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Review Article

Spinal Muscular Atrophy : A Clinical Review

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ABSTRACT

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder that primarily affects motor neurons, leading to progressive muscle weakness and atrophy. It is caused by mutations in the SMN1 gene, which result in reduced levels of the survival motor neuron (SMN) protein, essential for muscle function. SMA presents in different types, ranging from severe infantile-onset forms to milder adult-onset cases, with symptoms affecting mobility, breathing, and motor development.This clinical review provides an overview of SMA's genetic basis, classification, symptoms, and diagnostic methods. It also examines advancements in treatment strategies, including gene therapy (such as onasemnogene abeparvovec), SMN2 splicing modifiers (like nusinersen), and supportive care to improve quality of life. The review further highlights challenges in early diagnosis, accessibility to therapies, and the importance of newborn screening programs for better outcomes. The goal is to offer a comprehensive understanding of SMA to inform clinicians, caregivers, and public health practitioners on effective disease management and emerging therapeutic options.

INTRODUCTION

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder characterized by the progressive loss of alpha motor neurons in the spinal cord. This degeneration leads to increasing weakness and paralysis of the muscles closest to the body's center. The condition was initially described in the 1890s by researchers Werdnig and Hoffmann. The genetic cause was identified a century later, in 1995, when scientists located the defect to a specific region on chromosome 5 (5q11.2-q13.3) and identified the survival motor neuron (SMN) gene as the culprit [1,2].

Overview:

1. Genetic Basis: SMA is inherited in an autosomal recessive pattern and is primarily caused by mutations in the SMN1 gene located on chromosome 5q13.2. The most common mutation is a deletion of exon 7 in SMN1, leading to a deficiency of the SMN1 protein.The SMN1 and SMN2 genes are nearly identical, but a key difference is a C to T transition in exon 7 of

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SMN2 [2]. This transition results in the majority of SMN2-derived mRNAs producing a truncated, nonfunctional SMN protein. However, 10-15% of SMN2 mRNAs retain exon 7, producing some functional SMN protein. [4].

2. Phenotypic Variability: The severity of SMA symptoms correlates inversely with the number of SMN2 gene copies. Patients with more copies of SMN2 typically experience a milder form of SMA.SMN2's role in producing some functional SMN protein partially compensates for the loss of SMN1, which explains some of the variability in disease severity among patients [5].

3. Clinical Implications:SMA severity generally varies with SMN2 copy number, with four or more copies being associated with a milder phenotype.Despite this compensation, the presence of SMN2 does not fully account for the range of clinical manifestations seen in SMA. [7].

Clinical description and Classification

1. Type I SMA (Severe SMA, Werdnig Hoffmann Disease, Acute SMA):

Onset: Between 0 and 6 months of age.

Motor Function: Infants cannot sit up independently; very limited head and trunk control; cannot swallow or feed well [12].

Life Expectancy: Historically less than 2 years due to severe respiratory complications and bulbar dysfunction, though survival has improved with advancements in care [15].

Symptoms: Weak cry and cough, progressive weakness of trunk and limbs, limited respiratory function due to involvement of intercostal muscles [16]

2. Type II SMA (Chronic SMA):

Onset: Between 6 to 18 months, but can be earlier.

Motor Function: Can sit up with or without support; may stand with support but cannot walk.[5]

Life Expectancy: Approximately 10 to 40 years.

Symptoms: Difficulty with swallowing, reduced weight gain, problems with coughing, scoliosis, and contractures. Fasciculations (muscle twitches) are also common.[9]

3. Type III SMA (Juvenile SMA, Kugelberg-Welander Syndrome):

Onset: After 18 months of age; divided into Type IIIa (onset before age 3) and Type IIIb (onset after age 3).[10]

Motor Function: Type IIIa patients can walk until about 20 years old; Type IIIb patients may walk for their whole lives.[13]

Life Expectancy: Indeterminate; generally good, with fewer respiratory and swallowing issues compared to Types I and II.[17]

Symptoms: Possible scoliosis development, less severe issues with swallowing or coughing, but independence in walking is a key characteristic.[13]

4. Type IV SMA:

Onset: Emerges after age 10, sometimes as late as 30 years.

Motor Function: Mild motor function impairment; patients retain the ability to walk.

Life Expectancy: Normal.[26]

Symptoms: No significant issues with swallowing or respiration; overall mild motor function involvement.[22]

Type	Age of on set	Severity	Life expectancy
Type I	0-6 months	Never sit	<2 years
Type II	7-18 months	Could sit, Never stand	>2 years Adults
Type III	>18 months	Stand and walk	Adulthood
Type IV	Adult	Walk during Adulthood	Adulthood

Table no 01

History of SMA:-

Historical Evolution of SMA Research

The history of spinal muscular atrophy (SMA) research can be segmented into three key periods:

1. **Early Period (1891–1994):** This phase marks the discovery of SMA and includes the initial

classification of clinical subtypes as well as the chromosomal mapping of the SMA locus.[14]

2. **Developmental Period (1995–2015):** During this era, significant advances included the cloning of the SMN genes. This period also saw drug repositioning efforts and the development of novel drugs aimed at treating and potentially curing SMA.[24]

3. **Modern Period (2016–Present):** This current phase began with the approval of the first SMA drugs by the FDA and includes advancements in newborn screening technologies for early diagnosis.[25]

In this article:

- Section 2 explores the Early Period.
- Sections 3, 4, and 5 detail the Developmental Period.
- Sections 6, 7, and 8 cover the Modern Period.

Figure 1. Milestones in SMA Research :-

- **1891:** The initial identification of spinal muscular atrophy (SMA) occurred when Werdnig documented the first two cases, initiating the clinical study of this disease. Subsequent research revealed a wide range of SMA phenotypes.[14]
- **1995:** The identification of the genes SMN1 and SMN2 marked a pivotal moment in SMA research. SMN1 is crucial for the development of SMA, while SMN2 functions as a modifier that affects disease severity. This genetic discovery laid the foundation for innovative drug development.[16]
- **2016:** The FDA granted approval for nusinersen, the first therapeutic agent for SMA, marking a significant step forward in treatment options.[23]
- **2019:** The FDA approved onasemnogene abeparvovec, a groundbreaking gene therapy that offered a new treatment approach for SMA.[8]
- **2020:** Risdiplam was approved by the FDA as an additional therapeutic option, expanding the range of available treatments for SMA.[20]

History of SMA

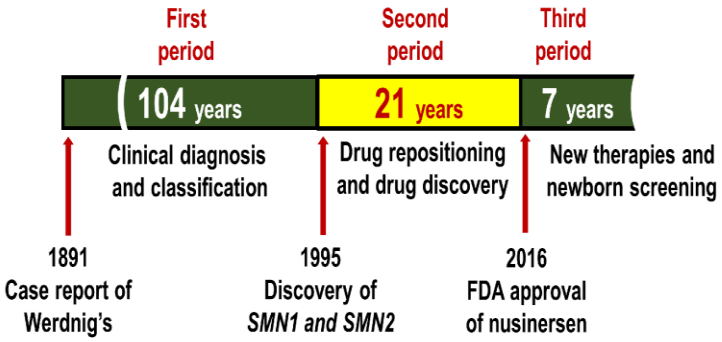

Fig 1: History of SMA

- **Signs and symptoms :-** The symptoms of severe SMA Type 0/I can vary based on the specific type of SMA, the disease's progression, and individual factors. The following signs are typically observed in this severe form:[18]
- **Absence of Reflexes:** Particularly noticeable in the extremities, indicating a lack of normal reflex responses.[9]
- **Muscle Weakness and Tone:** Marked by overall weakness, poor muscle tone, and a tendency to be limp or floppy.[30]
- **Delayed Motor Development:** Challenges with reaching developmental milestones such as sitting, standing, or walking.[7]
- **Characteristic Sitting Posture**: In small children, a distinctive "frog-leg" position with hips spread and knees bent while sitting.[15]

Respiratory Muscle Weakness: Reduced strength in the muscles responsible for breathing, leading to weak coughing and crying in infants, as well as potential accumulation of secretions in the lungs or throat, and difficulty breathing.[16]

Bell-Shaped Torso Appearance: A pronounced abdominal area resulting from the reliance on abdominal muscles for breathing in severe cases.[7]

Tongue Fasciculations: Visible twitching of the tongue.[22]

Feeding Difficulties: Issues with sucking, swallowing, and general poor feeding.[10]

SMA Diagnosis:-

Genetic Testing: SMA is primarily confirmed through genetic analysis, which detects the homozygous deletion of the SMN1 gene in over 95% of cases. For the remaining cases, genetic testing reveals a compound mutation in the SMN1 gene.[10] Typically, this testing involves a blood sample. Multiplex Ligation-dependent Probe Amplification (MLPA) is a commonly used technique for this purpose, as it not only identifies SMN1 gene mutations but also measures the number of SMN2 gene copies, which holds clinical relevance.[10]

Symptomatic Diagnosis: In cases where genetic testing is not immediately conclusive, SMA can be diagnosed symptomatically, particularly in children with acute forms of the disease.[12] Key symptoms include progressive disease progression, paradoxical breathing patterns, low muscle tone in both legs and arms, and absent tendon reflexes.[12]

Early Detection: Detecting SMA at an asymptomatic stage is essential for effective intervention. Early diagnosis enables the prompt introduction of causative treatments, potentially preventing or mitigating the development of symptoms and improving patient outcomes.[12]

Tretment :-

Overview of SMA Treatments

Nusinersen (Spinraza)

Approval: In December 2016, the FDA approved nusinersen as the first treatment for spinal muscular atrophy (SMA) in both children and adults.[15]

How It Works: Nusinersen helps increase the production of a protein called SMN, which is missing in people with SMA due to genetic mutations.[5]

Clinical Trials:

o Endear Trial: In infants with Type 1 SMA, 40% of those treated with nusinersen reached key motor milestones, compared to none who received a placebo. The treatment also reduced the death rate.[18]

o Cherish Trial: In children with later-onset SMA, those treated with nusinersen showed significant improvement in motor skills over 15 months.[18]

Onasemnogene Abeparvovec (Zolgensma)

Approval: This gene therapy is for children aged 2 or younger with Type 1 SMA.[13]

How It Works: It delivers a working copy of the SMN gene using a virus.

Clinical Trials:

o In trials, all treated patients were alive and healthy at 20 months, compared to a much lower survival rate in historical data.

o Patients showed significant improvements in motor skills, like sitting and rolling over.[13]

Risdiplam (Evrysdi)

Approval: This treatment is for SMA types 1, 2, and 3 in people 2 months and older.[14]

How It Works: It modifies the way the SMN2 gene works to produce more SMN protein.[16]

Clinical Trials:

o **Firefish Trial:** In infants with Type 1 SMA, many were able to sit up and most survived without needing ventilation after 12 months.[9]

o Sunfish Trial: Older children showed meaningful improvements in motor function.[17]

Other Therapies

 Some older medications were tested but did not show significant benefits for SMA patients.

 Supportive treatments focus on improving quality of life and independence, including physical therapy and nutritional support.[21]

 Prognosis And Management Of Spinal Muscular Atrophy (SMA):-

 Prognosis:-

Type 0/I: Severe form, often leading to significant motor and respiratory issues early in life. Life expectancy can be limited, but treatments have improved outcomes.[25]

Type II/III: Intermediate forms, with a range of severity. Many individuals live into adulthood and can maintain good quality of life with proper care.[9]

Type IV: Mild form, with a slower progression. Most individuals have a near-normal life expectancy and quality of life.[10]

Management:-

• **Medical Treatments:**

- Use medications like Spinraza, Zolgensma, and Evrysdi to address the disease's underlying cause.

• **Physical and Occupational Therapy**:

-Physical Therapy: Helps maintain muscle strength and mobility.

-Occupational Therapy: Assists with daily activities and improving function.

• **Respiratory Care:**

- Support for breathing issues, including respiratory devices and techniques.

• **Assistive Devices:**

- Use of wheelchairs, braces, and other aids to support mobility and daily tasks.

• Regular Monitoring: - Frequent check-ups to manage symptoms and adapt treatments as needed.[23]

 Rational Of Work:-

Aim of work :

This review aims to clearly examine Spinal Muscular Atrophy (SMA) by looking at its genetic causes, symptoms, and how it is diagnosed. It will also assess current treatments and recent developments in therapy.

1.Patient and Family Support: Offers valuable information for patients and families, helping them understand the condition and available resources.

2.Evaluate Treatment Options: Analyze the efficacy and safety of existing and emerging treatment modalities, enabling clinicians to make informed choices for their patients.

3.Educational Resource: Provides healthcare professionals, researchers, and students with a comprehensive understanding of SMA, including its genetics, clinical features, and treatment options.

4.Awareness Raising: Increases awareness of SMA among healthcare providers and the general public, promoting earlier recognition and intervention.

Objectives:-

1.Understand Genetic Causes: To explore the specific genetic mutations that lead to SMA and their effects on motor neuron health.

2.Review Diagnostic Techniques: To evaluate the current diagnostic criteria and methodologies, including genetic testing and neurophysiological assessments, for effective identification of SMA.

3.Evaluate Diagnostic Approaches: To review current diagnostic criteria and methods, including genetic testing and clinical assessments, for accurate identification of SMA.

4. Discuss Impact on Quality of Life: To explore how SMA affects the daily lives, emotional well-being, and social interactions of patients and their families.

 Litrature review :

Jablonka, S., Hennlein, L., & Sendtner, M. et al (2022) : RNA-based therapies offer chances for therapy development of complex neurodegenerative disorders such as amyotrophic lateral sclerosis, muscular dystrophies, Parkinson's and Alzheimer's disease. The experiences made with these new drugs for SMA, and also the

experiences in AAV gene therapies could help to broaden the spectrum of current approaches to interfere with pathophysiological mechanisms in neurodegeneration.

Keinath, M. C., Prior, D. E., & Prior, T. W.et al (2021): The most robust response to SMA treatments has clearly been shown to occur in treating presymptomatic patients. Thus, early detection through newborn screening is paramount to ensuring efficient treatment access prior to manifesting symptoms of the disease. [16]Prenatal cases identified as a result of carrier screening will also allow for early treatment. Biomarkers and outcome measures to assess disease response to therapy are needed, particularly in determining use of additional or combination treatments. Future research is needed to understand the long-term effects of the therapies alone or in combination.

Messina, S., Sframeli, M., Maggi, L., D'Amico, A., Bruno, C., Comi, G., & Mercuri, E. et al(2021): Spinal muscular atrophy is a motor neuron disease of infancy, childhood and adulthood and the genetics and pathophysiology has received extensive study over the last twenty years. This increased focus has led to an improvement of our understanding of the natural history of the many sub-types of SMA and to the development and distribution of standard-of-care recommendations. The dramatic preclinical results in SMA models systems, has also led to incredible cooperation between clinicians, scientists, government, industry, and volunteer organizations on an international scale to develop the guidelines needed for clinical trial readiness.

Schorling, D. C., Pechmann, A., & Kirschner, J.et al (2020). We are facing an exciting era with three available therapeutic options in a disease considered incurable for more than a century. NBS leading to early treatment is vital to provide optimal care. Each therapeutic strategy has its weaknesses and strengths and clinicians need to know them to optimize clinical care. Once these approaches will be available for all SMA types, the final choice will be based on patient's clinical features and compliance and on the feasibility of drug administration. Since post-symptomatically treated patients are not cured, patients and parents ask for combined approaches. Additional therapies to complement present and forthcoming *SMN*-targeted treatments are needed in order to optimize their effects. Combinations of different drugs that increase *SMN* level or with muscle enhancing therapies must be tested in clinical trials.

Kariyawasam, D., Carey, K. A., Jones, K. J., & Farrar, M. A. et al (2018)SMA is now a treatable neurodegenerative disease, and early detection and treatment are crucial. As a result of the availability of novel, time-critical treatment options, GPs are now playing a key part in the early recognition of this condition. It is important that all GPs consider urgent referral for a child with delayed motor milestones and signs of symmetrical weakness.

 Summary & conclusion:-

Spinal Muscular Atrophy (SMA) is a genetic disorder that causes progressive muscle weakness due to the loss of motor neurons. Advances in genetic understanding and treatment have significantly improved outcomes. Early diagnosis is crucial, and treatments such as Spinraza, Zolgensma, and Evrysdi offer hope by addressing the underlying genetic cause. Supportive therapies and assistive devices help manage symptoms and enhance quality of life. While the prognosis varies by SMA type, ongoing research and treatment innovations continue to improve life expectancy and functionality for individuals with SMA.

 Future Scope :

Advancements in Gene Therapy

Recent developments in gene therapy for spinal muscular atrophy (SMA) have transformed treatment landscapes. Zolgensma (onasemnogene abeparvovec), a one-time gene replacement therapy, has shown remarkable efficacy in infants with SMA type 1. Clinical trials indicate

significant improvements in motor function, with many patients achieving milestones that were previously unattainable. This therapy delivers a functional copy of the SMN1 gene, addressing the root cause of SMA and dramatically altering the disease's trajectory. Ongoing research focuses on optimizing delivery mechanisms and expanding treatment indications to older patients and those with different SMA types.

Long-Term Outcomes

Long-term studies of patients treated with Zolgensma and other therapies like nusinersen (Spinraza) are crucial for understanding their lasting effects. Data suggest improvements in motor skills, respiratory function, and overall survival rates, with many patients showing sustained benefits over multiple years. Research is also investigating quality of life measures and potential late-onset side effects, which will be essential for informing treatment strategies and clinical guidelines moving forward.

Personalized Medicine

The future of SMA treatment is increasingly leaning toward personalized medicine. Genetic profiling can help identify specific SMN2 copy numbers and mutations that influence disease severity and treatment response. Tailored therapies based on individual genetic backgrounds could enhance efficacy and minimize adverse effects. Advances in understanding the genetic basis of SMA could facilitate the development

Research on Pathophysiology

Emerging research into SMA's pathophysiology is uncovering new therapeutic targets. Studies are exploring the role of non-SMN factors and their contributions to the disease, which could lead to novel drug developments. Understanding the interplay between motor neurons and supportive glial cells is also shedding light on potential pathways for intervention, paving the way for future research directions.

Clinical Trial Innovations

Innovative methodologies in clinical trials, such as adaptive trial designs, are being adopted to enhance the efficiency of SMA research. These designs allow for modifications based on interim results, potentially speeding up the development of effective therapies. Additionally, incorporating real-world evidence into trial designs can provide insights into treatment effectiveness outside of controlled clinical settings, informing better patient care strategies

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