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Duchenne muscular dystrophy- disease characterization and emergent genetic therapy- literature review

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Abstract

Introduction

The goals of this paper are to present the complexity of Duchenne muscular dystrophy phenotype, genetic background, and substantial progress that has been made due to the development of genetic engineering techniques in diagnosing and treating this condition.

Review methods

A thorough review was conducted using the PubMed database, Google Scholar, and relevant subject literature. The paper focused on presenting the latest knowledge available from research on etiology, the course of the disease, and new trends in the treatment of Duchenne muscular dystrophy.

Summary

Duchenne muscular dystrophy, despite being mainly associated with motoric difficulties, is connected with abnormalities in other areas, even cognitive function. Thanks to progress in genetic engineering, new opportunities have emerged in DMD treatment, including the application of several genetic therapies: adeno-associated virus (AAV) vectors, CRISPR-Cas9, termination codon read-through, and exon skipping agents.

Conclusions

Newly emerging medications, acting at the genetic level through various mechanisms, provide hope for further advances in Duchenne muscular dystrophy treatment. Although the application of gene therapy showed a noticeable effect, it was still not satisfactory. At this moment, the most reasonable approach is combined therapy with glucocorticosteroids, interdisciplinary care, and the introduction of a selected type of gene therapy.

Keywords: “gene therapy”, “Duchenne muscular dystrophy”, “Duchenne muscular dystrophy therapy”.

1. Introduction

Duchenne muscular dystrophy is one of the most common neuromuscular disorders. It belongs to a group of dystrophinopathies in which the function of dystrophin, a protein essential for maintaining the integrity of the cytoskeleton and cell membranes of myocytes, is absent or impaired. This exact group of diseases also includes Becker muscular dystrophy, intermediate forms, and symptomatic dystrophinopathy women carriers. The complete absence of dystrophin is responsible for the most common and severe muscular dystrophy, which is called Duchenne muscular dystrophy. This rapidly progressive, lethal genetic neuromuscular disorder mainly affects men, with an estimated male birth rate of 1/3,500 -1/9,300 [1].

2. Pathogenesis

The role of dystrophin is to link the cytoskeleton to the ECM is thought to allow the transmission of force from the contractile elements inside the cell to extracellular matrix structures, providing integrity of muscle fibres. In DMD patients, the permeability of sarcolemma is aggravated. It becomes most noticeable after imposing mechanical stress or electrical stimulation [2]. Other biological functions are accomplished through an assembly of the dystrophin-associated glycoprotein complex. The element of this compound, nNOS, is

involved in a number of muscle activities, including metabolism, regeneration, and muscle perfusion. During contraction, a high concentration of intracellular calcium activates sarcolemmal nNOS to produce nitric oxide. Diffusion of NO to the surrounding tissue prompts vessel dilatation, and hence, an increased supply of oxygen for working muscles is provided. In DMD, nNOS is delocalized from the sarcolemma [3]. Lack or presence of non-functional dystrophin protein results in the development of disease symptoms.

3. Etiology and mutation detection

Duchenne muscular dystrophy is inherited in a recessive manner linked to the X chromosome. The mutation affects the Xp21 region, containing the dystrophin gene, the largest one present in humans. It consists of 2.5 Mb, with 79 exons, which make up 0.1% of the capacity of the entire human genome. Due to the gene's enormous size, ⅓ of the mutations can arise de novo [4]. Genetic testing is necessary to demonstrate the presence of a defective gene. Approximately 70% of the MPLA test finds major duplications or deletions involving one or multiple exons. Failure to show a mutation in the MPLA test does not exclude the diagnosis of Duchenne muscular dystrophy. The next step in detecting abnormalities is to perform sequencing of the patient's genome [5]. This is necessary to detect, for instance, point mutations responsible for the shift of the reading frame, in which small insertions or deletions create a non-divisible by 3, nucleotides sequence. It results in a different amino acid sequence from the original one, leading to the formation of a non-functional protein. On the other hand, some minor in-frame deletions are not detected as the individuals with such mutations are either asymptomatic or exhibit non-DMD/non-BMD clinical features. This finding was intriguing by suggesting the size of deletions in the *DMD* gene is not strictly correlated with the severity of the disease [6]. In sporadic cases, both of the aforementioned DNA analysis methods are unable to show abnormalities in the DMD gene. This occurs when complex rearrangements and changes within introns arise, and methods such as RNA analysis must be used to reveal these changes. The result of all the above-mentioned abnormalities is the complete absence of dystrophin and the onset of DMD symptoms. Accurate analysis of the mutations is not only crucial for making an appropriate diagnosis and predicting the course and clinical picture of the disease but also for selecting an appropriate personalized therapy [5].

4. Clinical presentation

The first noticeable symptoms of Duchenne muscular dystrophy typically appear before the age of 3, but discrete developmental abnormalities can be seen as early as in the first year of a child's life [7]. The acquired milestones in psychomotor development are delayed. In addition to predominantly observed motor abnormalities, like weakness of the muscles of the hip girdle, causing difficulty in standing up and walking on their own, speech development disorders are also found in a large proportion of young patients. Intellectual disability can be identified, and its background seems to be associated with the pleiotropic effect of the DMD gene [8][9]. Distinctive for DMD is Gowers' sign, which involves the patient propping his hands against his own legs while standing up. In the course of the disease, there are characteristic gait abnormalities (swaying of the hips, tiptoe walking) and calf hypertrophy. Patients, as a result of abnormal muscle function, develop curvatures of the spine- deepened lumbar lordosis and scoliosis, which, in addition to limited mobility, can lead to impaired respiratory function, with progression of the disease [10]. Gradual loss and degradation of myocytes lead to loss of mobility at the age of 6 to 13 years (median 10 years) [11]. As the patient grows, symptoms from systems other than the musculoskeletal become more expressed. There appeared development of cardiomyopathy, gastrointestinal and urinary motility disorders, and significant disturbances of the respiratory system in the form of hypoventilation, leading to respiratory failure. Gradually increasing symptoms lead to cardiopulmonary failure, resulting in premature death of patients. With the introduction of cardioprotective therapy into the standard medical practice and the early introduction of assisted ventilation, the life expectancy of DMD patients has been extended from a median of 17 years found from studies in the 1990s to about 30 years based on recent publications [11][12]. Advances introduced in the multidisciplinary approach therapy have significantly extended the lives of patients and enabled them to enter adulthood. This has made Duchenne muscular dystrophy no longer a typical pediatric condition. The symptoms mentioned are related to the amount of functional dystrophin available throughout the patient's organism. The presence of even a defective protein, as is the case in Baker muscular dystrophy, manifests a milder phenotype and is associated with a better medical prognosis.

5. Conventional and new approach to DMD therapy

For many years, the primary therapy for DMD was based on the reduction of symptoms and slowing the progression of the disease. The primary off-label drug used to reduce inflammation caused by myocyte degradation was glucocorticosteroids. However, it was an introduction of widely performed multidisciplinary treatment, including respiratory support, cardioprotection, exercise rehabilitation, and orthopedic treatment of scoliosis to impose a gradual extension of patients' lives duration and increase in quality [10][12][13]. In the treatment of DMD, new opportunities are emerging due to the development of gene therapy, which aims at modification of disease course. Technological advances have enabled the development of gene therapies and the routine usage of genetic tests both for confirmation of the diagnosis and determination of the type of mutations present in Duchenne muscular dystrophy patient's genome. Reducing the cost and increasing the availability of genetic testing makes it possible to choose personalized therapy for the patient, a treatment idea that modern medicine is striving to achieve. There appeared several approaches to genetic therapy of DMD: gene transduction mediated by adeno-associated virus (AAV) vectors, exon skipping agents, termination codon read-through, and revolutionary genome editing therapy using CRISPR [14][15]. Because the full-length dystrophin cDNA exceeds the packaging capacity of the first-generation adenoviral and retroviral vectors, even an intramuscular injection of DNA plasmid was tested, but the results of the research show it was an insufficient method of gene therapy [16].

5.1. Adeno-associated virus (AAV) vectors in DMD gene therapy

AAV is a group of parvoviruses that demand the presence of adenoviruses for proper replication. This group of viruses does not integrate with host DNA, preventing the activation of proto-oncogenes, which can lead to severe complications of gene therapy [17]. AAV advantages as vectors derive from their ability to elicit minimal immunological response and sustain long-term therapeutic expression of the gene they carry. Their limitation is the capacity of 4,5 kb, which, acknowledging the enormous size of the dystrophin gene, is a significant obstacle [18]. Additionally, some epidemical studies show that 40–80% of the human population contains antibodies against AAV, indicating previous exposure to the virus and causing the threat of eliminating vectors by patients' immune systems [19]. This exerts pressure on early treatment administration in children, as they do not come into contact with many wild adeno-associated viruses and therefore do not acquire a specific immune response against them. Despite the

outlined difficulties, in October 2012, a milestone was reached as the first AAV-mediated gene therapy, Glybera, a medication for lipoprotein lipase deficiency, was approved by the US Food and Drug Administration (FDA). Since then, several severe diseases have received approvals for commercialized effective therapies, such as SMA with Zolgensma and inherited retinal dystrophy with Luxturna, while dozens of other treatments are currently under clinical trials [20]. Multiple challenges associated with the development of viral vector effective treatment in DMD include not only required miniaturization of the DMD gene to be compatible with vector capacity but also a substantial mass of target muscle tissue distributed throughout the body and unknown changes at the cell membrane level that might alter vector uptake and binding [21]. Due to the discovery of highly functional *Δ17–48 mini-dystrophin* protein by Kay Davies's laboratory, it is known that even a half-sized protein can provide muscle protection [22]. However, *mini-dystrophin* gene size still exceeded AAV capacity. The crucial problem arising during the creation of therapy was connected with the development of synthetic microgens that are less than 4 kb. In 2006, the first AAV *micro-dystrophin* gene therapy was performed in human patients at Nationwide Children's Hospital in Columbus, Ohio, USA. However, the level of dystrophin gene expression in this trial appeared to be far from clinically efficient [23][24]. It was contrary to optimistic reports regarding the effectiveness of high-dose AAV therapy in other neuromuscular conditions like SMA and X-linked myotubular myopathy [25]. There are still clinical trials in the United States and Europe examining different mini/micro variants of the DMD gene and transporting it various serotypes of AAV vectors. The use of AAVrh74 serotype vectors in reports showed some effectiveness, as evidenced by statistically significant clinical improvement, but failed to meet the endpoint of medical trials. The advantages of this type of modified AAV are that it is significantly more efficient in transducing primary human skeletal muscle cells *in vitro* and has a better safety profile [26]. During testing of AAV9 and AAV9-CRISPR, fatalities appeared among patients [27] [28]. The vast majority of recipients of AAVrh74-mediated DMD therapy also experience some mild adverse effects, such as nausea and vomiting. Regardless of the controversy surrounding its efficacy, in June 2023, the first viral vector gene therapy for DMD, delandistrogene moxeparvovec (Elevidys), was approved under the Accelerated Approval pathway [29]. The importance of AAV-mediated gene therapy lies in its ability to be applied to all types of DMD gene mutations. Because of this, studies using viral vectors are ongoing and continually developed to achieve the undeniable effectiveness and safety of the treatment.

5.2. CRISPR-Cas9 Application in DMD

CRISPR (clustered regularly interspaced short palindromic repeat, CRISPR-associated) was primarily recognized during the exploration of the E.coli iap gene. The detected structure was made up of homologous repeated sequences of nucleotides separated by spacer sequences [30]. Further research has shown that these sequences carry the DNA of invasive agents from past infections. CRISPR system enables Bacteria and Archaea to incorporate encounter pathogenic viral genetic material into a new spacer sequence. The following processes are significant for the detection and destruction of pathogens. In genetic engineering mostly used is CRISPR-associated protein 9 (Cas9). This construct uses a chimeric single-guide RNA (sgRNA) to direct Cas9, a nuclease, to distinct targets [31]. Application of this tool induces cuts in the DNA of patients with DMD. Later, it allows the performance of more complex modifications like the deletion of complete exons, the skipping of an exon following a splice modification, the restoration of the normal reading frame by inducing micro-insertions or micro-deletions (INDELs), or the formation of a hybrid exon [32]. The CRISPR-associated protein 9 (Cas9) complex can be put into AAV and injected to a patient to potentialise the therapeutic effect of both agents. Due to the ability to impose permanent changes in the patient genome, this kind of treatment has the potential to restore dystrophin expression. Another advantage is the potential efficiency in every type of mutation within the DMD gene. The vision of definitive stopping Duchenne muscular dystrophy progression makes CRISPR/Cas9 a promising treatment. With all these benefits, it is clear that Cas9 can trigger genotoxic effects that include large insertions/deletions, chromosomal translocation, and chromothripsis [33][34]. CRISPR technologies are still under medical trial in numerous hereditary and non-hereditary conditions, including DMD.

5.3. Termination codon read through

The representative of this group of drugs is ataluren. The mechanism leading to it’s therapeutic effects is based on retarding recognition of premature termination codons during transcription. The result is the production of some proportion of fully functional dystrophin. Unfortunately, termination codon read through therapy is reserved for a narrow group with nonsense mutations. These genetic changes affect only 10-15% of patients with DMD [5]. Although ataluren was granted conditional marketing authorization by EMA in 2014 on 28 March the conditional marketing authorization was not renewed. The reason justifying such a statement was the lack of confirmation of the medicine's effectiveness [35].

5.4. Exon skipping agents in DMD

During numerous inquiries, it has been demonstrated that even the presence of biochemically abnormal dystrophin results in a milder phenotype of Becker muscular dystrophy. Patients with this condition present onset of symptoms as late as in the third decade of their lives [36]. The aim of exon skipping treatment is to convert out-of-frame into in-frame deletions (reverting DMD into less severe BMD). Out-of-frame mutations refer to the insertion or deletion of nucleotide bases in numbers that are not multiples of three. Every codon, made of 3 nitrogenous bases, corresponds with a specific amino acid. The exclusion of one nitrogenous base can cause the substitution of inaccurate amino acids. From the spot of a mutation, further transcription proceeds incorrectly. The result of the process mentioned above is the creation of unfunctional or lack of specific protein. For exon-skipping, there are three different experimental approaches: single-stranded antisense oligonucleotides (ASOs), DNA editing (CRISPR), and U7 snRNP-mediated splice blocking [37]. Of these, ASOs can be considered as one of the most advanced RNA-based therapeutic modalities, because of the highest number of New Drug Application approvals [38]. Usage of oligonucleotide drugs (ASOs) cause the exclusion of exons, where mutation occurs, from mRNA. Therapeutic particles bind to pre-mRNA to hybridize and mask the exonic splicing enhancer (ESE) sequences normally contained in all exons [5]. After the splicing process defective exon is “skipped’ and shortened, but still functional, particle can be formed. Most widely applied as oligonucleotide drugs are PMO compounds. Morpholino chemistry (PMO-phosphorodiamidate morpholino oligomer) are uncharged molecules and are difficult to transfect into cells in vitro, but in dystrophic muscles, contrary to unaffected ones, attain high concentration. Enhanced next-generation PMO additionally includes a cell-penetrating peptide (CPP), which triggers increased tissue uptake mediated by electrostatic interactions between the cationic charges of the CPP and the anionic charges of the cell-surface proteoglycans during endocytosis [39]. To date, there are four FDA-approved ASO drugs for DMD treatment: eteplirsen(induce exon 51 skipping), golodirsen (induce exon 53 skipping), viltolarsen (induce exon 53 skipping) and casimersen (induce exon 45 skipping) [40][41][42][43]. Data collected have shown a good tolerance and safety profile of PMO ASOs following weekly intravenous administrations [44][45]. A considerable disadvantage of using ASOs is that each registered medication is suitable for a narrow group of patients who have a mutation within a specific exon.

6. Conclusions

DMD is a lethal genetic neuromuscular disease, and so far, there is no cure for this disease. Patients with this condition present a broad spectrum of symptoms, not only connected with motor functions. In recent years, considerable progress has been made in the treatment of many medical conditions due to the introduction of genetic therapies. That raised hopes for a more effective and riveting primary cause, genetic mutation, treatment of Duchenne muscular dystrophy. Although several drugs acting through various mechanisms, such as adeno-associated virus (AAV) vectors, CRISPR-Cas9, termination codon suppression, and exon skipping agents, have appeared, in most cases, the therapeutic effect was noticeable but not satisfactory. Additionally, some highly effective approaches, such as exon-skipping therapy, are not suitable for all patients. Furthermore, each registered PMO-based drug is designed to target the specific exon where mutations occur. It makes the cost of such medication even higher when the demand is so low. Financial aspects are often overlooked but are crucial matters. Even for patients' families from wealthy countries, the prices of the newest genetic DMD medication are tremendous. That aspect led to the withdrawal of the first genetic treatment for the hereditary disease, Glybera [46]. Another aspect is the safety of medications, as deaths of patients were observed after the administration of adeno-associated virus (AAV) vectors and CRISPR-Cas9 [27] [28]. It should be noted that many patients and caregivers are willing to take greater risks for a treatment that may slow clinical deterioration or delay the loss of functional milestones [47]. Acknowledging all the mentioned prospects, many improvements are still needed to make gene therapy more efficient, accessible, and secure in Duchenne muscular dystrophy. At this moment, the most reasonable approach is to combine steroid therapy, which has been applied for many years, with multidisciplinary care based on alleviating symptoms and complications, and matching it with the type of gene mutation therapy [48]. Despite the odds, considerable progress has been made in DMD therapeutic design and innovative fields of investigation, not only for the disease discussed in this review, but also for other congenital conditions.

Disclosure

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