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# Spinal Muscle Atrophy: A Costly Battle against a Rare Genetic Disorder Worth 16 Crore

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***Abstract***

Spinal muscle atrophy is a disease of inheritance due to homozygous deletion of survival motor neuron gene 1 (SMN1) in the brain stem and spinal cord indicated as slowly advancing muscular dysfunction and atrophy. The 95% of cases reported of spinal muscle atrophy (SMA) depict deletion of the SMN1 gene. Targeted therapeutic strategies to combat SMA mainly focus on enhancing the level of full-length SMN protein. Currently, three drugs approved by FDA are Nusinersen, Zolgensma, and Risdiplam for treating SMA. With the advent These drugs have transformed the therapeutic approach of managing the fatal genetic disorder, treating number of patients worldwide along with the active participation of the organizations raising funds for the affected patients.

## Introduction

Spinal muscle atrophy is a rare hereditary condition characterized by the degeneration of lower motor neurons in the anterior horn of the spinal cord and brain stem nuclei which results in debility and wasting of muscles. It is thought to be the primary genetic contributor of neonatal deaths. SMA affects approximately one in 10,000 to 20,000 live births, and the carrier frequency in the general population ranges from 1/40 to 1/70. The First clinical manifestation of spinal muscle atrophy dates back to 19th century when Austrian neurologist Guido Werdnig reported symptoms resembling SMA in 2 infant brothers in 1891 and 7 additional cases were reported by Johan Hoffmann from 1893 to 1900. SMA is an incurable disease and till now no therapeutic has proven 100% effective to cope with this fatal condition. However, the identification of the disease-causing gene SMN1, has led to significant advancement in our knowledge of the molecular pathophysiology of this condition which in turn have opened new door for the impending advancement in therapeutic approaches to fight against this deadly disease (Nishio *et al*., 2023).

### *Case reports of SMA*

A girl named Teera from Mumbai was diagnosed with the rare genetic disorder SMA at 2 months of age. As the disease progressed, she was unable to perform basic functions like sitting, swallowing, or even



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breathing due to dysfunction of the nerve cells. She was advised to undergo gene replacement therapy with Zolgensma, a drug made by Novartis. Her parents started raising funds for this single shot gene therapy through digital platforms and they successfully managed to raise Rs. 18 crores, which helped the patient recover from the fatal disease.

Similarly, another incidence of SMA was reported in June 2021, affecting a one-year-old kid named Zainab who needed the expensive, powerful medicine Zolgensma to combat this fatal genetic condition. Her parents lost one of their children to SMA in 2018. This time, Zainab's father came to know about some children that had survived SMA after getting Zolgensma. He entered his daughter's name with Cure SMA, a foundation that raises funds to treat SMA, and fortunately, her daughter received the miraculous medicine Zolgensma through a lottery ticket, saving the girl.

***Molecular genetics of SMA***

The distinctive genetic profile is the primary cause behind the special attention given to SMA by research institutions, pharmaceutical industry, and specialized programs from the NIH. Genetic alterations like mutation or deletion that affect the SMN1 gene are primarily responsible for SMA. This SMN1 gene is located at 5q13 position on chromosome 5 (Melki *et al.*, 1994). This area is center for chromosomal rearrangement, comprises a 500 kb inverted repeat along with locus for the telomeric SMN1 and centromeric SMN2 genes, these genes show substantial similarity (Gilliam *et al*., 1990) (Figure 1). The occurrence of SMA is manifested when either there is SMN1 gene deletion (both copies), or conversion to SMN2 by genetic recombination (Boda *et al*., 2004). Although SMN2 and SMN1 both have a similar potential to code for proteins but exon 7 of SMN2 has a translationally silent mutation that is C to T alteration which leads to activation of different pathway of mRNA maturation and thus exclude exon 7 (Lorson *et al*., 1999). The entire length of SMN protein is translated from almost 95% of SMN1 mRNA which includes exon7 while around 85% of SMN2 mRNA lacks exon7 leading to compressed form of the protein (SMNΔ7) (Gavrilov *et al*., 1998). As this compressed SMNΔ7 protein lacks stability thus cannot fulfill the deficiency of normal SMN protein (Burnett *et al.*, 2009).

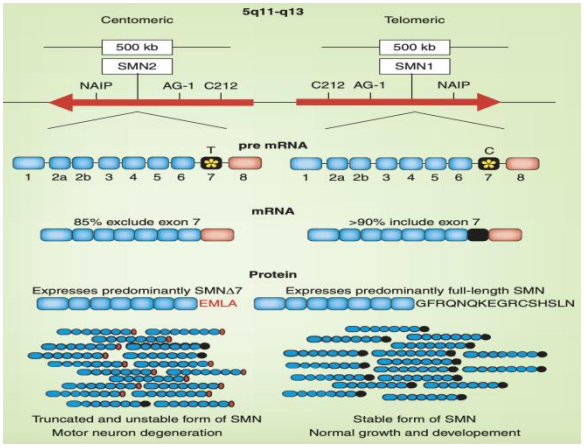


**Figure 1**: The figure depicts the position, mRNA Splicing and the protein expression of SMN1 and SMN2 gene (Cherry and Androphy, 2012).

***Classification Of SMA***

The extent of SMA can vary greatly, from severe instances that appear in infants and early childhood to milder forms that may not show symptoms until adolescence (Figure 2). Depending on the age of onset and the level of muscle weakness, the disease can be categorized into 4 main types:



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1. **Type 1** is the most severe one and is often referred to as Werdnig-Hoffmann disease. Infants suffering with Type 1 SMA cannot sit unassisted and has been found to be fatal at <2 yrs.
2. **Type 2** also known as Intermediate SMA, occurs between six and eighteen months of age characterized by infants that can sit unsupported and has been found to be fatal at >2 yrs.
3. **Type 3** is the mild one and is often referred to as Kugelberg-Welander Disease. Infants suffering with Type 3 SMA can stand and walk unassisted and has been found to be fatal in adulthood.
4. **Type 4** SMA, the mildest form of SMA, frequently manifests in adults.

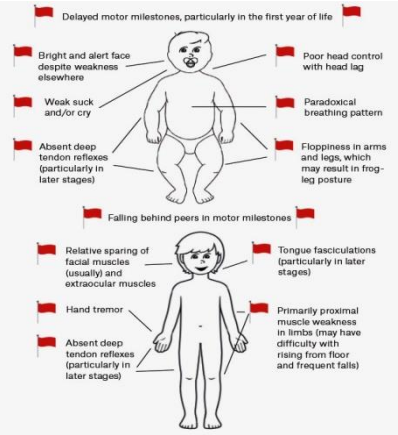


**Figure 2**: Clinical signs of SMA in infants and children (Davidson and Farrar, 2022).

***Therapeutic Strategies to combat SMA***

The unraveling of the inheritance of SMA provides valuable insights into understanding the pathogenesis of SMA which in turn forms the basis for the development of novel therapeutics to combat this fatal condition. The distinct architecture of the SMN genes enables development of a potential therapeutic strategy by altering the SMN2 gene's expression in SMA patients in order to enable these SMN2 copies to operate similarly to the SMN1 gene (Figure 3). This concept inspired the scientific community to look for approaches to enhance the SMN proteins expression by altering SMN2 mRNA through exon 7 inclusion, decreased alternative splicing, increased SMN2 transcription through promoter activation, regulation of SMN protein translation, and diminished SMN protein breakdown. In this regard, the identification of endogenous transcription factors altering SMN2 gene expression was extremely intriguing. One such discovery of Htra2-β1, a splicing factor facilitated full-length SMN2 expression by interaction of Htra2-β1 with an exon-splicing enhancer sequence on exon 7. This revelation prompted for investigation of innovative lead compounds which can activate endogenous splicing factors, such as Htra2-β1 thus facilitating the inclusion of exon 7 during SMN2 mRNA maturation.

Currently, available therapies try to address the underlying genetic etiology of SMA, which is a lack of the SMN protein as a result of mutations in the SMN1 gene. The key therapeutic approaches for SMA include:

1. Gene Replacement Therapy: Onasemnogene Abeparvovec, also known as Zolgensma, is the therapeutic candidate that first used gene therapy to treat SMA. FDA has approved this single-dose gene therapy for use in children under the age of two. It uses an AAV9 capsid vector to deliver a functional copy of the SMN1 gene to the motor neuron cells in the central nervous system. It is given as an i/v infusion. Zolgensma has shown exceptional benefits in terms of increasing motor function and survival in newborns with SMA,



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especially Type 1 SMA (Stevens *et al*., 2020). It is the costliest medicine in the entire globe. The development of Zolgensma by Novartis Gene Therapies has received British government approval produced by Novartis, a multinational pharmaceutical firm located in Switzerland. According to the official announcement from NHS England, the medicine costs Rs. 18 crores for every dose.

2. SMN Protein Modulating agents: Nusinersen (Spinraza) is an antisense oligonucleotide that alters the SMN2 gene's splicing to increase the synthesis of entire SMN protein. It is administered through intrathecal injection and associates with a specific sequence in SMN2 mRNA which in turn leads to alteration in SMN2 gene's splicing. It is the first ever therapeutic approved by FDA for treatment of SMA, Spinraza has shown significant improvements in motor function and survival (Meylemans and Bleecker, 2019). Other than Nusinersen, Risdiplam (Evrysdi®) is a first oral SMN2 splicing modifier that increases the synthesis of entire SMN protein. It is authorized to treat SMA in patients above 2 years of age and has shown positive outcomes in phase 2/3 clinical trials in patients suffering from TYPE1 SMA, leading to its approval for SMA treatment in various countries (Paik, 2022).
3. Neuromuscular Support and Symptomatic Care: Supportive care measures are essential for controlling symptoms and enhancing the quality of life even though they do not directly address the genetic basis of SMA. These include orthopedic interventions, dietary management, respiratory assistance, physical therapy, and occupational therapy (Cherry and Androphy, 2012).

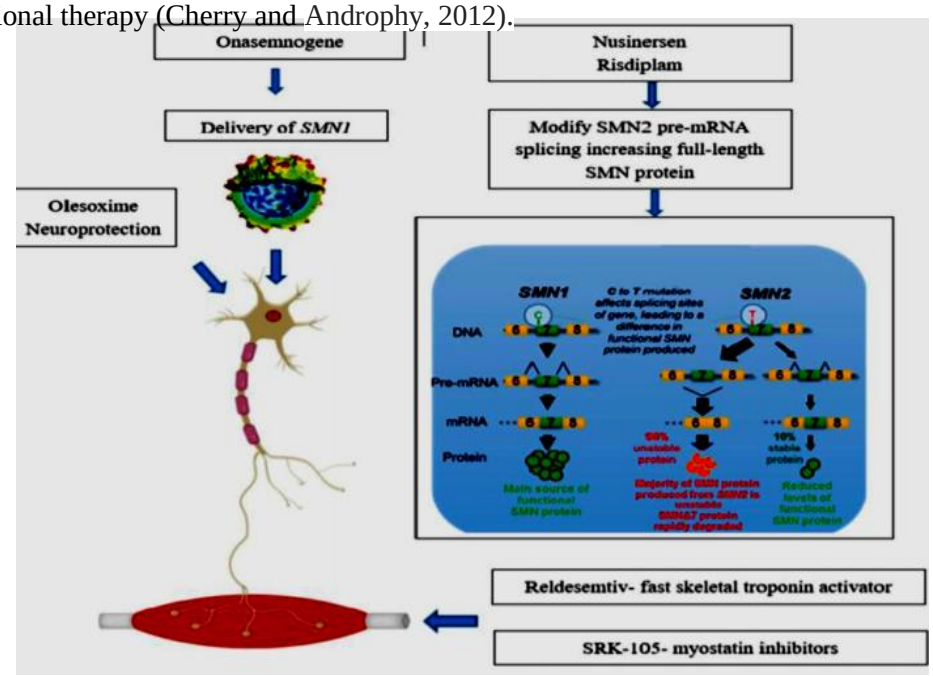


**Figure 3:** Mechanism of different drug therapies: Nusinersen, Zolgensma, and Risdiplam (Vengurlekar *et al*., 2021).

## Conclusion

Spinal muscle atrophy is a uncommon hereditary condition of SMN in the brain stem and spinal cord. It is the main genetic contributor to neonatal fatality. SMA is an untreatable hereditary disease, however, since the identification of SMN gene 27 years ago, numerous studies have been carried out all over the world to make this fatal disease curable to some extent using Zolgensma or Spinraza. Numerous programs to raise funds for kids with SMA are ongoing in order to deal with the enormous financial load brought on by these therapies.



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