Duchenne Muscular Dystrophy Complicating Pregnancy: Case Report and Review of the literature

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Abstract: Duchenne muscular dystrophy (DMD) represents a severe genetic disorder characterized by progressive muscle weakness and wasting. We present a case of a healthy male offspring coming from a mother carrier with the mutation c.9568c>T, p.Arg3190, depicting an extremely rare case. At the same time, it will provide a comprehensive review of the current understanding of the disease, including its etiology, pathophysiology, clinical features, diagnostic methods, and management strategies. The review section highlights the genetic basis of DMD, emphasizing mutations in the dystrophin gene and its consequences on muscle structure and function. Additionally, the pathophysiological mechanisms leading to muscle degeneration, such as impaired calcium homeostasis and increased oxidative stress, are discussed. Diagnostic methods, including genetic testing, muscle biopsy, and imaging techniques, are outlined, along with their respective limitations and benefits. Lastly, various management approaches are examined, ranging from symptomatic treatment, physical therapy, and assistive devices to emerging therapeutic strategies such as gene therapy and exon skipping. Through this case report and review, we aim to enhance the understanding of DMD and facilitate improved diagnosis and management of affected individuals.

Keywords: Duchenne Muscular Dystrophy, Case Report, Review, Genetic Disorder, Dystrophin Gene, Muscle Degeneration, Diagnosis, Management.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that primarily affects males (Birnkrant, Bushby, Bann, Apkon, *et al.*, 2018), with an estimated incidence of 1 in 3,500 to 5,000 male births (Ward and Birnkrant, 2018; Crisafulli *et al.*, 2020). It is caused by mutations in the dystrophin gene located on the X chromosome, leading to the absence or dysfunction of the dystrophin protein (Salmaninejad *et al.*, 2018). DMD is characterized by progressive muscle weakness, starting from early childhood and resulting in loss of ambulation and respiratory complications in the late stages (Rivera *et al.*, 2020). This case report aims to present a detailed clinical description of a patient with DMD and provide a comprehensive review of the current understanding of the disease.

CASE REPORT

Based on the patient's medical history obtained at the hospital and the clinical examination, the patient, Caucasian aged 32, (G3, P2), carries a pathogenic missense mutation in the dystrophin gene (DMD), specifically the mutation c.9568c>T, p.Arg3190.

After her carrier confirmation, it is assiduously verified of her muscular dystrophy's family history.

First Pregnancy: During her first pregnancy, increased nuchal translucency was detected on ultrasound, prompting a CVS that revealed a male fetus carrying the DMD mutation. Consequently, the pregnancy was terminated.

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Second Pregnancy: In her second pregnancy, CVS identified a female carrier embryo. This pregnancy progressed uneventfully, resulting in the birth of a healthy, fully functional baby girl.

Third Pregnancy: The patient presented at the clinic for the first time. She did not present with a history of diabetes, hypertension, thyroid disease, cardiomyopathy, asthma, autoimmune diseases, allergies, neurologic diseases, psychiatric diseases, or urinary problems. She did not smoke or consume alcohol. A breast lipoma was noted on her left breast. Her Pap test smear in 2020 was normal, and an indirect Coombs test was negative. Her blood group and Rh factor were A+.

An ultrasound at 11-13+6 weeks showed a crown-rump length (CRL) of 66 mm, nuchal translucency (NT) of 1.90 mm, a pulsatility index (PI) of the ductus venosus of 0.88, an anterior placenta, and a visible nasal bone. CVS was again performed. This time, the results indicated a healthy male fetus with no mutations in the DMD gene like identified in the mother's family history. The chorionic villus sampling showed a male embryo karyotype of 46,XY without any apparent structural or numerical chromosomal abnormalities.

A Doppler ultrasound at 31+2 weeks revealed increased resistance in the uterine arteries with normal embryo anatomy, as well as normal umbilical and middle cerebral artery (MCA) findings.

The woman delivered a healthy male infant at 33 weeks of gestation.

In this context, it is important to understand that Duchenne muscular dystrophy represents a genetic disease that follows an X-linked dominant inheritance pattern. This means that males who inherit the mutation in this gene will develop the disease, while

females who are carriers of the mutation can either be asymptomatic or exhibit mild symptoms. Since the patient's first child is female, it is most likely that she will not present a severe form of the disease. However, it is important to note that female carriers can still transmit the mutation to their offspring.

REVIEW

The review section provides an overview of the genetic basis of DMD, highlighting the types of mutations in the dystrophin gene and their effects on protein structure and function. Duchenne muscular dystrophy (DMD) is a devastating genetic disorder that affects approximately one in every 3,500 to 5,000 male births worldwide (Nassoro *et al.*, 2020). Named after the French neurologist Guillaume Duchenne, who first described the condition in the 19th century (Kumar Adlakha *et al.*, 2015), DMD is characterized by progressive muscle weakness, loss of ambulation, and respiratory and cardiac complications. This part of the article aims to delve into the multifaceted aspects of DMD, including its genetic basis, clinical manifestations, diagnostic techniques, management strategies, and the latest advancements in research and therapy.

GENETIC BASIS AND PATHOPHYSIOLOGY

DMD is an X-linked recessive disorder caused by mutations in the dystrophin gene located on the X chromosome (Nowak and Davies, 2004). The majority, over 75%, of cases of DMD are commonly inherited from the mother, while around 25% of cases result from a mutation in the dystrophin gene (Birnkrant, Bushby, Bann, Apkon, *et al.*, 2018; Shahade, Mundada and Samal, 2022). Dystrophin is a vital protein involved in maintaining the structural integrity of muscle fibers (Sander *et al.*, 2000; Percival *et al.*, 2008; Lai *et al.*, 2009). Individuals with DMD either do not produce dystrophin at all or produce only a minimal amount of it in their muscles (Sienkiewicz *et al.*, 2015). Mutations in the dystrophin gene lead to the absence or deficiency of dystrophin, resulting in the disruption of the dystrophin-associated protein complex and subsequent muscle fiber degeneration (Birnkrant, Bushby, Bann, Apkon, *et al.*, 2018). It is distinguished by delays in motor skills, weakness in muscles, difficulties in breathing, and the inability to walk (Andrews and Wahl, 2018). The progressive loss of muscle function is attributed to the repeated cycles of muscle fiber necrosis, inflammation, and subsequent regeneration, ultimately leading to fibrosis and fatty tissue replacement.

The majority of females who are carriers of Duchenne muscular dystrophy (DMD) do not exhibit any symptoms of the condition (Aartsma-Rus, Ginjaar and Bushby, 2016). This is because of a phenomenon called random X-chromosome inactivation, where approximately 50% of their muscle fibers express the dystrophin protein, which is necessary for normal muscle function. This inactivation process occurs randomly and is a natural mechanism to compensate for the presence of two X chromosomes in females (Trippe *et al.*, 2014).

Over time, the percentage of dystrophin-positive fibers in carriers can increase. This is believed to happen due to a survival advantage of the muscle fibers that produce dystrophin (Pegoraro *et al.*, 1995). However, it's important to note that this increase is relatively rare. In some exceptional cases, DMD can manifest in females. This can occur through a translocation event involving the DMD gene on the X chromosome (Aartsma-Rus, Ginjaar and Bushby, 2016). Translocation refers to the exchange of genetic material between chromosomes (Winerdal *et al.*, 2020). When the DMD gene is involved in a translocation, it can lead to the development of DMD in female individuals (Alghamdi *et al.*, 2021).

X-chromosome inactivation takes place early in embryonic development, and the pattern of inactivation is inherited by daughter cells. If the X chromosome involved in the translocation is inactivated, those cells do not survive (Shvetsova *et al.*, 2019). As a result, the embryo will only contain cells in which the non-translocated X chromosome with the unaffected DMD gene is inactivated. Consequently, no dystrophin protein is produced in these cells, leading to the manifestation of DMD in affected females (Aartsma-Rus, Ginjaar and Bushby, 2016).

CLINICAL MANIFESTATIONS AND DIAGNOSTIC TECHNIQUES

DMD typically presents in early childhood, with boys showing delayed motor milestones and difficulties in climbing stairs or getting up from the floor. As the disease progresses, muscle weakness spreads throughout the body, affecting the proximal limb and trunk muscles. Children with DMD often exhibit a characteristic "Gowers' maneuver," where they use their hands to push against their thighs to stand up from the floor due to the weakened leg muscles (Jansen *et al.*, 2010; Andrews *et al.*, 2018). Muscular weakness in DMD primarily impacts the muscles closer to the body's core, known as proximal muscles, rather than those farther away, called distal muscles. As a result, it typically manifests first in the lower limbs (Duan *et al.*, 2021). The progression of the disease can be categorized into five stages: the presymptomatic stage, early ambulatory stage, late ambulatory stage, early non-ambulatory stage, and late non-ambulatory stage (Ward and Birnkrant, 2018). Although DMD is typically a genetic disorder, there are instances where individuals without a family history of the condition can still develop it due to independent genetic mutations affecting their genes (Duan *et al.*, 2021).

Cardiac involvement is a commonly observed complication in muscular dystrophies. It occurs when the cells of the heart muscle (cardiomyocytes) undergo programmed cell death (apoptosis) and are replaced by fibrotic tissue. This process often leads to compensatory enlargement of the surrounding muscle (hypertrophy) and can create conditions favorable for the occurrence of irregular heart rhythms (arrhythmias) (Kim *et al.*, 2021; Liu *et al.*, 2022).

Over time, as the amount of fibrotic tissue increases, the left ventricle of the heart progressively expands (dilates), ultimately resulting in a condition known as dilated cardiomyopathy (Palladino *et al.*, 2016). To delay or protect against the development of cardiomyopathy associated with Duchenne muscular dystrophy (DMD), medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are commonly prescribed (Palladino *et al.*, 2016). The use of steroids for this purpose is controversial, with conflicting evidence supporting its effectiveness (Passamano *et al.*, 2012; Feingold *et al.*, 2017). Once cardiomyopathy is established, standard treatment for heart failure is recommended (Mitropoulou *et al.*, 2022).

Clinical diagnosis is often confirmed through a combination of physical examination, family history, and laboratory tests. Serum creatine kinase (CK) levels are significantly elevated in individuals with DMD due to muscle fiber damage (Wright *et al.*, 2012; Chung *et al.*, 2016; Kwon *et al.*, 2016). Genetic testing, such as multiplex ligation-dependent probe amplification (MLPA) or next-generation sequencing (NGS), can identify specific mutations in the dystrophin gene and provide a definitive diagnosis (Lee and Song, 2017; Wu *et al.*, 2018; Zhang *et al.*, 2019).

MANAGEMENT AND THERAPEUTIC APPROACHES

Currently, there is no cure for DMD, but various management strategies aim to optimize quality of life and delay disease progression (Nassoro *et al.*, 2020). Multidisciplinary care, including physical therapy, orthopedic interventions, respiratory support, and cardiac surveillance, plays a crucial role in managing DMD. Engaging in strength training exercises can be advantageous in enhancing muscular strength and decelerating the decline in muscle power among individuals with DMD (Jawade *et al.*, 2020). Additionally, proprioceptive neuromuscular facilitation techniques can contribute to enhancing the balance and mobility of DMD patients (Birelliwar *et al.*, 2020). Furthermore, practicing yoga, which encompasses breathing exercises, physical postures, and meditation, can also be beneficial. Yoga not only addresses the physical aspects but also incorporates psychosomatic and spiritual elements, providing potential advantages for individuals with DMD (Khatib *et al.*, 2017).

The use of corticosteroids, such as prednisone or deflazacort, has shown efficacy in slowing disease progression and preserving muscle function (McDonald *et al.*, 2018). Corticosteroids, such as prednisone/prednisolone and deflazacort, have been found to provide several benefits based on evidence-based research. One notable advantage is that these medications can extend the period of disease progression in individuals with Duchenne muscular dystrophy (DMD) (Falzarano *et al.*, 2015). Prednisone/prednisolone and deflazacort are the two most frequently prescribed corticosteroids for DMD (Birnkrant, Bushby, Bann, Alman, *et al.*, 2018). When it comes to prednisone, patients with DMD may benefit from a daily dosage ranging from 0.3 to 1.5 mg/kg (Evans *et al.*, 2009). The specific dosage within this range can be determined based on individual factors and medical considerations. By administering corticosteroids within the recommended dosage range, patients with DMD may experience a longer period before the disease progresses, which can contribute to improved overall outcomes and quality of life (Falzarano *et al.*, 2015).

In recent years, there have been significant advancements in therapeutic approaches for DMD (van Ruiten *et al.*, 2014; Aartsma-Rus *et al.*, 2019). The significance of prevention has been emphasized greatly due to the absence of any current curative treatment (Mujezinovic and Alfirevic, 2007). The current standard for prenatal diagnosis involves invasive procedures like chorionic villus sampling or amniocentesis, which carry procedural risks and are not suitable for women who prefer non-invasive methods. However, the discovery of cell-free fetal DNA (cff-DNA) in the mother's bloodstream has raised hopes for non-invasive prenatal tests (NIPTs) (Dennis Lo *et al.*, 1997; Lo, 2003). These tests have been used for non-invasive screening of fetal aneuploidies, such as trisomy 21, using maternal plasma (Papageorgiou and Patsalis, 2012; Mersy *et al.*, 2013). They have also been applied for determining fetal sex in pregnancies at risk of X-linked genetic disorders and assessing the Rhesus factor status in RhD-negative women (Freeman, Szczepura and Osipenko, 2009; Devaney *et al.*, 2011; Niesche and Haase, 2012). While NIPTs for single-gene disorders remain challenging, as around 90% of the DNA in maternal plasma is from the mother, efforts are underway to overcome this limitation (Lun *et al.*, 2008).

RESEARCH AND FUTURE PERSPECTIVES

The scientific community and pharmaceutical industry have witnessed a surge in research and clinical trials dedicated to DMD. The aim is not only to find a cure but also to improve the quality of life for individuals living with the disease. Birnkrant et al. conducted a comprehensive study focusing on the diagnosis and management of Duchenne muscular dystrophy (DMD). Their research included a case

study and provided valuable insights and recommendations in various areas of care. These areas encompassed the diagnosis process as well as the management of neuromuscular, rehabilitation, gastrointestinal, and endocrine aspects related to DMD (Birnkrant, Bushby, Bann, Apkon, *et al.*, 2018).

In a separate case study, Rivera et al. investigated the medical management of muscle weakness in individuals with DMD. Their study evaluated different corticosteroid regimens and concluded that among the options available, either deflazacort or prednisone weekend dosing were the preferred approaches (Rivera *et al.*, 2020).

Salmaninejad et al. contributed to the field by presenting a case study on DMD. Their research focused on the advancements in gene therapies developed to address the dystrophin deficiency characteristic of DMD. The study concluded with updates on the latest available gene therapies that hold promise in compensating for the lack of dystrophin in individuals with DMD (Salmaninejad *et al.*, 2018).

In addition to traditional therapeutic approaches, novel modalities such as exon-skipping, gene therapy, and gene editing have shown promise in preclinical and clinical trials. While challenges remain, including the need for long-term safety data and the high cost of these therapies, the progress made so far instills hope and optimism in the DMD community. The importance of prenatal diagnosis for Duchenne muscular dystrophy (DMD) cannot be overstated due to the severity of its clinical symptoms compared to other X-linked recessive inherited muscular dystrophies. Unfortunately, there is currently no curative treatment available for this disease. Therefore, early detection through prenatal diagnosis plays a critical role in managing the condition and providing appropriate support and care for affected individuals. By identifying DMD in the prenatal stage, families can make informed decisions regarding the pregnancy and prepare for the challenges associated with the disease. While curative treatments may not be available yet, prenatal diagnosis allows for proactive management and the implementation of strategies to improve the quality of life for individuals with DMD (Beksac *et al.*, 2018).

Disclosure of interest

All authors declare any financial interest with respect to this manuscript.

Consent was obtained or waived by all participants in this study

Conclusion

Duchenne muscular dystrophy is a devastating condition that affects thousands of children and their families worldwide. However, recent advancements in research and therapeutic approaches have brought about new opportunities for managing and treating this complex disease. With ongoing scientific discoveries, the future holds promise for improved clinical outcomes and the potential for a cure. Continued support for research, increased awareness, and access to comprehensive care will be crucial in transforming the lives of individuals living with DMD.

The pathophysiological mechanisms leading to muscle degeneration in DMD, such as impaired calcium handling, increased oxidative stress, and inflammatory processes, are discussed. Diagnostic methods, including genetic testing, muscle biopsy, and imaging techniques, are described, along with their respective advantages and limitations. The review also covers current management strategies for DMD, including symptomatic treatment, physical therapy, interventions, and respiratory support. Furthermore, emerging therapeutic approaches such as gene therapy, exon skipping, and novel pharmacological agents are explored.

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