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Duchenne muscular dystrophy overview

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Abstract

This literature review addresses Duchenne muscular dystrophy (DMD), a serious muscle disease related to the X chromosome. DMD causes progressive loss of walking ability and dependence on wheelchairs in adolescence. Patients' quality of life and survival have been improved through the use of corticosteroids and a multidisciplinary approach to orthopaedic management. DMD is caused by partial or total absence of dystrophin protein due to specific mutations in the DMD gene (Xp21. 2 locus). The disease is characterized by progressive muscle weakness, deformities in the musculoskeletal system, problems in the nutrition of the person and digestive problems, also presents a decrease in bone density. Diagnosis is based on clinical evidence, elevated levels of creatine phosphokinase in the blood and electromyography, and its confirmation is made with muscle biopsy. Early diagnosis is recommended to initiate proper management and carry out treatment. Treatment focuses on preserving muscle strength, preventing spinal deformities, managing respiratory and cardiac complications, and improving quality of life. In some studies, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists has been shown to be beneficial for long-term cardiovascular management resulting from DMD. In conclusion, a multidisciplinary approach is required to counteract clinical outcomes and improve the quality of life of patients with DMD.

Keywords: DMD; Dystrophin; Angiotensin II; Rehabilitation

1. Introduction

Duchenne muscular dystrophy (DMD) is a serious muscle disease that is closely related to the X chromosome. Its name comes from the French physician Duchenne de Boulogne, who in 1868 made significant contributions to define the clinical characteristics of this genetic disease [1]. This pathology is diagnosed around the age of 5 and is characterized by a progressive loss of the ability to walk, which results in people depending on a wheelchair at approximately 12 years. The life expectancy of those affected ranges to 20 years, due to respiratory complications or heart failure, which are accompanied by this pathology. However, when early intervention is applied with treatment, life expectancy can be extended up to 30 years [2].

Duchenne muscular dystrophy (DMD) belongs to a group of genetic pathologies that are dystrophinopathies, these are set of hereditary muscle diseases that are characterized by progressive muscle weakness. In the case of DMD, muscle weakness follows a standardized pattern that is also predictable. Something important is that, without any medical intervention, patients have loss of the ability to walk before reaching adolescence and, unfortunately, complications such as respiratory or, to a lesser extent, heart problems. At present, no curative treatment has been found for Duchenne Muscular Dystrophy (DMD). However, improvements in patients' quality of life and survival have been observed through the use of corticosteroids and an orthopaedic approach, which has led to changes in disease progression [3].

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The purpose of this article was to conduct an exhaustive literature review on the most up-to-date and recent information on the most relevant clinical manifestations of Duchenne muscular dystrophy. In addition to providing updated information in order to keep us abreast about advances in the knowledge of this debilitating disease. I also contribute to the medical community to expand knowledge about this dystrophinopathy.

2. Genetics and Pathophysiology

Duchenne muscular dystrophy (DMD) is an inherited disease closely related to the X chromosome that mostly affects males and is characterized by the partial or complete absence of the dystrophin protein due to specific mutations in the DMD gene that is located on the short arm of the X chromosome (area P21.2) [4]. These mutations can also lead to other related genetic diseases, such as Becker muscular dystrophy (BMD) and cardiomyopathy 3B [5].

Dystrophin is a protein composed of 3,685 amino acids and is composed of four distinct domains. The first domain exhibits similarity to the association areas of actinin A and spectrin B at its amino terminal end. The second domain consists of 24 repeats of 109 amino acids that adopt a triple helical structure interrupted by proline regions that function as molecular hinges, providing flexibility to the molecule. The third domain is similar to the calcium-binding region of A-Actinin, and the last domain forms a complex with membrane-present glycoproteins [6, 7]. Dystrophin is expressed in various cells and in the following structures which are: sarcolemma, striated skeletal muscle, smooth muscle, heart muscle, as well as in some types of neurons such as Purkinje cells and neurons of the cortex. Although its precise function has not yet been fully elucidated, dystrophin is believed to play a fundamental role in stabilizing the plasma membrane during muscle contraction, this is done by binding the amino terminal domains to actin, while the carboxyterminal end binds to the DGC protein and, in turn, it binds to laminin outside the sarcolemma membrane [8].

Duchenne muscular dystrophy is the result of a genetic alteration affecting the X chromosome [5]. As genetics dictates, males inherit one X chromosome from their mother and one Y chromosome from their father [3]. Only one X chromosome can carry a genetic variant associated with DMD. Even if a woman has one X chromosome with the DMD gene variant, her second X chromosome usually produces enough dystrophin to keep muscles strong [4].

Gowers WR tells us that, in order to understand the pathology of Duchenne muscular dystrophy at the molecular and cellular level, it is important to consider two important clinical features [9]. First, DMD manifests as a chronic and debilitating disease, resulting from degeneration and necrosis of skeletal and cardiac muscle. Secondly, a very close relationship has been observed between muscle contraction and the pathogenesis of DMD [5].

3. Clinical Manifestations

Duchenne muscular dystrophy (DMD) is a genetic disease characterized by the absence of dystrophin in skeletal muscle, heart muscle, and brain [3]. López Hernández, in his reference article, describes that patients with DMD suffer rapid progressive muscle weakness of proximal dominance, starting with weakness in the muscles of the pelvic region, pseudohypertrophy in the muscles of the lower limbs and certain changes in gait that can be diagnosed before the age of 5 [9]. Around the age of 9, most patients have lost their motor skills, which results in an appearance of deformities in the musculoskeletal system, for example, contractures and scoliosis in 75% of cases [10]. Over time, muscle weakness is also expressed in the respiratory and cardiac muscles, leading to respiratory (75%) and/or cardiac (25%) failure and death [9].

It has been found that apart from muscle weakness and musculoskeletal deformities they are pathognomonic findings in this genetic disease [11]. Patients with DMD may also have other clinical changes that worsen the prognosis of the disease. These include nutritional problems, such as malnutrition or overweight, as well as digestive disorders such as constipation or gastroesophageal reflux. On the other hand, findings of a decrease in bone density and an increase in the risk of fractures have been found in these patients [10].

To summarize the clinical manifestations observed in patients with DMD, it has been found that there is also weakness and atrophy of the distal muscles, instability and difficulty walking, frequent falls, as well as loss of the ability to walk and stand upright, usually after 12 years. These symptoms differ slightly from those mentioned above, which occur around age 9 [12, 13]. It is important to clarify that DMD usually causes death in the second decade of life, due to the most common causes respiratory and cardiac problems [11]. A summary of clinical findings by stage of onset is presented in Table 1.

Table 1 Characteristics of patients with DMD [12]

Early	Slow gait Language delay Developmental delay in general
Intermediate	Difficulty to walk Frequent falls, wobbling when walking. Walk on the balls of your feet. Proximal predominant muscle atrophy Calf pseudohypertrophy
Late	Loss of ability to walk. Weakness in the upper limbs Joint and tendon contractures Heart failure

Note: Some patients have mild mental retardation. But this is rare.

3.1. Diagnosis

In the branch of medicine, there are several methods used to detect the presence of this disease. One of them is the detection of the most distinctive changes observed in the laboratory which are the levels of creatine phosphokinase (CPK) increased in the blood serum [8]. During the first 14 to 22 months of life, a large elevation in CPK values is observed, which then tend to decrease. In addition, it has been proven that these increases in CPK may be accompanied by elevated levels of serum aldolase and lactate dehydrogenase (LDH), although their importance is not as relevant as CPK in the diagnosis, but they are part of DMD [5].

To suspect the diagnosis of DMD, it is important to consider a number of clinical findings, regardless of family history. These findings are grouped into the presence of muscle dysfunction in children, elevated serum CK levels and, in some cases, elevation of AST and ALT transaminases, produced by liver and muscle enzymes [5]. In addition, electromyography is a practical and reliable medical test that allows to observe the myopathic patterns related to DMD [6]. This test is performed at the same time as the polymerase chain reaction (PCR) test, this in order to detect deletions or duplications of the dystrophin gene. However, the definitive diagnosis is made by muscle biopsy, a test that involves the removal of a portion of tissue using a needle to be examined later and in turn reveals the loss of dystrophin, changes in the diameter of muscle fibers, as well as infiltration of fatty and connective tissue. Therefore, from the clinical evidence, muscle biopsy is considered a complete diagnostic test [14].

Based on the average age for diagnosis of DMD, it has been observed that in Europe and North America it remains around 4-5 years [16, 17]. These age ranges are considered in diagnoses globally. It is important to make the diagnosis as early as possible, and although there is currently no definitive cure for the disease, a focus in different medical areas is recommended [18] It is important to remember that DMD can also present cognitive problems, such as language delays, general development, or behavioral disorders [18, 19].

3.2. Treatment

The therapeutic approach of Duchenne muscular dystrophy (DMD) focuses on neutralizing the onset of myocardial dysfunction and preventing further deterioration of the quality of life of affected patients [18]. In the early stages of the disease, there is discussion about the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists in patients younger than 10 years. However, several studies have been found to have shown that these drugs contribute to improved long-term cardiovascular and cerebrovascular outcomes [20, 21].

The treatment of DMD focuses on four fundamental areas of the patient's quality of life: preserving muscle strength, preventing the development of spinal deformities, controlling respiratory impairments, and preventing and treating heart diseases that lead to DMD [10]. Management of this disease remains primarily supportive, and it has been shown that physical therapy and daily muscle stretching can help avoid the need to subject the patient to surgical release of contractures [15].

In conclusion, recommendations have been reached where patients with DMD are cared for in specialized units. These should be made up of a multidisciplinary team of health professionals with experience in the management of this disease [3]. It is important to note that a comprehensive and coordinated approach, covering all the treatment areas mentioned, is essential to reduce clinical outcomes and improve the quality of life of individuals affected by Duchenne muscular dystrophy [24, 25]

4. Conclusion

I have concluded that Duchenne muscular dystrophy (DMD) represents the most common form of muscular dystrophy in humans and is caused by mutations in the dystrophin gene, located on the short arm of chromosome X. Progress in understanding the pathophysiology of DMD has promoted the development of new molecular therapeutic strategies. However, at present there is no specific treatment, so better control of patients is required, as well as an adequate characterization of genetic variants for future studies related to steroid treatment, therapeutic response and phenotype modifying disorders, thus establishing a genotype-phenotype correlation.

The early diagnosis of DMD plays a fundamental role in the management of this disease, since it allows to establish a multidisciplinary therapeutic approach that involves different fields of medicine. The primary goal of this approach is to slow the progression of loss of muscle function and ultimately loss of walking ability. The use of corticosteroids has been shown to improve the clinical course of the disease and has therefore been incorporated as part of standard treatment for patients with DMD. However, it is important to note that the dosing regimen of corticosteroids may be adjusted according to possible side effects that may arise.

In conclusion, DMD represents an allelic form of muscular dystrophy that is caused by mutations in the dystrophin gene. Despite advances in the understanding of its pathophysiology, no specific treatment is yet available. It is crucial to establish an early diagnosis to implement a multidisciplinary therapeutic approach that includes the use of corticosteroids to delay the progression of the disease. However, better characterization of genetic variants and greater genotype-phenotype correlation are required to improve understanding of the disease and develop more effective therapeutic strategies in the future.

Compliance with ethical standards

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Disclosure of conflict of interest

The author shows no conflicts of interest with collaborators or third parties.

Statement of ethical approval

Inclusion and equitable access to health care for people with Duchenne muscular dystrophy.

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