



Duchenne muscular dystrophy – novelties in diagnostics and treatment

Duchennova mišična distrofija – novosti pri diagnosticiranju in zdravljenju

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Abstract

Duchenne muscular dystrophy (DMD) is the most common and one of the most serious childhood diseases. It is an X – linked recessive neuromuscular disease, caused by mutations in the dystrophin gene, primarily resulting in skeletal and heart muscle abnormalities. In most boys, the first signs of the disease appear as progressive muscle weakness between the ages of 3 and 5 years. The muscle weakness is more pronounced in the proximal muscles, initially affecting the lower limbs to a greater extent than the upper limbs. Untreated, the disease progresses and will cause a serious decline of motor function by the age of 10 to 11 years, when the patients require wheelchairs even for travelling short distances. The progressive respiratory muscle failure results in chronic respiratory insufficiency and the patients require ventilatory support. Heart muscle involvement is consistent, studies showing that cardiomyopathy is present in all patients by the age of 18.

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The diagnosis of DMD is based on laboratory and genetic testing in patients with suspect clinical manifestations. If genetic testing is negative, muscle biopsy is necessary to confirm the diagnosis in highly suspect cases. Treatment of DMD patients requires a multidisciplinary approach, which coupled with corticosteroid treatment, physical therapy, supportive treatment and specific aids, have led to increased longevity and improved quality of life in these patients. Several drugs are being developed, targeting both the reduction of muscle damage, as well as the basic genetic cause of the disease.

Izveček

Duchennova mišična distrofija (DMD) je najpogostejša in ena najresnejših mišičnih bolezni otroške dobe. Gre za na kromosom X vezano recesivno živčno-mišično bolezen, ki jo povzroča mutacija v genu za distrofin. Primarno prizadene skeletne mišice in srčno mišico. Pri večini dečkov se klinični znaki bolezni izrazijo z napredujočo mišično šibkostjo med 3. in 5. letom starosti. Mišična šibkost je bolj izražena v proksimalnih kot distalnih mišicah in v začetni fazi bolj vpliva na poslabšanje funkcije spodnjih kot zgornjih udov. Bolezen postopno napreduje. Pri nezdravljenih otrocih večinoma po 11. do 12. letu starosti vodi v takó resno zmanjšanje zmožnosti gibanja, da le-ti že za premagovanje krajših razdalj potrebujejo invalidski voziček. Napredujoča šibkost dihalnih mišic vodi v kronično dihalno odpoved in potrebo po pomoči pri predihavanju. Okvara funkcije srca je splošno prisotna, kajti po študijah so klinični znaki kardiomiopatije prisotni pri vseh bolnikih po 18. letu starosti. Na podlagi klinične slike diagnozo DMD potrdimo z laboratorijskimi in genetskimi preiskavami. V primeru negativnih rezultatov genetskih preiskav, a ob močnem kliničnem sumu za DMD, pa se za potrditev diagnoze poslužujemo mišične biopsije. Zdravljenje bolnikov z DMD zahteva multidisciplinarno obravnavo. Z uporabo kortikosteroidov (KS), fizioterapije, podpornega zdravljenja in opreme s pripomočki sta se življenjska doba in kakovost življenja bolnikov z DMD izboljšala. V fazi razvoja je več zdravil, katerih delovanje se usmerja v zmanjšanje okvare mišic, a tudi zdravil, ki bi odpravile osnovni, tj. genetski vzrok bolezni.

1 Introduction

Duchenne muscular dystrophy (DMD) is the most common muscular disease in children, with an incidence of 1 in 3,500 to 5,000 live-born boys (1-3). It is an inherited, X-linked recessive neuromuscular disease (NMD) caused by a mutation in the dystrophin gene that mainly affects men. The main symptom is progressive skeletal and heart muscle damage. However, there are also other associated health issues which jointly usually lead to loss of mobility and premature death. The diagnosis of DMD is usually made at the age of 5, when a difference in motor skills of sick children compared to healthy peers becomes apparent. In the early 1990s, the life expectancy of children with DMD was 20 years. With advances in treatment, however, both quality of life and life expectancy have improved; the latter now reaches 30–40 years, and many patients may reach an even higher age.

The article presents an overview of knowledge about DMD and novelties in the treatment and rehabilitation of children with DMD.

2 Genetics

DMD is an inherited, X-linked recessive disease caused by a mutation in the DMD gene at the Xp21 locus, which encodes the skeletal muscle protein dystrophin (2,4). Dystrophin is located on the sarcolemma

(plasma membrane) of skeletal muscle and is a component of a large glycoprotein complex. It acts as a mechanical link between the cytoskeleton and the extracellular matrix (5).

The primary consequence of this genetic mutation is skeletal muscle and heart muscle damage. Dystrophin provides stability, strength and functionality to muscle fibres, and its deficiency leads to their degeneration (6-8). The DMD gene is the largest gene in the human genome, containing 79 exons and is transcribed into a 14 kb-long mature messenger ribonucleic acid (mRNA). The size of the DMD gene contributes to a high rate of mutations in it (in a third of cases these occur *de novo*). They can shift the reading frame or form a premature stop codon, thus interrupting gene translation or causing the formation of a shortened and unstable dystrophin protein (1,5). The “reading frame” rule can explain most of the phenotypic differences between DMD and Becker muscular dystrophy (BMD); the latter is a milder form of dystrophinopathy. Mutations that shift the reading frame usually cause the formation of abnormal and shortened dystrophin and cause DMD. However, mutations that preserve the reading frame produce a shorter and partially functional dystrophin, which results in the milder clinical picture of BMD (9,10). The majority of mutations in DMD are intragenic deletions, which account for 65–70% of all mutations and most

commonly occur in exons 45–53. Duplications are present in 7% of patients, and point mutations or small deletions/insertions are present in the rest (9,11,12). Thus, the clinical picture and prognosis of disease outcome can vary drastically depending on the type and location of the mutation (12).

3 Clinical picture

In most boys with DMD, the clinical signs of the disease are expressed between the ages of 3 and 5. Development is usually normal in the first few years of life, or there is only a slight delay in reaching developmental milestones (usually children start walking by the age of 18 months) (13). During infancy, the disease may manifest as mildly decreased muscle tone and poor head control. Muscle weakness usually begins to show between the ages of 2 and 3, with gait abnormalities (e.g. walking on toes), difficulty running, difficulty walking up stairs or getting up from the floor, and frequent falls. Less commonly, the disease manifests as speech or global developmental delay. The random discovery of elevated serum creatine kinase (CK) or hepatic transaminases can also raise the suspicion of the disease in pre-symptomatic children. Since these findings may already be elevated when the child is still asymptomatic, considering the differential diagnosis of DMD in these instances is important. It is characteristic for DMD that initially the proximal muscles of the lower limbs and the muscles of the trunk are more affected, but later also the muscles of the upper limbs and the distal muscles (3,6,14).

Clinical symptoms and signs that gradually develop are: waddling gait, positive Gower's sign (a result of weakness of the hip and thigh muscles and a characteristic manner of getting up from a lying and/or sitting position to an upright position; for a person to get up from a sitting or supine position, they must first turn around and become prone on the elbows and knees and extend them so that they can lift their torso; then, leaning on the ground, they gradually bring their arms and their legs closer in order to move their body's centre of gravity over the legs; at this point, the person can release one hand and take hold of or lean on one knee, which is followed by the same movement with the other hand; then they gradually 'climb' up the legs to reach an upright or standing position; Gower's sign is considered positive as soon as a person has to turn to a redirected position to lift themselves from a supine position, as 'climbing' up the legs in mild proximal muscle weakness might not take place; Gower's sign is

a non-specific sign of proximal muscle weakness that is not pathognomonic for DMD), (pseudo)hypertrophic and stiff calves, which are also occasionally painful, and in later stages, shortening of the Achilles and other tendons of the lower limb muscles and weakness of the neck muscles also occur. As the disease progresses, the tendon reflexes, distal following proximal, also gradually dissipate (13,15,16).

Most boys progress in muscle strength and motor skills (albeit to a lesser extent than their peers) by about the age of 6; after this age there is a progressive deterioration of muscle strength (14). The disease progresses rapidly after the age of 7 to 8, and untreated children become wheelchair dependent between the ages 11 and 12. Scoliosis and joint contractures develop due to loss of muscle function, ability to maintain posture and movement. A typical form of scoliosis is a long paralytic C-curve involving the thoracic and lumbar spine, and in the advanced stage, pelvic tilt also occurs in most cases. Scoliosis progresses faster compared to idiopathic scoliosis. At the same time, the risk of vertebral and long bone fractures increases with the development of osteoporosis due to inactivity. After the loss of the ability to move, problems with the heart, respiratory system and the already mentioned orthopaedic problems become more pronounced. It is also known that patients with DMD are more likely to develop puberty later, they are of shorter stature, and have an increased risk of malignant hyperthermia with anaesthesia and the use of depolarizing muscle relaxants (3,13,17).

As already mentioned, the disease also affects the heart and lungs. Cardiac involvement is usually manifested by dilated cardiomyopathy and cardiac arrhythmias (10). The degree of cardiomyopathy in 50–80% of patients is not proportional to muscle weakness (18). Heart disease, which mostly manifests by persistent tachycardia, is present in up to 25% of children under the age of 6. Despite the high proportion of boys with heart muscle involvement, most of them are relatively asymptomatic due to physical inactivity (10). Nigro et al. (19) in a study published in 1990 found that clinical signs of cardiomyopathy are expressed after the age of 10 and are present in 30% of patients up to the age of 14, while after the age of 18 they are present in all patients.

Lung damage occurs due to the progressive weakness of the respiratory muscles. The latter leads to ineffective coughing, reduced nocturnal respiration (nocturnal hypoventilation) and sleep-disordered breathing, and respiratory infections are also more common than in the general population (3,20,21). Progressive scoliosis often impairs respiratory function even further.

Chronic respiratory failure as a result of restrictive lung disease is a common feature of these patients. Studies have shown that the vital capacity of this group of children increases until about 12 years of age, and then begins to decline by 4–8% per year (22,23). Respiratory complications are also a major cause of morbidity and mortality in patients with DMD (3,20,21).

Various dystrophin isoforms have also been shown to be present in the brain, retina, and Purkinje cells. Mutations in these specific isoforms are most likely to cause extramuscular manifestations of the disease, manifested by delayed speech development, cognition disorders, behavioural and learning difficulties, as well as attention and hyperactivity disorders, and autism. Various studies have shown that some degree of non-progressive cognitive impairment is present in some boys with DMD, but not all. In addition, the results of studies have also shown that mutations in the distal parts of the dystrophin gene are more likely to be associated with cognitive impairment and that cumulative loss of dystrophin isoforms expressed in the central nervous system increases the risk of cognitive deficits (13,17). The described average IQ in boys with DMD is 85 or 1 standard deviation below the population average (3).

Girls who carry mutations in the DMD gene are usually asymptomatic, but it is known that they may develop symptoms of skeletal and heart muscle damage; these patients are defined as 'symptomatic carriers' (24). The authors of some studies report that the prevalence of skeletal muscle damage in carriers is 3–46%, the prevalence of elevated serum CK values is 53–100%, and dilated cardiomyopathy is 8–18%. Dilated cardiomyopathy, in particular, is a serious problem, as its incidence increases with age even in carriers with normal electrocardiogram (ECG) and without symptoms associated with skeletal muscle damage (25). Cardiac dystrophinopathy is also a risk factor for myocarditis. Because of all this, female carriers need proper treatment and regular monitoring by a cardiologist (8,21,25,26).

4 Diagnostic tests

DMD should be considered by any physician who comes in contact with a boy whose parents say he often falls, that he has weak muscles, and who finds a positive Gower's sign in the boy's clinical status. These problems can also be accompanied by delayed speech development. The disease should also be considered in any boy with global developmental delay or any girl with unexplained impaired heart function.

Serum analysis of blood shows elevated levels of muscle enzymes which are released into the bloodstream – CK and transaminases (mainly alanine aminotransferase – ALT and aspartate aminotransferase – AST). Based on the previously described clinical picture and laboratory results, the decision to perform genetic tests for DMD confirmation is made. Given that deletions and duplications in one or more exons are present in most patients (up to 70%), the multiplex ligation-dependent probe amplification (MLPA) method is the genetic test of choice. While MLPA detects deletions and duplications in exons, it does not detect mutations in introns. For this purpose, microarray-based comparative genomic hybridization, aCGH, is used as a second test. In addition to these two, single-condition amplification/internal primer and multiplex amplifiable probe hybridization are used to diagnose DMD. If by using one or more of these methods a mutation in dystrophin is identified, no further testing is required. However, if the deletion or duplication cannot be determined by these methods, it is necessary to perform sequencing of the dystrophin gene, which means carrying out a targeted search for point mutations or small deletions or insertions.

Muscle biopsy is not required in case of a positive genetic result for DMD. However, if genetic testing is negative while CK levels are elevated and DMD-consistent clinical symptoms and signs are present, muscle biopsy should be performed to quantify the dystrophin expressed in the sample. The latter should also be performed in case of suspicion of DMD and a positive family history of a still unknown family mutation. Nowadays, electrophysiological examinations (electromyography, nerve conduction studies) are rarely required in the process of diagnosing DMD. They are not mandatory in diagnosing DMD (8,25).

The comprehensive patient evaluation also includes genetic counselling of family members of a patient with DMD in order to identify who is a potential carrier of the mutation in the dystrophin gene. Such testing is recommended to female relatives of a boy with a confirmed diagnosis of DMD. If the test confirms that the woman is a carrier, a prenatal genetic diagnosis is available to her (7,18). At the Department of Child, Adolescent and Developmental Neurology of the University Children's Hospital, University Medical Centre (UMCL) Ljubljana, all female relatives of an ill boy are advised to undergo genetic counselling with a clinical geneticist; further genetic diagnostics is in the domain of the clinical geneticist.

5 Treatment

In January 2018, The Lancet Neurology published new recommendations for the holistic treatment of patients with DMD (8,21,28). They emphasize the importance of early detection of the disease, earlier identification and treatment of possible and expected complications, all with the aim of prolonging the life expectancy as well as improving the quality of life of patients with DMD.

5.1 Corticosteroids

The exact cellular mechanism of the positive effects of corticosteroids (CS) in the treatment of DMD has not been fully elucidated. By working on mouse models with muscular dystrophy and in patient studies, researchers found that the positive effects of CS may be due to the following possibilities of their action: 1. altering the mRNA levels of structural, signalling, and immune response genes; 2. reducing the number of cytotoxic T lymphocytes; 3. lowering calcium influx and concentration in the cytosol; 4. increasing laminin expression and muscle regeneration; 5. inhibiting muscle apoptosis and cellular infiltration; 6. increasing dystrophin expression; 7. affecting neuromuscular transmission; 8. protecting against mechanical damage to the fibres; 9. slowing down muscle fibre necrosis; 10. slowing down the rate of skeletal muscle breakdown; 11. increasing the level of taurine and creatine in the muscles. It was concluded that additional studies are needed to identify cellular mechanisms of action that contribute to the positive effects of CS in the treatment of DMD (29).

One of the goals of CS treatment is to prolong the time when the patient walks independently or has the preserved ability to move. Using CS extends the ability to move independently without the use of a wheelchair for roughly three years (30). Randomized controlled studies have shown that CS significantly improve muscle strength and movement ability in boys with DMD (8,31), maintain respiratory and cardiac function, upper limb function, and reduce the need for scoliosis surgery, at least in the short term. Therefore, this treatment is also included in the latest international recommendations for the treatment of children with DMD (8,10,32,33).

The authors of the current recommendations of CS treatment initiation believe that CS should be introduced when the child's motor skill development stops at the latest, but prior to their loss, which is between the ages 5 and 15. Prednisone (at a final dose of 0.75 mg/kg BW/day) or deflazacort (at a final dose of 0.9 mg/kg

BW/day) are recommended for treatment. If the child does not tolerate the administered dose or more severe side effects occur, it is advisable to reduce the dose by 25–33% and re-evaluate the treatment after one month. If the functional movement ability is reduced, it is advisable to re-increase the dose of CS to the target dose according to the weight and based on the initial dose and to re-evaluate after 2 to 3 months. The introduction of CS is also recommended for patients who are no longer able to move independently. We also follow these recommendations at the Department of Child, Adolescent and Developmental Neurology of the University Children's Hospital, University Medical Centre (UMCL) Ljubljana.

Despite the instructions given, the preferred CS, the optimal dose and the dosing regimen are not known. In some studies, daily doses of prednisone/prednisolone or deflazacort have been shown to be more effective than intermittent dosing regimens regarding the effect on preserving the ability to move, but such doses have been associated with an increased risk of side effects (34,35).

On the other hand, studies have also been published in which prednisone administered once weekly has been shown to be as effective as daily prednisone intake. Phase 3 of double-blind, randomized controlled trials compared deflazacort 0.9 mg/kg BW/day, deflazacort 1–2 mg/kg BW/day, prednisone 0.75 mg/kg BW/day, and placebo. In all groups treated, improved muscle strength was observed compared to the placebo group. They also found that deflazacort was associated with lower weight gain compared to prednisone. However, a study comparing the safety and efficacy of deflazacort with prednisone is ongoing (8,36–38).

We believe that additional studies are needed to further define the effect of CS on prolonging the time when a child is still able to move independently and other positive effects on the health of children with DMD, the most appropriate time to start treatment, type of CS and dosing regimen, but also studies that, in addition to the already known side effects of CS (the most common being overweight, short stature, behavioural changes, Cushingoid appearance and excessive hair growth) (36,38), would exactly specify the long-term side effects of their use in patients with DMD.

The desire for a drug that would be as effective or more effective than CS and at the same time have fewer side effects, has led to the development of vamorolone. Vamorolone is a new (first in its class) anti-inflammatory synthetic steroid drug that appears to optimize the classic anti-inflammatory effects of CS. Studies on the efficacy and safety of vamorolone in animal models with

chronic inflammatory conditions, including mouse models with DMD, have shown, when comparing vamorolone with prednisolone, that the anti-inflammatory effects of prednisolone are maintained and that there are no side effects. The maintenance of anti-inflammatory effects and loss of side effects in preclinical models is consistent with the mechanism of action of vamorolone; namely, it blocks the nuclear factor κ B (NF- κ B) associated proinflammatory signals as a ligand/receptor in the monomeric state, instead of in the classical molecular model of ligand/receptor dimer complexes (39,40).

Conklin et al. (39) conducted a multicentre, open-label, two-week phase IIa study involving 48 mobile boys with DMD aged 4 to <7 years who had never received CS. The boys were divided into four groups of 12 children to study the effectiveness and safety of different doses of vamorolone; in the first group, children received vamorolone at a daily dose of 0.25 mg/kg BW/day, in the second at a dose of 0.75 mg/kg BW/day, in the third at 2.0 mg/kg BW/day and in the last group at a dose of 6.0 mg/kg BW/day. The results showed that vamorolone was safe and well tolerated by patients even at the highest daily dose studied (6.0 mg/kg BW/day). The pharmacokinetics of vamorolone were also found to be similar to the pharmacokinetics of prednisolone. The study also showed better safety of vamorolone compared to glucocorticoids, as the results showed a decrease in insulin resistance, positive effects in bone turnover and a decrease in adrenal inhibition. In addition to the above, the anti-inflammatory mechanism of action and a positive effect on the stability of the plasma membrane were also noted; all of this was demonstrated by a decrease in serum CK, dependent on the dose of vamorolone.

The positive effects of vamorolone for the treatment of DMD were also found in a recently published study by Hoffman et al. (40). After 24 weeks of vamorolone treatment, improved muscle function (estimated by the time to rise) and an increase in osteocalcin (a biological marker for bone formation) were observed. In addition, lower values of adrenal inhibition and insulin resistance biomarkers were found when comparing the results with previously published studies in patients with DMD treated with glucocorticoids.

To optimize the treatment of DMD, various authors have studied the safety and efficacy of many drugs of different groups (anticholinesterase drug galantamine; antioxidants acting on biochemical and metabolic pathways, such as allopurinol, creatine, glutamine, idebenone; drugs that affect growth, height and muscle function – mazindol, growth hormone; drugs that cause

changes in sarcolemma and calcium accumulation – verapamil; drugs that affect blood flow in the muscles, anti-inflammatory drugs – azathioprine, cyclosporine, CS ...). For the time being, CS (prednisone/prednisolone/deflazacort) are still considered a credible treatment that can change the natural course of the disease. Coenzyme Q10 and creatine had a positive effect on certain muscle functions in individual studies without side effects, whereas based on the results of a 52-week study of 31 patients with DMD, idebenone (a synthetic analogue of coenzyme Q10) was found to supposed to have a long-term positive effect on pulmonary function (41).

5.2 Treatment of cardiovascular problems

Cardiovascular complications are the leading cause of disease-related morbidity and mortality in patients with DMD. Dystrophin deficiency in the heart muscle is manifested by cardiomyopathy. As the disease progresses, heart function deteriorates, so clinical signs of heart failure develop; besides aforementioned there is also a risk of developing life-threatening arrhythmias (21).

As already mentioned, according to a study published by Nigra et al., dilated cardiomyopathy is present in all patients with DMD after the age of 18 (19). However, the age at onset of dilated cardiomyopathy and its degree vary widely and do not depend on an individual mutation in the dystrophin gene (42). In addition, it is important to realize that the signs and symptoms in patients who have a greatly reduced ability to move (and do not walk) are often subtle (21). Because of all of the above, boys with DMD need regular monitoring by a cardiologist for the early detection of left ventricular (LV) ejection fraction decline (42). Recent recommendations for the treatment of children with DMD, published by Birnkrant et al. (21), also state that a cardiologist should be included in the multidisciplinary treatment of these children at an early stage, if possible with additional knowledge of the treatment of cardiomyopathy and heart failure associated with NMD.

When DMD is diagnosed, patients who are still able to walk and patients who have recently been able to do so are advised to have a regular, yearly examination (up to the age of 10) by a cardiologist, including an ECG and cardiac imaging. The method of choice for follow up is magnetic resonance imaging (MRI) of the heart, which, due to the need for anaesthesia, is generally performed from the age of 6 to 7 on; until this age, regular yearly heart ultrasound examination (US) is recommended. After the age of 10, however, due to the increased risk of LV dysfunction, an annual cardiac assessment

is advised. However, if symptoms and/or signs of heart failure occur during examination or upon imaging (e.g. LV enlargement, LV dysfunction), the cardiologist will assess whether more frequent monitoring is required.

The biggest change in recent recommendations is that angiotensin-converting enzyme inhibitors (ACEI) may be introduced into treatment in asymptomatic boys less than 10 years of age, with no signs of abnormality in cardiac MRI or cardiac US. ACEI selection as well as dosing are in the domain of the cardiologist (21). Studies conducted by Duboc et al. (2005 and 2007), which examined the effect of the ACEI perindopril on the onset and progression of LV dysfunction in patients with DMD, have shown that early introduction of ACEI was associated with later onset of LV dysfunction and lower mortality (43-45). However, pharmacological treatment, regardless of age, should be initiated in the case of abnormal US or MRI of the heart or in case of clinical symptoms of heart failure in accordance with the general guidelines for the treatment of heart failure. In addition to ACEI or angiotensin receptor blockers (ARBs), additional beta-blocker and mineralocorticoid receptor antagonist therapy is initiated after an observed deterioration of LV function. With further deterioration of LV function, anticongestive treatment is intensified further (21).

In patients in the late stage of the disease, i.e. long after they have lost the ability to walk, in light of the expected progression of the deterioration of cardiac function or escalation of heart failure and for the purpose of early optimal treatment, more frequent treatment by a cardiologist is recommended within the time frame at their discretion. Symptomatic heart failure is difficult to diagnose in patients who have lost independent movement, as the initial symptoms of heart failure are identified on the basis of physical performance (NYHA heart failure classification). In these patients, only signs of already advanced heart failure are visible, such as inability to perform daily activities, weight loss, vomiting, abdominal pain, and sleep disturbances. It is also extremely important to provide optimal respiratory support, as abnormal pulmonary function affects heart function.

In addition to heart failure, patients with DMD with severely impaired LV function are also at risk of thromboembolism and cardiac arrhythmias. Most common rhythm disorders include atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. In patients with impaired LV function or myocardial fibrosis, a 24-hour Holter ECG is recommended once a year. Among patients with episodic, non-sustained rhythm

disturbances, the method of choice are event monitors/event recorders. The introduction of antithrombotic agents, antiarrhythmics or the insertion of specific cardioverter defibrillators is in the domain of the cardiologist (21).

5.3 Treatment of respiratory problems

As DMD progresses, the strength of the muscles of the chest, the diaphragm (the most important respiratory muscles) and the abdominal wall gradually deteriorate, especially after the loss of independent movement. Inactivity, incorrect posture, obesity and changes in the shape of the chest further contribute to deepening respiratory failure and impaired coughing efficiency and lead to respiratory complications: ineffective shallow breathing patterns, uneven distribution of ventilation within the lungs with the formation of atelectasis, severe pneumonia, and chronic respiratory failure. Without effective respiratory support, disease progression leads to chronic respiratory distress, long-term and severe respiratory infections, and exposes the patient to a high risk of poor disease outcome with respiratory failure or deepening cardiomyopathy. If left untreated, patients are at high risk of developing severe dyspnoea, the need for long-term hospitalizations due to atelectasis or pneumonia, and the risk of death as a result of respiratory failure or cardiac arrhythmias due to respiratory problems (7,21).

The latest guidelines specifically emphasize the importance of early treatment, which aims to maintain long-term pulmonary function and to “delay” the decline in pulmonary function. The decline in pulmonary function initially shows no symptoms, so patients do not detect it in time. Therefore, at the stage when patients are still able to move independently, regular monitoring of pulmonary function by spirometry is recommended once a year – especially FVC.

In addition, nocturnal polygraphy/polysomnography (PSG) is recommended in patients who move independently and have symptoms and/or signs of sleep-disordered breathing, and in those who experience weight gain during CS therapy with the aim to objectively assess sleep-disordered breathing.

Leading NMD centres perform nocturnal polygraphy/PSG routinely once a year in patients who no longer walk independently (independent of FVC), as well as in all patients who still walk and have a FVC <50%. The presence of clinical signs of sleep-disordered breathing or frequent/severe respiratory infections are a warning sign of the need for additional targeted analysis of sleep breathing (46).

In addition to causing increased daily fatigue and headaches, obstructive sleep apnoea, which often co-occurs with snoring, also increases the risk of cardiovascular complications, namely hypertension, stroke, and heart failure (47). Apart from snoring, these are late signs of nocturnal hypoventilation, which we want to avoid with a proactive approach.

Sleep studies can also be used as an alternative method to monitor respiratory status in those patients who are unable to participate in routine pulmonary function tests.

As already mentioned, more respiratory complications are expected after the loss of the ability to move independently. Therefore, monitoring of pulmonary function every 6 months is advised at this stage of the disease. In addition to FVC, monitoring of maximal inspiratory and expiratory pressure, cough strength, blood oxygen saturation by pulse oximetry (SpO_2) is recommended; transcutaneous measurement of the partial pressure of carbon dioxide in the blood ($P_{tc}CO_2$) or partial pressure of carbon dioxide in expired air ($P_{et}CO_2$) is also recommended every six months or whenever room air SpO_2 is $\leq 95\%$.

Based on the results of these examinations, the patient is advised to use respiratory physiotherapy devices in accordance with their needs and abilities (e.g. vibrating/oscillating device – a device that by causing the chest wall to vibrate and by using appropriate manual technique allows easier clearing of the lower respiratory tract; aspirator; expectorant...). If the criteria are met, non-invasive ventilation during sleep is introduced and, where necessary, also during the day (mouth-breathing support) and, in the case of markedly advanced disease, consideration should be given to the appropriateness of invasive respiratory support.

Progressive scoliosis often worsens pulmonary function. These patients should undergo surgical correction of scoliosis. A characteristic type of scoliosis in patients with DMD is a long paralytic C-curve involving the thoracic and lumbar spine with pelvic tilt. It is usually necessary to correct scoliosis and fixate the spine, extending from the 4th thoracic to the 1st sacral vertebra by also fixing it to the pelvis.

Regular follow-up of the patient and the provision of this respiratory support reduces the number of respiratory complications and improves the quality of life as well as prolonging survival. Adequate respiratory support is provided by a team of pulmonologists and respiratory physiotherapists/nurses with specialized skills who provide parents with appropriate education to provide optimal respiratory support at home.

Regular vaccination against infectious diseases is recommended for all patients, regardless of the stage of the disease. However, those who receive a high dose of CS (more than 20 mg or more than 2 mg/kg body weight prednisolone per day) should not be vaccinated with live vaccines. If a child with DMD has not had chickenpox, it is advisable to vaccinate them with two doses of live, attenuated vaccine at 6-week intervals before initiating CS treatment, but if this is no longer feasible, it is recommended that those family members who have not had chickenpox be vaccinated. Patients with DMD should be vaccinated against influenza every autumn, and pneumococcal vaccination is also recommended. The best protection against pneumococcal infections is achieved by using the conjugate vaccine in the required number of doses for the age, followed by another dose of the polysaccharide vaccine after two months. Since 2015, the pneumococcal conjugate vaccine is available to all children in Slovenia, in patients with DMD aged 5 years and older who are already on a high dose of CS. Due to immune deficiency, the costs of the pneumococcal conjugate vaccine are covered by the Health Insurance Institute of Slovenia, otherwise patients over 5 years of age who do not receive CS treatment have to pay the costs of the conjugate vaccine themselves, but the costs of the polysaccharide vaccine are borne by the Health Insurance Institute of Slovenia (21,48).

5.4 Treatment of endocrinological and metabolic co-morbidity

Impaired muscle strength due to the progression of the underlying disease and treatment with CS are two major risk factors for decreased bone density and increased risk of bone fracture. A fracture can occur even after a minor fall. The most common are fractures of the bones of the lower limbs and vertebrae. In addition to clinically detectable fractures, asymptomatic fractures, especially of the vertebrae, occur in boys with DMD. Untreated fractures cause chronic back pain and spinal deformities, and fractures of limb bones can lead to premature loss of mobility. In recent guidelines for the treatment of boys with DMD, Birnkrant et al. (21) therefore emphasize the importance of early detection, identification and treatment of individuals at increased risk of bone fractures. The detection is aided by bone mineral density measurements with double X-ray absorptiometry (densitometry), and even more important is the routine X-ray imaging of the spine in lateral projection in individuals at increased risk due to CS treatment or physical inactivity. Thus, in addition to

periodic densitometry, periodic X-ray imaging of the thoracic-sacral part of the spine is also advised; in boys treated with CS every 1–2 years, and in others every 2–3 years. In addition to imaging tests, blood tests are also used to assess bone health: calcium, phosphate, alkaline phosphatase, parathyroid hormone, vitamin D and bone turnover parameters are determined. An endocrinologist plays a major role in planning primary and secondary prevention and treating low bone density. The basis of prevention and treatment is adequate calcium intake, maintenance of normal vitamin D levels and reduction of risk factors for reduced bone density (CS, physical inactivity). Mild asymptomatic fractures should be closely monitored. In moderate and severe asymptomatic fractures and in all fractures with symptoms in the thoracolumbar spine, Birnkrant et al. recommend treatment with intravenous bisphosphonates (21).

As part of endocrinological treatment, it is also important to monitor physical growth, pubertal development and possible adrenal dysfunction. In boys with DMD treated with CS, decreased growth rate is quite common. As part of monitoring, it is therefore necessary to determine body height at each examination (at least every 6 months), and in the case of immobile patients, other auxological measurements can be used to determine growth, such as measurements of the length of individual long bones. In case of short stature and/or slower growth, endocrinological treatment is required as in other children. Recombinant human growth hormone therapy has also been mentioned. Delayed or incomplete puberty as part of the treatment with CS or with poor nutrition is consistent with secondary-tertiary hypogonadism. With the exclusion of the causes of hypogonadism, testosterone treatment prescribed and dosed by an endocrinologist is warranted. An important goal of the testosterone treatment is to maintain bone health or treat decreased bone density as a consequence of hypogonadism. Iatrogenic adrenal insufficiency has also been described during treatment with CS. Patients receiving CS should be aware of the possibility of acute adrenal insufficiency, which is a life-threatening condition. In people with DMD, especially those receiving high doses of CS, with symptoms or clinical signs consistent with the Addisonian crisis, immediate hydrocortisone treatment is urgently needed.

A holistic approach to the treatment of DMD also includes the identification of CS and reduced physical activity-related metabolic complications such as obesity, so-called prediabetes and various components of the metabolic syndrome.

5.5 Treatment of gastrointestinal problems and ensuring adequate nutritional status

Constipation is one of the most common gastrointestinal (GIT) problems in patients with DMD, as they usually have several risk factors present (inability to move, weakness of the abdominal muscles, prolonged passage of stool through the colon, dehydration). To prevent the development of constipation, it is necessary to take care of a balanced diet with sufficient intake of ballast substances and adequate fluid intake, and if this is not enough, regular/daily use of oral osmotic stool softeners and laxative suppositories, which accelerate intestinal peristalsis, is recommended.

Gastroesophageal reflux disease (GERD) is also a common GIT problem, mainly due to impaired oesophageal motility, delayed gastric emptying (gastroparesis) and the presence of scoliosis, as well as treatment with CS. GERD is primarily treated with drugs, namely proton pump inhibitors. However, it should be taken into account that long-term treatment with proton pump inhibitors is associated with an increased risk of reduced bone density, vitamin B12 deficiency, and infections such as pneumonia. It is also necessary to advise on proper nutrition, in terms of smaller and more frequent meals, and appropriate reduction of fat intake.

Gastroparesis can lead to postprandial abdominal pain, nausea, vomiting, and loss of appetite. When gastroparesis is confirmed by appropriate examinations, an attempt is made to treat it by changing the diet as in the GERD treatment, by prokinetic therapy and, in case of failure, also by inserting a gastro-jejunal feeding tube.

Patients may also experience difficulty swallowing and contractures of the jaw muscles, especially in the later stages of the disease. These factors make feeding very difficult and affect the patient's general condition (weight loss accelerates the gradual loss of respiratory muscle strength), so it is extremely important to inform patients and their parents/guardians in a timely fashion about the possibility of feeding via feeding tubes either through a nasogastric tube or especially through percutaneous gastrostomy tube.

In light of all the above, it should be emphasized that ensuring optimal body weight of patients with DMD is crucial. Namely, patients with DMD have an increased risk of being overweight in early life (mainly due to CS and loss of ability to move), but later, due to problems with feeding and swallowing and contractures of the jaw muscles, they are at risk of being underweight. Nutritional imbalance, as already mentioned, has a negative effect on skeletal muscle as well as on the respiratory

and cardiovascular systems. Therefore, it is important that the multidisciplinary team includes a dietitian who, by regularly monitoring the patient's clinical condition, weight and height, advises the patient on a healthy, balanced diet, which must ensure optimal intake of calories, protein, fluids, as well as vitamins and electrolytes, especially calcium and vitamin D (8,49).

5.6 Psychological aspects of treatment of children and adolescents with DMD

Psychological treatment is one of the important aspects of holistic treatment of children and adolescents with DMD (28), as living with this disease requires patients and their relatives to adapt to different, disease-related health and physical limitations. At the same time, the quality of life of patients is also affected by frequent associated neuro-developmental and psychopathological disorders.

In children and adolescents with DMD, specific cognitive impairments and intellectual disabilities are more common. In tests of intellectual ability, they achieve on average about one standard deviation lower results compared to healthy peers. In a review study, Cotton et al. (50,51) found in 1,224 patients with DMD that as many as 35% of children with DMD achieved scores in the intellectual disability range ($IQ \leq 70$), significantly more than in the general population of children (approximately 2%). In addition, research over the last ten years has shown that such problems are more common in patients with a defect of the distal part of the DMD gene associated with the regulation of prenatal central nervous system development (52,53).

In addition to differences in general intellectual abilities, various studies have also confirmed a higher incidence of deficits in specific cognitive abilities. These include problems with verbal comprehension and expression, verbal memory and automation of thought processes, which increases the risk of specific learning difficulties in children with DMD, such as dyslexia, dyscalculia and dysgraphia (54-57).

Due to the described problems in the field of cognitive abilities and physical limitations resulting from the disease, children and adolescents with DMD often show poorer adaptive skills in the areas of communication and social skills, practical everyday skills and motor skills (58).

Increased symptoms of various psychopathological disorders have been reported in children and adolescents with DMD (59). In many cases, they are clinically significant (56,60), most often in the form of anxiety (29.3%),

depression (27.4%), obsessive compulsive disorder (4.8–11%) and/or autism spectrum disorders (3.1–21%). In conjunction with the latter, but also possibly independent of it, boys with DMD may also have more difficulty processing sensory stimuli. Hyper- or hyposensitive reactions to auditory, visual, tactile, olfactory, oral, and vestibular stimuli have been reported (61). One of the most commonly associated disorders in DMD is attention deficit hyperactivity disorder (ADHD) (9–45%). Hinton et al. (56) observed significant attention problems in about a quarter of boys with DMD, accompanied by frequent behaviour regulation difficulties, low frustration tolerance, aggression, defiant behaviour, and mental rigidity.

DMD, however, does not affect only patients, but as a complex and chronic progressive disease it is a great burden for the whole family. The burden that the family feels is reflected on a daily practical and mental level. At the daily practical level, the impact of the disease is reflected in altered family relationships and the extent of social and leisure activities of family members, as well as in financial challenges. At the mental level, the effect of illness is recognizable in the emotional responses that family members experience due to illnesses such as feelings of loss, sadness, tension, feeling unable to cope with the situation (62). A bigger challenge for parents of children with DMD is also their upbringing (63). Compared to parents of healthy children, they report higher levels of stress (63,64) and feelings of guilt, sadness, and depression associated with the child's illness (62,65). The severity of these problems and the effectiveness of parents in dealing with them depend on the level of progression of the child's illness, experiencing the illness as a burden, interpersonal support and the financial burden that the illness poses to the family.

An important group that is often overlooked in the treatment of children and families with NMD are their healthy siblings. The illness of their brother or sister affects them as well. Research on their psychological adjustment shows at least double the risk of them developing emotional and behavioural problems than with their peers in the normative comparison group (66,67).

Families of children with DMD, however, do not only report that coping with chronic NMD is difficult and burdensome, but often also emphasize the positive effects of the disease. Two thirds of parents of children with DMD and BMD report positive psychological effects of their own parenting experience. They point out as particularly valuable the possibility of personal growth, the development of an enhanced sense of power in coping with difficulties, and cite the beneficial effect

of the disease on the interconnectedness of family members (62,67).

Psychological assistance to patients with DMD and their families includes diagnostic procedures to identify associated neurodevelopmental and psychopathological disorders, as well as various psychotherapeutic measures to help cope with the disease. As members of the professional team, clinical psychologists use standardized psychodiagnostic tools to identify the presence of possible intellectual disabilities and/or specific deficits and to assess the child's adaptive skills. Based on the psychological assessment, they also offer support in integrating the child into the school and social environment, and advise schools and kindergartens on various adjustments, assigning a companion and on the possibility of providing additional professional assistance if the child needs it. They provide psychological support and counselling to parents regarding family relationships, siblings and partnerships, and help them integrate into various self-help groups. They provide psychological help and support in communicating with the child about their illness and strive to provide psychological support to healthy siblings. By providing appropriate psychological measures, they thus contribute to the empowerment of the family and the child with DMD and strive to strengthen the strong areas of all family members and the family as a whole.

5.7 Rehabilitation and supportive care programs

The rehabilitation of children with DMD involves specialists in physical and rehabilitation medicine, physiotherapists, occupational therapists, speech therapists, special teachers, social workers, psychologists and specialists in orthotics and prosthetics at the University Rehabilitation Institute of the Republic of Slovenia (URI-Soča). A key element in planning a rehabilitation programme is the assessment of functional status, especially in the area of movement and daily activities. When assessing functional status, it is important that the assessment is performed by a therapist who has the appropriate knowledge and experience and understands the relationship between test results and the clinical picture in a child with DMD (8).

According to the recommendations of Birnkrant and his colleagues, mobility assessments should be performed every six months. They recommend regular assessments of muscle strength, the range of passive lower limb joint mobility, and walking tests (6-minute walking test, 10-metre walk, stand-up and walk test) (8). Among

functional tests in Slovenia, regular clinical practice uses MFM, the motor function measure scale for neuromuscular diseases (68). A child with DMD should regularly perform stretching exercises for the lower limb muscles 4 to 6 times a week. To maintain physical fitness, the authors of the guidelines recommend swimming, low-resistance exercise, and exercises to improve or maintain respiratory function. The physiotherapy programme is also important at a time when the child loses the ability to move independently. They advise exercising to the extent that the child does not get too tired and that exercise does not cause pain (myoglobinuria in the 24-hour urine is a sign of excessive effort and additional muscle damage). To prevent contractures and prolong the ability to move, the guidelines recommend the use of orthoses for the ankle and foot at night (to stretch the gastrocnemius muscle), the use of orthoses for the knee, ankle and foot (stretching the muscles that bend the knees) and stand-up chairs (stretching all the muscles of lower limbs, when the child can no longer walk). Therapeutic bikes are available to strengthen the muscles of the lower limbs and overcome the medium distances. In the case of deformities of the lower limbs, orthopaedic surgical treatment is considered (8,21,28).

An often-overlooked problem is pain. The authors of the guidelines have pointed out that little is known about this. Experts are encouraged to ask a child with DMD about possible pain. It is believed that pain is often the result of improper posture and inability to change position. In view of this, it is recommended that the child be provided with a suitable sitting chair, a seat for the wheelchair and an adaptive bed with a cushion for pressure ulcer prevention. In the event that scoliosis has already developed due to muscle weakness and asymmetrical posture, a well-adjusted and individually made chair or wheelchair is especially important. Scoliosis is measured on an X-ray with a Cobb measurement, which is still considered a useful standard clinical method. When determining the curvature, we first determine the upper and lower vertebrae that still belong to this plane. A line is then drawn along the upper border of the upper vertebrae and the lower border of the lower vertebra and perpendiculars to this line. The sharp angle between these two lines is called the Cobb angle (69). With established scoliosis, regular monitoring, devices with a spinal orthosis and timely surgical treatment are important. The authors of the guidelines recommend that this be done in a child who is still growing and is not undergoing CS therapy, at a Cobb angle above 20°, or in a child with CS therapy at a Cobb angle above 40° (8,21,28).

As the gross motor function decreases, difficulties

arise in performing daily activities. To make dressing and undressing easier, soft elastic clothing with simple fastening systems is recommended, as well as the use of a toilet chair and a shower chair. When contractures in the joints of the upper limbs begin to develop due to muscle weakness, it is appropriate to make an orthosis for the hands (most often for the wrist and palm with the fingers) to maintain a neutral position. In addition to testing and learning how to use these aids, occupational therapists at URI-Soča also monitor the child's ability to perform fine movements and graphomotor skills. To help the latter, it is possible to use thicker pens with a softer filling, so that the child leaves a clear enough trace on the paper with less pressure. Later, the adolescent with DMD may also be offered the use of a computer to make notes of the subject matter more easily and to use handouts.

In case of gross motor ability loss, we offer the child the use of a wheelchair. There are several types of wheelchairs available (transport, manual, electric). Testing takes place at URI-Soča. It is important to decide on the model together with the child and parents, and at the same time provide the child with a good sitting position and an effective way to overcome longer distances. In the later stages of the disease, adolescents with DMD are usually equipped with a very complex electric wheelchair, which has an adapted cushion, backrest with the possibility of tilting back, a seat with a cushion for skin protection, footrests that can change the tilt, wheelchair control lever with switches very sensitive to touch, and brackets for possible respiratory assist devices.

Speech therapists usually meet a child with DMD early in case they have difficulty developing speech, but always with a young person late in the course of the disease when they are no longer able to effectively produce voice and form words. The programme includes articulation learning, exercises to improve exhalation and volume, alternative strategies to improve speech, and the introduction of an alternative communication programme. At this time, it is important to talk to the adolescent with DMD in a calm environment, to take into account their state of fatigue, to repeat the question several times if necessary, and to give them enough time to answer the question. If a young person needs an alternative communication device for communication, they are referred to URI-Soča. There, the child rehabilitation team selects the appropriate device, prescribes it and then teaches the adolescent and their parents how to use it.

All these devices, which significantly improve the ability to move, slow down the development of joint contractures and scoliosis, improve independence in

performing daily activities, participation in activities and quality of life, are available to children and adolescents free of charge (up to the price standard); the costs are covered by the Health Insurance Institute of Slovenia. The prescribing procedure is precisely determined by the Rules on Compulsory Health Insurance (70).

5.8 New drugs and drugs that change the course of the disease

In recent years, several specific drugs have been developed that alter the natural course of the disease and whose action is aimed at reducing muscle damage or reducing/eliminating the effect of the genetic cause of the disease.

The first such drug to treat DMD is ataluren. It has been registered in Slovenia since August 2017 for patients who are able to move independently, nowadays for those older than two years (initially only for those older than 5 years) who have a nonsense mutation leading to the formation of a premature stop codon in the messenger RNA. Ataluren acts on the so-called principle of the read-through mechanism. With its action, it strengthens the connection between the ribosome and the mRNA and enables the read-through of a premature stop codon instead of termination of transcription, thus enabling the formation of functional dystrophin (71,72). It is estimated that 10–15% of patients with DMD/BMD have a nonsense mutation, meaning that they are candidates for treatment with ataluren (73). The effectiveness of ataluren has been studied in several studies. Preclinical studies have shown encouraging results, as more dystrophin is formed in the muscle cells of patients treated with ataluren (74). In the second phase of the study, which included 26 boys with DMD with a nonsense mutation, they found that, both *in vitro* and *in vivo*, dystrophin expression increased and that serum levels of muscle enzymes decreased after 28 days of treatment; however, only minimal changes were observed in muscle strength and timed tests during ataluren treatment (75). Bushby et al. performed a double-blind, randomized, placebo-controlled multicentre study of the efficacy of ataluren in 173 patients with DMD aged 5 to 20. After 48 weeks of treatment, a 6-minute walk test (6MWT) showed a slower reduction in walking distance (up to 13 m) in the group of patients receiving 40 mg/kg BW/day of ataluren (but not in those receiving ataluren at a dose of 80 mg/kg BW/day) compared with placebo (up to 44m) (76). However, the results of a study conducted by McDonald et al. did not show a statistically significant difference in 6MWT

compared between the group of treated and untreated subjects (77).

In addition to ataluren, eteplirsen and golodirsen, which are antisense oligonucleotides, are also used to treat DMD. They work by recognizing exon 51 or exon 53 on the dystrophin gene, respectively, and affect the transcription mechanism so that exon 51 or 53 is skipped. This preserves the reading frame and produces a shorter but functional dystrophin protein (78,79).

Eteplirsen was approved by the US Federal Food and Drug Administration (FDA) under the fast-track procedure in September 2016, while golodirsen was approved by the FDA under the fast-track procedure in December 2019. Most current data on the efficacy of intravenous eteplirsen are the result of four clinical studies (NCT00844597, NCT01396239/NCT01540409 and NCT02255552).

In the NCT00844597 study, treatment with eteplirsen improved dystrophin expression in 7 of 19 patients. NCT01396239/NCT01540409 is an extended clinical study carried out to address the preceding studies insufficiency– the duration of the NCT00844597 study. The results of these studies, which showed a statistically significant increase in dystrophin-positive fibres (demonstrated by the immunohistochemical method) in patients treated with eteplirsen, contributed to the FDA's accelerated approval of eteplirsen (78). Data collection from a post-marketing efficacy study of eteplirsen for use in DMD patients with an appropriate mutation was completed on 14 June 2019, the results of which are not yet known (80).

The FDA decided to accelerate the approval of golodirsen based on the positive results of clinical studies (phase 1/2) conducted in Europe that evaluated the safety, tolerability, pharmacokinetics and efficacy (dystrophin expression) of golodirsen in 25 boys (6–15 years) with DMD with confirmed deletions in the dystrophin gene corresponding to golodirsen treatment. The first part was a 12-week, double-blind, placebo-controlled phase one study in which patients were randomized to receive intravenous golodirsen at 4 incremental doses (4 mg/kg BW/week to 30 mg/kg BW/week for 2 weeks for each dose) and into a comparable group receiving placebo once a week. The second part was a 168-week, open-label phase 2 study evaluating the long-term efficacy and safety of intravenous administration of golodirsen 30 mg/kg BW/1x/week in 12 patients who participated in the first part and in 13 untreated patients. The results of the interim analysis at 48 weeks of the second part showed that the average dystrophin level (assessed in muscle biopsy using the Western blot test) was

statistically significantly increased compared to baseline ($p < 0.001$); the mean and median change from baseline was + 0.92% and + 0.88% of normal levels. Based on the underlying error in DMD (dystrophin deficiency), it can thus be predicted that this increase in dystrophin synthesis will result in a slower disease progression. A post-marketing confirmatory study (ESSENCE) is currently underway; in the latter, patients are currently still being recruited; it is expected to be completed by 2024 (78,81).

These medications have not yet been approved by the European Medicines Agency, so eteplirsen and golodirsen are not available in Slovenia. In Slovenia, we are trying to obtain eteplirsen for patients who are suitable candidates, but under the compassionate use protocol.

Other drugs still in clinical trials include myostatin-targeting drugs, newer CS, anti-inflammatory molecules and antioxidants, substances which reduce fibrosis, drugs that improve vasodilation, mitochondrial function, and utrophin modulator drugs. Under development are the CRISPR/Cas9 technique, which alters genomic DNA, cell therapy with myoblast and stem cell transplantation, and also gene therapy that would, with the help of the so-called adeno-associated virus (AAV), transmit mini/microdystrophins to cells. Studies on the efficacy and safety of these medicines will be needed before they actually enter the market (8,82-84).

6 Protocol for the treatment of children with DMD at the University Children's Hospital Ljubljana

Duchenne muscular dystrophy with its low incidence is considered a rare disease. Therefore, it is beneficial for patients to be managed in centres where a larger number of patients accumulate and where they are treated by specialized experts in various fields. Patients with DMD (as well as patients with other rare diseases) require a multidisciplinary approach (8).

The Department of Child, Adolescent and Developmental Neurology of the University Children's Hospital, University Medical Centre (UMCL) Ljubljana is the only tertiary centre for the treatment of children with DMD in Slovenia. To establish an optimal team and uniform treatment of patients and to reduce the number of visits to various wards and clinics for children and the burden that this posed for the children as well as their families, we reorganized the treatment of children with DMD and other NMD in 2017, so that the DMD patient plays a central role. All activities have been adjusted so that the treatment is optimal for the patient.

A team for NMD was formed, linking experts of various specialties. The core team includes paediatric neurologists, paediatric endocrinologists, paediatric pulmonologists, paediatric gastroenterologists, clinical psychologists, physiotherapists and occupational therapists, dieticians and other staff with specific knowledge in the field of NMD; and last but not least, the nurses and technicians who make the first contact with the patient on the ward and are the link between the other team members. Depending on the individual needs of patients, specialists in physical and rehabilitation medicine, ophthalmologists, orthopaedists, surgeons, otorhinolaryngologists, geneticists, speech therapists, social workers and other professionals are also included.

With the help of a coordinator, all patients with DMD (as well as those with other forms of NMD) are invited annually for a two day inpatient stay, during which patients undergo assessment by all sub-specialists that they require. Children are admitted to the Department of Child, Adolescent and Developmental Neurology or to the Unit of Pulmonary Diseases (children with non-invasive or invasive respiratory support), and specialists from various subspecialties perform examinations/tests in the department and plan further follow ups. If more frequent assessments are required, the coordinator tries to combine these examinations. As part of the treatment, attention is also paid to psychological support for patients and their families. A social worker also offers assistance in managing the rights and adjustments related to schooling and the social status of children and families.

In April 2020, we manage 29 boys with DMD/BMD and one girl, who is a symptomatic carrier. In accordance with the recommendations, in the case of the appropriate clinical picture or at the first signs of mobility decline, patients and their parents are advised to introduce CS therapy and all other forms of treatment.

Treatment with ataluren is also available in Slovenia and fully covered by the Health Insurance Institute of Slovenia. Thus, this therapy has already been introduced to three patients who have the appropriate mutation and meet other necessary criteria.

We believe that such multidisciplinary treatment contributes to reducing the burden on patients, contributes to the establishment of good cooperation and patient trust, reduces the financial burden for patients, provides the best long-term outcome and, last but not least, ensures uniform treatment in accordance with state-of-the-art guidelines. Therefore, we advise that all children whose doctor suspects that they may have DMD or any other NMD be referred for treatment to the University Children's Hospital, which can be arranged by doctors by telephone, No. 01 522 5189.

7 Conclusion

DMD is a serious muscle disease that affects boys and their families and for which we still do not have an effective treatment to eliminate the basic, i.e. genetic cause of the disease. In recent years, there has been significant progress in understanding the natural course of the disease. With this knowledge, with the earlier diagnosis of the disease and with multidisciplinary treatment, with the use of CS, and in cases of appropriate mutations with the use of newer drugs, physiotherapy and supportive care, the duration and quality of life of patients with DMD have improved. There are several drugs in development, whose aim is reducing muscle damage, as well as drugs that would eliminate the basic, i.e. genetic cause of the disease. They raise hopes that in the future the disease will only be a thing of the past.

Conflict of interest

None declared.

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