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Identification and Therapeutic Development of Spinal Muscular Atrophy

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Abstract: The most prevalent condition in children is spinal muscular atrophy (SMA), for which there is presently no efficient treatment. It is characterised by atrophy of skeletal muscle motor neuron in the spinal cord are deterioting, and widespread weakness. The survival motor neuron 1 (SMN1) gene is disrupted in homozygous fashion as a result of detection, conversion, or mutation. Given the high carrier frequency, siblings of parents or of parents of SMA children are required to undergo carrier testing, which aims to collect data that may aid in reproductive planning. In the event that a request for carrier testing on siblings of an affected SMA newborn is made, it is advised. There are a number of potential therapeutic agents that have been found and are at various stages of research. Clinical trials continue to be carried out, and translational research on spinal muscular atrophy is very prominent. A thorough discussion of clinical symptoms, diagnosis, molecular genetics, therapeutic development, and therapy is provided in this Review.

Key words: Spinal muscular atrophy, SMN1, SMN2, Neuron motor, newborn screening, genetic.

1. Introduction

The survival motor neuron (SMN1) gene deletion or mutations are the cause of the rare autosomal recessive neuromuscular disease known as spinal muscular atrophy (SMA), it is characterized by increasing symmetrical muscle weakening and atrophy as well as lower motor neuron (anterior horn cells) loss in the spinal cord and brainstem nuclei. Over 95% of instances of SMA are caused by the autosomal-recessive condition known as the most common SMA, in which the SMN1 gene has a homozygous deletion or mutation. SMA occurs in 1 in 6,000–10,000 live births [1-3]. SMA has four different clinical subtypes: type I, which is the most severe and primarily affects newborns; types II and III, which are intermediate forms. The mildest kind, type IV, develops in adults. Increasing the amount of SMA protein in tissues and cell types that are important to the disease is the current aim of SMA therapy development. Promising medicines have advanced to clinical trials thanks to recent work in small-molecule screening and the creation of trustworthy animal models [4].

1.1 Epidemiology

With a carrier frequency of 1/40 to 1/6 and an estimated prevalence of 1 in 6,000 to 10,000 live births. SMA is the second most frequent fatal autosomal recessive illness after cystic fibrosis [5]. Among general, a 2005 study found that type I spinal muscular atrophy is less prevalent among Cubans (3.53 per 100,000 live births). Additionally, there is a higher rate among those of African ancestry [6, 7]. In order to ascertain the carrier frequency in various ethnic groups in North America, in 2009 an epidemiological examination was carried out. Caucasians had the highest carrier frequency (1 in 37, or 2.7%), while Hispanics had the lowest (1 in 125, or 0.8%), and African Americans (1 in 56, or 1.8%) had an intermediate frequency [8]. Moreover, despite the high carrier frequencies, the incidence of spinal muscular atrophy is lower than expected.

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1.2 Clinical Manifestations and Classification

When motor neurons in the spinal cord deteriorate, it results in spinal muscular atrophy which is characterized by hypotonia and muscle weakness. Electromyography and muscle biopsy were previously used to confirm the diagnosis [9, 10]. Although the majority of people with spinal muscular atrophy have homozygous mutations in the SMN1 gene, there are three distinct clinical categories based on age of onset and level of motor function. Severe type I, intermediate type II, mild type III, adult-onset type IV, which now includes extremely mild disease, and severe type I. The maximum level of motor function, such as sitter or walker, is used by most studies to describe the kind of spinal muscular atrophy [11, 12].

- Type I spinal muscular atrophy

About 50% of patients diagnosed with spinal muscular atrophy have type I spinal muscular atrophy, also referred to Werdnig-Hoffman disease. Type I SMA is characterised by the onset of the disease before the age of six months and death within the first two years of life. They have poor head control, areflexia, hypotonia, which causes them to "slide through" on vertical suspension, and a "frogleg" posture while lying down. Infants with type I SMA also develop a bell-shaped chest and a kind of paradoxic breathing known as "belly-breathing" due to weakening of the intercostal muscles and relative diaphragm sparing. These individuals lack control over head movement, have flaccid paralysis that is symmetrical, and exhibit severe hypotonia. They require assistance to sit down. Additionally, it weakens the protection of the airways and raises the possibility of aspiration pneumonia, a significant cause of morbidity and mortality [13-16].

Prior to recently, spinal muscular atrophy was only considered to be a motor neuron condition. Recent research suggests that severe type I SMA muscle atrophy can occur in a number of organs other than the spinal cord motor neurons, including the brain, the heart and blood vessels, and even the sensory nerve. Recent postmortem studies showed growing evidence of congenital cardiac problems in severe spinal muscular atrophy, with hypoplastic left heart syndrome being the most prevalent relationship [17]. In a biopsy study by Rudnik-Schoneborn et al. demonstrated that among the 19 patients with infantile spinal muscular atrophy, significant sensory nerve pathology was evident in those with severe spinal muscular atrophy type 1, whereas no sensory involvement was evident in patients with spinal muscular atrophy II and III. Of these, axonal degeneration was noted in seven patients, and abnormal nerve conduction study results were followed by biopics that revealed a marked reduction in muscle mass [18].

- Type II spinal muscular atrophy

The start of type II disease, between the ages of 7 and 18 months, is characterized as being of intermediate severity. The ability to sit unassisted is present in the patients. With the aid of leg braces, a few can stand, but none can walk by themselves. As they age, they also experience growing scoliosis, which when combined with intercostal muscular weakening cause's serious restrictive lung disease [14, 16]. The high relative fat mass index puts them at risk of becoming overweight even while their body mass index may be low [19]. Survival rates were 98.5 percent at age 5 and 68.5 percent at age 25 in a study of 240 type II patients. The likelihood of respiratory impairment reduces life expectancy even if patients may live into their third decade [20].

- Type III spinal muscular atrophy

The symptoms of Kugelberg-Weiland disease, type III spinal muscular atrophy, are extremely diverse. Usually, they accomplish all significant motor milestones, like self-sufficient walking. While some people may require wheelchair help as children, others may walk and lead fulfilling lives as adults despite having a few small physical weaknesses. Scoliosis frequently develops in these patients. Joint overuse

symptoms, which are typically brought on by weakness, are frequently observed. They might have hand tremor or polyminimyclonus. Their life expectancy is similar to that of the general population in a small but significant way [14, 17, 20].

- Type IV spinal muscular atrophy

Weakness usually appears in people with type IV disease in their second or third decade of life. Patients are able to walk as adults despite minor motor impairment and the absence of respiratory or dietary issues [20].

1.3 Molecular Genetic

Investigations in 1990 employed linkage analysis to pinpoint the SMA gene's location on chromosome 5q13. With recombinant mapping, cloning of the disease-gene region with yeast artificial chromosomes, and identification of multicopy repeats of microsatellites and other genomic sequences, the initial 10 cM interval was later limited to a 1-2 cM zone [21] hums have two different forms of the SMN gene: a telomeric form (SMN1) and a centromeric form (SMN2). When the SMN1 gene is translated, full-length messenger RNA (mRNA) transcripts encoding the SMN protein are produced during the translation of the SMN1 gene. With the exception of a C to T change in an exonic splicing enhancer that causes exon 7 to be excluded during transcription, the SMN2 gene is the same as the SMN1 gene. The resulting, incomplete protein is rapidly destroyed and is not functional. Importantly, exon 7, which encodes the normal SMN protein, is retained in a small percentage of the total transcript obtained from the SMN2 gene (about 10%-15% of the total mRNA transcript) because exon 7's removal from SMN2 mRNA is incomplete [22]. A favourable connection between SMN2 copy quantity and a milder phenotype was verified by numerous subsequent genotyping analyses. Although it is now known that the primary variable impacting the severity of SMA is the SMN2 copy number, it is clear that there are other phenotypic factors as well. According to prior and colleagues, in order for this to happen, our understanding of the genetic factors influencing disease severity must be improved [23].

1.4 Diagnosis

Clinical traits, particularly in the severe variation of a floppy baby or feeble youngster, are highly suggestive for the diagnosis of SMA. The mental acuity and attentiveness are always good. Typically, more proximally than distally, the weakening is symmetrical, and more pronounced in the legs than the arms. According to this clinical classification, the degree of weakness is correlated with the age at which it first appears with delayed motor milestones. Depending on the age at disease beginning and the length of the illness, sensitivity is maintained and deep tendon reflexes are more or less affected. Additionally, other clinical characteristics in the most severe form include: cough, poor head control, trouble eating and swallowing, atrophy and fasciculation of the tongue, and the infant's reliance on the diaphragm for breathing [24, 25]. A DNA sample is obtained for genetic testing, which is a volumetry process. These could be buccal (mouth check) swabs, samples of saliva, blood, or prenatal tissue. An SMA diagnosis or carrier status may be confirmed through testing [26].

There are different types of genetic testing related to SMA:

Diagnostic - confirms if you have SMA

Familial - Verifies whether you carry the particular mutation discovered in your family.

Carrier - whether you are a SMA carrier

Parental - Determines if your unborn child has inherited SMA from your parents.

1.5 Newborn Screening

The development of SMA disease-modifying therapies has brought attention to the value of early diagnosis, which enables presymptomatic treatment. Indeed, motor neuron loss in SMA is a progressive

process, and presymptomatic treatment of newborns has resulted in noticeably better outcomes [27, 28]. At least 32 US states have implemented newborn SMA screening. The fact that newborn screening only detects exon 7 deletions and not point mutations should be noted because this means that 5% of cases will not be discovered at birth [29]. SMN2 copy number is the main factor considered when deciding whether to start treatment after receiving a presymptomatic diagnosis of SMA. Due to the advantages of early intervention and the potential difficulties with gene transfer in older children, we now advise gene transfer in infants with 2-4 copies of SMN2 [30]. In addition to newborn screening, many prospective parents can now access carrier testing, which the American College of Obstetricians and Gynecologists has currently authorized [31, 32].

1.6 Therapeutic Strategies

Actually, SMA has no recognized treatments, and its pathophysiology is still poorly understood. However, there have been significant advancements in recent years in our understanding of the disease's molecular underpinnings, and new therapy strategies are emerging [33].

- Pharmacological therapeutic

In SMA therapeutic trials, a number of mechanisms have been studied, including albuterol for its anabolic qualities and the molecular impact on SMN2 gene expression, as well as neuroprotective medicines to rescue motor neurons (like riluzole), creatine to improve energy metabolism, and SMA. Histone deacetylase (HDAC) inhibitors, such as suberoylanilide hydroxamine acid (vorinostal), phenylbutyrate, sodium butyrate, and valproic acid, were used in early attempts to increase the expression of SMN2. Phenylbutyrate and valproic acid showed modestly improved clinical and molecular outcomes in early open-label clinical trials. The apparent advantage, however, was not maintained in further randomised, placebo-controlled trials. The proteasome inhibitor bortezomib, which prevents the breakdown of SMN protein, is one of the several small compounds that have been examined in SMA animals but have not yet made it to human trials. Bortezomib improved the architecture of the neuromuscular junction and improved muscle performance but did not increase the lifespan of SMN7 mice when taken alone. However, bortezomib increases SMA mouse survival to a median of 20 days when combined with trichostain. Furthermore, as in the case of bortezomib. CNS penetrance of small molecules is a major consideration in the development of small molecules therapies for SMA [33, 34].

- Gene therapy

Approaches to gene therapy for SMA have also been studied, employing viral vectors to replace SMN1 in addition to potential medication therapy. [34]. The primary agent for monogenic diseases receiving human gene therapy is adeno-associated virus (AAV). AAV is a nonpathogenic virus that can express transgenes for a long time without integrating into the host genome and with low innate immune response activation [35, 36]. In a series of studies, self-complementary drugs were injected into the CNS of SMA-like mouse models, lengthening the median life span of the affected animals to 50 days compared to the unaffected controls 15 days [37].

AAV9, which is employed for SMA gene delivery, demonstrates tropism for the muscles and the central nervous system. The viral capsid is preserved for distribution in this application. However, a recombinant SMN transgene replaces the rep and cap genes [38, 39]. In a crucial clinical trial, 15 newborns with the SMA type I phenotype received AUXS-101 gene therapy. In all 15 patients, gene therapy increased ventilator-free life over the past 20 months, compared with only 8% of historical controls [40, 41].

- Stem cell therapy

As a cellular replacement technique for the therapy of SMA, stem cell approaches show promise and are currently the subject of a lot of research [42, 43]. Cell

replacement can be accomplished by either activating endogenous stem cells in the CNS or by transplanting stem cell-derived cells that have completed in vitro maturation. The only stem cell therapies currently in use are mesenchymal and bone marrow transplants, but no experience with these treatments has been reported in SMA research. However, significant advancements have been made using primary neural stem cells derived from the spinal cord, showing improvement of the spinal muscular atrophy phenotype in mice, despite the fact that this primary source has few translational applications [44]. A significant breakthrough in producing genetically suitable neurons for stem cell therapy was made most recently with the successful production of induced pluripotent stem (iPS) cells from patient fibroblast [45].

2. Conclusions

In conclusion, there have been numerous advancements in the study of SMA over the years. There is no proven cure for the inherited, persistent motor neuron illness known as spinal muscular atrophy. However, there is reason for hope because the field is dynamic and learning more and more about the molecular genetics and pathogenesis of spinal muscular atrophy. The inclusion of participants in these researches has been made easier by the spinal muscular atrophy patient registry. To improve the long-term interdisciplinary management of individuals with spinal muscular atrophy, standards of care were also developed. Some people may still exhibit disease symptoms, particularly if they receive treatment after developing symptoms. Therefore, more work is necessary to see if therapy efficacy can be increased. There may be multiple treatments. Further research will be needed to assess the effectiveness and effects of gene therapy over the long run.

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