlying causes such as atelectasis or hypoventilation (4), and lead to decreased respiratory drive and worsen hypercapnia in cases of chronic hypoventilation (5). With prolonged glucocorticoid therapy, the patient may have a reduced stress response during surgery or acute illness, and the need for stress doses of hydrocortisone must be considered.

Heart and lung function should be checked and optimised before elective surgery and actively monitored pre- and postoperatively (4, 5). There is a risk of anaesthesia-induced rhabdomyolysis and cardiac arrest with the use of depolarising muscle rela-

xants, which are therefore contraindicated in these patients (4). The use of inhalational anaesthesia is not recommended due to uncertainty regarding the risk of malignant hyperthermia-like reactions (4, 5).

Bone health and endocrine disturbances

Several studies have shown reduced bone mineral content in patients with Duchenne muscular dystrophy as assessed by dual-energy X-ray (DXA), and prolonged glucocorticoid therapy seems to exacerbate this tendency (26, 27). Some studies have shown an increased risk of osteoporotic vertebral fractures when patients are treated with glucocorticoids (26–28). Annual monitoring of bone turnover markers, vitamin D levels and DXA scans (which require expertise to perform and interpret for the age group in question), and a low threshold for X-ray examination in the case of symptoms such as back pain, are recommended in Duchenne muscular dystrophy (5). There is some evidence that optimal serum levels of calcium and vitamin D may counter the development of osteoporosis (28).

Delayed puberty and short stature are known problems in adolescents with Duchenne muscular dystrophy (17). To date, testosterone and growth hormone replacement therapy have been attempted in individual cases. With increased life expectancy and improved levels of functioning, there is a need for further research into bone health and endocrine disturbances (17, 27).

Cognitive and neuropsychiatric problems

Dystrophin is present not only in striated muscle, but also as distinct isoforms in areas including the central nervous system (29). Around one third of patients with Duchenne muscular dystrophy have cognitive difficulties (30). Generally speaking, average IQ is one standard deviation lower than in healthy boys (29, 30). This cognitive impairment is not progressive.

There is an increased incidence of ADHD, autism spectrum disorders, obsessive compulsive traits and specific language, reading and learning disabilities (1, 31, 32). Specialist teachers and neuropsychologists with expertise in the condition should be involved at an early stage to assess the child's needs and to provide guidance on the need for intervention.

Quality of life

It is reported that children with Duchenne muscular dystrophy have lower physical and psychosocial health-related quality of life than healthy children (33). Nevertheless, there does not seem to be any clear relationship between physical functioning and perceived psychosocial quality of life (33). A

study from Denmark suggests that young adult men with the disease have a good quality of life (3).

More knowledge is required about the relationships between level of functioning, age, participation, mental health and quality of life in Duchenne muscular dystrophy.

Conclusion

Duchenne muscular dystrophy is a very severe muscle disease that eventually affects many organ systems. Comprehensive and active care targeting those aspects of functioning mentioned here has been shown to improve patients' quality of life and life expectancy significantly. Provision of this comprehensive care is a specialist task.

The Scandinavian consensus programme for Duchenne muscular dystrophy (9) has been a useful tool for several years. In 2010, updated international guidelines were published in *Lancet Neurology* (1, 5). Ongoing research offers hope for better treatment options in the future. At the same time, prolonged survival presents many new challenges for patients, families and the support services. There is a need for more knowledge about problems arising in adolescence and adulthood. This group illustrates well the challenges faced by patients and their families who receive comprehensive and close multidisciplinary care throughout the patients' childhood, as these patients now increasingly become adults.

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