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Perspective

Duchenne Muscular Dystrophy in Pediatrics: Updates on Management and Prognosis

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Duchenne muscular dystrophy (DMD) is a profoundly severe and rapidly progressive neuromuscular disorder belonging to a cohort of inherited conditions typified by muscular weakness, resulting in an amplified degree of disability. There are numerous variants of muscular dystrophy, which exhibit substantial variations in terms of severity, onset age, and life expectancy [1]. This condition gives rise to significant muscle atrophy, manifesting initially as weakness of the limb-girdle muscles by the age of 5 years, and culminating in an incapacity to ambulate between the ages of 8 and 12 years. Additional clinical features include pseudo hypertrophic calf muscles, diminished levels of activity, cognitive impairment, and a variable presentation among patients and with advancing in age [13,14], which usually culminates in mortality before age of thirty [2]. This is primarily due to cardiorespiratory complications, which are recognized as the primary cause of death in advanced neuromuscular diseases. Despite that the mortality rate can decline by early basic pulmonary function assessment, such as vital capacity [5].

This disorder primarily affects young boys, with an incidence of one in 5,000 boys, or 200 per million births. Females typically act as non-symptomatic carriers, but there are rare unconfirmed cases of mild symptoms [3-6].

Dystrophin, a cytoskeletal protein of pivotal significance, serves as a linchpin in preserving the stability and functionality of myofibers in muscle. Its critical function entails establishing a mechanical linkage between the cytoskeletal actin in muscle fibers and the extracellular matrix, achieved through the dystrophin-associated protein complex (DAPC) [7]. The dearth of dystrophin, hence, culminates in the rupture of the muscle fiber membrane during contraction and the concomitant disruption of intracellular signaling, thus inevitably leading to profound impairment of muscle function [8,9]. DMD pathophysiological consequences usually arise from mutations in the dystrophin gene. This particular gene holds the distinction of being the largest gene in the human genome. The mutations in this gene can lead to a variety of pathophysiological effects. Approximately one-third of DMD cases result from new mutations, while the remaining two-thirds are inherited from the mother through X-linked inheritance. In such cases, the mother typically serves as an asymptomatic carrier of the mutation. The substantial variability of DMD mutations, which can include significant deletions, duplications, and minor mutations, can be traced to the large size of the gene and its high mutation rate [4].

Duchenne muscular dystrophy is diagnosed through a battery of three tests, namely measurement of creatine kinase (CK) and other enzyme levels, genetic testing, and muscle biopsy. The initial stage of diagnosis entails conducting a blood test to determine CK levels. CK, an enzyme released during muscle damage, can signify that abnormal processes, such as muscular dystrophy or inflammation, are inducing muscle disintegration. Although elevated CK levels do not provide specific details on the type of muscle disorder, they indicate that the muscle itself, rather than the nerves controlling it, is the probable source of weakness. Notably, elevated CK levels can be present in newborns with DMD and may be detected before the onset of symptoms. These levels peak by age two and then gradually decline,

with CK levels eventually returning to normal as muscle tissue is replaced by fat and scar/fibrotic tissue [10]. The second test, genetic testing, involves analyzing DNA from cells, usually blood cells, to identify the presence and location of a mutation in the dystrophin gene. Healthcare professionals at MDA Care Centers can provide detailed information regarding testing options, which are readily accessible in the United States. Genetic testing is typically performed in individuals with clinical features of dystrophinopathy and elevated serum CK levels. A definitive diagnosis of DMD is established by confirming a gene mutation in the dystrophin gene. Large deletion or duplication mutations are commonly assessed, although small mutations may also be evaluated if the initial analysis is negative. Additionally, female relatives of male patients with DMD may undergo DNA testing to determine whether they carry the disease and can transmit it to their male offspring while also potentially passing on their carrier status to their daughters. The third test, muscle biopsy, is less frequently used due to advances in genetic testing. However, it can still provide detailed information about a patient's muscular function, differentiate muscular dystrophies from inflammatory and other disorders, and distinguish between various types of muscular dystrophy. For example, the amount of functional dystrophin protein present in a biopsy sample can indicate whether the patient has DMD, which is characterized by the absence of dystrophin, or the less severe Becker muscular dystrophy (BMD), which involves the presence of partially functional dystrophin. BMD symptoms are typically milder and onset later, and life expectancy is longer than that of DMD. In cases where a definitive diagnosis cannot be established through genetic testing, western blot analysis or staining with selective antibodies may be used to detect dystrophin in muscle tissue, enabling the prediction of disease severity [11,12].

Therapeutic strategies for DMD

Despite significant therapy progress over the past 30 years, DMD is incurable. Yet, a multimodal medical, surgical, and rehabilitative strategy focusing on the symptoms of DMD can change the course of the illness naturally, enhancing patients' quality of life and extending life [15]. Although this disease affects mainly skeletal and cardiac muscles, a wide range of extra-muscular symptoms and indirect effects of muscle weakening may result.

Guidelines for DMD are already suggested. As there aren't many large-scale randomized controlled trials for this disease, these guidelines are frequently not supported by evidence-based medicine. Nevertheless, they are based on the recommendations of highly expert physicians. These recommendations should be viewed as guidelines for the treatment and management of DMD, but they should be modified to the needs and preferences of specific patients and updated in light of emerging research on the subject.

As this disease is caused basically by a mutation resulting in the absence of dystrophin protein, many therapeutic strategies have been suggested based on the type of this mutation.

Stop-codon read-through can theoretically be used for all nonsense mutations, which account for up to 10% of all DMD cases [16]. In read-through therapy, smaller molecules are used to interact with the ribosome, which causes the insertion of an alternative amino acid at the site of a premature termination codon, enabling translation to continue and producing a dystrophin protein that is largely functional. On the basis of this concept, many drugs have been created. This was proved by many clinical trials using the aminoglycosidic antibiotics gentamicin, in which the greatest levels of dystrophin reached 13 to 15% of normal, with lower serum Creatinine Kinase (CK) favoring drug-induced read-through of stop codons. These increases in dystrophin levels were observed after 6 months of gentamicin treatment. Strength stabilization and a little rise in forced vital capacity provided support for this [16,17]. Unfortunately, clinical investigations on humans revealed conflicting results, making the overall usefulness of gentamicin unclear and potentially rather restricted. Furthermore, despite their potential medicinal benefits, aminoglycosides have side effects. There have been reports of varying degrees of ototoxicity and/or nephrotoxicity [18], as well as they put individuals at risk of antibiotic resistance. Negamycin, another antibiotic, and its synthetic

equivalents were created to minimize the side effects of gentamicin. 2017 saw the development of two negamycin analogs: leucyl-3-epi-deoxynegamycin and 3-epi-deoxynegamycin, which could boost dystrophin synthesis and improve read-through efficiency, without any antimicrobial effect [19]. Another newer drug has shown a promising effects. In a high yield study, showed that in comparison to standard of care, ataluren plus standard of care was linked to a 2.2-year delay in age at loss of ambulation (LoA) and a 3.0-year delay in the fall of predicted forced vital capacity to 60% in nonambulatory patients (SoC) [20]. Patients with nonsense mutation DMD (nmDMD) who are ambulatory and nonambulatory both benefit from ataluren with SoC's slowing of disease development. In a recently published clinical trial, however, a newer drug- 2-guanidino-quinazoline (TLN468) -was shown to be more effective than gentamicin and to work on a wider variety of sequences without causing the read-through of normal stop codons [21].

Another method, known as AON-mediated exon skipping, in which Antisense oligonucleotides (AONs) of 20 - 30 bp in length are used to skip exons. The intron and the exon next to it are excluded when AONs precisely hybridize to splice motifs required for pre-mRNA processing and cover up the splicing signals on the RNA. As a result, an in-frame mRNA missing the targeted exon is produced, allowing for the translation of a shortened but still partially functional dystrophin [16]. Exon skipping is mainly based on mutations, therefore a large number of drugs is needed to cover all patients. Exon skipping and dystrophin restoration have been demonstrated to be induced by 2OMePS and PMO backbone alterations in DMD patients and animal models. In the negatively charged oligonucleotide 2OMePS, sulfur is substituted for the oxygen that would typically be present in a phosphodiester linkage at the phosphorothioate backbone (PS), while oxygen is still present at the 2' position of the ribose (PO). In contrast, the PS backbone boosts AONs resistance to nucleases, boosting AON stability. This is because 2OMePS AONs have an increased attraction to target transcripts and can limit their translation via steric blockage of the ribosome [22]. Furthermore, the PS backbone increases the bioavailability of AONs by reducing renal clearance of AONs through high-affinity binding to serum proteins [23]. Preclinical experiments using muscle cell lines, mouse, and dog disease models (requiring the skipping of 2 exons) as well as non-human primates were used to investigate the efficacy of 2OMePS and PMO AON therapy in DMD. It has been demonstrated that dystrophic muscles absorb 2OMePS and PMO AONs more effectively than healthy muscles. Both also demonstrated acceptable pharmacokinetics, were stable and safe, and could restore dystrophin expression [24-26]. However, Peptide-conjugated morpholino oligomer (PPMO) has been created to improve PMO penetration of cell membrane. PPMO can be administered to cells effectively and is more stable in the circulatory system than PMO [27]. The limited delivery effectiveness of PMO, particularly into cardiac muscles, may therefore be resolved by PPMO. On the other hand, PPMO and PMO can produce off-target effects, as they are created using AONs that have modification molecules randomly positioned at each nucleotide linkage [28]. A group of AONs produced stereoselectively that are more uniformly distributed is called a stereopure AON. With the use of this stereochemistry, crucial constructs can be optimized into a single, consistent profile that is both safer and more efficient.

All these agents' AONs are associated with variant degrees of efficacy and efficiency. Because that cardiomyopathy is the primary cause of death in DMD patients, the effectiveness of skipping in the cardiac muscles is a crucial factor in DMD therapy. Unfortunately, compared to skeletal muscles, AON has minimal effects on the repair of dystrophin in cardiac muscles [29]. To increase the potency of antisense medications, a number of strategies have been used, including tricyclo-DNA, peptide-conjugated PMO (B peptides, PNA/PMO internalization peptides, and phage peptides), octaguanidine morpholino, ultrasonic and microbubbles, and nanoparticles [30]. Only one of these medications, PPMO therapy, significantly increased dystrophin expression in the cardiomyocytes of dystrophic animals [31], making it a viable AON for therapeutic development. Drug safety is still another issue. The toxicity of these arginine-rich peptides remains problematic even though PPMO exerts effective cellular absorption [32].

Vector-mediated gene therapy, is another significant arm in the treatment of DMD. When it was first suggested, inserting the normal DMD gene into dystrophic muscles made logical therapeutic sense. The dystrophin gene's huge size and the extensive distribution of muscles make it difficult, though. The two main methods used in vector-mediated gene therapy are mini-/microdystrophin transfer by

adeno-associated virus (AAV) and dystrophin delivery using artificial chromosomes [33]. Although microdystrophin gene transfer utilizing AAV vectors has demonstrated exceptionally excellent therapeutic results in large animal models of DMD so far, there is still need for numerous optimization steps in the transition of this advanced therapy medical product from lab to clinic [34].

With the human artificial chromosome (HAC), which is created through native chromosome de novo synthesis, it may be possible to provide patients access to the entire DMD gene [35].

Precision medicine now has more options thanks to the CRISPR-Cas (clustered regularly interspaced short palindromic repeat, CRISPR-associated) system, which was discovered ten years ago. At the beginning, CRISPR-Cas was found to protect bacteria and archaea against foreign genetic elements during viral infections. The use of this method to fix various Duchenne muscular dystrophy (DMD) gene mutations resulted in the development of a number of prospective therapy strategies for DMD patients. The CRISPR nuclease variations utilized in this method are intended to cause a double strand break in a particular DNA sequence. Dystrophin expression can be restored in the cells of DMD patients by using CRISPR-Cas9 to cause DNA breaks. In order to achieve this, whole exons can be deleted, an exon can be skipped after a splice alteration, the normal reading frame can be restored by creating micro-insertions or micro-deletions (INDELs), or a hybrid exon can be created [36].

The last method, in which Watt and Morgan made the initial suggestion to transplant mice with myoblasts, or muscle progenitor cells. The injected myoblasts express donor genes and merge with host myofibers [37]. According to clinical evidence, muscles treated with myoblast transplantation have a larger maximal voluntary force than muscles on the opposite side. Western blot analysis of patient biopsies, however, revealed a low percentage of dystrophin expression, which can be partially accounted for by immunological rejection or poor myoblast survival after transplant [38,39].

Considering the level of functional Dystrophin protein required for clinical efficacy, many studies have examined how to best treat DMD using a varied dosage of all these genetic approaches. It has been demonstrated that 30% dystrophin levels in DMD patients are adequate to avoid muscular dystrophy [40]. Dystrophin abundance in healthy individuals differs from threefold to fivefold, thus the minimum dystrophin production required in dystrophic patients may also vary among individuals [41].

Prognosis

In the year 2021, a meta-analysis was conducted to examine the life expectancy of individuals who have been diagnosed with Duchenne muscular dystrophy (DMD). The findings of this study brought to the forefront the substantial influence of age and birth year on the mortality rates of DMD patients. Specifically, the study demonstrated that mortality rates were initially low for patients between the ages of 0 and 10, but exhibited a gradual increase with advancing age. The study also reported an annual mortality rate of 86 deaths per 1,000 DMD patients between the ages of 20 and 25, which rose significantly to 336 deaths per year for individuals aged above 40. Furthermore, the research identified a clear association between birth year and mortality rates among DMD patients. It was found that patients born before 1970 experienced a substantially higher mortality rate as compared to those born after 1990. For instance, the study reported a mortality rate of 265 per 1,000 DMD patients between the ages of 25 and 30 for those born before 1970, in contrast to just 27.6 per 1,000 for those born after 1990. These findings hold great significance for healthcare professionals, policymakers, and families of individuals with DMD, emphasizing the need for effective measures to improve the life expectancy of DMD patients [42]. It is noteworthy that although gene therapy has been shown to improve the disease course and decrease complications associated with DMD, there is currently no empirical information regarding its effects on mortality, morbidity, and life expectancy rates in DMD patients.

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