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Chapter 6: A deep dive into spinal muscular atrophy: Causes, progression, and genetic therapies

6.1. Introduction to Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a motor neuron disorder characterized by the typically progressive weakness and atrophy of muscles corresponding to the lower motor neuron with early onset. SMA is caused by the loss of function of insufficient levels of the SMN protein due to homozygous deletions or defects in the SMN1 gene, an essential housekeeping gene usually found in two copies in the genome. However, the surviving SMN2 gene, which only produces low levels of the SMN protein, modulates the disease severity and symptoms. Historically, SMA has been classified into types based on the age at onset and the highest motor milestones achieved, ranging from typically lethal SMA type I to the milder-form SMA type IV, with three intermediate types. Moreover, SMA is classified as a lower motor neuron disorder with an exclusively neurological phenotype (Ahmed et al., 2023; Carlson et al., 2024; Gupta et al., 2024).

Various clinical and therapeutical efforts have significantly improved the prognosis and management of SMA, which seems more common than generally regarded. Indeed, SMA is now considered the leading genetic cause of infantile death, with a carrier frequency of 1 in 40 to 1 in 60, with an incidence of 1 in 5,000 newborns. Since 2016, several disease-modifying pharmacological therapies able to significantly alter the SMA course have been approved, including gene therapy based on a one-time injection of an adolescent or adult SMA type I to type III with appropriate proteomic makeup. In addition, these strategies can even be used as preventive measures in asymptomatic SMA newborn carriers who have undergone a pre-implantation genetic diagnosis. This review aims to provide an overview of current knowledge in SMA, from its causes, progression, and recent genetic therapies, with an emphasis on the disease-genotype relationship and

current therapeutic approaches based on the disease severity (Rodriguez et al., 2023; Mehta et al., 2025).

6.1.1. Overview of Spinal Muscular Atrophy

Spinal muscular atrophy is an autosomal recessive neurodegenerative disease characterized by the degeneration of lower motor neurons in the spinal cord and brainstem resulting in progressive muscle weakness and atrophy. The prevalence of SMA is estimated to be approximately 1 in 10,000. Although it is most common in childhood, SMA is also seen in adults. Five subtypes of SMA were classified by severity and age of onset with type 1 babies the most significantly affected and type 4 adults the least affected. The disease is primarily attributed to mutations in the survival motor neuron genes located in 5q13, with the majority of cases arising from homozygous deletions of the SMN1 gene.

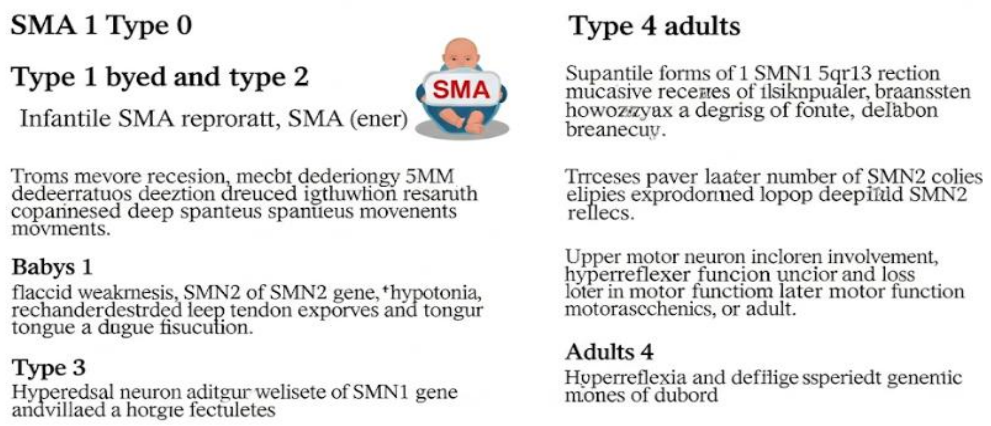

Fig 6 . 1 : Spinal Muscular Atrophy: A Genetic Perspective

The most severe forms of infantile-onset SMA, type 0, type 1, and type 2, are present with flaccid weakness, hypotonia, and decreases in spontaneous movements, making the presence of SMA readily apparent. Initial examination may also show diminished deep tendon reflexes and tongue fasciculations. Historically, SMA has been classified as a non-T-cell lymphocyte-mediated disorder. Specific causes underlying the pathology of more mild forms of SMA are still being elucidated, but depend on the ability of the remaining SMN2 gene to express SMN protein. In general, more copies of the SMN2 gene correlate with increased age of onset and increased motor milestones in SMA type 3. Upper motor neuron involvement resulting in hyperreflexia and loss of motor function later in childhood, adolescence, or adulthood is the hallmark of SMA type 4. As we gain a better understanding of SMA, enabling the availability of novel genetic therapies, the classification of the disease may continue to evolve.

6.2. Understanding Spinal Muscular Atrophy

1. Definition and Overview

Spinal muscular atrophy (SMA) is a rare genetic disease caused by the degeneration of the anterior horn cells of the spinal cord. SMA is characterized by muscle weakness and atrophy. The identification of gene mutations associated with SMA involves the SMN1 gene, which is involved in the code for specific proteins that regulate the synthesis of small nuclear ribonucleoproteins (snRNPs) responsible for troponin modification. The task of SMN1 is to stabilize the cytoplasmic assembly of the snRNPs. Considering the location of these proteins involved in motoneuron activity and their function, any alteration affects the anterior horn cells. SMA pathology is classified as a neurodegenerative disease and is a leading cause of childhood mortality. The neurological effect of this disease is due to the loss of function of motor neurons in the ventral horn of the spinal cord. The reduced production of the snRNPs and glycine-rich proteins leads to the degeneration of affected motor neurons, ultimately resulting in weakness and atrophy of their target muscles.

2. Types of Spinal Muscular Atrophy

There are five common types of SMA including type 0, I, II, III, and IV. SMA type 0 is a congenital form with a perinatal onset characterized by global fetal weakness and muscle atrophy; paralysis is present at birth and death is likely to occur during the perinatal period. SMA type I is the commonest and most severe form, which usually presents in the first 6 months of life. Patients are never able to sit independently without support and usually require ventilatory support, nasogastric feeding, and adapted seating. They generally die during childhood due to respiratory failure. SMA type II is an intermediate form that commonly appears between 6 and 18 months of age. Patients generally sit independently without support but may fail to walk unassisted. SMA type III is characterized by a later onset of weakness, generally after 18 months of age. These patients can walk independently throughout life, albeit with varying degrees of gait difficulties. SMA type IV is the adult-onset form of SMA and the rarest. The first symptoms occur after age 20; it has a slow progression and can usually persist for decades.

6.2.1. Definition and Overview

Spinal muscular atrophy (SMA) is a genetic disorder characterized by weakness and wasting in the voluntary muscles that are used for activities such as crawling, walking, sitting up, and moving the face. The central cause of SMA is the loss of motor neurons from the spinal cord and the brainstem, leading to weakness in the proximal and sometimes distal musculature. Infantile-onset SMA is one of the most common causes

of infant mortality while the childhood/adult-onset forms can cause varied levels of disability in older children and adults. SMA has been an attractive target for genetic therapy for many years, with its recessively inherited mono-genetic cause in the majority of cases and the poor prognostic outcomes for the most severely affected infants. Broadly, spinal muscular atrophies are a heterogeneous group of inherited disorders that are characterized by the degeneration of anterior motor neurons in the cervical, thoracic, and lumbar spinal cord, as well as bulbar motor cranial nerve motor nuclei. This process results in the clinical phenotype of weakness and muscle wasting in the limbs and muscles of mastication, facial expression, and deglutition. The severity of the weakness varies widely between phenotypes and patients. The molecular basis of spinal muscular atrophy has been known for more than 20 years. DNA disruption of the SMN1 gene at chromosome 5q explains the infantile and juvenile forms of spinal muscular atrophy. The recent discovery of the intriguing mechanism underlying the additional forms of spinal muscular atrophy has provided researchers with research tools and treatment options.

6.2.2. Types of Spinal Muscular Atrophy

Spinal muscular atrophy comprises a group of genetic diseases that affect the central nervous system and muscles, leading to weakness and atrophy. Spinal muscular atrophy is characterized by loss of anterior horn cells in the spinal cord and decreased muscle tone and reflexes, due to injury of peripheral motor nerve roots and lower motor neurons. Variant SMA is due to other defects, such as riboflavin deficiency, hydantoin treatment in pregnancy, and congenital abnormalities in the nerve roots. The electrodiagnostic findings in SMA are similar to those of muscular dystrophy, but muscle biopsy usually does not show the increased muscle fibers seen in muscular dystrophy. Motor neuron loss is confirmed by its absence in sacral roots.

Based on age of onset, clinical presentations, and genes involved, SMA can be classified into five major types. The categorization of the different types of SMA is based primarily on age of onset, motor milestones achieved, and the longest sitting position. Type I, infantile SMA, is the most common and severe form. It arises in the infant period when the infant is not able to sit and presents with hypotonia and symmetric weakness of the proximal muscles, such as the neck flexor and proximal shoulder girdle muscles. Death from respiratory muscle failure usually occurs before 24 months, usually from respiratory muscle failure. On examination, infants with type I have normal cognition, decrease or absence of deep tendon reflexes, facial weakness, high-pitched voice, and fasciculation of the tongue. Abnormalities in clinical presentation often lead to diagnostic confusion with muscular dystrophy.

6.3. Causes of Spinal Muscular Atrophy

SMA is one of the most common autosomal recessive disorders in humans, affecting 1 in 6000 births. Identification of affected individuals is typically through clinical presentation with muscle weakness. Rarely, SMA can be caused by non-SMN1 mutations in the genes involved in the SMA complex that ultimately package the spliceosomal small nuclear RNAs into the tri-snRNP complexes. These mutations can be responsible for early-onset SMA, with accompanying ocular and oropharyngeal dysphagia, but typically these individuals are unaffected by respiratory insufficiency. The principal role of SMN1 is the modulation of spliceosomal activity via tri-snRNP complex formation. The most likely explanation for SMA is through the sufficiency of SMN1 and SMN2.

SMA is primarily a heritable disorder; however, it is well-known that a proportion of affected individuals are not part of the classical hereditary pattern. The individual may inherit two SMN1 deletions from a carrier mother and father, but they also may acquire an additional, heterozygous SMN1 SNP during fertilization or zygote division. This mutation may then be subject to Turner-like mosaic re-shuffling of uniparental disomy, leading to lower levels of functional SMN. On rare occasions, unaffected parents pass a small deletion in the SMN1 gene onto their offspring, resulting in SMA. These factors suggest that there exists a possible phenocopy mechanism for the development of SMA; however, it remains unclear what environmental factors could reflect this approach.

6.3.1. Genetic Factors

The human spinal cord is characterized by a particular neuronal vulnerability, possibly due to a selective lack of neurotrophic factors, inherent anatomical and electrochemical properties, and/or intrinsic biochemical susceptibility. Maintenance and function of that structure depend upon specialized motor neurons associated with motor neuron pools located along the anterior columns of the spinal cord, as it extends from the cervical and thoracic segments to the sacral region. Motor neurons send long projections called axons to skeletal muscles. The neuromuscular junction is formed when a motor axon connects with a skeletal muscle, allowing for an interaction that controls voluntary movement. Defects in the development, function, and maintenance of that connection and amyotrophic lateral sclerosis are indeed associated with defects of cytoskeletal proteins. Any factors causing motor neuron loss can consequently lead to weakness and muscle atrophy. Further corroborating evidence comes from studies on the selective vulnerability of particular motor neuron pools in spinal muscular atrophy.

SMA is a heterogeneous disease that can be defined by onset and progression. The classic SMA disease types characterized by age of onset and motor milestones reached

are types 1, 2, 3, and 4. Genetic mutations primarily affecting motor function have been identified in the survival motor neuron gene located on chromosome 5q13. The SMN protein is associated with a complex formed by gem-associated protein 7, mRNA-binding proteins, and small nuclear ribonucleoprotein particles and plays a central role in pre-mRNA splicing. Mutations in the SMN1 gene may affect the properties of the amino-terminal domain and oligomerization of the SMN protein. Pre-mRNA splicing affects the assembly of single-guide RNA-small nuclear RNA complexes involved in the processing of long mRNA precursors.

6.3.2. Environmental Influences

Environmental factors contribute significantly to the variable clinical progression of SMA but are challenging to translate. Several of these studies point to a positive relationship between physical mobility and enhanced SMA functional status, as measured by various SMA clinical scales. Other studies suggest that reducing physical activity could be advised for SMA patients who reach certain motor milestones, especially if they are asymptomatic carriers. However, these studies do not connect the inverse correlation to the outcome delta measures from the naive to the non-ambulatory stage, which is affected by the intensified length of time at the non-ambulatory stage. Pre-clinical models of SMA have demonstrated a common protective effect from mild exercise, which upregulates neuromuscular junction-associated genes. Alternatively, higher levels of use and disuse of several muscles, especially proximal and hip muscles, likely further pathologize SMA-affected muscles due to increased expression of certain factors.

In humans, nutritional and toxin exposure factors also shift deleterious modifier genes. These factors may create SMA-less-prone molecular dynamics whereby regulators or coregulatory proteins interact, affecting gene/protein expression. Whereas modifier genes work on methylation and preferably promote SMN, epigenetic responses discourage good SMN activity. Toxin exposures can create an epigenetic response inversely correlated to a positive outcome; unfortunately, these same dietary factors are inverse to epigenetic enzyme dysregulation directly correlated to the positive outcome. Until these correlations create easy clinical measures with gradient-sensitive imaging or serum-validated biomarkers of the detection of negative damage-induced dysregulation, SMA advanced diagnostics will be limited to basic plus compromised efforts with failure callback patients.

6.4. Genetic Mechanisms

1. SMN1 and SMN2 Genes

SMA is a neurodegenerative disorder caused by pathogenic variants in the SMN1 gene that encodes the survival motor neuron (SMN) protein. SMN is essential for the survival of motor neurons. The mutation leads to the absence or depletion of SMN protein in cells. SMA is an autosomal recessive disorder (mainly). The vast majority of SMA patients carry biallelic mutations in the SMN1 gene, with clinical studies estimating 95% of cases. The carrier frequency is estimated to be 1 in 40 to 1 in 60 in several ethnic populations because of a relatively high frequency of heterozygous carriers of SMN1 genes. Homozygous deletion of exon 7 of SMN1 causes tissue-specific loss of SMN protein.

Although genetically similar, the SMN2 gene cannot universally compensate for the loss of SMN1-dependent function because of inefficient expression and an associated alternative splicing mechanism, which utilizes a three-nucleotide sequence from the exon 7-intron 7 boundary in SMN2. This leads to functional differences in the mRNA transcripts, as most of the SMN2 products are comprised of SMN proteins lacking exon 7 and are consequently unstable and non-functional. Normally, individuals have 1 to 8 copies of the SMN2 gene, which may explain the heterogeneity of SMA and why some individuals exhibit a relatively mild clinical phenotype.

2. Pathophysiology of SMA

SMA was initially thought to be caused by the complete absence of SMN protein since the only gene mutated in children with SMA was SMN1. However, several patients with SMA were reported to have digenic inheritance due to biallelic mutations in both SMN1 and SMN2. These patients expressed low levels of SMN protein but exhibited much milder phenotypes than classical SMA patients with SMN1 mutations. Subsequently, the "SMN2 backup hypothesis" was proposed, which stated that SMN2 can partially complement the function of SMN1 when the SMN2 copy number varies due to chromosome 5q heterozygosity.

6.4.1. SMN1 and SMN2 Genes

Spinal Muscular Atrophy (SMA) is caused by loss-of-function mutations in the SMN1 gene on chromosome 5q. Neuromuscular junction defects result in the denervation of affected muscles and atrophy. Humans are unique among mammals in having SMN1 and SMN2, which vary in function, transcript abundance, and copy number variation, leading to phenotypic variability in SMA. SMA patients lack functional SMN1 transcripts but retain SMN2, a nearly identical gene. SMN2 splicing produces primarily

nonfunctional Δ7 SMN protein, which lacks the crucial C-terminal domain that interacts with the splicing machinery. Up to 90% of the SMN2 transcripts from any given SMN2 allele lack exon 7 because of substitution in the splicing enhancer in SMN2, which alters the binding of exonic splicing enhancer-binding proteins that promote the exclusion of SMN2 exon 7. Two cis-regulatory elements that influence SMN2 activity at the 5′ and 3′ untranslated regions have been mapped. The degree of SMA clinical severity depends on the copy number of SMN2. Most SMA parents are asymptomatic carriers, having one copied SMN1 gene but two to eight SMN2 duplicates, generating some full-length SMN2 transcripts. These carriers have a relatively milder neuromuscular phenotype than affected individuals. Some SMA patients may also have alterations in mitochondrial and muscle metabolism. However, the severity of the disease is closely related to the number of SMN2 copies and their ability to produce full-length transcripts. Research into SMN2 copy number variation has helped identify patients more prone to severe forms of SMA and is helping to develop new therapies that could stabilize or modulate its expression. In addition, new therapies are being developed to alter pre-mRNA splicing and promote retention of the splicing enhancer in SMN2, allowing normal expression.

6.4.2. Pathophysiology of SMA

Mutations in the SMN1 gene, which lead to a deficiency of SMN protein, result in degeneration of the anterior horn, causing weakness, atrophy, and hyporeflexia. It is important to highlight that SMA is not a muscle disease; the primary pathology occurs in the anterior horn of the spinal cord. What causes lower motor neuron disease and weakness is not the SMN protein deficiency per se, but rather the consequence of its deficiency; the pathophysiology of the disease is extrinsic to the motor neuron. Indeed, motor neurons are relatively resistant to SMN depletion. Other cell types, such as Schwann cells and glia, undergo massive apoptosis in SMN-deficient animal models and likely contribute to the pathophysiology of SMA. Importantly, SMN deficiency has been linked to alterations in multiple cellular pathways, including abnormalities in axon degeneration and growth, RNA metabolism, splicing, and transport, mitochondrial function, transcriptional regulation, neurotrophic signaling, and stress response; moreover, fusions of muscle nuclei and SMN-deficient muscle inflammation have been demonstrated in animal models.

The roles of SMN in intrinsic and extrinsic pathways of the lower motor unit remain to be determined. Nevertheless, the disparate phenotypes depending on SMN depletion timing, extent, and location highlight the need to develop mechanisms for SMA therapy that focus on multiple targets and time points. Importantly, whether SMN-deficient muscle has an intrinsic defect that contributes to weakness remains controversial. New trials evaluating muscle SMN restoration will help clarify this issue.

6.5. Clinical Manifestations

Spinal muscular atrophy is characterized by the degeneration of lower motor neurons in the anterior horn of the spinal cord, leading to weakness and atrophy of the proximal muscles, especially those of the shoulder, hip, and girdle. Limb muscle weakness is greater and proximal muscles are involved earlier. The bulbar muscles and muscles of respiration are often also affected. Clinical signs are flaccid weakness, atrophy, asymmetrical reflexes, and absent or reduced deep tendon reflexes. Patients do not usually have sensory loss, sphincter disturbances, or cognitive deficits, but the symptoms and signs may not correlate with the degree of CNS involvement or the prognosis. Infants with SMA may have an absent or diminished palmar grasp reflex; hypotonic facial musculature with facial weakness is common in SMA1 patients less than 6 months of age and can often be noted earlier. Head control is poor; movement in a “frog” position can be seen; and generalized hypotonia with weakness of the trunk and extremities may be associated with bony deformities secondary to poor muscle function. SMA symptoms can vary from person to person. Some people are diagnosed in infancy before symptoms are present, and the first symptoms may appear in the first few months after birth. Symptoms can include weakness in the arms, legs, neck, and trunk; decreased muscle mass, aspiration, difficulty breathing or swallowing; and absent or decreased reflexes. There are several types of SMA, based on age of onset and maximum level of weak muscle function during life, with types 0, 1, 2, 3, and 4. SMA type 0, also called prenatal, is the most severe and rare form, with fewer than 10 cases reported per year in the US. Kids with SMA type 0 have low muscle tone, limited or no movement in the arms and legs, and severe swallowing problems and breathing failure in infancy.

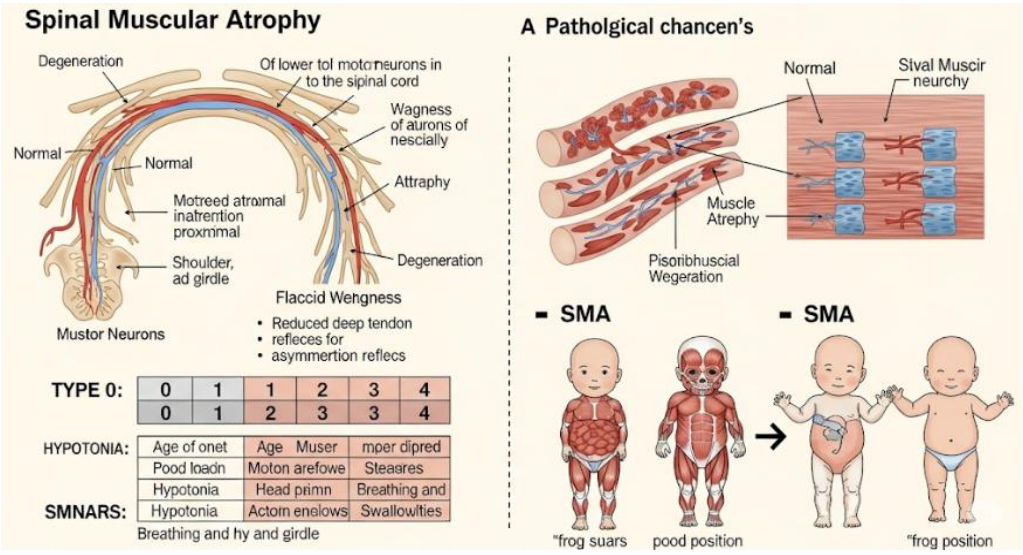

Fig 6 . 2 : SMA: A Closer Look at Muscle Degeneration

6.5.1. Symptoms and Signs

Spinal muscular atrophy (SMA) is a hereditary neuromuscular disorder characterized by progressive loss of anterior horn cells in the spinal cord and is associated with muscle atrophy and weakness. Typically, symptoms appear in infancy, childhood, or young adulthood, but some adults present with symptoms late in life. The symptoms of SMA differ markedly by subtype, primarily determined by the age of onset and the maximum size of weakness.

The earliest signs in the infant with SMA type 1 are decreased fetal movement and muscle weakness evident at birth or within the first few months of life. Death usually occurs by the age of 2 years as a result of respiratory failure. The infant is hypotonic ("floppy") with difficulty in sitting up and head control and presents with symmetric proximal muscle weakness (greater weakness of shoulder girdle and pelvic girdle muscles than distal limb muscles), absent deep tendon reflexes, and muscle atrophy (which becomes more obvious with age). As the weakness progresses, the infant develops facial weakness, possibly with a prominent forehead, narrow nasal bridge, and a "saddle-shaped" mouth. Tongue fasciculations and weak (or absent) sucking-swallowing reflexes are also found. Joint contractures may be present. The infant may develop respiratory insufficiency (with hypoventilation and hypoxemia) and aspiration pneumonia (the most common cause of death by the age of 2 years). The child may present with loss of motor milestones, positive family history, and genetic screening results. The parents may also be carriers. However, if there is no family history, and the child has a common duplicative disorder and deficiency, the central nervous system is normal.

6.5.2. Diagnosis and Assessment

The diagnosis of SMA may be complicated by the small size of the baby, the lack of clinical diagnostic features, and the nature of the clinical complaints, which may be subtle and nonspecific. A considerable proportion of SMA infants present with decreased fetal movements, arthrogryposis multiplex congenita, or bulbar symptoms such as difficulty swallowing or feeding. However, these features cannot be used exclusively for the differential diagnosis of SMA. For example, congenital myopathies may also result in arthrogryposis multiplex congenita.

Loss of antigravity head control at 1–2 months and abnormal negative or positive craniofacial signs while lying supine at 2–6 months are significant clinical features associated with the diagnosis of SMA. Evidence suggests that the likelihood of observing progressive weakness within the first year of life is greater than 98% for infants with type I SMA, approximately 50% for those with type II SMA, and 0% for

type III SMA. However, features at these ages are not confirmed predictive indicators of diagnosis. Due to this clinical heterogeneity and the lack of disease-specific clinical findings or biomarker tests, detailed molecular genetic testing of tissue samples is essential for the differential diagnosis and confirmation of SMA.

Subsequently, confirmed SMA patients require clinical assessment and testing every six months until age two and yearly thereafter. Clinical assessments include the Hammersmith Functional Motor Scale-Expanded, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, Modified Ashworth Scale, and prompts to encourage spontaneous movement use. MRI may also be performed for assessment, as characteristics include muscle atrophy, fatty replacement, my intestinal tissues, and motor unit number estimations.

6.6. Progression of Spinal Muscular Atrophy

The symptoms of SMA can be similar, but the age of onset and affected muscles can be different depending on the subtype of SMA. However, generally speaking, SMA is a progressive disease and will worsen with time. SMA is a progressive neurodegenerative disorder caused by degeneration of alpha motor neurons in the brainstem and spinal cord. In contrast with ALS, which causes denervation and reinnervation of muscle by higher numbers of motor units, SMA causes denervation without reinnervation by a diminishing number of motor units. Muscle fatigue, disuse, and hypotonia are linked with the important clinical findings of contractures, joint deformities, weakness, muscle atrophy, and breathing dysfunction of SMA. As the age of onset for different SMA subtypes varies greatly, the timing of the onset of symptoms will manifest diminished strength of the specific affected muscle groups over time. The effect on quality of life will depend on the specific muscles affected and the patient's lifestyle. Proximal weakness will impose gait and ambulation loss more and more after onset, causing problems in participating in normal daily activities for older children with type II SMA. Symptomatic treatment can postpone the time of these losses. However, eventually, surgeries to improve walking ability and joint mobility may not be enough to alleviate the effects on ambulation and independence for the patients during adolescent and adult life. Complications associated with motor function impairment and loss of ambulation worsen the quality of life.

The quality of life in people with SMA has been reported to be worse than in both the general population and specific rehabilitation patient populations. However, there is an indication that people with SMA differ greatly in terms of emotional health, support, and satisfaction with their physical health. Quality of life in people with SMA also appears to be determined more by non-clinical factors, such as social support, than clinical variables, such as the usual clinical markers of disease severity and physical function.

While it is important that treatment approaches be aimed at improving the clinical status of people with SMA, it is also essential to consider how to improve their quality of life.

6.6.1. Stages of Disease Progression

The most catastrophic form of SMA is known as SMA Type I or Werdnig-Hoffmann. Classic Type I presents very early in life, but the illness is not diagnosed usually until weeks to months after birth when the baby does not demonstrate normal muscle movement and head control, and experiences weakness and hypotonia. Usually, by the age of two months, the baby stops moving and exercising its limbs because of profound weakness. Also, tongue fasciculations or tremors may be seen. If the baby survives until the age of 5–6 months with no major crisis, the child will probably reach the landmark of never sitting independently due to choking, chest infection, difficulty swallowing, scoliosis, and joint contractures, and will die usually by age 1–2 years. The second form is SMA Type II. The onset is typically between approximately 6 months to 1 year of age when the patient presents with hypotonia and muscle weakness and is noted to have lost a few skills learned such as crawling and pulling to standing. It is diagnosed with clinical history, familial studies, genetic determination, and electromyographical studies, in which the child reveals weak muscles that like to be tested and exercised. This SMA Type II is divided into two branches: Classic Type IIA, where the baby will not be able to walk independently, and Type IIB, where the patient will walk with support and requires assistance with joint positioning around the age of 1–2 years. It is also characterized by scoliosis and joint contractures, with preservation of heart and ocular muscles. The prognosis is variable: approximately 10% of patients survive until their 30s, but most patients die between ages 5 and 20 years.

6.6.2. Impact on Quality of Life

SMA can cause significant disability in affected individuals due to the progressive weakness and muscular atrophy caused by the degeneration of anterior horn motoneurons. Disease severity is variable, but severely affected individuals require assistance for all aspects of daily care, such as fixing hair and clothing, bathing, feeding, oral hygiene, and mobility, including communicating and using the toilet. Individuals who do not meet their nutritional needs with oral feeding require the placement of a gastrostomy tube. Airway protection and clearance become more complicated as bulbar weakness rises, increasing the risk of respiratory illness. Feeding safety decreases if bulbar weakness compromises swallowing function, and aspiration may lead to recurrent pneumonia, esophageal reflux, and pulmonary aspiration. Most patients will be unable to walk, and limitations will increase in standing, sitting, and arm, hand, and finger

movements as SMA progresses. Cervical and trunk muscle weakness leads to the head and neck imbalance seen in SMA, requiring head and neck support. Musculoskeletal deformities, including scoliosis and stiff joints, may develop in the spinal and hip regions, and orthopedic surgery may relieve or limit disease consequences and complications.

The observed negative results show significant interference from the disease in all aspects of quality of life for all types of SMA. Conversely, the treatment has a significant positive impact on quality of life. A better quality of life has also been reported for patients with ASMD and those suffering from a type of loss of function through mutations, possibly due to longstanding bias benefits. Quality of life is positively affected by better health in patients.

6.7. Current Treatment Approaches

Despite the emergence of disease-modifying therapies for SMA in recent years, supportive care remains an essential aspect of managing the condition and reducing its impact. The exceptional benefit of the newly established gene-modifying treatments was revealed in clinical trials, accumulating evidence from early treatment, and clinical experience. The antiparticulate effect is thought to preserve neuronal function, delaying disease progression and disabling conditions that necessitate supportive measures; some patients still require supportive aids and machinery to conserve and ventilate vital functions. In addition, supportive treatment is indispensable for patients who do not meet the eligibility criteria for available disease-modifying drugs. Moreover, a clinical diagnosis of SMA can be triggered by the acute onset of weakness in newborns or children, which could lead to a disability in the respiratory and motor systems. For these patients, the supportive approach is important because recovery is possible even if the diagnostic workup for SMA takes several weeks until the treatment initiation.

Rehabilitation services may also contribute to a better quality of life through the facilitation of adaptive skills and devices. Therefore, SMA management usually comprises a multidisciplinary team of health professionals, who provide seamless intensive support in a motoneuron shortage, including geneticists, neurologists, clinical geneticists, functional assessment experts, therapists, dietitians, pediatricians, nurses, social workers, psychologists, palliative care specialists. However, the details of supportive management differ among patients with distinct motor abilities and requirements, necessitating close cooperation with the family or caregiver.

6.7.1. Supportive Care

Patients with spinal muscular atrophy (SMA) face various challenges and complications in daily life regardless of whether they are amenable to gene replacement therapy. SMA management consists of supportive care, which includes assessments and recommendations from professionals from diverse specialties to optimize the patient's quality of life. The timing and method of implementing supportive treatments and the professionals' priorities should be adapted to the patients' and families' needs while considering the natural course of the disease, the patient's age and SMA type, and the presence of comorbidities and complications. These measures may become more intensive with age and disease progression. Systematic multidisciplinary care can be facilitated using a multidisciplinary team or through a designated key worker. Family-centered care is also important, given the lack of treatment for SMA up to only recently. Family concerns should be taken into consideration during the hospitalization and clinical consultations to support caregiving and create a good childrearing environment. Common issues include poor muscle strength, dysphagia, and respiratory insufficiency. Assessments should include a neurological examination, dysphagia and nutrition assessments, a respiratory assessment with polysomnography, and a yearly scoliosis assessment. Supportive care treatments for SMA include a nasogastric tube or gastrostomy in the event of dysphagia with impaired caloric intake due to a lack of chewing ability; nighttime non-invasive ventilatory support in the event of upper airway obstruction due to sleep apnea; and non-invasive ventilatory support for daytime use or tracheostomy if symptomatic respiratory failure due to poor cough aides arises. Scoliosis surgery may be attempted to reduce the need for non-invasive ventilatory support; however, scoliosis and kyphosis may worsen due to underlying weakness and postoperative hypotonia. Management should be tailored to the patient, and caregivers should be supported during planning and execution.

6.7.2. Physical and Occupational Therapy

In SMA type 1, physical therapy should focus on the joint range of motion to prevent contractures, especially of the hips, knees, and ankles. If stretch-relaxation techniques, splints, night positioning, and casting are insufficient in prolonged sitting posture patients, it may be necessary to increase the surgical correction of scoliosis to prevent deterioration of respiratory function. Since the difficulty in pulmonary function increases proportionally with spinal deformity, the timing of surgery is very important. The perioral, pharyngeal, lingual, and cervical muscles should be mobilized in children who are infinitely or partially fed by enteral tube feeding. In addition, supportive respiratory care must be the foundation of motor function and quality of life. In sitting-type patients, it might be helpful to improve and maintain body posture by adding pelvic, lumbar, and

thoracic supports, or rigid or soft corsets for long periods. Patients should receive passive or active-assisted physical therapy, especially with seated posture, from infancy to stimulate reach and play skills. But while doing it, respiratory problems should be continuously monitored because hypoxia may occur easily.

In SMA type 2, physical therapy is about joint range of motion and strengthening. Since, in patients whose voluntary movement is reduced, the risk of secondary scoliosis and joint range of motion limitation increases. If ankle-foot orthoses are used, carefully decide with the patient and family members, and do not limit the ankle-foot function. In SMA types 2 and 3, since the risk of scoliosis increases and more energy is consumed due to prolonged sitting posture, scoliosis surgery should be carefully considered. In addition, in SMA type 2, which is frequently caught, hip surgery should be carefully considered by deciding the timing with the patient and family.

6.8. Genetic Therapies

SMA has a genetic cause, and therefore the rationale for a possible cure is intuitive. The great hope created by modern medicine is rapidly coming to fruition. The first wave of genetic treatments for SMA has been approved and is already in widespread clinical use. In addition to providing an exciting possible cure for SMA, the urgency to provide these therapies has also stimulated research into potential treatments for other genetic diseases.

1. Overview of Gene Therapy

Because SMA is caused by the absence of SMN, the easiest way to provide a “cure” would be to restore the production of SMN. This could be achieved by expressing the SMN1 gene in affected patients. Gene therapy can be undertaken either by delivering the normal SMN1 gene directly to target cells using a viral vector or by introducing DNA into target cells using techniques derived from those used to generate genetically modified organisms. For most patients, the simplest. Worryingly, for the first twelve SMA patients to receive intramuscular injection of SMN1 DNA without any special modifications, some patients developed paralytic disease resulting from without any special modifications, gene therapy is expected to be the most effective route of gene therapy.

2. Approved Treatments

SMA patients often have difficulty swallowing and may have significant respiratory compromise making surgery orotracheal placement and to a lesser extent percutaneous endoscopic gastrostomy difficult, if not impossible. Therefore explored the intrathecal delivery of an adeno-associated viral vector that expresses SMN1. Following encouraging results in a small number of SMA patients treated at a single center, the

manufacturer-sponsored a multi-center Phase II clinical trial. In total, fourteen SMA type I patients with ages between 2-7 months were treated. The results of this trial were extremely impressive.

3. Clinical Trials and Future Directions

The panoply of the SMA Type I animal model has provided an opportunity to initiate GMP preclinical programs before gene therapy in SMA infants. The coordination between the US FDA and sponsors has been so efficient that there are Safety and Efficacy for both systemic administration of viral vectors expressing SMN1 for Secretion and Intrathecal delivery of vectors expressing SMA for postsynaptic Transmission. However, exciting the results of the clinical trials of therapies are. The tremendous preclinical expertise that has been rapidly imported into SMA is key.

6.8.1. Overview of Gene Therapy

Gene therapy is the direct modification of a person's genetic material to counteract disease. For SMA, gene therapy is a promising approach because the conditions that cause the disease have been unraveled and, unlike many genetic diseases, SMA may be treatable by simple augmentation of an affected protein. The first major gene therapy studies involved the use of viral vectors to deliver an SMN1 transgene to the peripheral nervous system in patients with type 1 SMA. Most of the initial studies focused on safety and tolerability rather than on effectiveness but nevertheless generated considerable excitement. Consistent with the proposed mechanism of action, the development of transient neurotoxicity and antibody formation against viral vector components during these early trials were seen as encouraging because they indicated that gene delivery was taking place in both muscle and especially motor neurons.

The first gene therapy product to receive approval was Zolgensma, an AAV9 vector carrying a copy of SMN1. Retrospective analysis suggested some effects on survival, motor milestones, and the need for invasive ventilatory support. Because of the natural history of patients, children with type 1 SMA who have received Zolgensma can only be followed for about 3 years following treatment. Nevertheless, the data have been compelling enough to lead to both approval of the drug. Zolgensma is indicated for patients aged less than 2 years with SMA and fewer than 3 copies of SMN2. Children with the severe type of SMA and other already developed neurological damage cannot produce SMN protein either in motoneurons or throughout the body; the severity of their condition, and the putatively fatal outcome, argue strongly against using a powerful SMN-enhancing product, such as Zolgensma, to see if it can reverse such damage. Hence the decision to restrict its use.

6.8.2. Approved Treatments

Over the last few years, three gene therapies have been approved to treat SMA. Zolgensma is an adeno-associated viral vector-based gene replacement therapy that delivers a functional copy of the SMN1 gene into the affected individual's motor neurons. The US FDA approved Zolgensma for SMA with a genetic diagnosis, less than 2 years old, and who are naïve to previous SMA Therapy in May 2019, on a priority review basis with breakthrough therapy designation as the first ever gene replacement therapy for a neurodegenerative disease. Subsequently, Zolgensma received accelerated approval for the use of SMA type 1 patients with no genetic testing age, up to 2 months, but were treated in this group at 6-9 months in June 2020. Zolgensma has been reported to have a very good safety and efficacy profile in treating SMA patients in early life, with an increase in lifespan and comparable long-term, multi-domain motor function to SMA children who were never treated due to SMA disease severity and non-inclusion in clinical trials.

AVXS-101 / Zolgensma has a component that is a code that produces the SMN protein, while the second approved gene therapy SC-SMN, is a modified SmaSc811p. It is also an adeno-associated virus vector, modified to express the same homozygous SMN2 transgene in muscle tissues, as I.V. in non-SMA children and adults. A third SMA treatment using gene therapy is Emsani, although more different than Zolgensma and the sc-SMN transgene, than SC-SMN. Emsani consists of a recombinant adeno-associated viral vector that expresses a neuronal targeting ultra-short artificial SMN1-M5 chimeric genes that are designed for SMA1-type patients.

6.8.3. Clinical Trials and Future Directions

Not unexpectedly, the success of onasemnogene abeparvovec at addressing SMA's core deficits prompted the exploration of new gene replacement therapies. These gene replacement candidates differ from approved gene therapies in several ways. Some are intended for intrathecal injection rather than intravenous infusion. Other candidates seek to fill open-accession gaps that preclude approval of onasemnogene abeparvovec before symptom onset. IV tracheal at birth administration of AV viral vector therapies is meant to be a whole-life cure more extensive and permanent than IT delivery and pre-symptom IT delivery of Zolgensma. A recent study utilized the design unique to putative branch execution gene therapies that replace only that part of the SMN1 genome responsible for producing SMN protein, rather than the entire gene, to successfully express SMN protein in a mouse model. While a whole gene replacement, such as Zolgensma, better addresses the pathogenicity of more genes than just SMN1, branch execution gene replacement therapies can have certain advantages. They avoid on-target risks to all organ systems other than neurodevelopment and muscle. They avoid potential gene delivery

bottlenecks characteristic of IV delivery of universal AV vectors for such larger therapeutic genes. Additionally, shortened large genome preparations should increase the likelihood of efficiently engineering personalized knock-in gene therapy approaches to treating SMA.

Regarding SMA-specific therapeutic targets, AAV delivery of splicing-modifying gene therapy shows promise but risks associated with pharmacological inhibition of ubiquitin-specific protease 22 have delayed its proposed progression. AAV2-delivered antisense oligonucleotide-mediated SMN-with-near-gene-construct-preservative exon skipping is being utilized in mice and soon non-human primates along with concurrent RNA-SMN modulation in stem cell-derived motoneuron networks to explore the unprecedented synergy conferred by dual-targeting delivery. Preclinical studies suggest di-auranofin therapy, which has both pro-gastrointestinal health and pro-ventilator capacity upside, can augment outcomes from ASO and AAVs therapies that utilize the more inexplicit standard adeno-associated viral delivery method and those whose micro AO dose loads to motoneuron nuclei have their concentrations further enhanced by a strategy that uses more prepared gangliosides in the di-auranofin therapy context.

6.9. Conclusion

As the pathophysiology of SMA has become increasingly clear, so too have our treatment options. The advent of small molecule treatments that stabilize the SMN2 protein and re-initiating embryonic SMA patterning via gene transfer have resulted in clinical successes, and the systematic exploration of diverse gene therapies is likely to accelerate further developments of safe and effective SMA treatments. Small molecule therapies and gene transfer approaches are most effective left to adolescent SMA patients, postponing future motoneuron cell death and paralysis and, in the case of gene therapy, addressing the new motor unit wave recruitment hypothesis. However, there remains a need to discover treatments that can do more and restore function in adolescents and adults already symptomatic and for whom motoneuron deaths are a common occurrence.

Advancements in modeling platforms, along with newly described motoneuron biology features and human disease movement patterns, can begin to inform critical path planning for future SMA therapeutic trial designs. Modeling has already begun to delineate SAEs and identify avenues for future therapy strategies. Modeling approaches will also be critical to the broader SMA compound discovery landscape, such as high throughput screening of novel small molecules. Finally, our impacted and diverse patient population(s) desirous of novel methodologies and conditions are critically needed to continue the rapid and collective translational pace that translates basic biological principles into societal neuro therapies in SMA and other complex genetic disease

conditions. In summary, SMA's study efforts have already begun to impact the accelerated pace of full spectrum SMA translation from bench to bedside and can do more with the help of impacted patient communities.

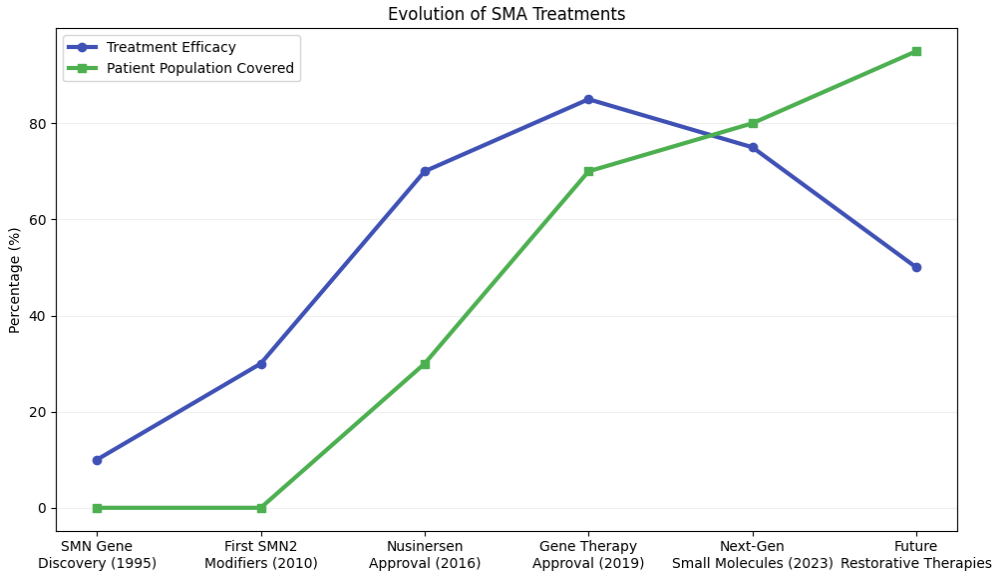

Fig 6 . 3 : Evolution of SMA Treatments

6.9.1. Final Thoughts and Future Perspectives on Spinal Muscular Atrophy

In a meta-perspective of spinal muscular atrophy (SMA) research, models have proven their worth in therapeutic options. Molecular modeling studies have identified functional domains of SMN, such as oligomerization or the interaction with other factors in metazoans. These domains can be further validated in mammals whose Smn expression can be knocked out. In mice, the interplay of developmental neurodegeneration is complex as mutant survival is analyzed, considering the conversion of lower to upper motor neurons with the lack of internode myelination in a demyelination/remyelination loop. Investigating cellular dysfunction in mouse SMA models needs more than the analyses of SMN protein levels or intranuclear SMN bodies in iPS-derived neurons and motoneurone cultures, which only observe a single cell type in a density culture system over time; the novel biophysicogenetic transgenic motoneuron and neuron SMA model allows timed monitoring of structural and functional pathology with selective readouts for both central periphery damage in living organisms.

Although we have identified basic aspects of the pathomechanism of the disease and the major regulators such as survival, we do not have a therapeutic or genetic disease modifier yet. Milestones in SMA research were the identification of the disease-causing

gene and our generation of the first mouse model, which made it possible to confirm and investigate loss of function and to identify low SMN levels as the common denominator across the types in a mouse model. The development of ASOs and new gene therapy approaches for the treatment of all SMA types in neonates and children, however, opened Pandora's box in treating all forms of the disease. We do not just want to cure motoneuron loss but also rebuild the connected neuromuscular junctions and muscle structures. In addition, to sophisticated specific RNA-targeted therapies for other motoneuron diseases, SMA research gave the impetus to study and develop novel strategies and cures for similar neurodegenerative diseases with loss-of-function mutations.

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