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Review

Clinical spectrum of manifestations in symptomatic female with Duchenne muscular dystrophy: A concise review

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Abstract. Duchenne Muscular Dystrophy (DMD) is a rare genetic disease, characterized by a severe, progressive muscle-weakening. Due to the localisation of the *dystrophin gene* in the X chromosome, DMD primarily affects males, but similar dystrophinopathies, that mimic DMD, can occur in females. The aim of this article is to present the main findings described in literature about these unusual dystrophinopathies clinical manifestations in females, in order to ease the practical approach to these conditions This article is a non-systematic review, with a view to presenting a critical review – all articles were researched in public databases PubMed, Medline, ScienceDirect, SciELO and Cochrane. Clinical presentation in female carriers shall vary from the traditional form in regards to the degrees and patterns of dysfunction, justified by the presence of a normal allele, as well as distinctive mutational mechanisms. Usually present with asymmetric bilateral leg weakness, myalgia, cramps, fatigue, calf muscles pseudohypertrophy, and dilated cardiomyopathy. Pathogenic variants in the DMD gene must be considered in the differential diagnosis of myopathic-suggestive clinical conditions, even in unusual presentations, such as female patients with muscular weakness or asymptomatic elevation of creatine kinase.

Keywords: Duchenne muscular dystrophy, female carriers, clinical manifestations, dystrophinopathies

1. Introduction

Myopathic disorders describe a wide group of diseases that share disturbance in the skeletal muscle's structure and/or function that can be classified as acquired or genetic but not necessarily hereditary. The latter reaches muscular dystrophies, congenital myopathies, channelopathies, and metabolic myopathies (including mitochondrial disorders), and the former encloses inflammatory, systemic-disease related and toxic myopathies [12, 14].

Even though a diverse range of pathophysiological mechanisms alter the muscular anatomy and physiology, some clinical manifestations are common amongst most of the myopathies, such as diffuse muscular weakness proximal, muscular fatigue, muscle pain, or atrophy, cramps, hypertonia or even myoglobinuria [12, 21]. It is also noted that in severe cases or advanced stages of certain myopathies,

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muscular dysfunction may lead to death related to diaphragmatic weakness or overlap with muscular and cardiac disorders. [7, 12, 17]

Further, due to the morbimortality related to such conditions, an early diagnosis and management are imperative, exceptionally in those linked to genetic mechanisms, since several start developing early in life, shortening the carrier's lifespan, e.g., Duchenne and Becker syndromes [25]. Both pathologies are caused by mutations in the dystrophin gene located in the X chromosome, causing primary degeneration of muscle fibers associated with fibrosis and lipo-substitution of the muscle tissue. Clinical work in recent years showed that Becker and Duchenne muscular dystrophies are part of a larger spectrum, where Becker constitutes the mild clinical endpoint and Duchenne the more severe and of the spectrum [21].

Therefore, as it has an X-linked hereditary pattern, Duchenne Muscular Dystrophy (DMD) diagnosis is exclusive to male patients, with well-defined clinical progression and pathophysiology. Female hereditary pattern carriers are quite common in many other diseases that are inherited X linked recessively [25]. Nonetheless, similar dystrophinopathies can occur in females, with different degrees and patterns of dysfunction, possibly justified by the presence of a normal allele but also due to distinctive mutational mechanisms [4, 25, 29]. Clinical manifestations described in the female population may vary from severe Duchenne-like dystrophy in childhood to mild muscular weakness in adulthood, even asymptomatic creatine kinase (CK) elevation and cardiomyopathy [12, 25].

Overall, due to these unusual dystrophinopathies' clinical manifestations in females, this article aims to present the main findings described in the literature about this topic in order to ease the practical approach to these conditions.

2. Material and methods

This article is a non-systematic review, with a view to presenting a critical review– all articles were researched in public databases PubMed, Medline, ScienceDirect, SciELO and Cochrane. Firstly, DMD related terms linked to the female population were searched in the mentioned databases, followed by the selection of the most relevant ones available in English or Portuguese. This selection process was supervised by two clinical neurologist practitioners with experience in neuromuscular diseases. Moreover, additional literature served as a source to deepen the general understanding of myopathies, specific classifications, previous treatments as well to illustrate historic descriptions of the disease.

3. Results

3.1. Duchenne muscular dystrophy (DMD) and genetics

DMD is one of the most common muscular dystrophies in childhood, with a prevalence of 3 cases per 100.000 people and its incidence is 1 in 3.500 to 5.000 male live births. Its pivotal clinical feature is a severe, progressive muscular weakness. It corresponds to an X-linked disorder caused by a mutation localized in the gene responsible to encode the dystrophin muscle isoform Dp427m [10], at the Xp-21 locus in the X chromosome short arm (Xp21.2), and only up to 10% of the carriers are symptomatic. Regarding the mutation mechanisms, 50–60% of the patients have deletions, 5–15% duplications, and 30% point mutations. Unlike the male patients, however, there are few studies comparing genotype and phenotypical manifestations in the female population. As seen in another study, the most affected individuals had generalized dystrophin absence, and one research showed that 23 of 24 patients presented dystrophin abnormalities [16]. Additionally, de novo pathogenic variants are frequent, and in fact, resulted in up to 33–39% of these mutations [6, 15].

It is also noted that although males correspond to the vast majority of patients affected by dystrophinopathies, 8% of female *dystrophin gene* pathogenic variant carriers present muscle weakness and may show cardiomyopathy as the disease progresses [25]. These manifestations are a result of the X chromosome inactivation (XCI), meaning that the expression of the unaffected gene is suppressed as the mutated one is favored. One study revealed that distorted XCI is involved in the initial DMD phenotype in carriers, with 95.2% presenting a skewed XCI pattern in lymphocytes [27].

Following, in females with myopathy of unknown cause, even without a clear history of X-linked disease, the muscle biopsy with dystrophin immunostaining is considered the best method of diagnosis, although tracking exon copy numbers can also be considered [16]. Thus, the diagnosis can be yielded by the genetic or anatomopathological method. In some cases, dystrophin positive and dystrophin mosaics help to confirm the diagnosis of carrier status [25]. Due to their less invasive nature, genetic testing may be preferred to muscle biopsy [26]. In addition, studies assessing the CK levels revealed to be an excellent screening method in dystrophin mutation carriers. It was also suggested in this study that female relatives of DMD carriers with negative genetic testing, especially those with high CK, should undergo muscular biopsy and immunohistochemical tests in order to assess dystrophin expression and detect carriers. Finally, a fair number of patients may be diagnosed by the multiplex linkage-dependent probe amplification (MLPA) method for dystrophin gene exons in association with next-generation sequencing for muscle diseases identification [29].

3.2. Clinical female presentation of DMD-like neuromuscular disorders

Duchenne muscular dystrophy is a progressive muscle-weakening disease that presents in boys in the first years of life with frequent falls, waddling gait, difficulties climbing stairs, toe walking, and the classic maneuver of "climbing up the thighs" while standing up, placing the hands on the knee in rising (Gowers's sign) [13, 21]. The progression is usually non-linear, being stable until the age of about 7, with a rapid progression to loss of deambulation, scoliosis, respiratory insufficiency, and cardiomyopathy. Also, many patients have cognitive deficits and autistic behaviors [1]. Hence, most patients die in their late teens, and older patients with multidisciplinary management, cardiac death is nowadays the most common cause of mortality [7, 17, 21].

Moreover, as females are considered disease carriers, the clinical presentation is different from the males, becoming symptomatic in about 10% of the cases. In a recent study, the age of onset of symptoms in women ranged from 1 to 50 years and are frequently milder than in boys. Also, the disease tends to be more severe when it starts at a younger age. These illustrate the heterogeneous features of the female clinical picture [25].

In addition, male patients are mainly seen, but only a small percentage of female patients have mild muscle weakness to a more severe course. For instance, females usually present with asymmetric bilateral leg weakness, myalgia, cramps, fatigue, calf muscles pseudohypertrophy, and dilated cardiomyopathy [9, 18]. Indeed, about 2.5–19% of carriers have skeletal muscle symptoms, and 7.3–16.7% develop dilated cardiomyopathy [15], and, thus, a recent clinical guideline recommends baseline cardiac assessment in early adulthood with electrocardiogram and, when available, Cardiovascular Magnetic Resonance and surveillance every 3–5 years. [2, 28].

Regarding musculoskeletal symptoms such as cramps and pain, they impact the daily lives of affected women in activities like walking, using stairs, or lifting objects, resulting in the use of compensatory muscles, also seen in men [25].

In short, laboratory tests display the abnormal high elevation of Creatine Kinase (CK) levels, which is common in asymptomatic and symptomatic patients, reaching values of up to 7,000 U/L and have a strong correlation with an elevation of AST/ALT levels. Thus, CK measurement can be an excellent screening method for patients carriers of DMD [29].

3.3. Asymptomatic versus symptomatic female carriers of DMD

Female heterozygous carriers of DMD-like phenotypic variations are mostly asymptomatic, and only 2.5 to 7.8% of these carriers have relevant clinical manifestations [26]. According to Silva et al, 8% of female DMD-like disease carriers have symptoms [25], and the prevalence is 15.9–19.5 cases per 100,000 women [29], while in boys 1 in 3,500 is affected [20].

Also, clinical manifestations are associated with chromosomal aberrations in DMD-like female carriers. For example, uniparental disomy of the X chromosome carrying the DMD mutation [23], Turner syndrome (45,X0) was associated with a DMD gene mutation on the single X chromosome and balanced X-autosome translocations with a breakpoint in the dystrophin gene [8].

Further, the skewed X chromosome inactivation is considered the potential mechanism that explains the dystrophic phenotype in manifesting carriers [22]. Preferential inactivation of one of the two X chromosomes may occur either by chance (primary non-random X-inactivation) or as a result of secondary cell selection [5]. In X-autosome translocations of carriers, it is generally accepted that the disease manifestations result from a non-random X-inactivation pattern, with the derivative X remaining active as a saving mechanism against the monosomy of autosomal regions [3]. Also, different patterns of X-inactivation have also been demonstrated in pairs of clinically discordant monozygotic female twins heterozygous for dystrophin gene mutations [24].

According to Brioschi et al, there were discrepancies about this hypothesis and X-inactivation etiology has been ruled out as an explanation of symptomatic phenotype in female carriers. The absence of a relationship between X inactivation and the transcriptional pattern of dystrophin suggests that the DMD gene escapes, to some extent, the X chromosome inactivation [4].

However, skewed XCI is the main factor determining the appearance of symptoms in DMD carriers. The autosome translocations involving the locus Xp21 were particularly associated with an early onset of symptoms [27].

4. Discussion

As Duchenne muscular dystrophy is the most common dystrophy in childhood, it must be considered in the differential diagnosis of myopathic-suggestive clinical conditions, even in unusual presentations, like female patients with muscular weakness or asymptomatic elevation of CK. The diagnosis remains mostly clinical but the genetic confirmation is crucial [26], not just to reassure this difficult diagnosis, but also for therapeutic purposes [21].

As genetic panels are not always available, CK remains a good initial parameter for the investigation (because of its easy accessibility, the sensitivity of 65.38%, and specificity of 92.1%) (7). Elevations of 20–100 times the normal value range are frequent in patients with Duchenne's muscular dystrophy [12]. It is important to emphasize that normal levels of CK do not exclude the diagnosis, once it can be in normal levels in advanced stages of the disease (because of extensive muscular fibrosis), or it can be mildly elevated in less severe forms of this condition.

Once established the diagnosis of muscular dystrophy is, the patient must undergo cardiac assessment looking for myocardiopathy and/or alterations in the electrical conduction of the heart since cardiac manifestations are one of the main causes of death [2].

Evidence on the best treatment for women with DMD is still scarce. However, one important medication in this condition is prednisone (0,75 mg/kg/day), which studies have shown to delay the loss of walking capability in males [19]. Other therapeutic approaches include physical therapy, an adaptation of the environment, management of cardiology abnormalities, respiratory evaluation regarding the necessity of ventilation methods, and orthopedic follow-up in cases of scoliosis and other spinal deformities [11, 17].

5. Conclusions

On the whole, it gets easier to outline the importance of Duchenne Muscular Dystrophy as a differential diagnosis in female patients with atypical presentation of the dystrophinopathies, like muscular weakness beginning at adulthood or even cardiomyopathies without other clear causes. Also, it aids to rationalize the process of diagnosis, investigation, treatment, and follow-up of those patients.

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Conflicts of interest

The authors declare no conflict of interest.

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