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REVIEW ARTICLE **OPEN ACCESS**

Spinal Muscular Atrophy

T. Rama Rao*1, R. Srujana2, J. Namratha2, Rabia Basri2
1. Professor & Principal, CMR College of Pharmacy, Medchal, Hyderabad, Telangana
2. Pharm. D students, CMR College of Pharmacy, Medchal, Hyderabad, Telangana
*Corresponding author: E-mail: tadikondarao7@gmail.com

ABSTRACT
Spinal muscular atrophy (SMA) is a neurodegenerative condition that causes weakness and paralysis as a result of the loss of motor neurons in the anterior horn of the spinal cord. A carrier frequency of 1/40 to 1/60 and an incidence of 1 in 6,000 to 1 in 10,000 live births are calculated. Generalized muscle weakness and atrophy, which mostly affect muscles in the proximal limbs, are the main symptoms of this condition. Based on the age at which symptoms first appear and the level of motor function attained, SMA is divided into four severity grades: SMA 1, SMA 2, SMA 3, and SMA 4. The majority of patients' diagnostic tests show that it is caused by homozygous disruption of the survival motor neuron 1 (SMN 1) gene by deletion, conversion, or mutation, which typically indicates the lack of SMN1 exon 7, is present in the majority of cases. Despite the lack of a cure, research has revealed potential processes explaining the disease's molecular etiology. The SMN1 gene region's distinctive genomic structure has been used to design treatment plans. In this, we provide a review that integrates etiology, types, clinical manifestations, pathophysiology, diagnostic strategy, and treatment.
Key words: Spinal muscular atrophy, SMN 1, SMN 2, genes, neurodegenerative.

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INTRODUCTION

A group of genetic disorders collectively known as spinal muscular atrophy (SMA) are characterized by the degeneration of anterior horn cells and the ensuing muscle atrophy and weakness. Over 95% of cases of the most prevalent form of SMA are autosomal recessive disorders caused by homozygous deletions or mutations in the 5q13 survival of motor neuron (SMN 1) gene [1].
Werdnig and Hoffmann first described the illness in the 1890s [2].
After cystic fibrosis, SMA is the second most common fatal autosomal recessive disorder [3] affecting between 1 in 6,000 to 1 in 10,000 live births, according to estimates [4].

CLASSIFICATION:

Based on the age of onset and the level of motor function attained [2], SMA is clinically divided into five phenotypes [5].
SMA type 0:
The term "spinal muscular atrophy type 0" is used to describe neonates who have a history of decreased foetal movements and present with severe weakness and hypotonia. In this instance, the weakness most likely began before birth [1].
SMA type 1:
Type 1 SMA, also known as Werdging-Hoffman disease, is characterized by hypotonia, poor head control, and diminished or absent tendon reflexes before the age of six months in infants [1]. Sometimes it can be detected while the baby is in utero (before birth) [5] type 1 SMA typically die in infancy and are never able to sit independently the severe neonatal variant, which at birth exhibits joint contractures and a paucity of movement, has a poor prognosis and frequently requires ventilator support as a neonate. It is possible to separate the clinical phenotype of type 1 into three fairly discrete groups with significantly divergent natural histories. With joint contractures and limited movement present at birth, type 1a has a poor prognosis and frequently requires ventilator support as a neonate. The typical SMA-1 patient, type 1b, has an intermediate prognosis, poor head control, and difficulty with oral secretions upon or shortly after the presentation. The minority of type 1 patients who are able to control their head or who can sit with support and have the best prognosis are type 1c patients[6].

SMA type 2:
SMA type 2 is characterized by onset between seven and eighteen months of age**.** A disease of intermediate severity on the clinical-genetic spectrum of infantile spinal amyotrophies, spinal muscular atrophy type 2 affects about one-third of patients. Can be diagnosed by using a quantitative polymerase chain reaction to look for homozygous deletion of the exon 7 SMN1 gene[7].
SMA type 3:
(Also known as Kugelberg-Welander disease, "walkers," or mild SMA) - shows up after 18 months like type ii with progressive proximal weakness predominantly affecting legs over arms; patients are ambulatory but may need a wheelchair as the disease advances. Restrictive lung disease does not typically affect patients, and life expectancy is unaffected. Type 3 can also be further divided into type 3a: presents 18 months-3 years, presents >3 years, and 3b [8].
SMA type 4:
Mutations in the SMN1 gene, which produces the survival motor neuron (SMN) protein, result in SMA type 4. The SMN1 gene cannot produce SMN protein because of the mutations. Due to alternative splicing of the mRNA, a second, related gene, SMN2,5, encodes for numerous different versions of the SMN protein. Only 10 to 15 percent of the SMN protein produced by the SMN2 gene is functional and full-length. Because it is too short, the remaining protein is quickly broken down by cells. Patients may have a waddling gait, yet they can walk for the rest of their lives. Electromyography can be used to diagnose [9].

ETIOLOGY:
Two genes are linked to the genetic basis of many cases (SMN1 or telomeric SMNt and SMN 2 or centromeric SMNc)
SMA is caused by a homozygous deletion of SMN1 on chromosome 5q13 in 95% of cases, although this does not explain how there can be significant clinical phenotypic heterogeneity **[10].** About 3% of affected individuals are compound heterozygotes for the deletion of one SMN1 allele and subtle intragenic mutations. All patients, however, retain at least one copy of SMN2, generally 2-4[2]. One copy of the SMN2 gene is typically present in new-borns with SMA type 0 or congenital SMA, which is inadequate to generate enough SMN protein to prevent the disease phenotype [10]. Two copies of SMN2 are usually connected to type 1 SMA [11]. People with type 2 or intermediate typically have three or more SMN2 genes. Degeneration of lower motor neurons in the spinal cord and brainstem nuclei results in SMA type 3 disease [12]. Mutations in the SMN1 gene, which codes for the survival motor neuron, result in SMA type 4 (SMN) [13].
Pathophysiology:
Spinal muscular atrophy (SMA) is a monogenic neurodegenerative disease characterized by the loss of alpha motor neurons, which results in muscle atrophy and weakness [14]. All eukaryotic cells have the SMN protein, which has been proven to be essential for all cells' homeostatic cellular mechanisms [15]. There are many theories on the SMN protein's function in SMA, but the two most prevalent ones concern the protein's roles in 1) the cytoplasm and 2) the nucleus of neurons. Actin dynamics, vesicle release at synapses, and mRNA transport via axons have all been shown to be critically dependent on the cytoplasmic SMN protein [16]. The SMN complex, a group of proteins that includes SMN, is present throughout the cytoplasm and nucleus. It is responsible for pre-mRNA splicing and spliceosomal small nuclear ribonuclear protein (snRNP) synthesis [15]. The affected person's parents both carry the problematic gene. As a result, kids won't exhibit any disease signs, which make SMA difficult to predict and treat with preventative treatments [17]. In the survival motor neuron 1 (SMN1) gene, homozygous deletions account for about 95% of SMA cases [18]. It is possible for SMN1 to develop point mutations, which cause SMA [19]. SMA may also result from mutations in genes other than SMN 1[20]. In 1995, two human SMN genes that express the SMN protein were discovered. 5 both the SMN1 gene, which has a telomeric form with 9 exons, and the SMN2 gene, which is a centromeric homolog, are found in a genomic instability region [20]. Spinal muscular atrophy, SMA, a genetic neuromuscular disorder with progressive muscle wasting due to mutation in the SMN1 gene, deficiency in SMN protein, and loss of motor neurons. Splicing in SMN1 resulted in a full-length mRNA that will produce a useful protein. Exon 7 is bypassed during the synthesis of SMN 2 mRNA, in contrast [21]. The result is the formation of SMN 7.2, an unstable and shortened version of the SMN protein. This protein is less effective inside cells and is swiftly and easily broken down by cells. Since the SMN2 gene is the only one in SMA patients who produce SMN protein, it has clinical value in these patients but is irrelevant in healthy people. Only around 10% of the SMN protein produced by SMN2 is fully functional [22]. A lack of the SMN protein results in the loss of certain motor neurons [23]. Mutations in genes other than SMN1 can also be regarded as causing SMA. In fact, more than 10 pathogenic variants have been identified as potentially responsible for leading to SMA [24]. The SMN2 gene has no relevance in healthy individuals, but does have clinical significance in SMA patients since it is solely responsible for SMN protein production in these patients. Nearly 10% of the SMN protein expressed via SMN2 is fully active [25]. This

means that a high copy number of SMN2 might partially compensate for the lack of SMN protein production and ease the severity of the disease. SMA patients carry at least one SMN2 copy, with this number of copies being variable among the SMA types. Milder SMA phenotypes have been associated with a greater number of SMN2 copies, 2, 5 however, this correlation is not absolute and other factors might be contributing to the disease severity [26]. SMN protein level in spinal muscular atrophy with congenital heart disorder associations and sensory nerve pathology observed in type 1 SMA patients, recent advances in our understanding of the SMN protein and its ubiquitous presence and multiple functions in all eukaryotic cells have led to conclusions that SMA is not purely a motor neuron disorder [27].

Signs and symptoms:

The main indication that chromosome 5 is (SMN-related) SMA is characterised by voluntary muscular weakness. The muscles closest to the body's centre, such as those in the shoulders, hips, thighs, and upper back, are those that are most severely impacted. Deep tendon reflexes are diminished, and the lower limbs appear to be more impacted than the upper limbs [28]. Hypotonic, respiratory distress, a weak cry, and poor feeding are among the clinical signs of type 0, which typically appear before delivery. Reduced intrauterine movement can also cause joint contractures [29]. Patients with type 1 SMA may exhibit some systemic symptoms and signs, including autonomic dysfunction, cardiac impairment, and, in rare cases, skin necrosis [29].

Patients with type 2 SMA are unable to stand or walk on their own, while some may be able to stand with the aid of bracing or a standing frame. Examination reveals lower limbs with the most acute proximal predominate weakness. Usually, reflexes are non-existent. Since the beginning of time, intermediate forms of the disease have been linked to a fine tremor (mini polymyoclonus), which is frequently present primarily in the distal limbs [30]. Proximal muscular weakness and hypotonia are characteristics of SMA type 3, although these patients appear normal during infancy, there is a slow but progressive weakness of the limbs and bulbar dysfunction may occur late in the disease [12]. Patients with type 4 SMA may have a waddling gait, but they continue to be able to walk throughout their lives. Other signs include finger trembling and calf muscle hypertrophy [13].

Diagnosis:

There are numerous extremely rare conditions of various etiologies (typically secondary to a genetic disorder) that can present similarly to SMA but often with distinguishing features not seen in SMA if genetic testing fails to identify pathological biallelic versions or absence of SMN1 despite clinical suspicion of SMA. A thorough clinical examination and a family history would be the initial steps in the diagnosis of SMA. The level of creatine kinase (CK) in the blood may need to be measured in order to determine whether any muscle damage has occurred. High blood CK levels do not harm the body directly, but they are a key sign of a condition called muscular dysfunction. If an electromyogram (EMG) indicates a motor neuron disorder, additional electrophysiological studies, such as a nerve conduction study, should be carried out [31].

The first level diagnostic test for a patient suspected to have SMA should be the search of SMN1 gene homozygous deletion. The absence of SMN1 exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMA. The test achieves up to 95% sensitivity and nearly 100% specificity [32].

Differential Diagnosis:

Congenital - 6 months: X-linked infantile spinal muscular atrophy, Pompe disease, Prader-Willi syndrome, Myotonic dystrophy type 1, Sellweger spectrum disorder. Congenital myopathies, metabolic, and mitochondrial diseases must all be taken into account. Childhood diseases include botulism, Guillain-Barré, hexosaminidase A deficiency, Duchenne muscular dystrophy, Fazio-Londe syndrome, and Hirayama illness. Adulthood: bulbar muscle atrophy, spinal atrophy, and amyotrophic lateral sclerosis [12][33].

Management:

In the past, SMA treatments have mainly been supportive with early paediatric palliative care specialists' involvement, especially for types 0, I, and II. However, novel therapies have recently been developed that are showing a lot of promise in reducing the extremely low morbidity and mortality linked to SMA I and II [1].

Spinraza: The medication selectively directs alternative splicing and increases SMN2 exon 7 inclusion, resulting in higher production of functional SMN protein by the use of antisense oligonucleotides (ASOs).

Zolgensma: It is a gene replacement therapy that is administered via intravenous (IV) infusion and is sold by Novartis Gene Therapies.

Evrysdi (risdiplam): Evrysdi, is a liquid oral drug sold by Genentech that encourages the SMN2 gene to create a more functional SMN protein [34][35].

Gene Therapy: The most cutting-edge treatment for SMA that specifically targets the malfunctioning SMN1 gene is gene therapy. Studies conveying an entire copy of wild-type SMN using an Adeno-Associated Viral serotype 9 (AAV9) vector in preclinical studies demonstrated that these constructs penetrate the brain-blood barrier and prolong the survival of treated SMA-mice [36].

Stem Cell Therapy: Cell transplantation for neuroprotection and ultimately cell replacement is another therapy option for SMA that is currently being intensively researched using retinoic acid, sonic hedgehog, and neurotrophic factors, embryonic stem cells can be differentiated into neural stem cells, which can eventually become functional motor neurons [37]. Cell replacement can be accomplished by either activating endogenous stem cells in the CNS or transplanting stem cell-derived cells that have completed in vitro maturation [2].

CONCLUSION

Although neurodegeneration is undoubtedly the main pathology in SMA, there is mounting evidence from clinical accounts and animal research suggesting additional tissues play a role in the disease's overall phenotype, particularly in its more severe forms. Autonomic nervous system involvement, congenital cardiac problems, dysfunction of the liver, pancreas, and intestines, and metabolic deficits are additional issues that affect patients. The capacity of doctors to anticipate and manage atypical consequences that may occur owing to the load on peripheral organs as a result of extended survival is one of the most crucial factors in the treatment of SMA patients using any therapeutic approach.

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