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Review Article

A review on spinal muscular atrophy: An inherited neuromuscular disease

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ABSTRACT

Spinal muscular atrophy is an inherited neurodegenerative illness characterized by muscle wasting and loss of spinal cord motor neurons. It results from homozygous loss, translation, or mutation of the survival motor neuron 1 (SMN1) gene. 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. Several stages of development have been recognized for a number of possible therapeutic agents. The standard of treatment for people having spinal muscular atrophy has evolved as a result of these and other healthcare technological advancements. In this review, we provide a comprehensive review of general introduction, types, symptoms, causes, diagnosis, and possible management of spinal muscular atrophy (SMA).

1. Introduction

A hereditary condition known as spinal muscular atrophy causes wasting and weakening in the muscles that allow for movement (skeletal muscles). It is brought on by the disappearance of specific nerve cells known as motor neurons, which regulate muscular action. As compared to muscles farther from the body's Centre, the weakening is often more pronounced in the proximal (near to the body's centre) muscles (distal). Age typically makes the muscular weakness worse. The same genes can alter in a variety of ways to induce spinal muscular atrophy. There is crossover seen between kinds, though they differ in terms of muscular weakening severity and age of start. Other types of spinal muscular atrophy and associated motor neuron diseases, including X-linked infantile spinal muscular atrophy and spinal muscular atrophy with bronchial discomfort type 1, are brought on by gene mutations. These conditions include spinal muscular atrophy with accelerated myoclonic epileptic seizures, spinal muscle atrophy with lower extremity predominance, and spinal muscle atrophy to lower extremity weakness.[1,2]

The survival motor neuron 1 gene (SMN1) on the fifth chromosome is primarily responsible for the majority of SMA variants, which impair the production of the SMN protein.[3] The survival motor neuron (SMN) gene codes for the production of the SMN protein. The spinal cord has the largest concentrations of the SMN protein, which is present throughout the body. The SMN complex, which includes this protein as one of its components, is crucial for the upkeep of certain cells known as nerve cells. The spinal cord and the area of the brain that connects to the spinal cord both contain these cells. The brain and spinal cord

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provide messages to motor neurons, which then instruct the skeletal muscles to tense (contract), allowing the body to function.[4,5]

SMA affects one in every 6,000 newborns. It is a common genetic condition that affects young kids and a leading cause of infant mortality. SMA may affect kids of any age. While patients who experience symptoms later in childhood or in adolescence often have a better prognosis, SMA in infancy and earlier life is linked to poorer results.[3]

Due to severely weak intercostals muscles in people with spinal muscular atrophy (SMA), regular breathing pattern is compromised. This can lead to shallow breathing or apnoea, especially during sleep, as well as weak and undeveloped lungs.[6]

2. Types of SMA

2.1. Type 1 (Severe)

60% of SMA patients have type 1, also known as Werdnig-Hoffman illness. A baby's initial six months of existence are when symptoms first manifest, or at birth. Babies having type 1 SMA have trouble sucking and swallowing. Kids don't reach common developmental stages including sitting or holding their heads up. Children are more likely to have lung infections and damaged airways as their muscles continue to deteriorate. Usually babies having type 1 SMA pass away before turning two.

2.2. Type 2 (Intermediate)

Type 2 SMA symptoms, commonly known as Dubowitz disease, start to show in infants between the six to eighteen months of age. Lower limbs are typically affected by this type. Although being unable to walk, children having type 2 SMA may be capable of sitting up. Most kids having type 2 SMA go on to reach adulthood.

2.3. Type 3 (Mild)

Type3 SMA symptoms, also known as Kugelbert-Welander or juvenile-onset SMA, start to show once a kid becomes 18 months old. Some type 3 peoples don't show symptoms until they are young adults. Mild muscular stiffness, trouble walking, and recurrent lung infection are examples of type 3 symptoms. Symptoms might eventually make it difficult to stand or move. Life longevity is not greatly decreased by Type 3 SMA.

2.4. Type 4 (Adult)

The uncommon adult version of SMA often does not manifest until the mid - thirties. Most persons with type 4 stay active and lead full lives despite the gradual progression of muscle weakening symptoms.[7,8]

Fig. 1: Common types of spinal muscular atrophy[9]

3. Causes[10,11]

All of the aforementioned kinds of spinal muscular atrophy are brought on by alterations in the SMN1 gene. The severity of the problem and which kind develops are influenced by the quantity of copies of the SMN2 gene.

The survival motor neuron (SMN) protein is synthesized using instructions from the SMN1 and SMN2 genes. The SMN1 gene typically produces the majority of functional SMN protein, while the SMN2 gene only produces a minor amount. The SMN2 gene generates many copies of the SMN protein, but only one of these copies is functional; the others are smaller and degrade more quickly. The SMN complex, which includes several other proteins including the SMN protein, is crucial for the upkeep of motor neurons. The spinal cord and brain provide messages to motor neurons, which then instruct the skeletal muscles to twitch, allowing the body to function.

The SMN1 gene is typically faulty in individuals with spinal muscular atrophy, which reduces the ability of the body to produce SMN protein. A lack of SMN protein causes motor nerve death, which prevents messages from being sent from the brain to the muscle cells. The signs and symptoms of spinal muscular atrophy are caused by the weakening and atrophy of numerous skeletal muscles, which occur because muscles cannot function without impulses from the brain.

Normally, every cell in an individual's body contains two copies of the SMN1 gene & one to two copies of the SMN2 gene. Some individuals have up to eight copies of the SMN2 gene, however this number fluctuates. Having several copies of the SMN2 gene is often associated with less serious characteristics of spinal muscular atrophy that appear later in life. The protein shortage brought on by SMN1 gene mutations can be partially compensated for by the SMN protein generated by the SMN2 genes. One copy of the SMN2 gene is typically present in each cell of individuals with spinal muscular atrophy type 0, compared to one or two copies in cells of individuals with type I, three copies in cells of individuals with type II, three or four copies in cells of individuals with type III, and four or more copies

in cells of individuals with type IV. The varying degree of spinal muscular atrophy is also influenced by other, mostly unidentified causes.

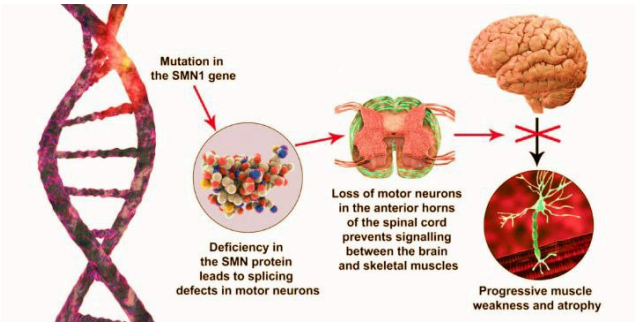

Fig. 2: Pathophysiology of spinal muscular atrophy [12]

4. Symptoms

The kind, intensity, and age at which SMA develops all affect the disease's symptoms. Typical signs include:

1. Muscular spasm and stiffness
2. Respiration and swallowing challenges
3. Muscular weakening that results in alterations to the form of the limbs, spine, and chest
4. Standing, moving, and sitting maybe uncomfortable

Babies with SMA type 1 have weaker limbs, low muscular tone, and difficulties in breathing and eating at birth. SMA type 3 symptoms might take up to a year to manifest in infants. Muscle atrophy and weakening are SMA's hallmarks in all of its manifestations. They happen as a result of the muscles' inability to receive the signal to contract from the motor neurons, the nerves that regulate movement. The muscles that are closest to the body's core are typically affected by the weakening. Normally, motor neurons' axons transmit these signals from the spinal cord to the muscles. Either the motor neuron or the axon itself ceases functioning in SMA. Being a progressive condition, SMA's symptoms usually get worse with time. [13]

Fig. 3: Common symptoms of spinal muscular atrophy [14]

5. Diagnosis

The preferred method for diagnosing SMA is molecular genomic analysis. Every newborn with weakness or hypotonia should be given early evaluation due to the effectiveness of molecular testing and the high frequency of SMA in the hypotonic or "floppy" infant. All other newborn causes of hypotonic weakness are included in the differential diagnosis of serious types of SMA. Muscular biopsy and electrodiagnostic examination used to be common assessment procedures, but now that molecular testing is widely accessible, these and other diagnosing examinations (such as MRI) are typically not required. [15]

5.1. Molecular diagnosis

Significantly, genetic screening for homozygous loss will confirm the condition in 95% of individuals with SMA, regardless of the severity of the disease, as individuals having SMA have homozygous impairment of activity of both SMN1 copies. [16] Almost all other SMN-related SMA patients will be compound heterozygotes, meaning that one copy of SMN1 has been deleted and the other copy has undergone a frameshift, nonsensical, or missense alteration. [17] Hence, SMN1 dosage analysis (to check for deletion of 1 copy) and decoding of the remaining SMN1 gene (to check for a mutation) should be carried out in a patient with suspected SMA if homozygous SMN1 loss is not obvious. Only one case with SMA and an accompanying homozygous dual variation in the SMN1 gene has been documented. [18]

5.2. Other testing modalities

Before to the development of molecular analysis, it was crucial to evaluate suspicious SMA using various diagnostic techniques to show the existence of nerve injury, such as electrodiagnostic examinations and muscle biopsy. The examination of atypical patients or patients who test negative for both SMN1 deletion and SMN1 mutation analysis should now generally exclusively use electrodiagnosis. Muscular biopsy is no more necessary since electrodiagnosis can more clearly show the characteristics of denervation. It is crucial to prevent intrusive and unneeded testing due to the prevalence of SMA and the effectiveness of genetic analysis. [19–21]

6. Management: [22–26]

Three drugs—nusinersen (Spinraza), onasemnogene abeparvovec-xioi (Zolgensma), and risdiplam (Evrysdi)—have received FDA approval to treat SMA

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6.1. Nusinersen (Spinraza)

The SMN2 gene is modified by this therapy, enabling it to produce more protein. All children and adults having SMA can utilise it. The medication will be injected by doctor into the spinal fluid. This will need to be performed numerous times, taking at least 2 hours into account preparation and recuperation time, and will thereafter need to be repeated every 4 months. According to studies, it strengthens patients and slows the sickness in roughly 40% of patients.

6.2. Abeparvovec-xioi onasemnogene (Zolgensma)

This replaces the problematic SMN1 gene. Children less than 2 years old can utilise it. The expert will insert a catheter—a thin tube—directly into a vein in hand or arm (an IV). Then, and use a tube to introduce a copy of the SMN gene into a particular collection of motor neuron cells. There will only need to be one instance of this. According to research, onasemnogene abeparvovec-xioi boosted kids with SMA achieve functional goals including head control and unassisted sitting more quickly.

6.3. Risdiplam (Evrysdi)

With the use of this medication, the SMN2 genes are prevented from interfering with the manufacturing of proteins, enabling the protein to access the neurons as required. Patients consume it orally once day, following a meal. In clinical studies, 41% of people taking it after a year had increased muscular performance.

In addition to gene therapy, doctor could advise the following approaches to treat the symptoms:

6.4. Movement

Workout and consistent regular exercises used in physical and occupational therapy can assist safeguard a patient's joints and maintain muscular strength. A therapist could advise using a walker, an automated wheelchair, or leg braces. In addition to helping with writing and sketching, specialized gadgets can operate phones and computers.

6.5. Breathing

Poor muscles keep air from passing readily into and out of the airways in SMA, particularly types 1 and 2. If a youngster experiences this, they could require a unique mask or mouthpiece. Children with serious issues may utilize a breathing assistance device.

6.6. Nutrition and swallowing

Babies and kids with SMA may struggle to suck and swallow when their mouth and vocal muscles are poor. Child might not receive a healthy diet in that scenario and might struggle to develop. Doctor could advise consulting a dietician. Some infants could require a feed intake tube.

6.7. Back problems

Children may develop a spine curvature if SMA begins in childhood. When the child's spine is yet developing, a doctor may advise wearing a back brace. They could have operations to address the issue once they finish developing.

7. Conclusion

The largest prevalent inherited condition affecting spinal motor neurons is SMA. It is the largest frequent hereditary cause of child mortality, and it can appear at any moment, from before birth to maturity, with different seriousness and illness effect. Despite the fact that the causal gene was discovered approximately 20 years ago, there are currently no disease-modifying medications accessible. Yet, well planned supporting care may diminish illness burden and enhance comfort of life. Nonetheless, supportive care still has to be improved. Our understanding of the biological effects of SMN decrease has advanced significantly, but the pathogenic mechanism of SMA—the process by which low levels of SMN protein cause the selective death of motor neurons—remains unknown.

8. Conflict of Interest

The authors declare no conflict of interest

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None.

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