Spinal Muscular Atrophy: review of a child onset disease

ABSTRACT

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 milestone 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. SMA type I is the leading cause of death in children under two years of genetic diseases in the world. Patients with SMA type 2 can sit but never walk independently. Patients with SMA type 3 have a normal life expectancy. Decline in muscle strength and motor function eventually occurs in SMA 2 and 3. 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.

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

1. INTRODUCTION

Spinal Muscular Atrophies are a genetic disorder with autosomal recessive trait, clinically 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 control of head movement. In severe cases of SMA, 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 genes are survival motor neuron (SMN) gene. Deletions of the telomeric copy of SMN gene (SMN1) have been reported in 88.5% to 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 6000 to 1 in 10,000 live births and with a carrier frequency of 1 in 40 to 1 in 60. 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 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 subtype of SMA. 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 the ubiquitously expressed protein survival motor neuron (SMN), 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 produces an stable SMN protein that meet the needs of the cell survival to continue, while the SMN2 produces an unstable SMN protein which cannot perform its function, therefore, apoptosis is induced.

Two hypotheses have arisen to explain SMA. Reduction of SMN is proposed to affect pre-mRNA splicing of certain genes or to disrupt its function in axons, resulting in reduced levels of certain transcripts in the distal axon. Recent papers provide evidence for both hypotheses.

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 “gene” 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 stability SMN protein RNA molecules that encode proteins essential for the development and function of motor neurons [8].
3.2 SMN1 gene

SMN1 gene is deleted or disrupted in 95% of patients whatever 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 any person with absence of both genes. It has been reported that in other species such as the mouse, the gene is not duplicated and its deletion causes early embryonic death. This suggests data that the absence of the SMN1 gene and its protein should be lethal to the organism.

According to Lorson et al., (2010) approximately 8% of the population lack the SMN2 gene but have a copy of the SMN1 gene, which allows them to be asymptomatic [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 their decline and therefore, they become the most vulnerable tissues in SMA; which all of this may explain the clinical manifestations.

3.3 SMN2 gene

All SMA patients have at least one copy of SMN2 gene (whose function does not prevent the development of the disease), and the greater the number of copies a patient has, the phenotype is generally less severe. [10]. Thus, it appears that the number of SMN2 copies have an important modifying effect on the disease severity and prognosis. 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 generate the copies of SMN2 gene; although, there are other modifying factors that are not yet known or remain unclear [11]. 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.

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**Fig. 1. SMN transcripts by gene splicing in healthy control vs. patient with SMA.**

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. 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.

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3.3.1 Number of SMN2 copies.
When SMN1 is mutated, SMA results because SMN2 cannot fully compensate for the lack of functional SMN protein. However, when the SMN2 copy number is increased, small amounts of full-length transcripts generated by SMN2 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 is correlated with a milder phenotype [12,13,14]. Data from Mailman et al. (2002), are summarized in table 1. More recently, Prior [2004] reported three asymptomatic unrelated individuals homozygous for an SMN1 deletion who had five copies of SMN2, demonstrating that expression levels consistent with five copies of SMN2 may compensate for the lack of SMN1 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 are affected with SMA type I to type III [15].

<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 (0%)</td>
<td>0 (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>7 (4.9%)</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
<td>43 (82.7%)</td>
<td>0 (0%)</td>
<td>43 (30.3%)</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>2 (3.9%)</td>
<td>70 (77.8%)</td>
<td>72 (50.7%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>20 (22.2%)</td>
<td>20 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>52</td>
<td>90</td>
<td>142</td>
</tr>
</tbody>
</table>

(Adapted from Mailman) [14]

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

3.3.2 SMN2 sequence variants

In contrast to the above observations, [16] recently described three unrelated individuals with SMA whose SMN2 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 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, thus resulting in the less severe phenotypes. These data demonstrate that the SMA phenotype may be modified not only by the number of SMN2 copies, but also by SMN2 sequence variants. Thus, it should not be assumed that all SMN2 alleles are equivalent and it is appropriate to investigate SMN2 for sequence changes that may have a positive or negative effect on SMN2 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.

4. EPIDEMIOLOGY
SMA is a rare disease (incidence of 1 in every 6,000–10,000 live births) with a heterozygosity frequency of about 1 in 35 people. 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 [17].

5. CLINICAL DESCRIPTION

Clinically, SMA disease severity is broad and for classification purposes, patients are categorized based upon the severity, the age of onset, and achieving (or failing to achieve) physical milestones (Table 2) [7].

Table 2. Clinical description of SMA 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-Hoffman, &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>
<tr>
<td>IV</td>
<td>Adult’s SMA.</td>
<td>20-30 years</td>
<td>They can walk without help</td>
</tr>
</tbody>
</table>

According to a clinical classification, SMA type I patients never achieve the ability to sit, type II patients will sit but will never be able to walk, and type III patients at some point of their lives will have ability to walk. Within individual SMA subtypes, there is significant phenotypic variation, such that a mild type II SMA patient and a severe type III SMA patient might present clinically with a similar 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. [18]

- Type 0 is extremely severe and initiates during prenatal development and results in death within weeks.
- Type I SMA (Werdnig–Hoffman disease) is a severe form characterized by an infantile onset ranging from birth to 6 months and accounts for approximately 50% of all newly diagnosed cases of SMA [19]. 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. [18]
- Type II SMA 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). [19]
- Type III SMA (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. [19] 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 [18].

- Type IV SMA patients can achieve a normal lifespan, and they will only present proximal leg weakness in adulthood.

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 and gradually there will appear paresthesias and hypotonia. (Figure 2) Depending on the SMA type, it will be the onset and severity of the clinical picture [21].

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

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 several theories which are related to the absence of the SMN1 gene, as it is reported that SMN protein is present at high levels in both axons and growth cones, and loss of its function disrupts axonal extension and pathfinding. 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. Another hypothesis
states that the SMN protein binds to a complex of more than 8 proteins that help to assemble uridine-rich ribonucleoproteins; and these are the main components of the splicesosomes performing for splicing pre-mRNA. With insufficient amounts of SMN protein in motor neurons entering apoptosis and nerve impulses are not transmitted between the brain and muscles resulting in some muscles cannot perform their normal functions, leading to weakness of the movement and finally atrophy [5].

SMA is often difficult to diagnose, because the symptoms can mimic other medical conditions. Each child may experience symptoms in different way [22]. 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. 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 both affected and carriers; and to increase the knowledge of its 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 deletion of SMN1 to the affected SMA. [1, 23]. Diagnosis of patients with SMA is mainly based on the identification of the deletion of exon 7 in SMN1 by Polymerase Chain Reaction (PCR) or allele-specific MLPA study (Multiplex Ligation-Dependent Probe Amplification).

The study of carriers in families with affected is performed with two methodologies. An indirect study, by analyzing markers 5'end of SMN1 gene, identifying risk haplotypes that segregate with the disease. And another direct, that is a quantitative method 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 [24].

Prenatal diagnosis of an affected patient with SMA is performed showing the fetal DNA sample of the existence of the homozygous deletion of the SMN1 gene [25]. Further study of the C212 and C272 markers, indicating whether it is a heterozygous carrier, while confirming that indeed no fetal and maternal sample is analyzed. Recently the methods of pre-implantation genetic diagnosis have joined as reproductive choice for those couples at high risk of disease recurrence [25].
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
- Assessment 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 establish 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.

Treatment should be directed according to the type of SMA, with some general considerations support, as described in the table below [7]. In recent years, there have been tested in vitro certain compounds such as valproic acid, hydroxyurea and phenylbutyrate salbutamol increasing RNA and SMN protein [10]. 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 [7].

Speaking of genetic counseling, it is the process of providing individuals and families with information on 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 [26,27,28]. Options for management, including ‘do not attempt to resuscitate’ status, should be discussed with the parents/care providers before respiratory failure [29]. 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 [30]. 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 [31].

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 spinal muscular atrophy 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 present 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 also fatal [30].

Bulbar dysfunction is universal in SMA type I, and gastrostomy should be considered early on the course of the disease. The bulbar dysfunction eventually becomes a serious problem for persons with SMA II and only very late in the course of disease for those with SMA 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 [30]. 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 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 persons with SMA II and in half of those with SMA III [32, 33, 34]. Before age ten years, approximately 50% of affected children, especially 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 does allow the affected individual to be upright rather than prone [34].
- 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 [35].

9. COMPLICATIONS OF SMA.

Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications of SMA [30].

An unexplained potential complication of SMA is severe metabolic acidosis with dicarboxylic aciduria and low serum carnitine concentrations during periods of intercurrent illness or fasting [35]. Whether these metabolic abnormalities are primary or secondary to the underlying defect in SMA is unknown. Some investigators have suggested that underweight individuals with SMA with minimum muscle mass are at risk for recurrent hypoglycemia or ketosis [36, 37]. The problem is self-limiting; individuals typically recover in two to four days.

10. LIFE EXPECTANCY AND PROGNOSIS OF SMA

SMA 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 [38, 39]. In a prospective study over a three-year period 31 of 34 children died before age two years [40]. However, there is some evidence that improved respiratory care and nutrition extends life expectancy [41].

SMA II. The life expectancy of persons with SMA II is not known with certainty. Anecdotal information shows that some live into adolescence and as late as the third or fourth decade [42, 43, 44, 45, 46]. Forced vital capacity decreases in all individuals with SMA, which will make them susceptible to have respiratory complications [30].

SMA 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 30s or 40s [47].

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 [44]. 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 individuals with SMA II and SMA III from Germany and Poland found that 68% of individuals with SMA II were alive at age 25 years and that life expectancy of individuals with SMA III was not different from that of the general population [46].

11. CONCLUSION

SMA is one of the most severe neuromuscular diseases with a child onset presentation. Worldwide efforts have been made to overcome this disease, scientific advances in the natural history of the disease and basic research as the most important contribution to the understanding of SMA and the search for the cure. The frequency of this condition is higher than expected, however the recognition of this disease is poor. In Mexico, little is known about SMA in which AMAME and the Desarrollo de envejecimiento y enfermedades neurodegenerativas (Development-Aging; Neurodegenerative Diseases) laboratory are the national reference for SMA. The molecular diagnose given free of charge to all the patients around Mexico that need it; leading a study in progress in which 37 patients with SMA has been reported. Those 37 patients positive for SMA were taken from 246 blood samples from all around Mexico. The type that predominates is the type III SMA because of a better prognosis with 17 patients, type I SMA is the second with 13 patients since all the patients live inside the hospitals. Type II SMA is the least common with 7 patients because of the poor information of the physicians. The main goal of this review is to inform more about SMA.

REFERENCES


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: Huntingtin
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