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A Review on Genetic Spinal Muscular Atrophy

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ABSTRACT:

SMA is a hereditary disorder that affects the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle).The majority of nerve cells that regulate muscles are found in the spinal cord, which explains why the disease's name includes the word spinal. The primary effect of SMA is on muscles, which do not receive impulses from these nerve cells. When muscles aren't stimulated by nerve cells, they atrophy, which is a medical term for shrinking.SMA is a motor neuron disease that causes the loss of nerve cells called motor neurons in the spinal cord. The most common form of SMA (chromosome 5 SMA, also known as SMN-related SMA) has a wide range of onset, symptoms, and progression rates. Types 1 through 4 of chromosome 5-related SMA, which is commonly autosomal recessive, are categorised to account for these variances.The age at which SMA symptoms appear generally coincides with the severity of motor function impairment: The stronger the influence on motor function, the younger the onset age. Children who show symptoms at birth or early in childhood usually have the lowest degree of functioning (type 1). SMA that develops later in childhood and has a milder course (types 2 and 3 in teenagers or adults, and type 4 in adults) is linked to greater levels of motor function. SMA is caused by a loss of SMN, or "survival of motor neuron," a motor neuron protein. As its name suggests, this protein appears to be essential for proper motor neuron function. SMN is a key regulator of gene expression in motor neurons. Its scarcity is due to genetic flaws (mutations) in the SMN1 gene on chromosome 5. The most common mutation in persons with SMA is exon 7Because there is 99 percent homology between these two genes, neighbouring SMN2 genes can partially compensate for non-functional SMN1 genes. Mutations in genes other than SMN1 cause other rare forms of SMA (non-chromosome 5).

Introduction:

Spinal muscular atrophy (SMA) is a genetic disease affecting the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle).

Johann Hoffman, a German scientist, and Guido Werdnig, an Austrian scientist, were the first to describe Genetic Muscular Spinal Atrophy. Both men had seen a number of babies in their first few months of life who had developed muscle weakness. They also noticed that the sickness seems to be handed on through the generations. They discovered that the motor neuron cells in these neonates appeared to be deteriorating as they investigated this strange condition, particularly in the anterior horn of the spinal cord. In contrast to other areas of the spinal cord that are involved with touch and other sensations, this segment of the spinal cord is located in the front and is connected to skeletal muscles. As a result of their observations, they were able to diagnose spinal stenosis.

Spinal muscular atrophy (SMA) is a hereditary condition characterised by muscle weakening and loss in skeletal muscles. It's caused by a lack of motor neuron cells, which are responsible for controlling muscle action and development. Muscles that are close to the centre of the body have more weakness than muscles that are farther away from the centre of the body. Muscle weakness usually worsens as people get older.

Genetics of spinal muscular atrophy:

Proximal SMA patients lack a functional SMN1 gene but have one or more copies of the SMN2 gene. Although the sequences of SMN1 and SMN2 are quite similar, SMN2 has a translationally silent C–T transition in exon 7 that changes an exonic splice enhancer motif. SF2/ASF, the SR protein that directs exon 7 inclusion, is generally recruited by this motif. This motif is broken in SMN2-derived transcripts, and an exon splicing silencer (ESS) motif is formed, which favours the recruitment of hnRNPA1 and RNA-binding protein (RBP) Sam68, resulting in frequent exon 7 exclusion. [M.A. Tarnopolsky et al., 2004] Exon 7 is missing from the resultant SMN transcripts, which code for a highly unstable SMN protein that is destroyed by the ubiquitin–proteasome system (UPS). A minority of SMN2-derived transcripts are spliced to include exon 7 which codes for a full-length SMN transcript and protein. SMA thus results from reduced expression levels of full-length SMN protein. The SMN protein is widely expressed and together with the Gamins forms a complex that is important in the assembly, recycling, and maintenance of small nuclear ribonucleoproteins (snRNPs), which are components of the spliceosome. Reduced SMN protein levels in cultured cells and SMA tissues has been associated with reduced fidelity of splice-site pairing causing a general splicing defect of multi-intron-containing

genes. These findings show that aberrant RNA splicing may be a direct cause of SMA. However, it has been postulated that SMN has other functions in motor neurons, which could explain why this cell type is especially vulnerable to SMN protein shortage. Axonal transport and b-actin mRNA translation are critical for axonal development and presynaptic differentiation. SMN has been demonstrated to traffic in motor nerve axons and to regulate b-actin mRNA translocation into the growth cone of cultured motor neurons with its binding partner hnRNP-R. SMN-deficient motor neurons also had shortened axons and tiny growth cones, as well as a lack of b-actin mRNA. As a result, the SMN protein could play a key role in b-actin mRNA trafficking and local translation, both of which are necessary for normal motor neuron cytoskeletal integrity and synapse stability.

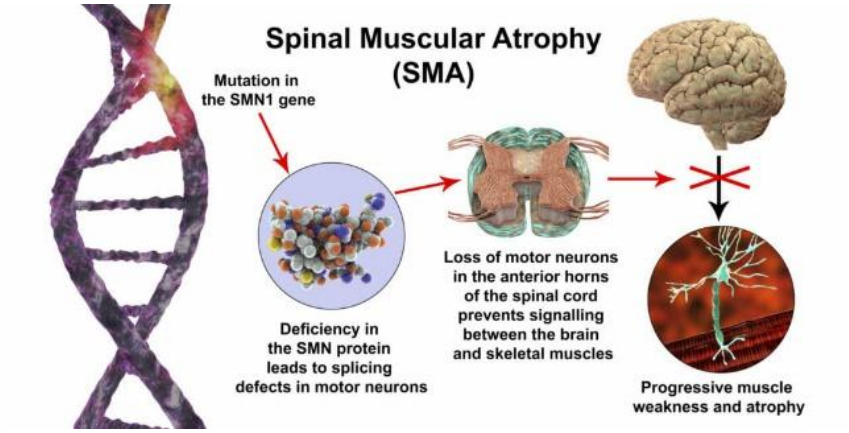


Fig. No. 01 Genetics of spinal muscular Atrophy

In female patients with SMA, there is a genetic modifier. A mutation in the survival Motor Neuron 1 (SMN 1) gene can result in the loss of Survival Motor Neuron protein, causing spinal muscular atrophy. This is partly explained by the paralogue gene Survival Motor Neuron 2 (SMN 2), which differs from Survival Motor Neuron 1 (SMN 1) by a single nucleotide polymorphism in exon. Exon 90 percent of the SMN2 mRNA is rejected as a result of this basic alteration, and the truncated unstable protein (SMND7) is rapidly destroyed. The SMN protein is globally transmitted and plays a critical role in cell homeostasis through a variety of functions that are still unknown. It's engaged in a variety of cell processes, including spliceosomal machinery construction, endocytosis, and protein translation. Because of its several functions, SMN depletion might result in systemic illness that extends beyond the motor neuron, which must be considered while developing new therapeutics. [J. Wan et al., 2012]

There are several types of genetic spinal muscular atrophy, all of which are caused by mutations in the same genes. The kinds of hereditary spinal muscular atrophy range in the time it takes for symptoms to appear and the severity of muscle weakening, but there is overlap between them. Other types of spinal muscular atrophy and disorders affecting the motor neurons. Other genes are involved in the development of spinal muscular atrophy with progressive myoclonic epilepsy, spinal muscular atrophy with lower extremity predominance, X-linked infantile spinal muscular atrophy, and spinal muscular atrophy with respiratory distress type 1.

The most unusual and serious type of spinal muscular atrophy is type 0 genetic spinal muscular atrophy, which manifests before birth. Affected infants move less in the womb and are born with joint contractions as a result. They are born with extremely weak muscles. Their respiratory muscles are weak, and they frequently succumb to respiratory failure and do not live for lengthy periods of time. Some infants with spinal muscular atrophy type 0 also have inborn birth abnormalities, which are heart problems that are present from birth. [2011, Namavan Y, et al.]

The most frequent type of ailment is spinal muscular atrophy type 1, commonly known as Werdnig- Hoffman disease. It is a severe kind of muscle weakness that appears at birth or within the first few months of life. The majority of the youngsters who are impacted are unable to control their head motions, development, or sit alone. Children with this type of defect may have swallowing issues, which can lead to feeding difficulties and stunted growth. [Ramser J, et al, 2008]

Muscle weakness develops in children between the ages of 6 and 12 months in spinal muscular atrophy type 2 (also known as Dubowitz illness). This sort of child can sit without assistance, yet they may require assistance getting to a seated position. However, if muscle weakness worsens later in childhood, affected children may require assistance in sitting. Individuals with type II spinal muscular atrophy are unable to stand or walk without assistance.Uncontrollable trembling (tremors) in their fingers, a twisting spine, and life-threatening respiratory muscle weakening are also common symptoms. The life expectancy of people with spinal muscular atrophy type II varies, however many live into their twenties or thirties.

Spinal muscular atrophy type 3 (also known as Kugelberg-Welander disease) causes muscle weakness after early childhood. Individuals with this syndrome can stand and walk without assistance, but walking and climbing stairs may become increasingly difficult over time. Many persons who are affected will require wheelchair assistance later in life. The life expectancy of people with type III spinal muscular atrophy is typical.

Type 4 spinal muscular atrophy is a rare condition that usually manifests in early adulthood. Slight to moderate muscle weakness, tremors, and mild respiratory issues are common in those who are affected. The life expectancy of people with spinal muscular atrophy type IV is typical.

The worldwide prevalence of hereditary spinal muscular atrophy, which affects 18,000 to 10,000 persons. The most frequent type of spinal muscular atrophy is type 1, which accounts for almost half of all cases. The next most prevalent types are 2 and 3, while types 0 and 4 are uncommon.

Spinal muscular atrophy is an autosomal recessive disease, meaning both copies of the SMN1 gene in each cell carry mutations. In most circumstances, the parents of someone with an autosomal recessive disorder each have one copy of the faulty gene, but they don't display any signs or symptoms of the disease. Rarely, a person with spinal muscular atrophy gets an SMN1 gene mutation from one parent and develops a new mutation in the other copy of the gene during the creation of reproductive cells (eggs or sperm) during early embryonic development. Only one parent is a carrier of the SMN1 mutation in these cases.

Individuals with more than two copies of the SMN2 gene are unlikely to inherit them from their parents. They usually occur as a result of a random error during the replication of DNA in an egg or sperm cell, or shortly after conception.

There have been significant improvements in our understanding of the genetic and molecular foundation of SMA recently. Since 2011, 13 SMA genes have been discovered thanks to next-generation sequencing technologies. To date, 33 genes have been identified as causal. Defects in RNA metabolism and splicing, axonal transport, and motor neuron development are all common pathological themes. There is now a lot of hope for developing a viable, disease-modifying treatment for SMN-related SMA, and a lot of work is being done in that direction.

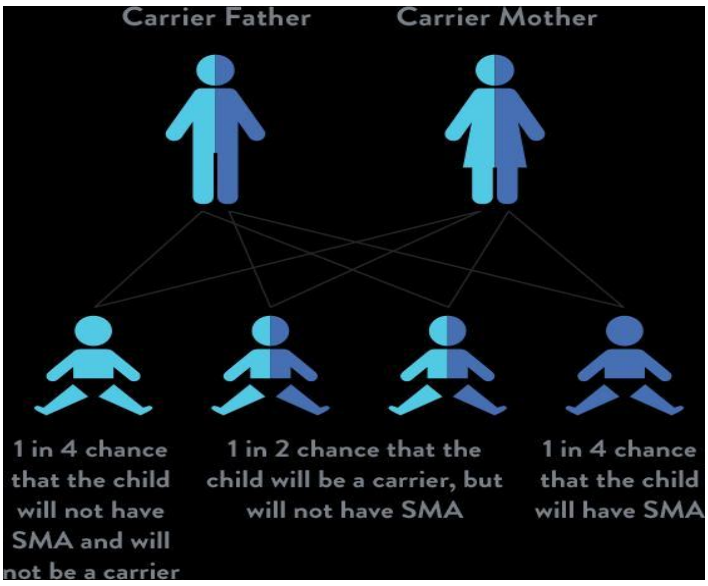
Small-molecule SMN enhancers, antisense oligonucleotides to correct SMN2 splicing, neuroprotectants, stem cell and gene treatments, and muscle function regulators are among the intriguing therapeutic options in research. Recent genetic findings in SMA, cellular mechanisms driving motor neuron degeneration, disease progression, and techniques to address "clinical trial readiness" and the development of innovative treatment options will be the focus of this study. 2012 [MF Messina and colleagues]

Supportive care is the current standard of care for SMAs. SMA can cause significant respiratory impairment and contractures in neonates and toddlers, as well as severe scoliosis.

Proximal SMA

SMN 1 related SMA

Respiratory support and spinal fusion operations may be required for these patients. Particular care should be made to vocal fold paresis in HMN7B or SPSMA, which produces stridor and finally airway blockage. Procedures such as vocal fold tie back or tracheostomy may be required. SBMA patients may have pharyngeal weakness, which can lead to aspiration. Patients with distal SMAs may benefit from distal weakness walking aids and/or ankle foot orthoses. The weakening is usually symmetrical, more proximal than distal, the legs are more afflicted than the arms, and the diaphragm, extra ocular, and face muscles are relatively unaffected. Despite the diaphragm's relative sparing, respiratory insufficiency is a serious consequence of SMA5q. Deep tendon reflexes are usually absent or severely weakened. There is a wide range of clinical



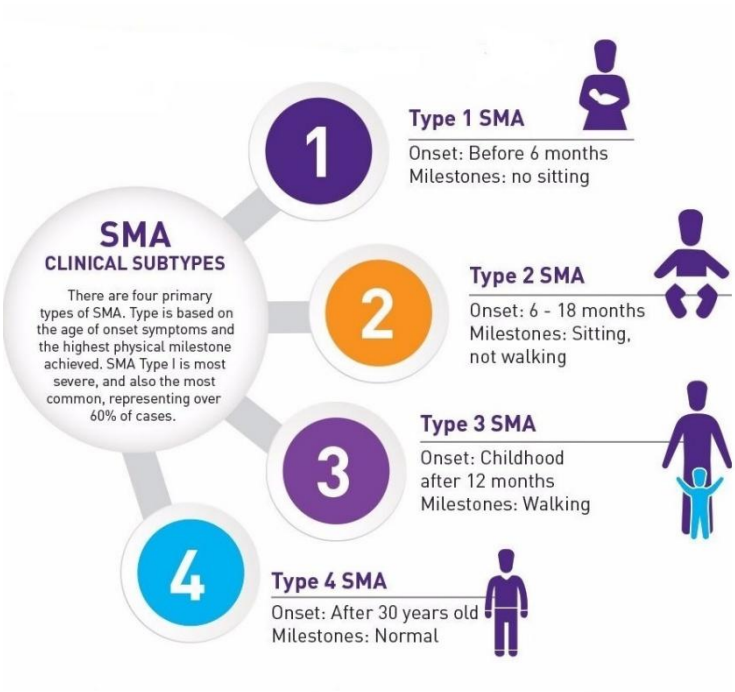
severity, with phenotypes classified as kinds 1–4 , based on the maximal motor milestone achieved and the age of beginning. With beginning before 6 months of age, infants with SMA type 1, or Werdnig–Hoffman disease, do not acquire unassisted sitting, and respiratory failure frequently leads to death within the first two years without breathing support. Before the age of 18 months, SMA type 2 causes weakness.

Patients can sit on their own but not stand or walk, and their life expectancy is frequently in the teens or early twenties. After 18 months of age, people with SMA type III (also known as Kugelberg–Welander disease) are able to walk unassisted. [MB Harms and colleagues, 2012]
The clinical history varies greatly, with some people needing wheelchair help as children and others walking as adults. The average lifespan is around 80 years. Adults are affected by SMA type 4.

NON SMN 1 related SMA

Infantile SMA variations or SMA "plus" syndromes, which have additional clinical symptoms like as arthrogryposis, anomalies of extra ocular movements, brainstem indications, or cardiomyopathy, account for less than 5% of infantile SMA. Congenital hypotonia, increasing postnatal weakness, and reflexion with anterior horn cell degeneration define these conditions. X-linked infantile SMA with arthrogryposis (XL-SMA), SMA due to mitochondrial failure, SMA with pontocerebellar hypoplasia (SMA-PCH/PCH1), and SMA with respiratory distress (SMARD) are among the differential diagnoses. Due to mutations in IGHMBP2, SMARD1 (or HMN type VI) is probably the second most frequent paediatric form of SMA. SMARD1 is characterised by early respiratory failure caused by diaphragmatic paralysis and weakness, which can be widespread or limited to the upper limbs and distal muscles. SMARD1 has recently extended its phenotypic to include mild weakness without substantial indications of respiratory dysfunction. While recessive SMN1 mutations account for the vast majority of proximal SMA cases, the genetic heterogeneity of proximal SMA beyond childhood has been recognised for decades, with autosomal dominant SMA accounting for only 2% of cases. This comprises SMA types 1 and 2, which affect the lower extremities and are caused by heterozygous mutations in the genes DYNC1H1 and BICD2, respectively. Muscle weakness and atrophy are more common in the proximal lower limbs, but upper limb and distal lower limb involvement is possible. Mild upper motor symptoms, foot abnormalities, or lower limb contractures may be seen in certain patients. The senses, bulbar, and cognitive capabilities are all intact. SMA that affects the lower extremities is either stable or progresses slowly over time. Late-onset autosomal dominant proximal SMA has been linked to dominant mutations in the vesicle-associated membrane-associated protein, protein B, allelic with ALS type 8.Although LMNA mutations are more commonly associated with muscle disease (particularly Emery–Dreifuss muscular dystrophy), the phenotypic spectrum also includes adult-onset autosomal dominants SMA followed by cardiomyopathy . Significantly, the phenotype of tauopathies has recently broadened to include lower motor neuron disease, with autosomal dominant mutations in MAPT producing proximal weakness of the upper limbs, and respiratory insufficiency without dementia, pyramidal, or bulbar involvement.
Recessive mutations in PLEKHG5 may also be linked to proximal SMA. Despite being classed as DSMA4, the clinical features are proximal muscular weakness with difficulties walking and ascending stairs that begins before the age of three years. Bulbospinal muscular atrophy, often known as Kennedy's illness, is the most prevalent adult-onset SMA and is linked to higher CAG repeats in the androgen receptor. Fasciculation's, muscle weakness and atrophy, dysarthria, and dysphagia are all symptoms of this X-linked recessive neurodegenerative illness. Patients may also develop endocrine symptoms, which are linked to mutations in the HSPB1 and HSPB8 genes, as well as HSPB3, GARS, FBXO38, and DYNC1H1 genes. The autosomal recessive types III and IV have been shown to have a link to 11q13 (synonymous with DSMA type 3). The development of weakness in the hand muscles distinguishes HMN type V, which may be linked to dominant mutations in BSCL2, GARS, or REEP1. Vocal cord paresis distinguishes HMN type VII, which could be caused by dominant mutations in SLC5A7 (CHT) or DCTN1. The discovery of recessive mutations in DNAJB2 (HSJ1), which cause a generic presentation of lower limb predominate slowly progressing weakness with young adult onset, known as DSMA type 5, highlights the genetic variability of HMN. [MB Harms et al., 2010]
The clinical range of dHMN/SMA is continuing to broaden, with congenital onset and X-linked or mitochondrial inheritance now being considered. Many of these illnesses are allelic with axonal Charcot-Marie-Tooth disease (HSPB1, HSPB8, BSCL2, GARS, TRPV4), juvenile variants of ALS (SETX), and hereditary spastic paraplegia (HSPB1, HSPB8, BSCL2, GARS, TRPV4) (BSCL2, HSPB1). In addition, an autosomal recessive dHMN with pyramidal symptoms has been described in the Jerash region of Jordan (dHMN-J), which is associated to 9p21.1-p12. Mutations in ATP7A (X-linked dHMN, allelic with Meknes disease) and LAS1L (SMARD2) may be connected to X-linked recessive dHMN/DSMA. TRPV4 mutations have recently been linked to congenital distal SMA and scapuloperoneal SMA. Vocal cord paralysis, scoliosis, contractures, or proximal upper limb weakness are some of the associated clinical characteristics. Mutations in MT-ATP6 and MT-ATP8 have recently been shown to cause less severe phenotypes, including recurrent attacks of symmetrical limb paralysis and a later-onset distal motor neuropathy, mimicking periodic paralysis due to channelopathies, challenging the dogma of varied and multisystem involvement in mitochondrial disease.

Types of SMA:



Genetic spinal muscular atrophy type -1:

Other Names: Werdnig-Hoffmann disease; Werdnig Hoffmann disease; Muscular atrophy, infantile.

Werdnig Hoffmann disease, also known as spinal muscular atrophy 1 (SMA1), is a hereditary neuromuscular condition that damages the nerve cells that govern voluntary muscles (motor neurons). SMA1 symptoms appear before 6 months of life and include progressive muscle weakness and poor muscle tone (hypotonia), which are caused by the loss of lower motor neurons in the spinal cord and brain stem. There are also issues with feeding and breathing. Changes (pathogenic variations, also known as mutations) in the SMN1 gene cause SMA1, which is inherited in an autosomal recessive pattern.

SMA1 is diagnosed when symptoms are present and genetic testing confirms the diagnosis. In the United States, SMA has been added to the list of recommended new-born screening tests, allowing it to be discovered before symptoms appear. This happened because new medicines are being created that are altering the disease's course. Nusinersen (Spinraza) was the first FDA-approved medication for SMA1 in December 2016. Many babies with SMA1 are achieving and maintaining age-appropriate developmental milestones, such as sitting, crawling, and walking, because to continued therapy with nusinersen. Breathing problems, dietary issues, and hospital admissions have all decreased on average. Treatment response, on the other hand, varies. Some babies with SMA1 may not respond to nusinersen at all, or they may have medical issues that prevent them from receiving it. Other treatments continue to be beneficial.

Symptoms:

Before the age of six months, infants with spinal muscular atrophy 1 (SMA1) have severe weakness. SMA1 is characterised by muscle weakness, a lack of motor development, and inadequate muscle tone (hypotonia). Infants with the worst prognosis have respiratory and eating (sucking and/or swallowing) issues. Scoliosis (spinal curvature) and other skeletal disorders affect some children. In most cases, intellectual development is normal. Affected children are unable to sit or stand, and the majority of them die before reaching the age of two owing to respiratory insufficiency. The symptoms that persons with this disease may experience are listed in this table. Symptoms of most diseases differ from person to person. All of the symptoms listed may not be present in all people who have the same condition. This information comes from the Human Phenotype Ontology database (HPO). The HPO compiles data on symptoms that have been described in medical literature. The HPO is regularly updated. To get more detailed information on a symptom, use the HPO ID.

Inheritance:

SMA1 (spinal muscular atrophy 1) is a disease that runs in families. This means that in order to be affected, a person must have a change (mutation) in both copies of the corresponding gene in each cell. Because they each contain one mutant copy of the gene, the parents of an affected person are known as carriers. Carriers, on the other hand, are normally unaffected by the disease and show no signs or symptoms. When two carriers of an autosomal recessive disease produce children, each child has a:

• There is a 25% chance of acquiring the condition.

• You, like your parents, have a 50 percent chance of being an unaffected carrier.

• A 25% chance of not contracting the disease and not being a carrier.

A person with SMA1's unaffected sibling has a 2/3 chance of being a carrier.

Only about 2% of people with SMA1 do not get it from both parents. In these situations, the affected person inherits one mutated copy of the gene from one carrier parent and develops a new mutation in the other copy of the gene for the first time.

Genetic spinal muscular atrophy type -2:

SMA2 (spinal muscular atrophy type 2) is a neuromuscular condition caused by a genetic mutation that affects the nerve cells that govern voluntary muscles (motor neurons). Between the ages of 6 and 12 months, kids with SMA2 have progressive muscle weakness if they are not treated. SMA2 babies can sit without assistance, but they cannot stand or walk on their own. SMA2 babies can sit without assistance, but they can't stand or walk on their own. Feeding and respiratory issues can also arise. SMA2 is inherited in an autosomal recessive way and is caused by alterations (pathogenic variations, also known as mutations) in the SMN1 gene.

Symptoms suggest SMA2 and genetic testing confirms the diagnosis. In the United States, SMA has been added to the list of recommended new-born screening tests, allowing it to be discovered before symptoms appear. This happened because new medicines are being created that are altering the disease's course. The first FDA-approved medication for SMA2 was nusinersen (Spinraza) in December 2016.Many babies and children with SMA2 are achieving and maintaining age-appropriate developmental milestones, such as sitting, crawling, and walking, thanks to continued therapy with nusinersen. In general, breathing problems, dietary issues, and hospital admissions diminish. Treatment response, on the other hand, varies. Some children with SMA2 may not respond to nusinersen at all, or they may have medical issues that prevent them from receiving it. Other treatments continue to be beneficial.

Symptoms

The signs and symptoms of spinal muscular atrophy type 2 (SMA II) usually appear between the ages of six and twelve months. Muscle tone problems can be detected as early as birth or within the first few months of life. Affected children may experience a sluggish progression of motor milestones at first. However, the capacity to sit independently is often the highest motor milestone obtained, and this milestone is frequently lost by the mid-teens. SMA II patients are unable to stand or walk without assistance. Finger tremors, breathing problems, dietary problems, and skeletal abnormalities are some of the other indications and symptoms (such as scoliosis and hip dislocation).

Symptoms of most diseases differ from person to person. All of the symptoms listed may not be present in all people who have the same condition. This information comes from the Human Phenotype Ontology database (HPO). The HPO compiles data on symptoms that have been described in medical literature. The HPO is regularly updated. To get more detailed information about a symptom, use the HPO ID.

Causes

Changes (mutations) in the SMN1 gene cause spinal muscular atrophy type 2 (SMA II). The severity of the illness is affected by extra copies of the SMN2 gene. These genes code for a protein that is required for the correct operation of particular nerve cells (known as motor neurons) that control muscle movement. Reduced levels of this protein and the loss of motor neurons are caused by mutations in the SMN1 gene. This, in turn, creates the SMAII-specific signs and symptoms.

Additional copies of SMN2 can compensate for some of the protein lost as a result of SMN1 mutations. As a result, those with extra copies of SMN2 may experience milder symptoms and develop the disease later in life.

Inheritance

SMA II (spinal muscular atrophy type 2) is an autosomal recessive disease. This means that a person must have a mutation in both copies of the relevant gene in each cell in order to be affected. The parents of an affected person are known as carriers because they each have one mutant copy of the gene. Carriers usually show no indications or symptoms of the disease. When two autosomal recessive disease carriers have children, each child has a:

• A 25% risk of having the ailment

• a 50% chance of being a carrier like each of the parents

• a 25% chance of not having the condition and not being a carrier

It's worth noting that affected people have a de novo SMN1 mutation in one copy of the SMN1 gene in roughly 2% of instances. Because just one parent has an SMN1 mutation in these circumstances, the affected person's siblings are not at risk of developing SMA.

Genetic spinal muscular atrophy type -3:

SMA type 3 is a milder form of proximal spinal muscular atrophy that causes muscle weakness and hypotonia due to degeneration and loss of lower motor neurons in the spinal cord and brain stem nuclei.

After ambulation has been acquired, the condition manifests after 12 months of age (typically between infancy and adolescence). Some publications have differentiated two subtypes (SMA3a and SMA3b): Patients with SMA3a onset before the age of three years are classified as SMA3a, whereas those with SMA3b onset after three years are classified as SMA3b. Walking, running, and stair climbing are all frequent difficulties. Muscle weakness starts in the knees and hips and spreads to the shoulders and arms. Legs are always impacted more severely than arms. Scoliosis and weak finger trembling are common, and the patellar reflex is missing.

SMA3 is caused mostly by deletions in the SMN1 gene, which codes for the SMN (survival motor neuron) protein, as with other forms of SMA. Although there is considerable variance, the number of copies of the second SMN gene is inversely associated to disease severity in SMA, with patients with MSA3 having three (SMA3a) or four (SMA3b) SMN2 copies. Deletions of the NAIP gene, which may play a role in disease severity modification, have also been found in SMA3 patients, however they are less common than in SMA1 and 2.

Genetic spinal muscular atrophy type -4:

Adult-onset proximal spinal muscular atrophy type 4 (SMA4) is characterised by muscle weakness and hypotonia caused by degeneration and loss of lower motor neurons in the spinal cord and brain stem nuclei. In most cases, SMA4 appears in the second or third decade of life. Muscle weakness starts in the knees and hips and spreads to the shoulders and arms. Waddling is a frequent gait. Finger trembling, fasciculation, and calf hypertrophy are all possible side effects. Although the clinical picture is similar to that of SMA3 (see this term), the motor impairment in SMA4 is less severe. SMA4 has been linked to deletions in the SMN1 gene, which codes for the SMN (survival motor neuron) protein, just like the other forms of SMA. Although there is considerable variance, the number of copies of the second SMN gene is inversely associated to disease severity in SMA, and some studies have found that patients with the mild SMA4 variant have several (four to six) SMN2 copies. However, some patients with SMA4 do not have SMN1 gene mutations, and the genetic abnormalities in these cases are still unknown.

Symptoms of SMA

Symptoms of SMA include:

The symptoms of SMA are varied, ranging from mild to severe. IN SMA, the muscles closer to the centre of the body are usually more afflicted than the muscles further away.

SMA symptoms vary depending on the type and severity of the disease, as well as the age at which it manifests.

Muscle weakness and twitching are common complaints.

• breathing and swallowing problems

• Muscle weakness causes changes in the form of the limbs, spine, and chest.

• standing, walking, and possibly sitting with difficulty

SMA type 1 babies are born with weak muscles, low muscle tone, and feeding and breathing issues. Symptoms of SMA type 3 may not develop until the child's second year of life.

Muscle weakening and atrophy are the hallmarks of SMA in all of its forms. These occur when the nerves that control movement, known as motor neurons, fail to send a signal to the muscles to contract. The muscles closest to the centre of the body are usually affected by the weakening.

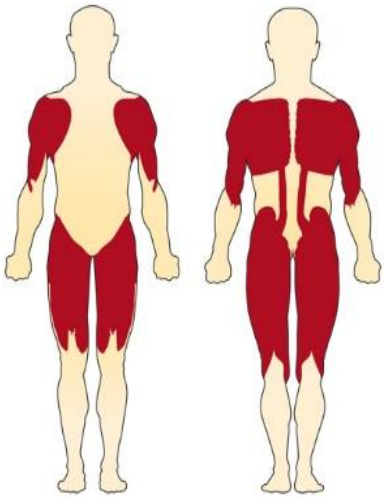
The axon of motor neurons ordinarily transmits these signals from the spinal cord to the muscles. In SMA, either the motor neuron or the axon stops working or does not work at all. SMA is a degenerative disease with symptoms that progressively deteriorate over time.

Many of the changes are problems of the underlying muscle weakness, rather than symptoms of SMA.

Therapy can help to alleviate some of these problems.

The predominant symptom of SMA caused by chromosome 5 (SMN-related) is voluntary muscular weakness. The muscles closest to the centre of the body, such as the shoulders, hips, thighs, and upper back, are the most impacted. Deep tendon reflexes are reduced, and the lower limbs appear to be impacted more than the upper limbs. 4

If the muscles that control breathing and swallowing are compromised, this might lead to anomalies in these actions. Spinal curvatures can develop if the back muscles weaken.In chromosome 5-related SMA, there is a lot of heterogeneity in the age of onset and the amount of motor



function achieved. These are broadly connected with the amount of functional SMN protein present in motor neurons, which is correlated with

the number of copies of SMN2 genes a person possesses. In chromosome-5 SMA, sensory, mental, and emotional functioning are all normal.

Some types of SMA aren't caused by a lack of chromosome 5 or SMN. The severity of these kinds, as well as the muscles that are most affected, varies widely. While most forms, such as the chromosome 5-related form, affect predominantly the proximal muscles, other forms, at least in the beginning, impact mostly the distal muscles (those further distant from the body's centre).

Variability of clinical features and Severity

Muscle weakness and atrophy are the most common clinical signs of SMA, which are caused by motor

neuron dysfunction and loss. Weakness is normally symmetrical and predominates in the proximal region. The severity of the condition can range from modest proximal limb weakness in adults to severe widespread weakness with respiratory failure in new-borns. Lower limbs are more involved than upper limbs, and bulbar and respiratory weakness are more common in cases when limb weakness is severe. In all but the most severe cases (type 0), the onset and evolution of weakness differs from that of many other motor neuron illnesses in that there is frequently a presymptomatic stage, followed by fast escalating functional loss and a later more static phase with gradual progression. Some families may even have brief moments of improvement after a period of growth. The rationale for this pattern of advancement is unknown, as is the natural history of the disease in its early stages. Some people have worsening weakness during times of stress, such as infection or pregnancy.

Clinicians observed a range of severity in SMA patients long before the causal gene was identified, which eventually led to a disease categorization. SMA has typically been divided into types 1–3, however some specialists advocate for a more comprehensive classification that includes other subtypes. The onset and severity of disease, and hence type, are primarily related to SMN2 copy number (and, presumably, SMN protein level), giving a molecular basis for the classification of SMA subtypes. SMA requires at least one copy of SMN2, and most infants with the most severe form of the illness (type 0) have only one copy. SMN2 is commonly found in two or three copies in infants with type 1 SMA. Three copies are frequently associated with type 2 SMA. Patients with type 3 have 3–4 copies, while those with type 4 have 4 copies or more. Variants within the SMN2 gene, in addition to copy number changes, can enhance full length SMN protein and thus alter phenotypic diversity. 859G>C in exon7 of SMN2 is one example, which raises exon7 inclusion by 20%. Discordant phenotypic severity in siblings with the same copy number of SMN2 suggests the presence of other genetic moderators. Plastin 3 expression has been found to be a modulator of severity in females with SMN1 deletions, but it has also been found to be high in severely affected female siblings.

Type 1 SMA is the most frequent and severe form of SMA, accounting for 45 percent of cases, and it is associated with onset after birth but before the age of six months. Before experiencing limb weakness, respiratory difficulty, a weak cry, and poor feeding, infants may appear completely normal. Affected babies acquire a splayed-leg or "frog-leg" lower limb posture as a result of significant hypotonic weakness in the lower limbs. A bell-shaped malformation of the chest may also be visible as a result of poor ribcage expansion combined with somewhat preserved diaphragm strength. During inspiration, paradoxical breathing is characterised by flattening of the chest wall (rather than expansion) and protrusion of the abdomen. There is flexic proximal-predominant weakness with sparing of the eye muscles and relative sparing of the face muscles, according to the examination. Tongue fasciculation’s are a very common occurrence. Cognition remains unaffected, and there is evidence of above-average intelligence. The ability to sit independently is never gained by definition, and in the vast majority of cases, death occurs before the age of two. The use of aggressive supportive treatment, such as breathing assistance, can significantly enhance survival rates. In some infants, a rare and very severe clinical phenotype has been identified, leading to the categorization of type 0 SMA. Hypotonia, respiratory distress, a weak cry, and poor feeding are all clinical symptoms of type 0, which usually begins before delivery and can lead to joint contractures due to decreased intrauterine movement. Respiratory insufficiency is present at birth, and mortality occurs within a few weeks. Some people

choose to divide SMA type 1 into a, b, and c instead of adopting the type 0 classification, with type 1a being the most severe and overlapping with type 0.

Type 2 SMA, which accounts for around 20% of all instances, usually appears between the ages of 6 and 18 months. Sitting ability is normally developed by 9 months, though it might be delayed. These children will never be able to stand or walk on their own, however some patients may be able to stand with the use of bracing or a standing frame. The lower limbs show the most severe proximal predominate weakness on examination. In most cases, reflexes are lacking. Fine tremor (minipolymyoclonus) is commonly seen in the distal limbs and has long been linked to intermediate stages of the disease. Tongue atrophy and fasciculation's are also common. Facial and ocular muscles are spared, just as they are in type 1. In type 2 diabetes, impaired swallowing and ventilatory insufficiency are common, especially in patients at the severe end of the spectrum. Scoliosis is a common occurrence in this group and is a major contributor to restrictive ventilation problems. Because of improved natural history associated with more active supportive care, the majority of patients with SMA type 2 live to be 25 years old, and many live considerably longer.

About 30% of people have type 3 SMA, which develops between the ages of 18 months and adulthood. Standing or walking without assistance is achieved by definition, though many individuals lose these abilities as their disease progresses. Type 3 patients are further divided into two groups: type 3a, which begins between the ages of 18 months and three years, and type 3b, which begins between the ages of three and thirty years. Patients generally complain of falls, difficulties ascending stairs, and other proximal weakening symptoms. Many people are able to continue ambulation despite significant weakness due to abnormal gait features developed to compensate for weakness. Patients that are ambulatory may have foot deformities. SMA type 3 has a typical lifespan. At the mild end of the spectrum, some SMA classifications contain one additional disease subtype. Patients with type 4 SMA may be diagnosed in this situation. Patients with type 4 SMA, which accounts for less than 5% of all SMA cases, are ambulatory and have the mildest form of the disease. The symptoms are quite similar to type 3's, with the exception of the later onset throughout maturity. Though the exact age of commencement of type 4 is unknown, it is commonly assumed to be around the age of 30.

In addition to the motor unit loss-related aspects of SMA, unusual observations in preclinical animal models and a small number of patient case series have revealed that non-motor symptoms may emerge on occasion. Sensory involvement, heart problems, gastrointestinal and autonomic dysfunction, and endocrine disorders are all possibilities. Because of the pervasive nature of the SMN protein and its universal requirement for cellular function, the likelihood of non-motor components of SMA is not surprising, but the exact prevalence and effect of these atypical traits remain unknown. This trend could be related to a threshold effect of susceptibility of other tissues to very low levels of SMN protein associated with type 0 SMA and a single SMN2 copy, and this trend could be related to a threshold effect of susceptibility of other tissues to very low levels of SMN protein associated with type 0 SMA and a single SMN2 copy.

Diagnosis

Some of the symptoms of SMA are similar to those of neuromuscular illnesses including muscular dystrophy. A physical exam and a medical history will be performed by your healthcare professional to determine the origin of your symptoms. To diagnose SMA, your doctor may request one or more of the following tests:

• Blood test: A blood test for enzymes and proteins can detect excessive levels of creatine kinase. This enzyme is released into the bloodstream by deteriorating muscles.

• SMN1 gene test: This blood test detects SMN1 gene abnormalities. A genetic test is 95% successful at detecting the changed SMN1 gene as a diagnostic tool. SMA is screened for in several states as part of regular new-born screenings.

An electromyogram (EMG) is a test that examines the electrical activity of nerves, muscles, and nerves.

• Muscle biopsy: A physician may do a muscle biopsy on a rare occasion. A little sample of muscle tissue is removed and sent to a lab for analysis in this process. A biopsy may reveal atrophy, or muscle loss.

During pregnancydiagnostic

Prenatal diagnostics can detect if your unborn child has SMA if you're pregnant and have a family history of the condition. These tests raise the chance of a miscarriage or pregnancy loss by a small amount. SMA prenatal testing include:

• Amniocentesis: Your obstetrician will inject a thin needle into your tummy to retrieve a little amount of fluid from the amniotic sac during amniocentesis. A pathologist (lab specialist) examines the fluid for SMA. After the 14th week of pregnancy, this test is performed. After the 14th week of pregnancy, this test is performed.

• Chorionic villus sampling (CVS): A tiny tissue sample from the placenta is removed through the mother's cervix or stomach by your obstetrician. A pathologist examines the sample for signs of SMA. CVS can occur as soon as the tenth week of pregnancy.

A full medical history and physical examination are performed on a patient with suspected SMA, such as a child who has unexplained weakness and hypotonia while seeming bright eyed and socially active. If there are no copies of SMN1, then reflex testing for SMN2 copy number should be done to discover pathogenic mutations in the SMN1 gene. If the patient is symptomatic and only one copy of SMN1 is found, a gene sequence analysis should be performed to rule out an SMN1 point mutation.

Other tests are not required to diagnose SMA, though they may be conducted initially to rule out other disorders with a similar clinical presentation. This could include genetic testing for other disorders, metabolic or biochemical studies, or an assessment of electrical signal

transmission from nerves to muscles (electromyography; EMG). When the above tests fail to disclose a diagnosis, a muscle biopsy may be considered.

In the United States, new-born screening for SMA is being implemented. As of January 2021, 39 states had screened for SMA, accounting for 86 percent of all babies born in the United States. New-born screening aids in the early detection of infants with SMA and, as a result, the early initiation of treatment. Infants who have been detected through SMA new-born screening are immediately directed for confirmatory testing, treatment discussion, and care. Early treatment, before symptoms appear, yields the best results. Because of a point mutation in the SMN1 gene, new-born screening will miss 3-5 percent of new-borns with SMA. These infants will acquire symptoms over time, necessitating prompt identification and treatment.

Complications

Possible Complications of SMA are,

- Aspiration (food and fluids get into the lungs, causing pneumonia)
- Contractions of muscles and tendons.
- Heart failure.
- Scoliosis.

Treatment

Neurologists, medical geneticists, physical therapists, speech pathologists, pulmonologists, respiratory therapists, medical social workers, dietitians, psychologists, and specialised nurses should all be part of the treatment team for SMA. Treatment that slows the progression of the disease (disease-modifying therapy) and therapy that helps control symptoms and improves quality of life are the two basic components of SMA care (supportive therapy). Affected individuals and their families should seek genetic counselling.

Symptomatic treatment

Physical therapy, occupational therapy, monitoring respiratory function and intervening as clinically indicated, nutritional status monitoring and intervention, spine curvature monitoring and intervention, and the use of orthotics and adaptive equipment as needed are all part of the symptomatic management of SMA. BiPAP (bi-level positive airway pressure) to control hypoventilation and a mechanical insufflation-exsufflation device to assist a mild cough are two types of respiratory support for SMA type 1 (infants symptomatic before to 6 months of age). Comfort and life expectancy have both been demonstrated to improve with supportive treatment. Some affected infants may only require ventilation support at night early in the disease. Children with severe respiratory failure may require more intrusive breathing treatments, such as the surgical installation of a breathing tube through the neck (tracheostomy). Nutritional support for newborns and children with dysphagia may necessitate the installation of a gastrostomy tube. Surgery may be required for musculoskeletal abnormalities such as scoliosis and/or hip dislocation in children with SMA.

Disease-modifying therapy:

Research has resulted in medications that can help people with SMA live longer. In 2016, the US Food and Drug Administration (FDA) approved the first disease-modifying treatment. These treatments have demonstrated encouraging benefits, including the achievement of developmental motor milestones and better survival in those who have received them. While the effects of these treatments are being investigated, keep in mind that they are not cures.

The FDA authorised nusinersen (Spinraza) as the first medicine to treat children and adults with SMA in 2016. Nusinersen is a drug that is injected into the fluid that surrounds the spinal cord (intrathecal administration). Nusinersen works by altering the splicing of the SMN2 gene product, mRNA, resulting in the production of more full-length and functional SMN protein.

The FDA approved onasemnogene abeparvovec-xioi (Zolgensma) for the treatment of SMA in children under the age of two in 2019. Onasemnogene abeparvovec-xioi is a gene therapy that uses a viral vector, AAV9, to deliver a fully functioning copy of the human SMN1 gene to target motor neuron cells. The medicine causes an increase in SMN protein in all cells, including motor neurons, after a single intravenous infusion.

The FDA approved risdiplam (Evrysdi) for the treatment of SMA patients aged two months and up in 2020. Risdiplam is the first medicine licenced for the treatment of SMA that is taken orally. Its mode of action is to alter SMN2 mRNA splicing, resulting in an increase in SMN protein.

SMN targeted therapies:

Since the discovery that SMA is caused by a homozygous loss of SMN1, researchers have concentrated their efforts on restoring SMN expression. Several potential ways of increasing SMN levels are currently in the late phases of clinical development. To begin, numerous techniques are being explored to boost the quantities of full-length mRNA and protein by targeting SMN2 splicing. Several antisense oligonucleotides (ASOs) targeting SMN2 sequences that either accelerate or inhibit SMN2 exon 7 splicing 12 (FIG. 1c) have been created and

have shown to be highly effective in preclinical investigations. Nusinersen is at the vanguard of these ASO-based therapies, and it has been approved for the treatment of all kinds of SMA in a number of countries throughout the world (including the United States, Europe, Canada, and Japan). Although nusinersen improves motor function in about half of people with type I SMA, it can have a more modest benefit in others. This difference is most likely related — at least in part — to time delays between diagnosis and treatment, as patients who began treatment early had significantly better outcomes than those who began treatment later in the disease course. The NURTURE experiment, which is now in progress, takes this issue a step further by involving only children who are presymptomatic for SMA. In addition, more studies are being conducted to determine the efficacy of nusinersen in older patients with SMA types II and III. These are important investigations, and the results will be crucial in generating a more full picture of nusinersen's efficacy in individuals with SMA. Most current ASO approaches have the disadvantage of requiring repeated intrathecal injections, which limits ASO distribution to the periphery, is costly, and can add to the burden on patients and clinicians because it is an invasive treatment that must be repeated on a regular basis during the initial loading phase. Next-generation ASOs may be able to address these difficulties by increasing effectiveness and allowing for less intrusive delivery methods. Furthermore, clinical trials in individuals with SMA are presently being conducted to determine the efficacy of orally administered small-molecule treatments that improve the inclusion of exon 7 in SMN2 splicing. Several of these drugs have shown to be particularly successful in rescuing SMA traits in preclinical investigations. . Other research have sought to boost SMN levels by inhibiting histone deacetylases, increasing signal transducer and activator of transcription 5A (STAT5; also known as STAT5A) activity, or blocking SMN ubiquitylation; nevertheless, clinical trials have so far proved disappointing. Additionally, gene replacement therapy is being used to try to restore SMN expression. AVXS-101, a self-complementing adeno-associated virus serotype 9 that intends to reintroduce SMN systemically following a one-time intravenous injection, is now in clinical development. Preclinical investigations have indicated that restoring SMN expression throughout the body, including the spinal cord, can significantly improve SMA phenotypes in several animal models. Several of these drugs have shown to be particularly successful in rescuing SMA traits in preclinical investigations. Other research have sought to boost SMN levels by inhibiting histone deacetylases, increasing signal transducer and activator of transcription 5A (STAT5; also known as STAT5A) activity, or blocking SMN ubiquitylation; nevertheless, clinical trials have so far proved disappointing. Additionally, gene replacement therapy is being used to try to restore SMN expression. AVXS-101, a self-complementing adeno-associated virus serotype 9 that intends to reintroduce SMN systemically following a one-time intravenous injection, is now in clinical development. Preclinical investigations have indicated that restoring SMN expression throughout the body, including the spinal cord, can significantly improve SMA phenotypes in several animal models. In patients with type I SMA, an initial clinical safety and efficacy research shows promising results94. There were no serious side effects observed, indicating that gene therapy was safe and well tolerated in young children. All of the patients in the research who got a high therapeutic dose lived longer than predicted and achieved motor milestones not generally linked with a diagnosis of type I SMA94. However, this research was conducted on a small, carefully chosen group of patients As a result, larger and more diverse multicenter trials are needed to determine the efficacy of this gene therapy strategy in a larger and more diversified population of SMA patients. Furthermore, despite its potential, viral gene therapy is not a widely used treatment in clinical practise. As a result, delivering safe and effective gene therapy to all people with SMA is likely to necessitate significant infrastructural improvements in order to make it widely available.

Muscle-enhancing and Neuroprotective therapies:

These muscle-enhancing and Neuroprotective treatments, when combined with exercise and physiotherapy suggestions, could provide further assistance for patients by limiting concerns linked to muscle fatigability and weakness. Furthermore, the nature of these therapeutic breakthroughs suggests that they are excellent candidates for the treatment of various neuromuscular illnesses due to their ability to provide general support and protection to the neuromuscular system.

Medication:

Nusinersen (Spinraza), onasemnogene abeparvovec-xioi (Zolgensma), and risdiplam have all been authorised by the FDA to treat SMA (Evrysdi). Both are types of gene therapy that work on the genes that cause SMA. The SMN1 and SMN2 genes direct your body to produce a protein that aids with muscle movement regulation.

• **Nusinersen**:. This medication modifies the SMN2 gene, allowing it to produce more protein. Both children and adults with SMA can benefit from it. The medicine will be injected into the fluid surrounding your child's spinal cord by their medical staff. This can take at least 2 hours, including preparation and recovery time, and will need to be repeated numerous times, with another dose every 4 months. According to studies, it benefits roughly 40% of people who use it by making them stronger and reducing the progression of the disease.

• **Abeparvovec**-xioi onasemnogene (Zolgensma). This necessitates the replacement of the problematic SMN1 gene. It's for kids under the age of two. Your child's medical team will insert a catheter, a small tube, into a vein in their arm or hand (an IV). They'll next inject a copy of the SMN gene into a specific set of motor neuron cells via the tube. This will only have to be done once. In studies, the onasemnogene abeparvovec-xioi helped children with SMA achieve certain developmental milestones more quickly, such as head control and sitting without assistance.

• **Risdiplam**: This medication prevents the SMN2 genes from interfering with protein creation, allowing the protein to reach the nerve cells when it is required. Once a day, after a meal, your youngster will take it orally. Their weight determines the dosage. In clinical trials, 41% of people who took it saw an improvement in muscular function after 12 months.

Aside from gene therapy, your doctor may advise a few additional options for symptom management.

• **Breathing**. Weak muscles in SMA, particularly types 1 and 2, prevent air from moving freely in and out of the lungs. Your youngster may require a specific mask or mouthpiece if this occurs. Your child may need to use a machine to help them breathe if they have significant issues.

• **Nutrition and swallowing.** Babies and children with SMA may have difficulty sucking and swallowing if their mouth and throat muscles are weak. In that case, your infant may not receive adequate nutrition and may struggle to grow. A nutritionist may be recommended by your doctor. A feeding tube may be required for some babies.

• **Movement**. Physical and occupational therapy, which incorporates exercises and routine everyday activities, can help your child's joints and muscles stay healthy. Leg braces, a walker, or an electric wheelchair may be recommended by a therapist. Computers and phones may be controlled with special tools, which can also assist with writing and drawing.

• **Back problems**. SMA can cause a curvature in a child's spine if it begins in childhood. While your child's spine is still growing, a doctor may recommend that they wear a back brace. They may need surgery to correct the condition once they've stopped growing.

Medical management

Respiratory muscle weakness is treated medically.

Respiratory muscle weakness is a severe issue in several types of SMA. It is the most common, but not the only, cause of death in chromosome 5 (SMN-related) SMA types 1 and 2.

When the respiratory muscles weaken, air does not move freely into and out of the lungs, resulting in negative consequences for overall health. Headaches, difficulties sleeping at night (insomnia), frequent yawning or sighing during the day, excessive tiredness during the day, poor concentration, difficulty lying flat, chest infections, and, eventually, heart damage and respiratory failure are all signs of deteriorating respiratory muscles.

The muscles between the affected baby's ribs are often quite weak in infantile-onset SMA, while the diaphragm muscle remains relatively strong. This causes a child's abdomen to move instead of their chest, giving the impression that they are breathing. The body might also have a pear-shaped appearance.

In recent years, the availability of portable, effective ventilation equipment has given new-borns with SMA additional alternatives and, in some cases, substantially extended their lives. Children and adults with various kinds of SMA may benefit from assisted ventilation. Many doctors recommend starting with non-invasive ventilation, which is delivering air under pressure through a mask or mouthpiece (typically ambient air that isn't enhanced with oxygen). This type of device is available in a variety of configurations and can be used at any time of day or night. It's simple to take it off for eating, drinking, and conversing. When non-invasive ventilation isn't enough, a tracheostomy – a surgical opening in the trachea, or windpipe — might be used to provide additional ventilation. The air is then given under pressure through a tube in the tracheostomy site. People who have a tracheostomy tube can normally eat, drink, and converse after a time of adjustment.

Clearance of respiratory secretions, which can occasionally be performed with a mechanical device, and infection control are other important parts of SMA respiratory care. One sort of equipment that can help clear respiratory secretions from the airway is an insufflator-exsufflator. The device simulates a normal cough by applying positive pressure to the airway and then swiftly reversing to negative pressure. The Philips Respironics Cough Assist is an example of this type of equipment.

A high-frequency chest wall oscillation device is another sort of airway clearance assistance. This is a vest that rapidly inflates and deflates, shaking the chest and causing "mini-coughs" that dislodge mucus from small airways and move it to larger airways, where it can be coughed up more readily. A good example is Philips Respironics' IN Courage system.

Almost everyone with SMA should get a flu shot every year to avoid respiratory infections. Staying away from crowds and obtaining enough rest and nourishment are also important considerations. A member of the MDA Care Centre team can provide you with information about respiratory care, flu vaccines, and other related topics.

Swallowing muscle weakness :

Swallowing issues develop when the mouth and throat muscles are weak.

Infants with infantile-onset SMA have difficulty eating and sucking. Sucking difficulties can result in dehydration and poor nutrition, whereas swallowing difficulties can result in airway blockage and respiratory infections from aspirated food or liquids (aspiration).

Alternative feeding methods, such as a feeding tube, also known as a gastrostomy tube or g-tube, can be used to feed babies with significant swallowing and sucking difficulties. A feeding tube is a thin, flexible tube approximately the size of a pencil that permits liquid sustenance (homemade or store-bought) to enter the stomach directly, bypassing the mouth, throat, and oesophagus.When not in use, some feeding tube systems are designed such that the tube can be disconnected from a "button" on the belly.

In addition to utilising the tube, some g-tube users can eat and drink by mouth. If the main issue is chewing muscle weakness, which makes eating difficult and time-consuming, it's good to eat by mouth for enjoyment and extra nutrition while using the g-tube for essential calories. If the tube is primarily used for aspiration of food and liquid, however, eating and drinking by mouth is unlikely to be safe.

Speech-language pathologists (SLPs) are trained to treat swallowing disorders as well as speech disorders. Your MDA Care Centre team can provide you with information on swallowing muscle weakness, such as particular meal preparation techniques and the use of gastrostomy tubes.

Back muscle weakness with progressive spinal curvature

In childhood-onset SMA, weakness of the back muscles that normally support the flexible, expanding spine is a serious issue. The kid may develop scoliosis, a side-to-side curvature of the spine, or kyphosis, a forward curvature of the spine, or both, if it is not treated. Some people may develop "pretzel" curvatures, which make it difficult to sit or lie comfortably.

In some situations, extreme spinal curvatures may impede pulmonary function if the bent spine compresses a lung, according to some doctors.

To try to control the spine as it grows, a back brace or corset that supports a kid in a specific position is frequently given. Braces don't cure the problem, although they can help a curve develop more slowly.

Spine-straightening surgery is usually always the best long-term remedy for spinal curvature, and it can be done if the child's respiratory condition allows it.

Back surgery can be difficult to time. Doctors prefer to wait until maximal spinal development has occurred since this allows them to employ a less invasive surgical procedure. On the other hand, if a patient's respiratory condition is deteriorating, surgery may be necessary sooner rather than later. Again, an MDA Care Centre can assist you in making this decision.

Conclusion

SMA is a category of inherited neuromuscular illnesses defined by the loss of nerve cells called lower motor neurons or anterior horn cells in the spinal cord. Lower motor neurons originate in the brainstem or spinal cord and transmit nerve signals from the brain's upper motor neurons to the muscles they regulate. Lower motor neuron loss causes gradual muscle weakening, atrophy (muscle wasting), and hypotonia (low muscle tone), which is most noticeable in muscles nearest to the body's trunk (proximal muscles), such as the shoulders, hips, and back. However, neurons that control most voluntary muscles, including those that control feeding, swallowing, and breathing, can be disrupted.

Newborns screening aids in the early detection of infants with SMA and, as a result, the early initiation of treatment. Infants who have been detected through SMA newborns screening are immediately directed for confirmatory testing, treatment discussion, and care. Early treatment, before symptoms appear, yields the best results.

Although symptom management and supportive care were historically the mainstays of SMA treatment, disease-modifying treatments (drugs that alter the course of the illness) have developed in recent years and have shown promising outcomes. The US Food and Drug Administration (FDA) has approved three SMN-enhancing therapies thus far.

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