Spinal Muscular Atrophy (SMA) is a group of inherited disorders that involve mainly bulbar and spinal motor neurons; causing muscle weakness and atrophy of proximal and symmetrical predominantly in lower extremities, without affecting the facial muscles and the intellectual ability. It is also unclear if SMA is a developmental or a neurodegenerative disease and occurs predominantly in childhood. The continuous clinical spectrum of SMA has been divided into 3 types based on the age at onset and highest motor milestones achieved. SMA type I was described by Hoffman in 1894 and in 1900 was reported as a disease characterized by hypotonia during the first 3 months of life, as well, is considered as the leading cause of death in children under two years of age among genetic diseases worldwide. SMA type II patients can achieve sitting but not walking. While SMA type III patients achieve full milestones with a progressive loss of walking ability. Deterioration in muscle strength and motor function eventually occurs in SMA type II and III. SMA occurs due to depletion of SMN, a ubiquitously expressed protein, which in all cells regulates RNA biogenesis and splicing through its role in the assembly of small nuclear ribonucleoprotein (snRNP) complexes.

**Keywords:** Spinal Muscular Atrophy, survival motor neuron, SMN genes, child milestones, SMA types

1. **INTRODUCTION**

Spinal Muscular Atrophies are genetic disorders with an autosomal recessive trait, that are considered clinically as a heterogeneous group of neuropathies characterized by the loss of motor neurons in the spinal cord and brain stem that affects the control of muscle movements. The loss of motor neurons causes muscle weakness and consequently the loss of activities such as crawling, walking, sitting and head control movements. In SMA severe cases, the breathing and swallowing muscles become affected and compromised. SMA is divided into types based on the milestone achieved and age of onset of symptoms [1,2,3].

The causative gene is the survival motor neuron called \( SMN1 \) gene. A deletion of the \( SMN1 \) gene has been reported in 95% of SMA cases. SMA occurs due to depletion of a ubiquitously expressed protein, SMN, which in all cells regulates RNA biogenesis and splicing through its role in the assembly of small nuclear ribonucleoprotein (snRNP) complexes. SMA has an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and with a carrier frequency of 1 in 40 – 60 persons. Currently, in Mexico we don’t have statistical data about SMA, therefore, is hard to know exactly the incidence and the actual prevalence of the disease. In Mexico, the...
Mexican Spinal Muscular Atrophy Association (Asociación Mexicana de Atrofia Muscular Espinal) gives support to patients with SMA.

2. ETIOLOGY

The classic SMA is an autosomal recessive inheritance trait. Approximately, it is estimated that 1 in 2,500 couples are carriers. The probability of a child of carrier parents for inheriting the disease is of 25%. [1,3,4]

Spinal muscular atrophies (SMA’s) are a group of disorders characterized by the loss of lower motor neurons and atrophy of muscle. The three main forms of SMA are caused by the deletion of exon 7 of the SMN1 gene, which has its locus on 5q11.2-13.3, and it’s made up of 70,220,767-70,248,838 pair of bases. Both genes, SMN1 and SMN2, have nine exons and eight introns genes that codify a protein named Survival Motor Neuron (SMN). The SMN2 gene is an inverted centromeric duplication from the SMN1 gene that produces a decreased functional protein. [5,6,7]

Proximal SMA (which we refer to simply as SMA) is a common genetic cause of infant death and the most frequent SMA type. SMA is among a number of neurological disorders associated with genes that have important roles in RNA metabolism. Although, SMA is caused by reduced levels of SMN, which is a ubiquitously expressed protein, it only affects the lower motor neurons. Several other neurogenetic disorders are caused by mutations in ubiquitously expressed genes, including amyotrophic lateral sclerosis (caused by mutations in superoxide dismutase 1 (SOD1)), Huntington’s disease (caused by a triplet expansion of CAG repeat in huntingtin (HTT)) and several others.

The SMN1 gene produces an stable SMN protein that meets the needs for the cell survival, while the SMN2 gene produces predominantly an unstable SMN protein which cannot perform its function, therefore, apoptosis is induced.

3. MOLECULAR PATHOGENESIS

3.1 SMN Protein.

The SMN protein is composed of 294 amino acids with a molecular weight of 38 kDa, and is involved in essential cellular functions such as RNA metabolism, splicing genes, more other specific functions like the survival and development of motor neurons (apoptosis, axonal transport). The function of the motor neurons located in the spinal cord and brainstem is to control muscle movement [5]. Using immunohistochemistry, it is observed that the SMN protein is located in the cytoplasm and in the nucleus, forming what are called "gems" or "coiled bodies". One function of the SMN protein is for the assembly of the small nuclear ribonucleoproteins (snRNP’s). These small nuclear ribonucleoproteins are used to remove introns from pre-mRNA in the nucleus. Each snRNP is composed with a small nuclear RNA, seven Sm proteins and other specific proteins. Motor neurons have a higher level of transcription of SMN than other cell types and possibly have a greater need for stable SMN protein. [8].

3.2 SMN1 gene

SMN1 gene is deleted or disrupted in 95% of patients whichever the clinical form of the disease. Instead, all patients with SMA have one to four copies of SMN2 gene, and there
has not been described in the literature any person with absence of both genes. It has been reported that in other species such as mice, this gene is not duplicated and its deletion causes early embryonic death. This suggests data that the absence of the \textit{SMN1} gene and its protein should be lethal to the organism. According to Lorson et al, (2010) approximately 8% of the population lack the \textit{SMN2} gene but have a copy of the \textit{SMN1} gene. \cite{7,9}. Expression studies indicate that SMN is present in all cells but the motor neuron-axon-board motor-muscle complex is very sensitive to its deficiency and therefore, they become the most vulnerable tissues in SMA. In \textit{SMN1} gene there has been found small intragenic mutations in the remaining affected individuals who do not lack both copies of \textit{SMN1} gene. \textit{SMN2} gene is almost identical centromeric \textit{SMN1} gene, with 8 nucleotide substitutions: five in the introns and three in exons 6, 7 and 8. Single-nucleotide transition of C to T at position 6 of \textit{SMN2} exon 7 does not change an amino acid, but causes disruption of a splicing enhancer site, which results in mRNA lacking exon 7 (\textit{SMN}\textsubscript{A7}). \cite{7,10,11}.

Most of the \textit{SMN1} gene transcripts are full-length whereas the majority of the \textit{SMN2} gene transcripts lack exon 7. Consequently, \textit{SMN2} gene is not able to compensate for the loss of exon 7 in \textit{SMN1} gene of the SMA patients. The \textit{SMN1} gene normally produces full-length SMN mRNA, whereas conversely approximately only 20 percent of the full-length SMN mRNA is produced from the \textit{SMN2} gene. This observation suggests a potential significant distinction in the FL-SMN transcript levels among healthy individuals, carriers and different types of SMA patients \cite{11}.

### 3.3 \textit{SMN2} gene

All SMA patients have at least one copy of \textit{SMN2} gene whose function does not prevent the development of the disease. Meanwhile the greater number of copies of \textit{SMN} 2 gene the phenotype of the patients are expected to be less severe. \cite{12}. We conclude that the SMA is the result of a decrement or a lack of SMN protein (Figure 1) and is directly influenced by the amount of protein that can be generated from the copies of \textit{SMN2} gene. \cite{13}. Therefore, it is necessary to find the link between in vitro cellular function of SMN protein and the etiology of the disease, especially to explain why motor neurons are the most affected in the disease.

\textbf{Fig. 1. SMN transcripts by gene splicing in healthy control vs. SMA patient.}

\textit{a) The SMN1 and SMN2 genes exhibit 99.9\% homology in their sequence. The only difference is a single nucleotide change from cytosine to thymine in exon 7. b) This promotes a change in the cleavage site in the SMN1 gene exon 7 to have an active sequence; while it does not in the SMN2}
gene and only 10% of the SMN2 transcripts are correctly spliced. c) In SMA patients, the SMN1 gene doesn’t produce SMN protein while SMN2 gene produces an unstable SMN monomeric protein that is rapidly degraded but a certain amount of stable SMN protein.

3.3.1 Number of SMN2 copies.

When SMN1 gene is deletioned, SMA results because SMN2 gene cannot fully compensate for SMN deficiency. However, when the SMN2 gene copy number is increased, small amounts of full-length transcripts generated by SMN2 gene are able to function and result in the milder SMA type II or SMA type III. Accumulating data indicate that the presence of three or more copies of SMN2 gene is correlated with a milder phenotype [14,15,16]. Data from Mailman et al. (2002), are summarized in table 1. More recently, Prior [2004] reported three asymptomatic unrelated individuals homozygous for an SMN1 gene deletion who had five copies of SMN2 genes, demonstrating that expression levels consistent with five copies of SMN2 genes may compensate for the lack of SMN1 gene expression. Furthermore, quantitative studies indicate that 80 to 90% of patients with SMA type I have 1 or 2 copies of SMN2 gene, and the SMA type II and III patients mostly have 3 or 4 copies of SMN2 gene (Table 1), although the model number SMN2 gene copies can be applied to most cases; however, this correlation is not absolute. For, instance, there have been cases reported where patients that have three copies of SMN2 gene are affected with SMA type I to type III [16].

Table 1. Number of copies of SMN2 gene in SMA I vs. SMA III type.

<table>
<thead>
<tr>
<th>SMN2 N° of copies</th>
<th>Normal</th>
<th>SMA I</th>
<th>SMA III</th>
<th>TOTAL (SMA I + SMA III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.4%</td>
<td>0</td>
<td>0</td>
<td>7 (4.9%)</td>
</tr>
<tr>
<td>1</td>
<td>32%</td>
<td>7 (13.5%)</td>
<td>0 (0%)</td>
<td>43 (30.3%)</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
<td>43 (82.7%)</td>
<td>0 (0%)</td>
<td>72 (50.7%)</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>2 (3.9%)</td>
<td>70 (77.8%)</td>
<td>20 (14.1%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>20 (22.2%)</td>
<td></td>
<td>20 (14.1%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>52</td>
<td>90</td>
<td>142</td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from Mailman) [14]

The number of copies of the SMN2 gene is proportional to the clinical phenotype in SMA type I and III patients; but it is not absolute the correlation.

3.3.2 SMN2 sequence variants

In contrast to the above observations, [17] recently described three unrelated individuals with SMA whose SMN2 gene copy numbers did not correlate with the observed mild clinical phenotypes; they were found to have a single base substitution, c.859G-C in exon 7 of SMN2 gene that created a new exonic splicing enhancer (ESE) element. The new ESE increased the amount of exon 7 inclusion and full-length transcripts generated from SMN2 gene, thus resulting in the less severe phenotypes. These data demonstrate that the SMA phenotype may be modified not only by the number of SMN2 gene copies, but also by SMN2 gene sequence variants. Thus, it should not be assumed that all SMN2 gene alleles are equivalent and it is appropriate to investigate SMN2 gene for sequence changes that may have a
positive or negative effect on SMN2 gene transcription. Those with the phenotype of SMA type I have as little as 9% of the normal amount of full-length SMN, those with SMA type II has 14%, and those with SMA type III, about 18%. Once full-length SMN levels approach 23% of normal levels, motor neuron function appears to be normal. Carriers usually have 45%-55% of the normal amount of full-length SMN protein.

### 3.3.3 Modifying factors

There exist modifying factors that are proposed that can help SMA to have a milder prognosis that have been discovered in recent years. It has been found that siblings with the identical SMN1 mutations and identical SMN2 copy numbers have different clinical findings. A protective modifier is the F-actin bundling plaslin 3 (PLS3) in which is a regulator of main processes that are depending on actin dynamic in motor neurons increasing the presynaptic F-actin amount, synaptic vesicle and the amount of neuromuscular junctions rescuing the axon length and outgrowth defects. [18] A modifying gene is ZPR1 gene that codifies the zinc finger protein that plays a role in the accumulation of SMN in gems and Cajal bodies. It has been found that the reduced expression of ZPR1 gene can cause a decreased motor neuron activity and increase the severity of SMA in mice. The overexpression of ZPR1 is reported to stimulate neurite growth and rescue axonal growth defect in SMA mice [18]. It is believed that a modifying factor such as Prolactin (PRL) has been found that by activating the STAT5 pathway it can promote the increase of SMN levels [19].

A modifying severity factor has been associated to DNA methylation was shown to be an important epigenetic modification altering gene expression pattern. Changes of this methylation pattern are associated with various disease processes. A differential methylation level of CpG sites near the transcriptional SMN2 start site was demonstrated between type I and III SMA patients in DNA samples isolated from leukocyte and fibroblast cell lines. In 2013, Zheleznyakova et al performed the first genome-wide methylation profiling of SMA patients and healthy individuals to study the association of DNA methylation status with the severity of the SMA phenotype, in which they found several differentially methylated candidate loci containing genes that could be possible modifiers of the SMA severity. The mainly identified strong significant differences in methylation level between SMA patients and healthy controls in CpG sites close to the genes CHML, ARHGAP22, CYTSB, CDK2AP1 and SLC23A2. As well, several of these identified genes, mainly CHML and ARHGAP22 are associated with the activity of Rab and Rho GTPases, which are important regulators of vesicle formation, actin dynamics, axonogenesis, processes that could be critical for SMA development because they appear to be associated with the cytoskeleton system, processes of neuronal development and maintenance, apoptosis and transcriptional regulation. Therefore, this allows hypothesizing that the proteins that influence Rab and Rho GTPase activity could be SMA severity modifying factors [20]. Meanwhile, such analysis could be relevant not just to identify new possible SMA modifying factors but also to predict the changes in genomic DNA methylation induced by potential SMA therapy agents, as most of them possess DNA-demethylase activity [21].

### 4. EPIDEMIOLOGY
SMA is a rare disease (incidence of 1 in every 6,000–10,000 live births) with a heterozygosis frequency of about 1 in 35 persons. After cystic fibrosis, it is the second most common lethal autosomal recessive disease in humans. And likewise, it is the most common fatal neuromuscular disease diagnosed in children under the age of eighteen [22].

5. CLINICAL DESCRIPTION

Clinically, SMA disease severity is broad and for classification purposes, patients are categorized based upon the age of onset, and milestone achievement (or failing to achieve) (Table 2) [8].

Table 2. Clinical description of SMA child onset types.

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Other names</th>
<th>Age of onset</th>
<th>Milestone achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Werdnig-Hoffmann, &quot;non-sitters&quot;</td>
<td>0-6 months</td>
<td>They never sit</td>
</tr>
<tr>
<td>II</td>
<td>Intermediate SMA, &quot;sitters&quot;</td>
<td>7-18 months</td>
<td>They can sit, but can't stand up</td>
</tr>
<tr>
<td>III</td>
<td>Kugelberg-Welander, Moderate SMA, &quot;walkers&quot;</td>
<td>&gt; 18 months</td>
<td>They can stand up and walk</td>
</tr>
</tbody>
</table>

According to a clinical classification, SMA type I patients never achieve head control, type II patients will sit but will never be able to walk and type III patients are able to walk but progressively will lose the ability. Within the types of SMA, there is a significant diverse phenotype. Such as mild type II SMA patients and a severe type III SMA patient might present clinically diverse phenotype. Moreover, SMA type III patients may lose ambulation with disease progression, and then fall into the same functional group as SMA II patients, "sitters", for stratification in clinical trials. [23]

- SMA Type 0 is extremely severe and initiates during prenatal development and results in death within weeks; which haven’t been totally accepted.
- SMA Type I (Werdnig–Hoffmann disease) is a severe form characterized by an infantile onset ranging from birth to 6 months and accounts for approximately 60% of all newly diagnosed cases of SMA [24]. These infants have profound progressive proximal weakness, usually affecting the legs more than the arms. They commonly present as ‘floppy’ babies, with poor head control and significant hypotonia, and are never able to sit independently. Infants with type I SMA usually develop respiratory failure, with death occurring by the age of 2. A clinically relevant increase in survival has been shown with the use of non-invasive, assisted ventilation. [23]
- SMA Type II onset occurs between 6–18 months and presents with progressive proximal weakness and hypotonia. It initiates with proximal limb weakness, with progressive weakness and respiratory complications, joint contractures and scoliosis appearing in childhood. At some point during childhood, type II patients can sit upright without assistance. Approximately 70% of type II patients live to adulthood; although, they have a shortened life expectancy (around 25 years of age). [24]
- SMA Type III (Kugelberg–Welander disease) presents past 1 year (>1 year for type IIIa; >3 years for IIIb) in most cases presents at 18 months of age. [23] These patients are able to stand and walk without assistance at some point in their lives and can have a normal lifespan, although many become wheelchair-bound during adolescence. They are affected
by progressive proximal weakness but develop little respiratory muscle weakness or scoliosis. Their life expectancy is generally in line with the general population [23]. SMA types are classified by the age of onset and the milestone achieved during childhood. The type IV is exclusive in adults and the progression is more benign than the others SMA’s.

6. PATHOPHYSIOLOGY

SMA is characterized by the degeneration of the anterior horn of the spinal cord, which causes a dysfunction of the neuromuscular system, therefore, the electrical impulse through the nerves cannot be transmitted properly causing hypotonia. (Figure 2) Depending on the SMA type, it will be the onset and severity of the clinical picture [26].

![Pathophysiology of the neuromuscular system in healthy control versus a SMA patient](image)

**Fig. 2. Pathophysiology of the neuromuscular system in healthy control versus a SMA patient**

*The dysfunction of the neuromuscular system in the neuromuscular junction causes the difficulty or lack of movement of the muscles causing it to atrophy on SMA patients*

There are hypotheses that have arisen to explain SMA. The first one states that the loss of SMN’s well-known function in snRNP assembly causes an alteration in the splicing of a specific gene. Reduced SMN levels result in reduced assembly of Sm proteins into snRNA. This unevenly alters the levels of specific endogenous snRNPs, such as those used to splice minor introns from pre-mRNA. The second hypothesis states that SMN is essential for mRNA transporting, by assembling LSm proteins. It is hypothesized that reduced levels of SMN affect the assembly of the LSm proteins complex. SMN is known to associate with the RNA-binding protein hnRNP-R, and together they are responsible for the transport and/or local translation of β-actin mRNA in the growth cones of motor neurons. It is important in
RNA localization, and leads to a disrupted splicing or axonal transport of mRNA of limited
target genes that are highly specialized to motor neurons, causing an impairment of synapse
and leading to SMA (8).

SMA is often difficult to diagnose, because the symptoms can mimic other medical
conditions. Each child may experience symptoms in different way [27]. The diagnosis of
SMA is made after the sudden or gradual onset of specific symptoms and after molecular
testing.

7. DIAGNOSIS

The idea of SMA starts first with the clinical manifestations such as the milestone delay and
the age of onset which will be determine for clinical diagnose. Before, neurophysiological
methods and muscle biopsies were used; nowadays, the diagnosis of SMA is done by the
molecular study by the identification of the deletion of exon 7 of the SMN1 gene. The
identification of the SMN1 gene as a determinant of SMA has opened new perspectives for
the diagnosis of the disease in affected and carriers and to increase the knowledge of the
pathophysiology. Confirmation of the diagnosis by molecular methods has significantly
improved genetic counseling of the disease. The fact that over 95-98% of cases of SMA
present a deletion in SMN1 gene in the exon 7; therefore, molecular analysis is the method
of choice to confirm the diagnosis in patients with a clinical suspicion of SMA, even before
the muscle biopsy. This deletion has been observed in a wide range of phenotypes from the
most severe type until virtually asymptomatic individuals. It is evident, therefore, that there is
no correlation between the deletion and a particular phenotype. Even domestic variation
exists, especially in chronic forms (type III), asymptomatic siblings have been described with
a similar SMN1 deletion to the affected SMA. [1,28]. Diagnosis of patients with SMA is
mainly based on the identification of the deletion of exon 7 in SMN1 by Polymerase Chain
Reaction allele-specific (PCR) or by MLPA (Multiplex Ligation-Dependent Probe
Amplification).

The study of carriers in families with affected is performed with two methodologies. An
indirect diagnose method is by analyzing markers 5’end of SMN1 gene, identifying risk
haplotypes that segregate with the disease. Another method, that is a quantitative that is
capable of measuring, if present, one or two copies of the SMN1 gene in the test sample. An
additional advantage of the quantitative method is its application to the diagnosis of SMA
carriers of individuals in the general population (generally spouses of carriers of the disease)
or gamete donors (although it is necessary to comment here that 4% of carriers can have
two copies of the SMN1 gene on one chromosome and none in the other). Also the
quantitative study to identify the remaining cases of clinically affected patients without
homozygous deletion (one copy and the other absent but present point mutation) and in
cases where the individual had died and was not available detecting DNA parents as carriers
[30].

Prenatal diagnosis of an affected SMA patient can be done by showing in the fetal DNA
sample, a homozygous deletion of the SMN1 gene [26]. Recently, the methods of pre-
implantation genetic diagnosis have joined as reproductive choice for those couples at high
risk of disease recurrence [30].

8. MANAGEMENT

8.1 Evaluations Following Initial Diagnosis.
To establish the extent of disease and needs of an individual diagnosed with SMA, the following evaluations are recommended (Figure 3).

**Nutrition/feeding assessment**
- Time required to complete a feeding
- Evidence of fatigue during a feeding/meal
- Weight plotted on standard growth curves

**Respiratory function assessment**
- Normal breathing pattern versus abdominal breathing pattern
- Forced vital capacity (FVC)

**Sleep assessment**
- Consideration of a sleep study if the child snores during sleep or awakes fatigued in the morning

**Activities of daily living**
- Assessment of equipment needed for independence, such as a power-chair and other equipment in the home to improve the quality of life for the affected individual and the caregiver

**Orthopedic Evaluation**
- Attention to the development of contractures, scoliosis, and hip dislocation

**Medical genetics consultation**

**Fig. 3. Evaluation following initial diagnosis to established the extent of SMA disease.**

Depending of the type of SMA will have different needs. **Type I will require major interventions in feeding assessment and respiratory function assessment.** **Type II will require power chairs, respiratory function assessment and orthopedic evaluation.** **Type III will require home equipment to improve the quality of life and continuous orthopedic evaluation.** All SMA’s require medical genetics consultation for the family.

Management should be directed according to the type of SMA, with some general considerations support, as described in the table below [8]. There have been tested in vitro certain compounds such as valproic acid, hydroxyurea and phenylbutyrate salbutamol increasing RNA and SMN protein [12]. Some of these compounds have passed extremely quickly from the laboratory to human trials with little or no information in animal models; the results are still unsatisfactory or incomplete [8]. Hopefully, there has been new research in which there might be the treatment for SMA. For example the following:

**Antisense Oligonucleotides (ASO’s)**

Currently, there are no effective therapies available for SMA. Since reduced SMN protein levels cause SMA, most treatments have focused and aimed on increasing the amount of SMN, with strategies that include SMN2 transcription promotion with drugs or small molecules and SMN1 gene replacement using viral vectors carrying wild-type SMN1. The modulation of SMN2 mRNA splicing to restore the functional protein production is considered as an important alternative and promising molecular approach for SMA treatment. This can be achieved with the Antisense Oligonucleotides (ASO’s), which are
nucleotide acids analogs that are able to bind both mRNA intronic and exonic sites, thus modifying splicing events. ASO's have become a possible therapeutic approach to redirect the splicing of the paralogous SMN2 gene, with a consequent increase in the production of functional SMN protein. Along the ASO's, Morpholino Oligomers (MO) are considered to have an excellent safety and efficacy profile, therefore, they are among the most promising candidates for this purpose. Numerous regions are involved in SMN2 splicing regulation, one of which is the negative intronic splicing silencer (ISS-N1), a 15-nucleotide splice-silencing motif located downstream of SMN2 exon 7. ASO's targeting the ISS-N1 region promote the inclusion of exon 7 without off-target effects. It has been hypothesized that hybridization of ASOs to the ISS-N1 region displaces transacting negative repressors and/or unwinds a cis-acting RNA stem-loop that interferes with the binding of U1 small nuclear RNA at the 50 splice site of exon 7. Since all these findings may suggest that ASO-induced splicing will most likely be one of the first molecular therapies for SMA, they are already in a Phase II trial. Nonetheless, there are critical issues remain to be resolved like the modality of administration and if a local injection is sufficient to rescue SMA or whether systemic injection is necessary [31,32,33,34].

- Stem Cell Therapy

Taking into account that the motor neurons are subject to degeneration in SMA, replacement of these lost motor neurons with stem cells and stem cell-derived cells is considered as another potential therapeutic approach for SMA patients. This type of therapy has two goals, the first being the cell replacement and the other one to promote cell survival. Through the secretion of neurotrophic factors, stem cell-mediated neuroprotection can be achieved. Corti et al investigated in a SMA model the injection of both neuronal precursor cells derived from embryonic stem cells and primary neuronal stem cells. The neuronal stem cells that were injected into the CSF showed migration into the spinal cord of SMA mice. As well, some of these cells also differentiated into motor neurons. By the means of the cell replacement and the secretion of trophic factors, improvement in motor function and survival in SMA mice was achieved. Induced pluripotent stem cells (ipS) represent another interesting approach for understanding SMA mechanisms and therefore, its treatment. The innovative of this therapeutic approach is that ipS cells derived from SMA patients can also be differentiated into motor neurons for further study of the disease pathology. Likewise, among this stem cell therapy, there is another alternative called auto-grafting, in which ipS cells derived from SMA patients can also be modified and transplanted back into the patients from whom they were obtained. This auto-grafting approach might eliminate the hurdle of graft rejection and need for immune suppression currently used for stem cell transplantation. Although, this type of therapy also has some disadvantages that have question its therapeutic use, first because they don't have the certainty that the cells obtained from a diseased patient, despite an initial modification of the disease, may revert to another phenotype over time. As well, there are recent investigations that have shown that ipS cells may have immunogenic properties, which need to be carefully evaluated [35,36,37,38,39].

- Gene therapy

Through viral delivery and insertion of the entire SMN1 gene or cDNA sequence into the genome of SMA patients, gene therapy is being considered as a future permanent solution for SMA. Although, there have been reported some risks if the exogenously delivered gene is inserted at a wrong location and/or is overexpressed. Despite that, the result of gene therapy aiming SMN1 delivery by scAAV9 in SMA mice and large animals seems like a promising alternative and it may offer one of the best therapeutic alternatives to a specific group of SMA patients who are too weak to receive frequent invasive treatments [40].
- Small Molecules

Olesoxime (TRO19622) is a small molecule with a cholesterol-like structure that displays strong neuroprotective properties. It targets and preserves mitochondrial integrity and function in stressed cells. Preclinical studies have demonstrated that Olesoxime promotes the function and survival of neurons and other cell types under disease-relevant stress conditions. It has been shown to be active in multiple preclinical neurodegeneration models including the NSE-Cre F7/F7 model of SMA. As well, it has demonstrated effectiveness in keeping motor neurons alive in cultures [40,41,42].

Speaking of genetic counseling, it is considered as the process of providing individuals and their families the information of the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. This implies to deal with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members.

8.2 Treatment of Manifestations

The management of children with SMA starts with the diagnosis and classification into one of the subtypes.

8.2.1 Pulmonary.

The key respiratory problems in SMA are as follows:
1. Impaired cough resulting in poor clearance of lower airway secretions
2. Hypoventilation during sleep
3. Chest wall and lung underdevelopment
4. Recurrent infections that exacerbate muscle weakness.

Pulmonary disease is the major cause of morbidity and mortality in SMA type I and II and may occur in a small proportion of patients with SMA type III. Without respiratory support, infants who are unable to sit usually die before the age of 2 years. Pulmonary compromise is caused by a combination of inspiratory and expiratory muscle weakness, with greater involvement of expiratory and intercostal muscles. Children with SMA type I can survive beyond age two years when provided tracheostomy or non-invasive respiratory support [32,33,34]. Options for management, including ‘do not attempt to resuscitate’ status, should be discussed with the parents/care providers before respiratory failure [31]. This discussion should be initiated when abdominal breathing is noted and/or the forced vital capacity is less than 30%. With non-invasive respiratory support, children have fewer hospitalizations after age five years [32]. Use of an intermittent positive-pressure breathing device in the treatment of children with neuromuscular diseases, including children with SMA, has proven effective in expanding lung volumes and clearing airway secretions [42].

Respiratory muscle weakness results in impaired cough and inability to clear lower airway secretions, lung and chest wall underdevelopment, and hypoventilation. Respiratory care of patients with SMA is essential to their survival and quality of life.

8.2.2 Nutrition.

Feeding and swallowing difficulties are common in non-sitters and sitters but are rarely a concern in walkers. The key symptoms of feeding difficulties that these patients will present include fatigue during oral feeding with a consequent prolonged mealtime, which can
predispose the patient to episodes of choking or coughing during or after swallowing. The presence of recurrent pneumonias is a major indicator of aspiration (due to all the difficulties for nutrition), which may be silent and fatal as well. [43].

Bulbar dysfunction is universal in SMA type I patients, and gastrostomy should be considered early on the course of the disease. The bulbar dysfunction eventually becomes a serious problem for SMA type II patients and only very late in the course of disease for those with SMA type III. Gastrointestinal dysmotility is considered as well a nutritional problem, because it can result in constipation, delayed gastric emptying, and potentially life-threatening gastroesophageal reflux [44]. Treatment should aim at reducing the risk of aspiration during swallow and optimizing efficiency of feeding and promote enjoyable mealtime. Because nutritional problems associated with SMA influence the patient’s pulmonary status and general well being, optimal management of these problems by a multidisciplinary team of physicians, speech therapists or occupational therapists, dietitians, and pediatric surgeons should greatly improve survival and mostly their quality of life.

8.2.3 Orthopedic Care.

Muscle weakness can occur in a different severity in each patient; regardless of that, it mainly limits the motor function of trunk and upper and lower extremities, resulting in contracture formation, spinal deformity, limited mobility and activities of daily living. As a result of these complications, these patients have an increased risk of pain, osteopenia and fractures. Infants and children with SMA should have an appropriate evaluation for their presenting musculoskeletal and functional deficits.

- Scoliosis is a major problem in most SMA type II patients and in half of those with SMA type III [45, 46, 47]. Before ten years of age, approximately 50% of affected children, particularly those who are non-ambulatory, develop spinal curvatures of more than 50 degrees, which require surgery. The use of an orthosis prior to surgical intervention does not prevent scoliosis but it does allow the affected individual to be upright rather than prone [48].

- Hip dislocation is another orthopedic concern in SMA. A retrospective review of a large series of cases suggests that asymptomatic hip dislocation does not require surgery [49].

9. SMA COMPLICATIONS.

Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common SMA complications [44].

An unexplained potential SMA complication is severe metabolic acidosis with dicarboxylic aciduria and low serum carnitine concentrations during periods of intercurrent illness or fasting [49]. Whether these metabolic abnormalities are primary or secondary to the underlying defect in SMA is unknown. Some investigators have suggested that underweight SMA individuals with minimum muscle mass are at risk for recurrent hypoglycemia or ketosis [50,51]. The problem is self-limiting; individuals typically recover in two to four days.

10. SMA’S LIFE EXPECTANCY AND PROGNOSIS

SMA type I - Children with SMA I typically manifest weakness prior to age six months and will never be able sit independently. The life expectancy in these patients is less than two years with some exceptions [52,53]. In a prospective study over a three-year period 31 of 34
children died before age two years [54]. However, there is some evidence that improved respiratory care and nutrition extends life expectancy [55].

SMA type II - The life expectancy of these individuals is not known yet with certainty. Anecdotal information shows that some live into adolescence and as late as the third or fourth decade [56,57,58,59,60]. Forced vital capacity decreases in all individuals with SMA, which will make them susceptible to have respiratory complications [44].

SMA type III - These individuals clinically manifest weakness after age 18 months, are able to walk independently, and have an indefinite lifespan. In some cases, those who are diagnosed prior to age 18 months still develop the ability to walk; although they lose their ability to walk by age 15 years, they are considered to have a “normal life expectancy.” Those who develop weakness after they have started to walk normally usually retain the ability to walk into their third or fourth decade [61,62,64]. Whether the loss of function observed in all individuals with SMA is caused by loss of motor units or other factors such as scoliosis, progressive contractures, and pulmonary insufficiency is difficult to determine [58]. In a physiologic outcome study, Swoboda (2005) showed a correlation between motor unit number estimation (MUNE) and disease severity. In addition to MUNE, the measurement of compound motor action potential can be used to help determine outcome.

A review of life expectancy of 569 German and Polish individuals with SMA type II and III found that 68% of individuals with SMA type II were alive at age 25 years and that life expectancy of those with SMA type III was not different from that of the general population [60].

11. CONCLUSION

Spinal muscular atrophy is considered as one of the most severe neuromuscular diseases with a child onset presentation. Quality of life can only be improved with the use of palliative care, including respiratory and nutritional support, as well as orthopedic and physiotherapeutic care. Management starts with the confirmed diagnose of SMA and posterior classification into one of the described subtypes. However, therapeutic developments and pre-clinical stages in SMA is a current challenge. Thus, the importance of this review is to inform and gather tremendous amount of evidence, to progress rapidly into a therapeutic strategy that can successfully be accomplished.

The increased attention to early diagnosis and to several aspects of management of SMA has stimulated the development of clinical guidelines and standards of care. In the past decade, many promising new therapeutic approaches have been tested in clinical trials of patients with SMA but with limited or no success. At the present, no effective therapy is available for SMA. The main therapeutic strategies that are now in use are based on symptomatic treatment and supportive care. Consequently, the development of novel therapies in SMA now has strong academic, government, and industry involvement, in addition to the interest of several parental organizations and foundations. However, both preclinical and early clinical trial results involving novel molecular therapies suggest that the clinical care paradigm in SMA will soon change.


41. Trophos. Therapeutic programs, spinal muscular atrophy


63. Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of


ABBREVIATIONS

SMA: Spinal Muscular Atrophy
AMAME: Asociación Mexicana de Atrofia Muscular Espinal
SMA’s: Spinal muscular atrophies
SMN: Survival motor neuron
SOD1: Superoxide dismutase 1
HTT: Huntington
SnRNP: Small nuclear ribonucleoprotein
ESE: Exon splicing enhancer
PCR: Polymerase chain reaction
MLPA: Multiplex Ligation-dependent Probe Amplification
MUNE: Motor unit number estimation
mRNA: messenger RNA