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Current diagnosis and treatment of Duchenne muscular dystrophy

D.D. Gaynetdinova, A.A. Novoselova

Kazan State Medical University, Kazan, Russia

Abstract

Duchenne muscular dystrophy (DMD) is an X-linked progressive disease from the group of primary myopathies caused by mutations in the *DMD* gene and a lack of dystrophin protein in the muscle fiber in males. The review considered the prevalence of pathology, the most common causes of dystrophinopathy, and the role of dystrophin not only in the functioning of muscles but also in the architectural organization of the Central nervous system. The disease classification based on stages and forms, initial clinical manifestations of the early and late stages of the disease, as well as neuropsychological, orthopedic, respiratory and cardiovascular disorders, are described in detail. The relevant to date diagnostic algorithm for suspected DMD, biochemical blood analysis, genetic, morphological (immunocytochemical staining of muscles with dystrophin antibodies) and instrumental (ultrasound, MRI) methods of examination are presented in detail. Particular attention in the diagnosis of DMD and objectification of disorders is given to assessment tests [Bailey's and Griffiths scales, Albert's Test of Infant Posture and Motor Assessment Scale, Expanded Hammersmith Functional Motor Scale (HFMSE), the Gross Motor Function Measure (GMFM), and the 6-minute walk test (6MWT)]. The review presents the advantages and disadvantages of modern invasive and non-invasive diagnostic techniques of the disease, indicating their reliability and the possibility of application at early stages, including prenatal. In conclusion, the treatment of DMD and its most frequent complications, both widely used in practice and at the stage of clinical research, is highlighted. It was emphasized the importance of rehabilitation measures that improve the duration and quality of life of patients with DMD. The main task of analyzing available sources on the most pressing issues of Duchenne muscular dystrophy was to stimulate research and social activity in resolving unsolved problems today.

Keywords: genetic disorders, Duchenne muscular dystrophy, myopathy, neuromuscular disorders, corticosteroids.

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Introduction. Duchene muscular dystrophy (DMD) is an X-linked progressive disease from the group of primary myopathies. Its clinical presentation was initially described in 1861 by the French scientist Guillaume-Benjamin-Amand Duchenne, who called the disease "paralyzing muscular pseudohypertrophy" [1]. The gene that causes the disease was identified in 1989, and the type of inheritance was established at the outset of the 20th century. The clinical presentation of DMD with a later onset and slow course (Becker disease) was first described in 1964 [2].

According to several reports, the prevalence of the disease varies from 1:3500 to 1:6300 live-born boys. Therefore, per 100,000 boys, there were 15.9 cases registered in the United States, 19.5 cases in the UK [3],6.64 cases in the Republic of Dagestan [4], 4.8 cases in the Rostov region [5], and 2.95 cases in the Chuvash Republic [6]. However, no special studies have been conducted in the Russian Federation as a whole; therefore, prevalence of DMD can be considered poorly understood.

Etiology and pathogenesis. The pathogenesis in DMD is caused by a deficiency of the dystrophin protein in the muscle fiber resulting from mutations in the *DMD* gene located in the region of the X chromosome short arm (loci Xp21.1–p21.2) [7]. The *DMD* gene consists of 79 exons. Dystrophinopathy in DMD is most commonly caused by intragenic deletions (65% of all cases) or duplications [8]. Most of the remaining cases are caused by nonsense (50%) and missense mutations (2%) [9]. Approximately two thirds of DMD cases are caused by maternal inheritance, and the remaining cases arise from spontaneous mutations [10].

The *DMD* gene product is the dystrophin protein that acts as a shock absorber that allows muscles

For correspondence: anetdina@mail.ru Received 31.01.2020; accepted 25.05.2020.

to contract and relax without damage. Dystrophin is part of the dystrophin–glycoprotein complex, which is a transmembrane protein complex, including dystroglycans, sarcoglycans, and dystrobrevins. Dystrophin is expressed in cardiac and skeletal muscles and is located on the intracellular surface of the sarcolemma, next to the sarcomeres. This protein provides a link between the intracellular actin cytoskeleton and extracellular matrix.

Lack of dystrophin leads to dysfunction of the dystrophin–glycoprotein complex, membrane instability, muscle degeneration, and necrosis of muscle fibers. Membrane instability causes excessive Ca^{2+} entry. Calcium, penetrating through microruptures, promotes the activation of inflammation and necrosis factors, resulting in fat and scar tissue replacing the muscles [3, 7, 11]. In addition, Ca^{2+} promotes the activation of phospholipase A_2, which allows the release of arachidonic acid. Prostaglandins and leukotrienes, which are arachidonic acid metabolites, are involved in inflammation and muscle pain, and contribute to the development of muscle weakness [12].

Dystrophin is essential not only in muscle function, but also in the architectural organization of the central nervous system; therefore, its deficiency leads to certain functional consequences, such as disorders related to the integrity of the synaptic terminals, decrease in synaptic plasticity, and integration of regional cellular signals. Mutations in the distal part of the *DMD* gene are associated with loss of the cerebral isoform of dystrophin, which may explain the decline in intellectual function in patients with DMD. This dystrophin isoform is most pronounced in the cerebellum and limbic system and is necessary in the modification of evoked synapse cell activity, synaptic maturation, and function. Therefore, the absence of dystrophin in the cerebellum may serve as a neurobiological explanation for neurological disorders [13]. Brain magnetic resonance imaging (MRI) of 14 boys with DMD showed a decrease in the volume of gray matter and the total volume of the brain in all examined patients [14].

Clinical presentation. Currently, DMD development has the following five clinical stages: preclinical (pre-symptomatic), early outpatient (with preserved ability to move independently), late outpatient (with preserved ability to move independently), early non-outpatient (with lost ability to move independently), and late non-outpatient (with lost ability to move independently) [3, 15].

The preclinical (pre-symptomatic) stage is characterized by a mild delay in motor and speech development. The diagnosis can be suspected based on the family history and biochemical blood test data showing increased activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine phosphokinase (CPK) along with its MB-CPK (a specific marker of myocardial necrosis) [16].

At the early outpatient stage, one of the first signs is retardation in early psychomotor development manifested by difficulty in raising the head and inability to walk by 15 months of corrected age [17]. Difficulties in walking, running, jumping, skipping, or climbing stairs, along with stumbling and frequent falls are also identified. The disease is characterized through a positive Gowers test, pseudohypertrophy in the gastrocnemius muscles— although less frequently in the gluteal and deltoid muscles— along with, walking with widely spaced legs or on toes, and waddling ("goose gait") [18, 19].

The late ambulatory stage is characterized by significant difficulty in walking, climbing stairs, and getting up off the floor. Achilles tendon retraction is formed. Due to abdominal muscle and hip extensor weakness, the pelvis tilts forward with the development of compensatory hyperlordosis in the thoracolumbar spine [20].

At the early stage, the patient is able to move independently at a distance of up to 10 m and maintain an upright body position. The use of a wheelchair becomes necessary. Shoulder girdle muscle weakness increases, and "winged scapulae" are noted on examination. With insufficient motor activity, contractures of the ankle, knee, hip, and elbow joints, along with the small joints of the hand develop rapidly [21]. This is accompanied by progression of respiratory and cardiovascular disorders [22].

The late period is characterized by severe muscle weakness and atrophy. The patient cannot independently maintain body position. Complications progress further and can be fatal [23–25].

The most common variant of DMD presents with the disease onset at the age of 3–5 years and loss of the ability to walk by the age of 11–12 years. However, the boys are physically well-developed, communicative, and good-natured.

A malignant, rapidly progressing course of the disease is characterized by onset at the age of 2–3 years, severe mental retardation (which often mask muscle weakness, and infantile cerebral palsy is mistakenly diagnosed), loss of independent movement by the age of 6–7 years, and death at the age of 15–18 years.

The third clinical variant of DMD develops rapidly in patients with cushingoid features (moon-shaped face, striae on the abdomen, typical fatty deposits), as the first symptoms occur at the age of 2–5 years, loss of ability to walk is noted at the age of 8–9 years, and death at the age of 18–20 years [2].

At DMD diagnosis, the mean age of patients is 4.2–5 years. Parents seek medical help because of incidental detection of a persistent increase in CPK activity (44.3%), delayed motor development (15.9%), muscle weakness (14.0%), increased blood serum aminotransferase levels (9%), family history of DMD (7.8%), walking on tiptoes (5.2%), mental retardation (2.6%), speech retardation (1%), and other symptoms (0.4%) [26].

Pain is one of the main problems in patients with DMD because ≥50% of children experience chronic pain predominantly in the neck/back and legs, which occurs several times a week [27,28]. Muscle pathology in DMD is accompanied by emotional and behavioral disorders, such as autism spectrum disorders (21%), hyperactivity (24%), impaired attention (44%), internalization (24%), and externalization (15%) [29]. Attention deficit hyperactivity disorder and autism spectrum disorder are more common among patients with DMD than in the general population [30].

P. Colombo et al, using the Wechsler Intelligence Scale and the Griffiths Scale, and taking into account the age, did not find a correlation between cognitive impairment and the severity of myodystrophy in 47 patients with DMD [13]. The study results showed that the discrepancy between the coefficient of verbal intelligence (VIQ) and indicators of the intelligence coefficient (IQ) occurs quite often, and that the verbal component is most deteriorated.

Mirski and Crawford showed a relationship between gait retardation and cognitive impairment, as with mental retardation, boys with DMD were thrice more likely to have a delay in the formation of gait function. Therefore, the researchers proposed to include in the diagnostic standards a mandatory sensitivity test for blood serum CPK level for the early detection of DMD in boys with global developmental retardation [17].

Mori-Yoshimura et al. diagnosed psychiatric diseases in 21% of patients with DMD, mental disorders in 24%, depressive tendencies in 32.5%, and high anxiety in all patients. They showed a higher incidence of schizophrenia and neurosis in boys with DMD than in the general population [14]. Compared with the entire pediatric population (0.5%–1%), patients with DMD have a higher prevalence of epilepsy (6.3%). Partial seizures are most often reported (43%), and generalized tonic–clonic seizures (28.5%) or non-convulsive forms of epilepsy (28.5%) are reported less often [14,31].

Complications occurring in the early non-ambulatory stage and causing the early death of patients are of the greatest significance in the clinical presentation of DMD.

Analysis of data over 10 years (2004–2014) suggested that the death of patients with DMD is most commonly caused by moderate or severe cardiorespiratory failure, with the proportions of the respiratory and cardiac components being equal [32]. The progressive loss of respiratory function leads to a restrictive type of lung injury and poses a significant risk of development of severe respiratory complications in patients [33]. They manifest as hypoventilation and periods of apnea during sleep, causing morning headaches, nausea, fatigue, loss of appetite, and cognitive impairment [29].

Lesions of the cardiovascular system in DMD are represented mainly by non-ischemic cardiomyopathy, at the onset of the restrictive-type disease, followed by the dilated type [34]. Rare causes of death include aspiration pneumonia, acute respiratory distress syndrome after physical exercise, cardiorespiratory arrest after minor injury without fractures, or multiple organ failure [32]. In addition to cardiological and respiratory complications, various orthopedic pathologies and muscle–tendon contractures occur as DMD progresses [35].

The average life expectancy in patients with DMD is 27.9 years; therefore, the disease prognosis is generally unfavorable, and death occurs as a result of cardiac, respiratory, and orthopedic complications [2,36].

Diagnosis. Because DMD has a 100% mortality rate in adolescence, intrauterine diagnosis becomes one of the most important aspects. Currently, prenatal diagnostics of DMD is allowed globally to terminate pregnancy in case of a positive test result. The Sanger sequencing and analysis of microsatellite markers of deoxyribonucleic acid (STR analysis) are used most frequently [37].

Currently, a diagnostic algorithm for suspected DMD has been developed, which includes a biochemical blood test, genetic, morphological (immunocytochemical staining of muscles using antibodies to dystrophin) and instrumental (ultrasound, MRI) research methods [2,3,29].

Changes in the biochemical blood test are represented by increased activity of ALT, AST, and creatine phosphokinase (CPK) [16,38]. Thus, Grinio, as a result of long-term studies, reported increased activity of ALT, AST, and CPK by 5 times, 4 times, and ≥11 times in patients with DMD, respectively. The author also emphasizes that the CPK level becomes normal and even reduced at the last stage of the disease [2], which was consistent with that of Nadarajah et al. [39].

Genetic testing includes multiplex ligation-dependent amplification of the probe to search for deletions and duplications, which allows identification of up to 70% of genetic mutations in DMD, as

well as gene sequencing (if amplification is negative) to identify point mutations and small deletions/insertions, which enables the identification of the remaining 25%–30% of genetic mutations [2,3,40].

In the presence of DMD, immunocytochemical staining of muscles with antibodies to dystrophin enables the determination of its absence in a muscle biopsy sample. In Becker muscular dystrophy, dystrophin is determined in part, just like in a female carrier of DMD [2].

Some researchers have noted the disadvantages of standard methods for diagnosing DMD. For example, increased serum CPK activity may be an unreliable sign of DMD because it decreases with disease progression due to loss of muscle tissue, or it may be increased in healthy people because of physical exertion, tension, or injury to skeletal muscle. In addition to the generally accepted diagnostic methods, the authors propose to study the aggregate levels of serum biomarkers (matrix metalloproteinase-9, tissue inhibitor of metalloproteinase, osteopontin) [39].

Genetic testing and muscle biopsy are the gold standard for diagnosing DMD. However, some researchers believe that it is necessary to search for effective non-invasive methods for diagnosing DMD in the early stages due to the increase in the number of young patients. Muscle MRI is a reliable non-invasive method for assessing the involvement of muscle fibers in the pathological process in neuromuscular disorders, and therefore can be widely used in practice. MRI detects replacement of muscles with adipose tissue and identifies edema in the early stages of muscle degeneration [41,42].

Wave elastography is another non-invasive method for assessing muscle involvement. It is an ultrasound imaging technique that detects deformity and compressibility of tissue when force is applied externally, which quantifies the tissue stiffness. The researchers concluded that wave elastography is a more advantageous method compared to MRI due to the greater sensitivity and the ability to monitor muscle changes even at an early age [42].

A special position in diagnostics of DMD is held by assessment tests to determine the level of psychomotor development of patients. The Bailey and Griffiths scales are considered by experts as a tool for assessing the rate of development in a child at a young age (up to 3 years) and identifying psychomotor retardation in the early stages of DMD. Some authors suggest using the 6-min walk test as an assessment tool [29]. The 6-min walk test is presumed to be challenging for physical therapists due to behavioral problems in patients with DMD. Patients with muscle pathology are also physically poorly developed and are at risk of falling during prolonged exertion. These problems can be solved by reducing the walking time to 2 min. Vill et al. showed that the 2-min walk test reliability was comparable to that of the standard 6-min walk test [43].

Some researchers suggested the examination of relatively older patients, who have lost the ability to walk, by using the Brooke Upper Limb Assessment Scale [3,29]. Hunt et al. proposed to assess motor development using a functional scale for assessing muscular dystrophy, which includes four sections, namely mobility (change in body position in space), daily activities, upper limb function, and movement disorders (for example, limb contractures). This scale is simple and easy to use to assess patients with DMD aged ≥6 years [27].

The treatment of DMD should be multidisciplinary, comprehensive, and adapted to the patient's profile, as well as to the stage of clinical progression [29]. Currently, glucocorticoids (GCs) are the most effective, particularly prednisolone (0.75 mg/kg /day) and deflazacort (0.9 mg/kg /day) [29]. According to the authors, this type of therapy can slow the disease progression by stimulating insulin-like growth factor synthesis and myoblast proliferation and reducing cytokine production and lymphocyte reactivity, which results in increased muscle volume and strength.

Osorio et al. suggested that intermittent administration of prednisolone and deflazacort (with alternation of days) is less effective but associated with fewer side effects than continuous administration for 10 days, followed by 10 days interval [29]. The same tendency was revealed with the administration of low doses of prednisolone (0.30–0.35 mg/kg /day). Increase in body weight and development of a cushingoid appearance should also be considered when high doses of GCs are administered [44]. In addition to slowing the progression of muscle weakness, prednisolone and deflazacort improve lung function, have a moderate cardioprotective effect in patients aged ≥20 years, and also reduce the need for surgical treatment of scoliosis [45].

In addition to GCs, a therapy aimed at the transcription and translation processes has been proposed. Currently, ataluren and eteplirsen are the only drugs that were subjected to preclinical development and have reached the clinical trial phase [29].

Ataluren modulates the mRNA[1] translation apparatus by inserting certain related tRNAs[2] near the site of nonsense codons, which promotes error-free ribosomal reading and enables to transform a non-functional truncated protein into a functional one. Ataluren was conditionally approved by the European Medicines Agency in July 2014 for the

treatment of DMD caused by an accidental mutation of the dystrophin gene in outpatients aged ≥2 years.

Eteplirsen is an antisense oligonucleotide produced to skip exon 51, which enables the restoration of reading in the central region of the gene (13% of DMD cases). It has been shown to increase the amount of dystrophin in muscle tissue in a pilot trial; therefore, the drug was approved by the Food and Drug Administration of the US Department of Health and Human Services [29].

Scientists pay special attention to search of drugs to minimize complications. McDonald et al. proposed to perform respiratory failure therapy in patients with DMD with the use of idebenone at a dose of 900 mg/day [33]. Camacho, in the recommendations for the support of respiratory function in patients with DMD, emphasizes the need to involve a pulmonologist, assess the forced vital capacity of the lungs annually, and assess the blood O_2 saturation and peak cough rate every 6 months [46]. The literature highlights the importance of timely sleep studies to identify periods of hypoventilation and apnea [47], the systematic use of physical therapy to prevent complications at the late stages of DMD [48], correction of orthopedic complications, and the use of technical means of rehabilitation [3,29,35].

Currently, experimental methods of treating DMD, particularly, gene replacement therapy, are actively being developed. It may be an effective treatment method for DMD, but its use is complicated by the size of the *DMD* gene, which is one of the largest in the human genome. Adeno-associated virus is considered the best way to deliver genes, despite its limited packaging capacity. Nusinersen has been proposed as one of the drugs for gene replacement therapy, which becomes the drug of choice for 5q spinal muscular atrophy associated with *SMN1* gene mutations, but some researchers reported that it can increase the probability of overall survival in DMD [45].

Conclusion. Thus, the clinical manifestations of DMD are well understood, but the pathogenetic mechanisms of the disease remain studied insufficiently. Despite the active search for drugs and therapy methods, no effective treatment has yet been developed. The main task of the analysis of available sources on the most topical issues of DMD was to stimulate research and public activity in solving currently unresolved problems. Further search for new therapies is required to increase life expectancy and improvement of rehabilitation assistance to improve the quality of life and alleviate the condition of the patients.

[1] mRNA — messenger ribonucleic acid.

[2] tRNA — transfer ribonucleic acid.

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