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An In-Depth Review on Spinal Muscular Atrophy : A Neurodegenerative Disease

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ABSTRACT

SMA, or spinal muscular atrophy, is a hereditary condition. This is an inherited recessive motor neuron disorder that is brought on by a missing copy or mutation of SMN1. Generalized muscular weakness and atrophy, primarily in the proximal limb muscles, are the hallmarks of this condition. Its phenotypic is categorized into five severity degrees (SMA-0, SMA-I, SMA-II, SMA-III, SMA-IV) based on the age at which it manifests. The motor neuron 1 (SMN1) gene is the source of homozygous mutations that cause this illness. The majority of patients have homozygous deletions of the SMN1 gene, according to the diagnostic test. Testing should begin with those who are at risk, and if a positive test result is obtained, the partner should be examined further. It is advised that the management of SMA be appropriately coordinated by a specialist who can organize a multidisciplinary intervention involving pulmonary and nutrition care. The categorization, signs and symptoms, diagnosis, etiology, and therapy of SMA are the main topics of this review..

KEY-WORDS: Spinal Muscular Atrophy, Neurodegenerative, Mutation, Electromyography, Chromosomes

INTRODUCTION

An autosomal recessive neurological illness called spinal muscular atrophy (SMA) is inherited. With a frequency of 1:6,000 to 1:10,000 newborns, SMA is the second most deadly illness with this genetic profile, behind cystic fibrosis (1:6,000).[1] One in 40 to 60 persons are carriers, or heterozygotes.[2] The survival motor neuron gene 1 (SMN1), which should be found in the telomeric region of chromosome 5q13, is homozygously mutated or deleted to cause this condition. The primary factor influencing severity is the quantity of SMN2 copies, a centromeric gene that resembles SMN1 in structure.[3]

The survival motor neuron (SMN) protein has decreased as a result of this genetic modification to the SMN1 gene. Because the SMN2 gene only generates 25% of the SMN protein, it cannot fully compensate for the lack of SMN1 expression.[4] Progressive and symmetrical muscular weakness and paralysis result from the degeneration of alpha (α) motor neurons in the ventral horn of the spinal cord caused by the absence of the SMN protein.[2]

SMA is a condition that is challenging to identify and has no clear treatment plan. The diagnosis is predicated on histology and electrophysiological evidence of muscle denervation.[3] These days, molecular study used to show the absence of SMN1 gene exon 7 confirms the diagnosis. [2]

Patients with SMA need specialized treatment since it is a neurological illness that advances over time, and it can stop the disease's progression and increase the patients' lifespan. This bibliographic review article aims to assist medical professionals in making timely diagnoses and providing appropriate therapeutic support by describing the clinical and laboratory profile of SMA patients, reporting on recent genetic and molecular discoveries, and outlining the treatment prospects for the future.

SIGN AND SYMPTOMS

The patient exhibits a variety of symptoms, including:

1. Areflexia, especially in the extremities
2. Generalized muscular weakness, low tone, sluggishness, or a propensity to collapse

3. Having trouble meeting developmental milestones, having trouble standing, sitting, or walking

4. In young toddlers, assuming a frog-leg sitting posture with flexed knees and abducted hips.

5. Loss of respiratory muscle strength seen as a weak cough, a feeble scream in babies, a build-up of secretions in the throat or lungs, and respiratory distress.

6. Bell-shaped torso in severe SMA type, which results from breathing utilizing just the abdominal muscles.

7. Tongue fasciculations (twitches)

8. Trouble swallowing or sucking, inadequate nutrition [5–9]

CLASSIFICATION

SMA can be described in following types:

Type 0 SMA :

Neonatals with a history of reduced fetal movements and significant weakness and hypotonia are classified as having spinal muscular atrophy type 0. In this instance, the weakness most likely has a prenatal origin. Upon inspection, newborns with type 0 may exhibit joint contractures, facial diplegia, atrial septal abnormalities, and areflexia. Early on, respiratory failure is a serious issue. Most people don't live to be older than six months, and life expectancy is decreased [10,11].

Type I SMA:

Other names for it include acute SMA, Werdnig-Hoffmann illness, and severe SMA. Its early start (between 0 and 6 months of age), inability to learn how to sit up, and extremely short life expectancy (less than 2 years) are its defining characteristics.Children with this type of diagnosis scream softly and cough, and they have very little control over their heads. Before they turn one year old, they lose their capacity to swallow and eat. Weakness in the trunk and limbs typically extends to the intercostal muscles, preventing the development of a regular breathing cycle. The diaphragm is initially spared, despite the fact that the intercostal muscles are damaged. The risk of early mortality is usually associated with bulbar dysfunction and respiratory complications.8 Historically, these children have a short life expectancy (less than 2 years), but, thanks to improved clinical care, over recent years survival has improved. [12]

TYPE II SMA:

At some point in their development, children with type 2 SMA can sit without assistance, but they are never able to walk on their own.Developing proximal leg weakening that is more pronounced than arm weakness is typically the presenting symptom of this intermediate variant of SMA. Upon inspection, there is areflexia and hypotonia. In the context of increasing scoliosis, muscle weakness, joint contractures, and mandibular ankylosis, many of the comorbidities in this patient population are associated with orthopedic difficulties of bone and joint development. Significant restrictive lung disease can also be brought on by scoliosis and intercostal muscular weakness. These kids have normal cognitive function [13].

Type III SMA:

Kugelberg-Welander syndrome or juvenile SMA are other names for it. The exact age varies widely, although it starts after 18 months. Wirth et al. [14] have classed the condition as Type IIIa SMA if it manifests before the age of three, and as Type IIIb SMA if it manifests after that age. The maintenance of walking capacity distinguishes the two. Type IIIb people can walk for the rest of their lives, but Type IIIa patients can only walk until they are 20 years old.[15] Although they are less frequent than in Type II individuals, issues with swallowing, coughing, or nocturnal hypoventilation can still be seen. These patients may have scoliosis as they become older.

The principal characteristic of these patients is that they are able to walk independently, and life expectancy is indeterminate.[3]

Type IV SMA:

Regarding the age of onset of Type IV SMA, there is no agreement. According to Russman [3], weakness usually appears after the age of ten, however Wang et al. [16] claim that weakness typically appears in the second or third decade of life, or around the age of thirty. There are no issues with breathing or deglutition, and there is only moderate involvement of motor function. These people have a normal life expectancy and can walk normally[3,16].

ETIOLOGY

Individuals who have SMA either have a mutant or missing portion of the SMN1 gene. An intact SMN1 gene produces SMN protein. Motor genes require this protein in order to live and function correctly. Motor neurons atrophy and eventually die in

people with SMA because they do not produce enough SMN protein. Consequently, the brain is unable to regulate voluntary movements, particularly those involving the head, neck, arms, and legs. Two nearly similar SMN genes are located on chromosome 5q13: the centromeric, or SMN2, gene, and the telomeric, or SMN1 gene, which determines spinal muscular atrophy. The coding sequences of SMN2 and SMN1 differ by a single nucleotide (840C>T), which causes alternative splicing of exon 7 but does not change the aminoacidic sequence. As a result, SMN2 genes produce varying amounts of mRNA (10% to 50%, SMN-del7) that result in truncated and unstable protein, as well as a decreased the amount of full-length transcripts (SMN-fl) and protein because of the alternative splicing of exon 7. Approximately 95% of patients exhibit homozygous disruption of SMN1 due to loss or gene conversion of SMN1 to SMN2 [20]. About 3% of affected individuals are compound heterozygotes for deletion of one SMN1 allele and subtle intragenic mutations. All patients, however, retain at least one copy of SMN2, generally 2-While the severity of the loss of SMN1 is essential to the pathogenesis of SMA loss of SMN1 is essential to the pathogenesis of SMA. While type 3 and 4 generally have three or four, most SMA type I patients have two copies of SMN2, three SMN2 copies are common in SMA type II [21,22].

DIAGNOSIS[23,24]

For the SMA diagnosis In the case of a weak youngster or a floppy newborn, clinical characteristics are especially indicative. Both intelligence and attention are consistently high. Usually, there is less weakness in the arms than in the legs, and it is symmetrical and more proximal than distal. The majority of SMA diagnoses are made using the following techniques.

- **Blood test:** Using a genetic blood test, spinal muscular atrophy is diagnosed.
- **EMG test:** The Electromyography test measures the electrical activity of a muscle or set of muscles.
- **Creatin kinase test:** The elevated levels of creatin kinase are measured by this test. Degenerative muscle releases this enzyme into the circulation.
- **Biopsy:** In this test, an examiner takes a little portion of muscle tissue and sends it to a lab for analysis.

TREATMENT

Patients with SMA require a variety of specialized therapies to slow the disease's progression and extend their lives because it is a progressive neurological condition.

Since there is now no pharmaceutical therapy available, supportive treatments account for the majority of care.

Supportive therapies

A multidisciplinary team is responsible for prolonging and improving the quality of patients' lives.[25] Care covers respiratory and nutritional support.

a) Respiratory care:

A small percentage of people with type III SMA may also be impacted by pulmonary illnesses, which are the main source of morbidity and mortality in patients with SMA types I and II.[16] Fast access to specialized clinical intervention and respiratory assistance (from noninvasive ventilation to tracheostomy and mechanical ventilation) when needed are provided for these patients. Pulmonary physiotherapy and postural drainage are two highly helpful techniques for clearing the Airways and moving secretions. These patients should also be on a vaccination regimen that includes several shots against substances that might cause serious lung infections, and they also require quick access to antibiotic medication.[16, 26]

b) Nutritional care:

Diverse gastrointestinal issues, including acid reflux, constipation, abdominal distension, and delayed gastric emptying, can affect children with sickle cell disease (SMA). [25] Because reflux is linked to silent aspiration, which can exacerbate the condition even more by resulting in aspiration pneumonia, reflux is a factor in determining mortality and morbidity. Foods high in fat should be avoided as they prolong stomach emptying and raise the possibility of reflux.[16] In addition to prokinetic drugs, patient care for gastroesophageal reflux involves pharmacological therapy with stomach acid neutralizers and/or gastric secretion inhibitors, such as proton pump inhibitors and histamine blockers.[25]

Pharmacological

a) Histone deacetylase inhibitors:

Due to its capacity to stimulate SMN2 gene transcription, this class of medications has been studied for the treatment of SMA. Histone acetylation, or inhibited histone deacetylase, increases transcription factors' accessibility to multiple genes, including SMN2, thereby promoting gene transcription.

Medications with a well-established clinical use, such phenylbutyrate, sodium butyrate, and valproic acid, are examples of substances that block the histone deacetylase enzyme. This characteristic, together with the fact that their pharmacokinetics and safety profiles have already been reported, makes them promising candidates for the therapy of SMA, especially valproic acid[27,28] and phenylbutyrate[29], which have been shown to be more able to reach the Neurological System.

b) Drugs to stabilize the SMNΔ7 protein:

This group includes indoprofen[30] (non-steroidal antiinflammatory) and some aminoglycosides antibiotics, such as amikacin and tobramycin.[31] These medications have the ability to improve the SMN2 gene-derived protein's translation efficiency, resulting in a more stable protein. Regretfully, aminoglycosides and indoprofen have low CNS penetration.[32] We eagerly anticipate the creation of substances that can cross the hematoencephalic barrier without sacrificing their stabilizing ability.

CONCLUSION

Notwithstanding our significant achievement in reducing infant mortality from the most prevalent genetic illness, spinal motor neutron, there are currently no disease-modifying therapies available. There are presently a number of SMArestoring treatments undergoing early-stage clinical studies. Since the most effective medication is expensive, research is not financially feasible. For the first time in SMA history, gene therapy is making it possible to significantly alter the clinical course. Presently, further therapeutic methods are being pursued at later phases of clinical research, which will probably broaden the range of pharmacological treatments available for SMA. Patients with SMA will require more sophisticated care as a result of this. To get the most benefit from treatment, prompt diagnosis and treatment commencement are crucial. In order to do this, it's still unclear when individuals with high SMN2 copy numbers should begin therapy. During the early years of life, children with early onset SMA exhibit a greater incidence of scoliosis, even if their motor development and survival are enhanced compared to individuals with symptoms. In order to respond quickly and allow the spine to be stabilized using medical orthoses, it seems that increased knowledge of this risk and careful observation of spinal abnormalities are essential. As many braces interfere with

breathing in the more severely affected patients, choosing the ideal device can be difficult. Surgical interventions entailing 'growing rod' systems have been reported to be feasible in children with SMA1. Further experience in this field however is needed to balance the risks and benefits of these interventions. There are orthopedic devices for example standing frames – have not been used in most SMA type 1 patients, but they appear promising for the prophylaxis of joint contractures and to allow age-appropriate positioning even in more severely affected patients.This evaluation might serve as a resource for improving SMA management. Considering the recent progress in treating SMA with drugs, given that many patients still have a substantial disease burden after receiving medication.

CONFLICT OF INTEREST

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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