Review Article

Spinal Muscular Atrophy: A Guide to Diagnosis and Treatment

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ABSTRACT

A hereditary condition known as spinal muscular atrophy (SMA) causes progressive motor neuron degeneration in the brain stem and spinal cord, which results in atrophy and weakening of the muscle. The absence of the survival motor neuron (SMN) protein, which is essential for the maintenance of motor neurons, is mostly brought on by mutations in the SMN 1 gene. Between severe infantile variants (SMA Type 1) and milder adult-onset forms (SMA Type 4), there is a vast range in the clinical appearance of SMA. While symptoms of late-onset types develop more gradually, those of early-onset forms are usually more severe and manifest during the first six months of life. Through genetic testing, the presence or absence of an SMN1 gene mutation is used to confirm the diagnosis of SMA. Patient outcomes have amended dramatically as a result of recent medical advancement, such as gene therapy and medications that enhance SMN. Not with standing these developments, controlling SMA still presents certain difficulties, such as the requirement for an early diagnosis and all-encompassing treatment to meet the patient's diverse demands. The goals of ongoing research are to better understand the disease's processes, develop effective treatment plans, and enhance the lives of those who suffer with SMA.

Keywords: Motor neuron degeneration, gene therapy, SMN protein, genetic problem, Spinal muscular atrophy.

INTRODUCTION

SMA is the second most frequent fatal autosomal recessive condition after cystic fibrosis. Degeneration of the spinal cords anterior horn cells is a characteristic of spinal muscular atrophy (SMAs), which beget gradual paralysis of the limbs and trunk that is accompanied by muscular atrophy. Grounded on the age of onset and clinical history, childhood SMA is separate into three clinical groups.

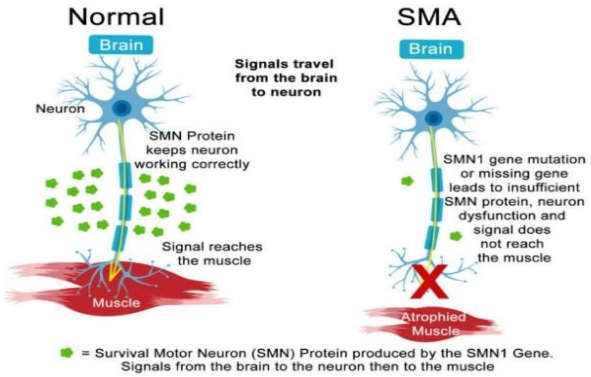

Figure 1: Spinal muscular atrophy

The chromosomes 5q11.2 – q13.3 are designed to all three types of SMN. A variety of yeast artificial chromosome (YAC) were erected, and the closest genetic loci were used to probe allele segregation.

Nine unrelated SMA patients showed evidence of inherited or de novo deletions, and deletions were highly suspected in at least 18% of SMA type 1 patients based on the finding of a significant heterozygosity deficiency for the loci under investigation.

The smallest rearrangement was setup in a region that was fully contained in the 1.2 mb YAC clone 903D1, and abutted by loci linked by C161 and C212 – C272. The tiny (140 kb) nested crucial SMA area has been characterized in SMA patients using a combination of genetic and physical mapping techniques. [1]

4.1. DEFINITION:

The loss of motor neurons in the brainstem and spinal cord results in spinal muscular atrophy (SMA), a genetic disorder that gradually weakens and atrophy muscles. The main cause of this disorder is mutations in the survival motor neuron 1 (SMN 1) gene, which leads to insufficient production of SMN protein, which is essential for the survival motor neurons.

Predicated on the age at which symptoms first appear and their severity, SMA is divided into four categories, with Type 1 being the most severe and Type 4 being the least severe. [2-5]

4.2. HISTORY:

- **4.2.1. Early Detection:**

1891: Austrian Neurologist **Guido Werdnig** gave the first thorough explanation of SMA. He talked about a condition that beget severe muscular atrophy & weakness in children.

1892: German Neurologist **John Hoffmann** gave a thorough description of the illness, which contributed to the complaint's early designation of Werdnig-Hoffmann complaints.

Figure 2: Guido werdnig

Figure 3: John Hoffmann

- **4.2.2. Genetic discoveries:**

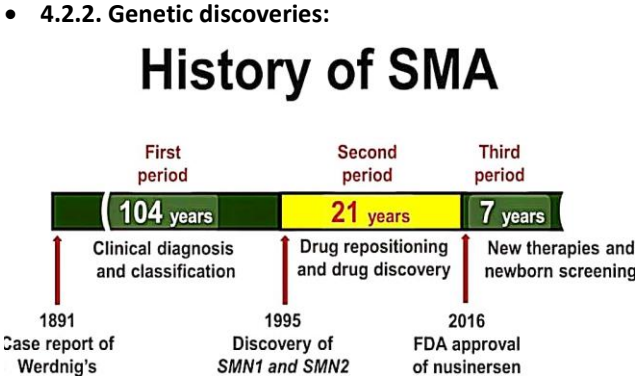

Figure 4: History of SMA

Genetic advancement made in the **1950s**&**1960s** paved the way for the understanding of SMA as a hereditary condition. Scientists discovered that SMA was inherited in an autosomal sheepish form, which means that for an off spring to be affected, a defective gene must be carried by both parents.

1955: The discovery that chromosomes 5 contain the SMA 1 (survival motor neuron) gene was a significant advance. SMA was determined to be caused by a mutation in this gene. The SMA 1 gene generates a protein that is necessary for motor neurons to survive. Motor neurons deteriorate when this gene is absent or imperfect.

- **4.2.3. Remedial Advance:**

2016 saw a critical turning point in the treatment of SMA with U.S Food and medicine administration's (FDA) blessing of Spinraza, also known as Nusinersen.

Spinraza is an antisense oligonucleotide that increase the quantum of functional SMA protein by altering the splicing of SMN 2, a gene that is nearly connected to SMN 1. This was the first SMA treatment that the FDA has approved.

2020 saw the FDA authorized Evrysdi (Risdiplam), an oral drug that also modifies SMN 2 gene splicing of SMA protein. [13,14,15]

4.3. CLASSIFICATION:

Based on the age of onset and clinical history, childhood SMA is traditionally separated into three clinical groups.

Type: 1

The most severe and prevalent kind, known as Werdnig-Hoffmann disease type 1, account for Roughly 50% of SMA cases.

Figure 5: SMA type 1

Typically, Newborns with SMA Type 1 Experience clinical symptoms Before the age of 6 Month, are unable to sit unassisted, & in the absence of intervention, typically do not live past the first two years of life.

Significant Hypotonia, Symmetrical flaccid paralysis and frequently no head control characterize these patients.

Based on the Severity of clinical signs, SMA Types 1 can be classified into at least three clinical sub groups;

1) Severe weakness from birth or the neonatal period, Head control is never achieved.
2) Onset of weakness after the neonatal period but usually within two months.
3) Onset of weakness after the neonatal periods but head control is achieved with assistance, a few of these kids might be able to sit.[6,7,8]

Type: 2

The onset period for SMA Type 2 is 7 to 18 months of age. Patients no longer develop the capacity to walk independently, but they do learn how to sit unassisted and some even learn how to sit stand.

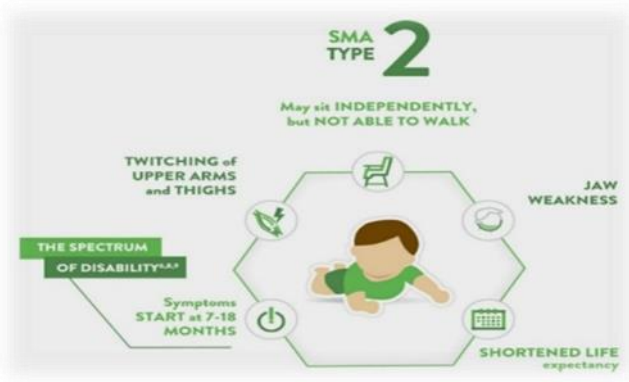

Figure 6: SMA type 2

In the early year of childhood, more severe type 2 patients can be Develop joint contractures and kyphoscoliosis, which are relatively prevalent conditions.

There is a range of severity from relatively stronger children with substantially stronger trunk, limb and respiratory muscle to weaker youngster who can hardly sit unassisted and are more likely to have respiratory symptoms & early scoliosis.

Type: 3

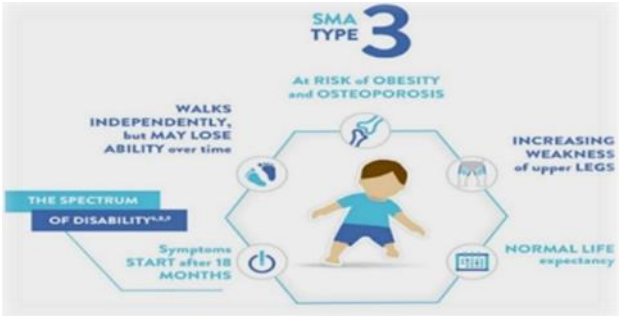

Figure 7: SMA type 3

Patient with clinical heterogeneity is included in SMA type 3[kugelberg welander illness] they usually accomplish all significant motor milestones and become independent walkers. while some people may require wheelchair help as children other may be able to walk and lead fulfilling liver as adults even if they have mild muscular impairment.[9-12]

4.4. EPIDEMIOLOGY:

Approximately 1 in 6,000 - 10,000 live births have SMA, making in the second most frequent fatal autosomal recessive illness after cystic fibrosis. The carrier frequency of SMA is 1/40 – 1/60[17,18]. According to a 2005 study, the incidence of type 1 spinal muscular atrophy was lower in Cuba than in other countries (3.53 per 100,000 live births), particularly among African Americans (0.89 – 0.93 per 100,000 live births.[20,21]

4.5. ETIOLOGY:

A mutation on chromosome 5q13 in the survival motor neuron (SMN 1) gene is the main cause of SMA. For the survival motor neuron (SMN) protein to be produced, which is necessary, the SMN 1 gene is required.

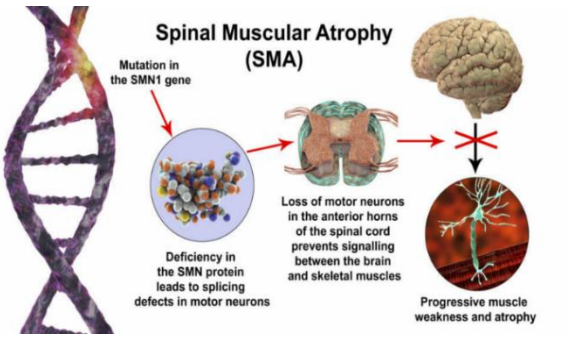

Figure 8: Causes of SMA

Muscle weakness develops gradually when there is a deletion mutation in the SMN 1 gene, which results in insufficient production of SMN protein and the degeneration and death of motor neurons.

The SMN protein is also produced by a separate gene, SMN2 although significantly less of it produced because of alternative splicing, which results in a shortened, less stable protein. Individual difference Exist in the amount of SMN 2 gene copies, which may impact the severity of the illness. [22,23]

Spinal muscular atrophy has been studied in yeast, worm, fly, zebrafish, and mouse animal models that alter SMN. These models facilitate high – throughput pharmacological and genetic screening as well as insights into disease mechanisms. Mutant mice can, however, be made to tolerate a considerable degree of illness.[19]

SMA pathogenesis is explained by two primary hypotheses: SMN has a motor neuron – specific function, such as mRNA transport down the axon, and its reduction may have an impact on snRNP assembly. SMN is implicated in snRNP biogenesis and mRNA splicing.

The SMN protein, together with eight other proteins, forms a complex that is essential for the assembly of the smith class core protein in uridine – rich snRNPs, or U snRNPs, spliceosomes. All somatic cells express it, however since motor neurons are susceptible to spinal muscular atrophy, it is possible that SMN protein has a special function.[24]

4.6. SIGN AND SYMPTOMS

- **4.6.1. Muscle weakness:**

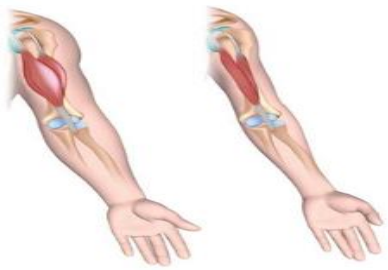

Figure 9: Muscle weakness

Usually begins in the proximal muscle (upper back, shoulders, hips, & thighs) which are the closest to the center of the body. This weakness may make it difficult to stand, walk or even sit up straight.

- **4.6.2. Poor muscular tone (Hypotonia):**

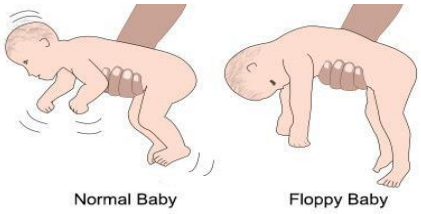

Figure 10: Hypotonia

Because of their hypotonia, newborns with SMA sometimes have **"FLOPPY"** appearances.

- **4.6.3. Loss of motor function:**

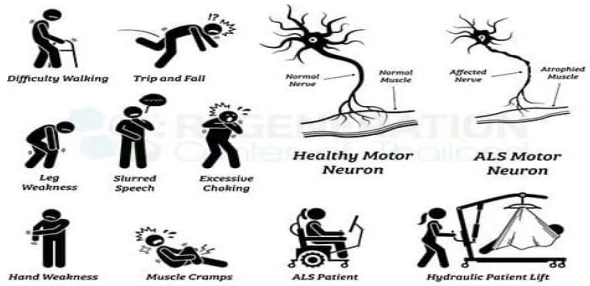

Figure 11: Loss of motor function

A steady decline in motor skills, such as the capacity to walk, crawl, or move one's head. In extreme circumstance paralysis may results.

- **4.6.4. Breathing problem:**

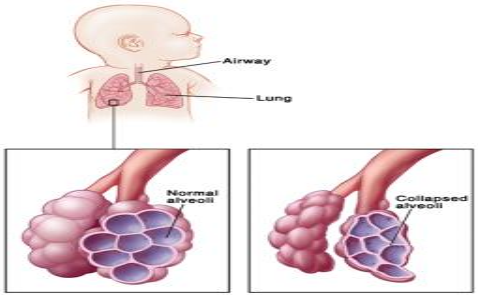

Figure 12: Breathing problem

Respiratory issues, which are common in severe cases of SMA, might be brought on by weakness of the breathing muscle.

- **4.6.5. Difficulties with swallowing & feeding:**

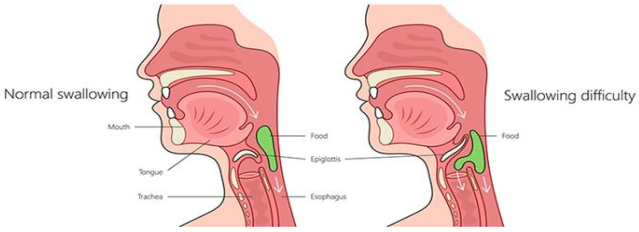

Figure 13: Difficulties with swallowing & feeding

Feeding difficulties and a higher risk of aspiration (Inhaling food or liquid into the lungs) can be caused by weakening in the muscles involved in chewing and swallowing.

- **4.6.6. Spinal curvature (Scoliosis):**

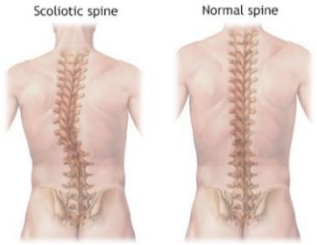

Figure 14: Spinal curvature

Scoliosis is a curvature of the spine that can develop over time as a result of weakening in the muscle that Curvature of the spine support it.

- **4.6.7. Joint contraction:**

Figure 15: Joint contraction

Restricted joint range of motion brought on by imbalanced & weak muscle, resulting in stiffness & abnormalities.

- **4.6.8. Tremors**:

Figure 16: Tremors

Hand & Finger tremors are a possible Symptoms of SMA in certain people.[14,13,16]

5. DIAGNOSIS

5.1. Clinical evaluation:

- **5.1.1. Medical history and physical examination:**

Both are essential. A thorough medical history should be obtained. Motor skill development delays, diminished muscle tone and muscle weakness are common symptoms.

Clinical characteristics are quite suggestive of SMA, especially when a weak or floppy newborn has the severe form. The intelligence and attentiveness are consistently good. Usually symmetrical, the weakness is more proximal

than distal, with the legs typically experiencing more weakness than the arms.

Additionally, in the most severe type, the new born has trouble swallowing & feeding, has weak crying & coughing, atrophy and fasciculation of the tongue & is dependent on the diaphragm for breathing (abdominal breathing).

- **5.1.2. Family History:**

Because SMA is inherited in an autosomal recessive manner, a history of the illness or symptoms associated with it in the family may offer crucial hints.

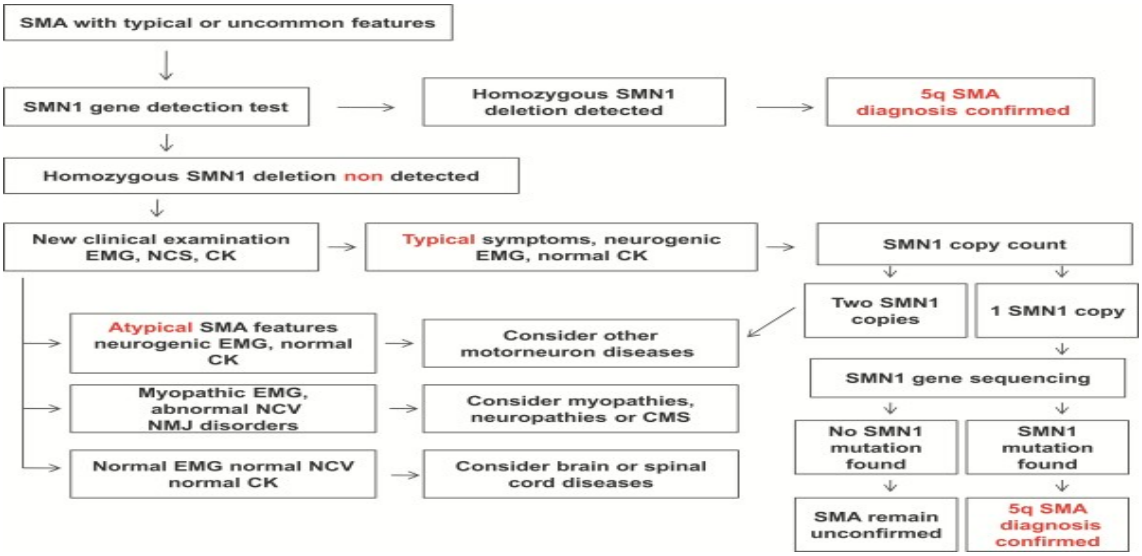

Figure 17: Summarize the diagnostic procedure algorithm that should sever as a reference for diagnosing SMA.

5.2. Genetic Testing:

- **5.2.1. SMN1 Gene mutation analysis:**

Finding mutations or abnormalities in the SMN 1 (survival motor neuron) gene is the main diagnostic procedure for SMA. The SMN 1 gene's homozygous deletion of exon 7 about 95% of SMA Cases.

- **5.2.2. SMN2 copy number analysis:**

The amount of the SMN 2 gene that is present can affect how severe the illness is a milder phenotype is often linked to more copies of SMN2.

5.3. OTHER TESTING:

- **5.3.1. Electromyography (EMG) and nerve conduction studies (NCS):**

These tests aid in evaluating the electrical activity of muscle and the health of motor neurons. A pattern consistent with chronic denervation & reinnervation may be seen in EMG.

- **5.3.2. Muscle Biopsy:**

Less frequently done due to the availability of genetic testing, muscle biopsy can show evidence of neurogenic atrophy.

- **5.3.3 Parental & Neonatal screening:**

If a family of SMA is known, prenatal testing for the disease can be done via amniocentesis or chorionic villus sampling (CVS).

Many localities are implementing newborn SMA screening programs, which will enable early diagnosis and treatment. [1,2,14,25,26]

6.TREATMENT

In recent years, there have been considerable advancements in SMN treatment options, with multiple medications certified to manage the disease. These are a few of the main medications used to treat SMN.

6.1. DRUGS

- ✓ Nusinersen
- ✓ Evrysdi
- ✓ Onasemnogene abeparvovec

6.1.1. NUSINERSEN:

❖ **Brand name:** Spinraza

It is used to treat the spinal muscular atrophy.

❖ **Mechanism of action:**

Designed to treat Spinal muscular atrophy brought on by mutation in the SMN1, gene, nusinersen is an antisense oligonucleotide. A defect in the survival motor neuron function, results from these mutations. In order to partially compensate for the SMN 1 gene, Nusinersen acts on the SMN 2 gene.

- **Splicing modification:**

The SMN 2 pre-mRNA's splicing is changed when Nusinersen binds to a particular sequence in the pre-mRNA.

As a performing, Exon 7 is included in the mRNA transcript, resulting in the synthesis of the complete SMN protein.

- **Enhanced SMN protein level:**

Nusinersen stimulates the inclusion of Exon 7, which raises the synthesis of functional SMN protein, which supports the survival and function of motor neurons.

❖ **Pharmacokinetics:**

- **Absorption:**

To insure direct to the central nervous system (CNS), Nusinersen is fitted intrathecally, that is directly into the cerebrospinal fluid.

- **Distribution:**

Nusinersen spreads widely throughout the central nervous system (CNS) after intrathecal treatment, eventually reaching the intended motor neurons.

- **Metabolism and Excretion:**

Exo nuclease - intermediated hydrolysis is the main mechanism by which nusinersen is metabolized slowly within the central nervous system. Eventually, it is excluded from the body by excretion.

❖ **Clinical Efficacy:**

Nusinersen treatment has been shown in clinical trials to significantly ameliorate motor function and increase patient survival rates. Notably, the ENDEAR research revealed that infants treated with nusinersen were more likely than those given a placebo to reach motor milestones.

❖ **Adverse Effects:**

- **Common side effects:** Lower respiratory infection**,** Constipation, Scoliosis**,** Respiratory distress**,** Fever
- **Severe side effects:** Coagulation abnormalities, Renal toxicity [27,28]

6.1.2. EVRYSDI:

❖ **Generic Name:** Risidiplam

It is authorized to treat spinal muscular atrophy (SMA). Muscle atrophy and weakening are the results of motor neuron loss in sickle cell anemia (SMA). The purpose of Evrysdi is to treat the underlying genetic etiology of SMA.

❖ **Mechanism of action:**

Evrysdi increase the synthesis of functional SMN protein by altering the splicing of the SMN 2 (survival motor neuron 2) gene. Mutations in the SMN 1 gene cause SMN protein deficiencies in SMA patients.

Due to a splicing error, the backup gene, SMN 2 gene, largely produces a docked, less functional version of the SMN protein. This splicing mistake is fixed by Evrysdi, performing in the synthesis of full-length, functional SMN protein.

❖ **Pharmacodynamics:**

- **Enhanced levels of SMN protein:**

Evrysdi enhances the body's amounts of functional SMN protein by correcting SMN 2 pre-mRNA splicing. This aids in motor neuron's survival and functionality.

- **Systemic distribution:**

When taken orally, Evrysdi acts on the central nervous system, when is important in the treatment of spinal muscular atrophy.

❖ **Pharmacokinetics:**

- **Absorption:** Evrysdi has a decent Bioavailability when taken orally.
- **Metabolism:** To produce its active metabolites, the medication is broken down by cytochrome p450 enzymes, principally CYP3A.
- **Excretion:** The main methods of excretion for Evrysdi and its metabolites in feces, with some renal excretion also being.

❖ **Clinical Efficacy:**

Studies on people with SMA have shown that Evrysdi enhances motor function. It was setup to be effective in both infantile-onset and later-onset SMA, performing in increased survival and the achievement of motor milestones.

❖ **Adverse Effects:** Fever, Diarrhea, Rashes, Respiratory infections.

Although it is well-permitted, Frequent monitoring is advised to treat any possible side effects. [29,30]

6.1.3. ONASEMNOGENE ABEPARVOVEC:

❖ **Brand Name:** Zolgensma

Spinal muscular atrophy (SMA) is a severe neuromuscular illness caused by mutations in the SMN 1 gene, which results in a shortage of the survival motor neuron (SMN) protein. Onasemnogene Abeparvovec is a gene therapy used to treat SMA.

❖ **Mechanism of action:**

- **Gene replacement therapy:**

Onasemnogene abeparvovec handed the patient's cell with a performing copy of the SMN 1 gene by exercising a modified adeno-associated virus (AAV9) vector. Because the AAV9 vector can target motor neurons and cut the Blood-Brain Barrier, it was named.

- **Expression of SMN protein:**

Following delivery, the patient's DNA integrates the performing SMN 1 gene, allowing the cells to produce the SMN protein – essential for the survival and proper operation of motor neurons.

❖ **Administration:**

Therapy is delivered as a single intravenous infusion using intravenous infusion. To guarantee that patients of varying sizes admit the proper therapeutic levels, the dosage is weight-grounded.

❖ **Pharmacokinetics:**

- **Distribution:**

The AAV9 vector spreads systemically following intravenous injection, showing a special predilection for motor neurons in the central nervous system.

- **Expression timeline:**

After delivery, SMN protein expression starts to be quite fast, and therapeutic levels are usually sustained for a long time.

❖ **Clinical Efficacy:**

- **Increase in motor function:**

Compared to the disease's natural course, clinical research on SMA patients treated with onasemnogene abeparvovec have demonstrated significantly better survival rates and improvements in motor function.

- **Milestone accomplishments:**

Infants entering treatment have shown the capacity to reach motor milestone like sitting alone, which are usually inaccessible for untreated SMA children.

❖ **Adverse effects:**

- **Common side effects:** Elevated liver enzymes, Vomiting, Thrombocytopenia
- **Serious risk:**

Severe liver damage is a possibility, especially in individuals, with liver diseases. It is essential to cover liver function both before and after administration. [31,32]

6.2. PHYSICAL THERAPY

➢ **Strengthening exercises:**

Acclimated to the patient's ability, with an emphasis on precluding atrophy and conserving muscle function.

➢ **Stretching and range of motion exercises:**

Maintain flexibility and avoid contractures.

➢ **Respiratory exercises**:

Enhance respiratory health, which is frequently bloodied in SMA patients.

➢ **Assistive Devices:**

Using wheelchairs, orthoses, and other devices to ameliorate mobility and freedom is known as the use of assistive devices.

➢ **Hydrotherapy**:

Exercises performed in the water can strengthen weak muscles and grease movement. [3,25]

6.3. SMA Dietary Management:

Muscle atrophy and weakness are hallmarks of the hereditary condition known as spinal muscular atrophy (SMA). Maintaining energy levels, limiting malnutrition, and promoting general health are all important aspects of nutrition in the management of sickle cell disease (SMA). The following are important food factors to take into the people with SMA.

6.3.1. High-Calorie Food Plan:

People with SMA frequently require more energy due to muscle atrophy and weakness. A diet rich in calories can support weight management and give you enough energy.

Calorie-dense foods including nuts, seeds, avocados, and full-fat dairy products may fall under this category.

6.3.2. Food High in protein:

Protein is necessary for the upkeep and repair of muscle. Lean meats, seafood, eggs, beans, and dairy products can all be included to help satisfy your protein demands.

6.3.3. Hydration:

Drinking enough water is important, particularly if swallowing is difficult. In addition to aggravating muscular weakness, dehydration can cause other issues.

6.3.4. Minerals and Vitamins:

As SMA can affect bone health, its critical to make sure you're getting enough calcium and vitamin D, among other vitamins and minerals. Fortified foods, fruits, and vegetables can assist fulfill these requirements.

6.3.5. Special considerations:

Some SMA patients may have digestive problems or trouble swallowing. Under the supervision of a healthcare provider, softer meals, dietary supplements, or tube feeding may be required in such circumstances. [3,25,33]

7. CONCLUSION

A hereditary condition Known as spinal muscular atrophy (SMA) affects motor neurons, causing gradual muscle loss and atrophy. As a result, it poses serious obstacles. As a result, it poses serious obstacles. A comprehensive strategy incorporating dietary, supportive, and medicinal intervention is necessary for the effective management of SMA. The treatment landscape for SMA has changed as a result of advances in genetic medicines, including as gene replacement therapy and antisense oligonucleotides, which have given patients new hope for improved outcomes. For those with SMA, nutritional management-which includes eating a high calorie diet, getting enough protein, and staying hydrated-is essential to preserving their health and quality of life. To maximize care strategies and ensure the best possible quality of life for person affected by SMA,

continuous collaboration among healthcare, and families is crucial as research continues to progress.

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