Review Article

Spinal Muscle Atrophy (Types I & II & III & IV): Literature Review

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis. Estimated incidence is 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1/40 - 1/60. This disease is characterized by generalized muscle weakness and atrophy predominating in proximal limb muscles, and phenotype is classified into four grades of severity (SMA I, SMAII, SMAIII, SMA IV) based on age of onset and motor function achieved. This disease is caused by homozygous mutations of the survival motor neuron 1 (SMN1) gene, and the diagnostic test demonstrates in most patients the homozygous deletion of the SMN1 gene, generally showing the absence of SMN1 exon 7. The test achieves up to 95% sensitivity and nearly 100% specificity. Differential diagnosis should be considered with other neuromuscular disorders which are not associated with increased CK manifesting as infantile hypotonia or as limb girdle weakness starting later in life. Considering the high carrier frequency, carrier testing is requested by siblings of patients or of parents of SMA children and are aimed at gaining information that may help with reproductive planning. Individuals at risk should be tested first and, in case of testing positive, the partner should be then analyzed. It is recommended that in case of a request on carrier testing on siblings of an affected SMA infant, a detailed neurological examination should be done and consideration given doing the direct test to exclude SMA. Prenatal diagnosis should be offered to couples who have previously had a child affected with SMA (recurrence risk 25%).

The role of follow-up coordination has to be managed by an expert in neuromuscular disorders and in SMA who is able to plan a multidisciplinary intervention that includes pulmonary, gastroenterology/nutrition, and orthopedic care. Prognosis depends on the phenotypic severity going from high mortality within the first year for SMA type 1 to no mortality for the chronic and later onset forms.

Keywords: spinal muscle atrophy; pathophysiology; epidemiology; diagnosis; types; treatment.

INTRODUCTION

In the 1890s, Werdnig and Hoffman described a disorder of progressive muscular weakness beginning in infancy that resulted in early death, though the age of death was variable. In pathologic terms, the disease was characterized by loss of anterior horn cells. Since then, several types of SMA have been described based on age when accompanying clinical features appear.

The most common types are acute infantile (SMA type I, or Werdnig-Hoffman disease), chronic infantile (SMA type II), chronic juvenile (SMA type III or Kugelberg-Welander disease), and adult onset (SMA type IV) forms. [1]

Definition

SMA is the second most common fatal recessive chromosomal disorder after cystic fibrosis.

Includes a group of autosomal recessive disorders characterized by degeneration of nerve cells (motor nuclei) within the lowest region of the brain (lower brainstem) and Progressive impairment of the lower motor neurons in the spinal cord (α-motor neurons) leading to muscle weakness of the truncal, and extremity muscles initially, followed by chewing, swallowing and breathing difficulties.

It is caused by homozygous disruption of the survival motor neuron 1 (SMN1) gene by deletion, conversion, or mutation (Figure 1).

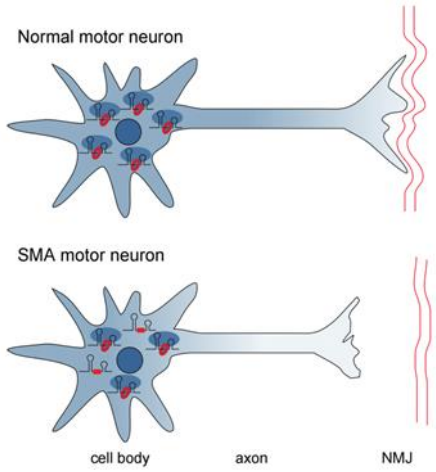

Figure1: Motor Neurons

Pathophysiology

The gene that causes SMA is called survival motor neuron (SMN). Each individual has 2 SMN genes, SMN1 and SMN2. More than 95% of patients with SMA have a homozygous disorder of the SMN1 gene providing 90% of the SMN protein on chromosome 5q, due to mutation, deletion, or rearrangement. However, all patients with SMN retain at least one copy of SMN2, which generates only 10% of the amount of full-length SMN protein versus SMN1. This genomic organization provides a therapeutic pathway to enhance SMN2, which is present in all patients, to function as the missing SMN1 gene.

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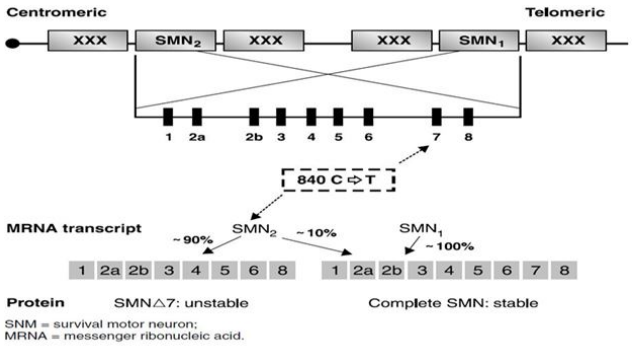

Figure2: Structure of the SMN gene in chromosome 5

Classification

SMA is clinical classified into four phenotypes on the basis of age of onset and motor function achieved.

Table1: SMA Classification

Type	Name	Age of onset	Function achieved
Type I	Werdnig-Hoffmann disease	0-6 months	Never sit
Type II	Intermediate (chronic infantile)	7-18 months	Sit never stand
Type III	Kugelberg-Welander disease (chronic juvenile)	> 18 months	Stand and Walk during adulthood
Type IV	Adult	2nd-3rd decade	Walk unaided

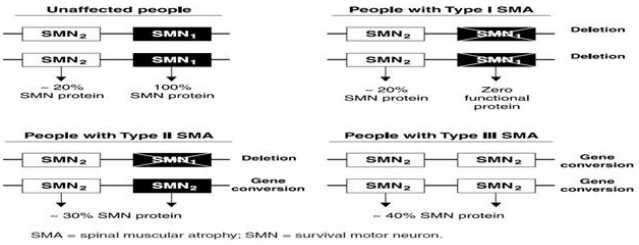

Figure3: Genotypes of people affected and unaffected by SMA

EPIDEMIOLOGY

Diagnosis

Since SMA is a low-incidence neurological disorder, diagnosis is difficult. Nevertheless, since SMA develops progressively, rapidly establishing a precise diagnosis is essential.

Children manifesting clinical signs characteristic of SMA, such as hypotonia, paresis, areflexia and fasciculation, should be investigated with care, 1 since these clinical signs can also be observed in other neuropathologies (Table 2)

Table 2: Most common causes of muscle hypotonia in childhood

Principal causes of muscle hypotonia by age at onset at birth	Other causes
Neuromuscular diseases	Systemic septicemia-induced diseases
Congenital myotonic dystrophy	Lung damage
Type I SMA	Intracranial pathologies
	Infections of the central nervous system
	Disorders of the peripheral nerves
	Diseases of the neuromuscular junction
	Prader-Willi syndrome
	Drug intoxication during pregnancy or delivery
After 6 months of age	**Other causes**
Neuromuscular diseases	Congenital heart disease
SMA, types II and III	Malnutrition
Polyneuropathies	Rickets
Childhood myasthenia gravis	Metabolic diseases
Muscular dystrophies	Nephropathies
Metabolic myopathy	Lung diseases

Since neuromuscular diseases are the main causes of childhood hypotonia28 and since the neuromuscular diseases that most often affect children are SMA and the dystrophies, (Table 2) provides a summary of the principal features that differentiate between the two groups.

Notwithstanding, it should be pointed out that not all of the features described here will always be present in every patient, since they vary according to the disease stage that each patient is in at the time of assessment.

Table 3: Principal differences between spinal muscular atrophy and the muscular dystrophie

Clinical features	SMA	Muscular atrophy
Symptoms	Weakness	Weakness
Signs	Muscle atrophy, lack of deep reflexes, fasciculations, rapid and discrete involuntary movements of muscles, such as trembling	Pseudo-hypertrophy of the calf, deep reflexes may be normal, reduced or absent, depending on the degree of muscle weakness
Test findings	Normal or reduced muscle enzymes, neurogenic electroneuromyography results, muscle biopsy with atrophic appearance	Very high muscle enzyme levels, myopathic electroneuromyography results, muscle biopsy with dystrophic appearance
Definitive diagnosis	Genetic test showing deletion of SMN, gene from chromosome 5	Genetic test showing deletion of the dystrophin gene from the X chromosome or by absent or deficient dystrophin in a biopsy (here we are only referring to Duchenne and Becker dystrophies. which are the most common types)
Disease mechanism	Degeneration of nerve cells in the spinal ventral horn	Degeneration of muscle cells
Genetic heredity	Autosomal recessive (the disease can manifest in both boys and girls, both parents are carriers and each pregnancy has a 25% chance of producing a child with the disease)	X-linked (the disease manifests in boys, mothers are carriers and there is a 50% chance that male children will have the disease or that female children will be carriers)

Treatment	First line treatment is physiotherapy (more details will be given later in the text)	First line treatment is physiotherapy (corticoids may be prescribed)
Most common complications	Respiratory problems, scoliosis, contractures	Respiratory and cardiac problems, scoliosis and contractures
Natural course of disease	SMA is a progressive disease; degeneration is faster or slower depending on type	Dystrophies are progressive diseases: degeneration is faster or slower depending on type (Duchenne, Decker, etc.)

In general, diagnosis of SMA is made on the basis of evidence of muscle denervation, found on electromyography and in muscle biopsy. Diagnosis is confirmed by molecular analysis demonstrating that exon 7 of the SMN1 gene is absent, irrespective of clinical classification.

Creatine phosphokinase (CPK) may be normal or as much as five times lower than normal. Serum CPK can differentiate neurogenic diseases, of which SMA is one, from myopathic diseases, such as dystrophies, in which muscle damage raises CPK levels.

Electromyography

Electromyography can be used to determine whether the disease has affected motor neurons, nerve roots, peripheral nerves, myoneural junction or muscle fibers.

In SMA there is electrophysiological evidence of denervation, while conduction is found to be intact in motor and sensory nerves. Fibrillation potentials are observed at rest in cases of denervation, whether located in the anterior horn or peripheral nerves, both duration and amplitude of motor unit potentials may be increased and there may be a reduction in motor conduction velocity in the earlier forms of AME.

Muscle biopsy

A range of abnormal muscle features can be observed in SMA patients. Certain histopathological findings are characteristic, such as the presence of atrophic muscle fibers, both type I and type II, hypertrophy of type I fibers or fiber-type grouping. However, these findings can also be observed in other causes of denervation. Therefore, this type of test does not confirm SMA, but provides additional clinical data. In the slower-progressing forms, superimposition of secondary myopathic abnormalities, such as angular fibers, central nuclei, splits and myofibrillar disarrangement, increase as the disease progresses.

Genetic investigation

Molecular genetic tests provide definitive diagnosis of SMA and could be the only tests performed. Genetic investigation demonstrates that exon 7 of the SMN1 gene is completely absent (with or without a deletion of exon 8). Since the SMN2 gene does not have this exon, its absence also demonstrates that the SMN1 gene is nullified. If a patient suspected of having SMA does have a copy of the SMN1 gene, then this copy should be investigated for mild mutations such as point mutations, insertions and deletions leading to a homozygous dysfunction of the gene. Molecular genetic diagnosis is more precise and less invasive than the other two tests described, but it is not widely available in Brazil. It should be pointed out that testing for deletions in the SMN gene can provide guidance during cases in which diagnosis is uncertain.

Alternatively, developed a technique for measuring the SMN protein in mononuclear cells (lymphocytes and monocytes), obtained from blood samples from patients with SMA. As would be expected, SMN protein levels were significantly reduced in the patients in comparison with the controls. The authors33 stated that their test could be used in the future to monitor clinical trials attempting to increase levels of MRNA and/or the SMN protein itself, but that it is not the best choice for diagnosing SMA.

Diagnostic algorithm for SMA

The first diagnostic test for a patient with suspected SMN should be to look for homologous deletions of the SMN1 gene. The absence of SMN1 exon 7 (with or without exon 8 deletion) confirms the diagnosis of SMA. The test achieves a sensitivity of 95% and close to 100% specificity. If the Level 1 test results are negative, further laboratory testing should be performed including the dose of creatine kinase and electrophysiological tests such as electromyography (EMG), and nerve conduction study. If the EMG suggests the presence of a motor neuron disease, further testing should be done for SMN mutations.

Genetic testing now

Delivering fast and reliable SMN1 gene copy number assay using linkage-based probe amplification (MLPA) or real-time PCR. Semi-quantitative assays improve diagnostic sensitivity by up to 98%. If a patient has one copy of SMN1, it is necessary to sequence the coding region of the non-deleted allele to identify the second causative mutation, and subtle changes in the sequence in general, including point mutations, insertions, and deletions. However, in about a third of patients with a typical clinical picture and one SMN1 transcript, the second mutation was not found in the SMN1 / SMN2 coding region.

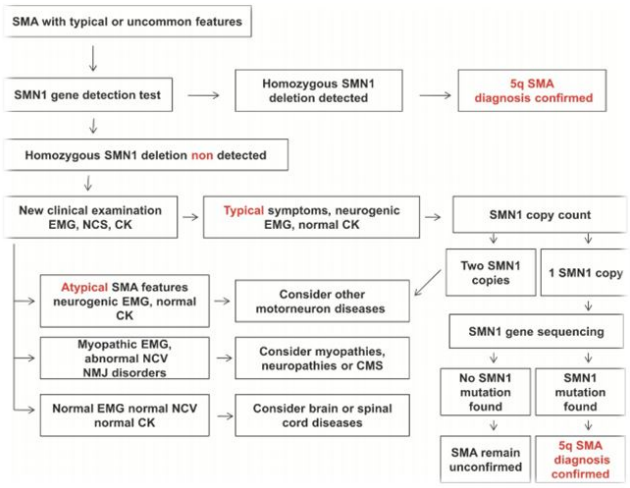

Figure 4: Diagnostic algorithm for (SMA)

If the electrophysiology examination excludes motor neuron disease, the child should be re-examined and he should undergo additional diagnostic tests taking into account other disorders.

Differential diagnosis

In general, the most important differential diagnoses of an infant with hypotonia and / or weakness are congenital myopathy, that is, myopathy with typical skeletal or ultrastructural features (rods, cores, central nuclei) on muscle biopsy, congenital muscular atrophy, myasthenia gravis Congenital syndromes, metabolic myopathy, congenital disorders of motor neurons and the peripheral nerve (congenital myeloid neuropathy), as well as non-neuromuscular conditions including genetic syndromes such as Prader-Willi syndrome, acute hypoxic ischemic encephalopathy, neonatal sepsis and anomalies Movement or metabolism.

Table 4: Other forms of SMA that are not related to the SMN gene

SMA variant	Inheritance/gene	Clinical features
Scapuloperoneal SMA	AD 12q24.1-q24.31	Progressive weakness of scapuloperoneal and laryngeal muscles
SMA with pontocerebellar hypoplasia	AR VRK1	Brainstem and cerebellar hypoplasia, early onset (0-6 mo)

X-linked infantile SMA with arthogryposis	X-linked Xp11.3-q11.2 UBA1	Contractures, onset at birth or infancy, early death
SMA with respiratory distress type I	AR-IGHMBP2	Early onset (< 3 mo), eventration of diaphragms, distal weakness, pes equines.
Congenital distal SMA	AD12q23-q24	Early onset with contractures, nonprogressive
Distal SMA-V/CMT2d	AD 7p15 GARS	Distal SMA with upper limb predominance

Types

SMA manifests itself in a wide range of severity, and affects infants through adults. The disease spectrum was divided into 4 types according to the highest milestone achieved in motor development.

Patients with SMA suffer from weakness and muscle wasting of the limbs, respiratory system, and brainstem muscles. They have no evidence of cerebral dysfunction or other central nervous system disease. Patients with SMA often have higher than average intelligence (IQs) and show high levels of intelligence.

The most used traditional types are as follows:

- SMA type I (acute infantile or Werdnig Hoffman).
- SMA type II (chronic infantile).
- SMA type III (chronic juvenile).
- SMA type IV (adult onset).

SMA type I - Acute infantile or Werdnig-Hoffman disease.

Patients present before 6 months of age, with 95% of patients having signs and symptoms by 3 months. They have severe, progressive muscle weakness and flaccid or reduced muscle tone (hypotonia). Bulbar dysfunction includes poor suck ability, reduced swallowing, and respiratory failure. Patients have no involvement of the extraocular muscles, and facial weakness is often minimal or absent. They have no evidence of cerebral involvement, and infants appear alert.

Reports of impaired fetal movements are observed in 30% of cases, and 60% of infants with SMA type I are floppy babies at birth. Prolonged cyanosis may be noted at delivery. In some instances, the disease can cause fulminant weakness in the first few days of life. Such severe weakness and early bulbar dysfunction are associated with short life expectancy, with a mean survival of 5.9 months. In 95% of cases, infants die from complications of the disease by 18 months.

SMA type II - Chronic infantile form

This is the most common form of SMA, and some experts believe that SMA type II may overlap types I and III.Most children present between the ages of 6 and 18 months.

The most common manifestation that parents and physicians note is developmental motor delay. Infants with SMA type II often have difficulties with sitting independently or failure to stand by 1 year of age.An unusual feature of the disease is a postural tremor affecting the fingers. This is thought to be related to fasciculations in the skeletal muscles.Pseudohypertrophy of the gastrocnemius muscle, musculoskeletal deformities, and respiratory failure can occur.The lifespan of patients with SMA type II varies from 2 years to the third decade of life. Respiratory infections account for most deaths.

SMA type III - Chronic juvenile or Kugelberg-Welander syndrome

This is a mild form of autosomal recessive SMA that appears after age 18 months. SMA type III is characterized by slowly progressive proximal weakness. Most children with SMA III can stand and walk but have trouble with motor skills, such as going up and down stairs. Bulbar dysfunction occurs late in the disease. Patients may show evidence of pseudohypertrophy, as in patients with SMA type II. The disease progresses slowly, and the overall course is mild. Many patients have normal life expectancies.

- SMA type IV - Adult-onset form.
- Onset is typically in the mid-30s.
- In many ways, the disease mimics the symptoms of type III.
- Overall, the course of the disease is benign, and patients have a normal life expectancy.

TREATMENT

There is no cure is present for SMA as pathogenesis is still not fully known.

Table 5: Treatments (benefits) tested

Treatment.1	Increased overall muscle strength (may include hips, neck, arms, legs, face, etc.) such that one is able to do something one was unable to do before.
Treatment.2	Consistent muscle performance/ strength (ie, muscles work relatively the same throughout the day muscle strength does not vary greatly from day to day).
Treatment.3	Improvement in ability to swallow.
Treatment.4	Improvements in ability to o speak/ communicate.
Treatment.5	Improvement in breathing function (may include, less infections, less time on BiPAP or vent,stronger cough, decrease in belly breathing)
Treatment.6	Improved proximal mobility/ functionality (getting up, balancing when sitting or standing, walking, jumping, running, climbing stairs, fewer falls).
Treatment.7	Increased core strength (to allow for greater and longer stability when sitting, better rolling while sleeping etc).
Treatment.8	Increased upper limb (arm) strength allowing the ability perform basic personal tasks (such as brushing teeth, washing face, writing with a pen, putting on glasses, scratching head, using the keyboard, opening doors, self-feeding, etc).
Treatment.9	Decreased fatigue, increased energy and ability to do more in a day.
Treatment.10	Lessening of symptoms' severity (decrease in, tremors, muscle weakness, etc.) or experiencing less symptoms than before treatment was introduced.
Treatment.11	Prolonging lifespan (Increasing length of life).

Treatment.12	Slowing or stopping of disease progression.

Nusinersen (Spinraza)

FDA has approved Nusinersen (spinraza) in December 2016, which regard the first drug that approved for treating adult and children with SMA. Nusinersen is an antisense oligonucleotide (ASO) that has been designed for treating SMA which caused due to mutation in chromosome 5q which will lead to deficiency of SMN protein. It also show increasing economic 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein.

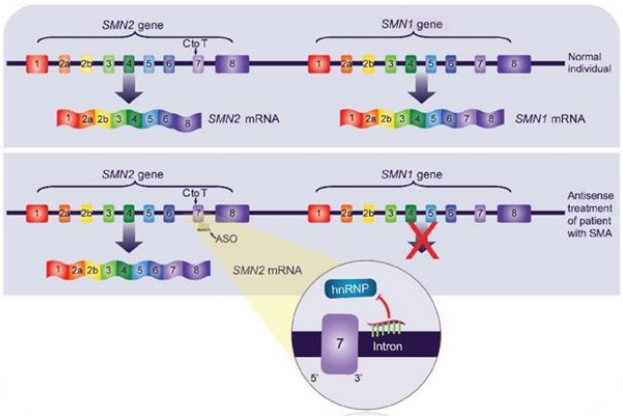

Figure5: Mechanism of action of Nusinersen

Onasemnogene abeparvovec (Zolgensma)

It is a single dose of approved adenoviral gene therapy for patients younger than 2 years of age. The expectation is that more severe type 1 patients who previously expired before childbearing age will have a much better prognosis. There is currently limited information on pregnancy mainly of types II and III that appear later which we hope will change as children currently treated reach adulthood. A number of successful pregnancy reports have been published. A recent review of the literature found that the incidence of maternal and fetal complications was not higher than that of the general population, but it is not surprising that rates of preterm labor and cesarean delivery were higher. Similar to the cases already discussed, local anesthesia and avoidance of depolarizing muscle blockers are preferred. Worsening weakness has been reported in a marked proportion of women. Weak respiratory muscles can impair delivery and administration of anesthesia. Spinal deformities and surgical devices can complicate epidural or spinal anesthesia and respiratory management during cesarean delivery.

It is recombinant AAV-9 based gene therapy which is designed to deliver a copy of the gene encoding the human SMN protein, it is applied for gene replacement therapy in children aged 2 years or younger with SMA Type 1 who has mutation in the Survival motor neuron 1(SMN1) gene.

Risdiplam (Evrysdi)

It is a survival of motor neuron 2 (SMN2) mRNA splicing modifier designed to treat mutations in chromosome 5q that lead to SMN protein deficiency. It is indicated for SMA, including types 1, 2, and 3, in adults and children aged 2 months or older.

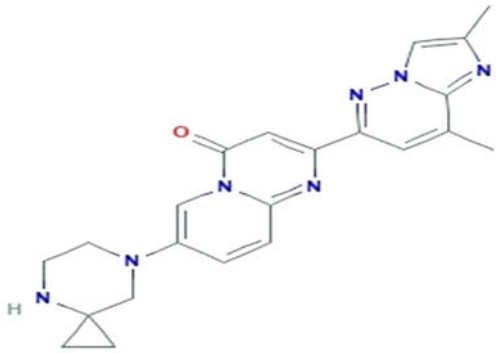

Figure6: Structure of Risdiplam

Other medications

Medications such as valproic acid, phenylbutyrate, hydroxyurea, and albuterol have been shown to increase SMN transcription in laboratory studies, but clinical trials have not demonstrated significant improvement in disease progression.

Supportive treatment should be aimed at improving the patients' quality of life and minimizing disability, particularly in patients with slow progression.

The goals are to maximize the patient's independence and quality of life at each stage of the disease. Multidisciplinary approach is essential. Once diagnosis is reached, overnight oximetry, respiratory muscle function tests, cough effectiveness, forced vital capacity (for patients >5 years), swallow study with video, physical and occupational therapy assessments, assistive equipment evaluation, and hip/spine radiography are appropriate. Recognition of mandibular dysfunction manifested as limited mouth opening is an important factor in prevention of aspiration.

Gene therapy

In addition to potential pharmacotherapy, gene therapy approaches to SMA have been evaluated, using viral vectors to replace SMN1. Adenovirus vectors (AAV) have also been used to deliver ASOs to the central nervous system via intrathecal infusion. Passini et al (2011) demonstrated a highly effective oligonucleotide transport rate, with increased expression of SMN-fl, and provided evidence that this pathway of administration has a higher efficiency than systemic delivery.

Diet

Ensuring optimal caloric intake enables patients to use weak muscles to their maximum capacity without incurring obesity as a comorbid condition.

Activity

Encourage mobility. The goal of active but nonfatiguing exercises is to maintain range of motion, increase muscle flexibility, and prevent contractures. These exercises should not produce pain or exhaustion. A small series showed that the risk of falls is strongly correlated to stride-length variability, so this variable should be a focus of physical therapy programs. Preventing spinal deformities (eg, scoliosis) and joint contractures is important. This goal is accomplished by using range-of-motion exercises, knee-ankle-foot orthoses, specialized wheelchairs and seats at home and school, and home assistance devices.

Surgical Care

Surgical revision may provide stable correction of the spine, and early orthopedic intervention may be indicated in patients in whom prolonged survival is anticipated. Hip subluxations and dislocations are common.

Nonsurgical treatment is generally preferred unless pain is severe, owing to the high rate of repeated dislocation.

Noninvasive ventilation and percutaneous gastrostomy reportedly improves the quality of life with no effect on survival. These modalities may be most effective in prolonging lifespan in patients with slowly progressive disease, whereas they may provide comfort care in rapidly progressive infantile forms.

Stem cell therapy

Stem cell approaches offer promising results as a cellular alternative strategy in the treatment of SMA, and they are currently receiving significant attention. Cell replacement can be achieved by implanting cells derived from stem cells that have undergone maturation in the laboratory, or by activating autologous stem cells in the central nervous system. Bone marrow and mesenchymal cell transplantation is the only stem cell therapy currently in use, but no experience has been reported in SMA research.

CONCLUSION

This literature review describes all required information about SMA in terms of its definition, pathophysiology, classification, epidemiology, diagnosis, types SMA type I - Acute infantile or Werdnig-Hoffman disease, SMA type II - Chronic infantile form, SMA type III - Chronic juvenile or Kugelberg-Welander syndrome, SMA type IV - Adult-onset form and treatment.

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