Spinal muscular atrophy: diagnosis, treatment and future prospects
Mariana T. C. Baioni,1 Celia R. Ambiel2

Abstract

Objective: To report on recent genetic and molecular discoveries and on future prospects for the treatment of spinal muscular atrophy (SMA), thereby helping healthcare professionals to make a quick diagnosis and provide appropriate and timely therapeutic support.

Sources: Information was collected from scientific articles published in the last 2 decades, retrieved from the databases SciELO, PubMed, and MEDLINE.

Summary of the findings: SMA is a neurodegenerative disorder with autosomal recessive genetic heredity. It is caused by a homozygous deletion of the survival motor neuron (SMN1) gene. This genetic alteration results in reduced levels of the SMN protein, leading to degeneration of alpha motor neurons of the spinal cord and resulting in muscle weakness and progressive symmetrical proximal paralysis. It is known that basic nutritional and respiratory care and physiotherapy can be important to delaying disease progression and prolonging patients’ lives. Several drugs are being tested, some new, others, such as valproic acid, already known; paralysis can be halted, but not reversed.

Conclusions: SMA is a difficult to diagnose disorder, because it is little known, and treatment is uncertain. Pharmacological treatments and supportive therapies are not yet able to recover motor neurons or muscle cells that have already been lost, but are aimed at delaying disease progression and improving patients’ residual muscle function, as well as offering better quality of life and life expectancy.


Introduction

Spinal muscular atrophy (SMA) is a neurodegenerative disease with autosomal recessive heredity. After cystic fibrosis (1:6,000), SMA is the next most fatal disease with this genetic profile, with an incidence of 1:6,000 to 1:10,000 births.1 The frequency of carriers (heterozygotes) is one in 40 to 60 people.2

This disease is caused by a homozygous mutation or deletion of the survival motor neuron gene 1 (SMN1), which should be located in the telomeric region of chromosome 5q13. The principal determinant of severity is the number of copies of SMN2, a gene that is similar to SMN1 and is located in the centromeric region.3

This genetic alteration to the SMN1 gene is responsible for a reduction in survival motor neuron (SMN) protein. The SMN1 gene does not completely compensate for the absence of SMN1 expression because it only produces 25% of SMN protein.4 The lack of the SMN protein leads to degeneration of alpha (α) motor neurons located in the ventral horn of the spinal cord, which leads to progressive and symmetrical muscle weakness and paralysis.2

Clinical classification of SMA is based on age at onset and maximum motor function acquired, with the following categories: 1) severe (type I, severe SMA or Werdnig-Hoffmann disease); 2) intermediate (type II or chronic

1. Especialista, Fisiologia Humana, Universidade Estadual de Maringá (UEM), Maringá, PR, Brazil.
2. Doutora, Biologia Celular. Professora, Fisiologia Humana, UEM, Maringá, PR, Brazil.

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SMA); 3) mild (type III, juvenile SMA or Kugelberg-Welander disease); and 4) type IV (adult SMA). Other authors classify SMA into just three categories: severe, intermediate and mild.

SMA is a difficult disorder to diagnose and treatment is uncertain. Diagnosis is based on evidence, both electrophysiological and histological, of denervation of the muscle. Nowadays, diagnosis is confirmed by molecular analysis to demonstrate an absent SMN1 gene exon 7.

Since this is a progressive neurodegenerative disease, patients with SMA require special care, which can halt disease progression and prolong their lives. The objective of this bibliographic review article is to describe the clinical and laboratory profile of SMA patients and report on recent genetic and molecular discoveries and the future prospects for treatment, thereby aiding health professionals to make rapid diagnoses and provide early and appropriate therapeutic support.

**Development**

**Classification of SMA**

There are four SMA classifications, based on age at disease onset and maximum motor function acquired.

Type I SMA: (also known as severe SMA, Werdnig-Hoffmann disease or acute SMA) is characterized by early onset (between 0 and 6 months of age), by a failure to acquire the ability to sit up and by very short life expectancy (less than 2 years). Children diagnosed with this form have very little control of their heads and cough and cry weakly. They lose the ability to swallow and feed before they reach 1 year of age. Trunk and limb weakness normally spreads to the intercostal muscles, making it unlikely that a normal respiratory cycle will develop. Although the intercostal muscles are affected, the diaphragm is initially spared. The risk of early mortality is usually associated with bulbar dysfunction and respiratory complications. Historically, these children have a short life expectancy (less than 2 years), but, thanks to improved clinical care, over recent years survival has improved.

Type II SMA: (or chronic SMA) generally becomes symptomatic at around 5 to 40 years, but it may emerge earlier. Some patients classified as having type II SMA are able to sit up unaided while others can remain sitting if they are positioned, but cannot sit up unaided. Better developed patients are able to remain standing if provided with support, but will nevertheless be unable to learn to walk. Bulbar weakness, combined with swallowing difficulties, can lead to reduced weight gain in some children. Furthermore, these patients may have problems with coughing and with cleaning secretions from the trachea, may have fine trembling (known as fasciculation) and can suffer from scoliosis and contractures as they age. Life expectancy is around 10 to 40 years.

Type III SMA: (also known as juvenile SMA or Kugelberg-Welander syndrome) onset is after 18 months, but the actual age varies greatly. According to Wirth et al., when the disease emerges before 3 years of age it is classified as Type IIIa SMA, whereas when onset is later, it is called Type IIIb SMA. The difference between the two is preservation of the ability to walk. Patients with Type IIIa are able to walk until they are 20, while Type IIIb patients will be able to walk for their whole lives. Problems with swallowing, coughing or nocturnal hypoventilation are less common than in patients with Type II, but may still be observed. As they age, these patients may develop scoliosis. The principal characteristic of these patients is that they are able to walk independently, and life expectancy is indeterminate.

Type IV SMA: there is no consensus on the age of onset of Type IV SMA. Russman reports that it emerges after 10 years of age, whereas Wang et al. state that weakness normally emerges during the second or third decade of life, or at about 30 years of age. Motor function involvement is mild and there are no problems with deglutition or respiration. These patients are able to walk normally and have normal life expectancy.

**Clinical features of SMA**

Since only α motor neurons are lost progressively, only motor function is compromised and sensory neurons are unaffected. This loss of function leads to weakness and to progressive symmetrical atrophy of the proximal voluntary muscles of the legs, arms and, sometimes, the trunk, as the disease progresses.

A number of unusual clinical features are observed in SMA. One of these is the distribution of muscle weakness, which is more compatible with a myopathic disorder than with a neurogenic disorder. Proximal muscles are more involved than distal muscles, legs are more affected than arms and arms are more affected than the face and diaphragm. In other words, muscle weakness and atrophy does not have a homogeneous distribution. The severity of muscle weakness is related to age at onset and children with the most severe form of the disease (Type I SMA) can appear normal at birth, but present muscle weakness a few months later.

Furthermore, the clinical course followed by SMA patients who survive beyond childhood demonstrates that loss of muscle strength is normally most evident at diseases onset and that, after this, residual muscle power can remain stable for months or years.

**Molecular genetic basis of SMA**

Genetic studies have shown that SMA is caused by absence of the SMN gene, which should be located in the telomeric region of chromosome 5. This gene was identified in 1995 by Lefebvre et al. and has nine
SNM = survival motor neuron; MRNA = messenger ribonucleic acid.

Figure 1 - Structure of the SMN gene in chromosome 5

The SMN1 gene is responsible for complete synthesis of the SMN protein. In contrast, the SMN2 gene is not capable of completely synthesizing the protein, being only responsible for a part of its production. SMN2 produces 10 to 25% functional protein while the remaining 75% produced is a protein that is truncated and unstable (SMN∆7) and is rapidly degraded (Figure 1). 

Another important point that should be highlighted is that the number of intact copies of SMN2 is a determinant of disease severity. Figure 2 illustrates the genotype of people who are affected and unaffected by SMA, characterizing type I, II and III patients. It also illustrates the quantity of SMN protein synthesized by each genotype. As the number of copies of SMN2 increases, the quantity of functional SMN protein increases and the severity of the disease reduces. The figure also demonstrates that gene conversion events are responsible for the milder phenotypes, while deletion of the SMN1 gene leads to more severe forms of the AME.

The SMN protein is widely distributed in all cells of the body. It is found in the nuclei of cells and within the nucleus it binds to certain structures involved with removing non-coding sequences (introns) from the pre-MRNA (messenger ribonucleic acid). Furthermore, it appears that SMN also participates in regulating transcription and expression of certain genes.

Despite advances in knowledge about the biochemistry of SMN, it is not yet clear how reduced levels in all different cell types are specifically responsible for degeneration of α motor neurons. This raises the possibility that SMN has an additional function that is restricted to these neurons. Immunohistochemical studies have identified SMN in dendrites, implantation cones and axons of motor neurons, suggesting it plays a role in transporting RNA along axons. Furthermore, it has been observed that the motor neurons of SMN-knockout mice and zebrafish exhibit failure to reach the motor end plate, having an axon with aberrant ramifications, indicating strong evidence that SMN plays an important role in morphological development and axonal migration. On the other hand, the SMN protein is also found postsynaptically at the neuromuscular junction and in the Z bands of striated muscle, indicating that pathogenesis does not exclusively involve the motor neuron cell body, but can also affect the muscle fibers themselves.

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No cases have ever been reported of people with complete absence of the SMN protein, i.e., patients who have SMA and also have an absent SMN<sub>2</sub> gene. This is probably because such a genotype would be incompatible with life and the SMN protein may play an essential role during embryo development<sup>19,25,26</sup> or may modulate neuronal apoptosis.<sup>27</sup>

**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,<sup>1</sup> since these clinical signs can also be observed in other neuropathologies (Table 1).

Since neuromuscular diseases are the main causes of childhood hypotonia<sup>28</sup> and since the neuromuscular diseases that most often affect children are SMA and the dystrophies,<sup>28,29</sup> Table 2<sup>30</sup> 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 1** - The most common causes of muscle hypotonia in childhood

<table>
<thead>
<tr>
<th>Principal causes of muscle hypotonia by age at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At birth</strong></td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Congenital myotonic dystrophy</td>
</tr>
<tr>
<td>Type I spinal muscular atrophy</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
</tr>
<tr>
<td>Systemic septicemia-induced diseases</td>
</tr>
<tr>
<td>Lung damage</td>
</tr>
<tr>
<td>Intracranial pathologies</td>
</tr>
<tr>
<td>Infections of the central nervous system</td>
</tr>
<tr>
<td>Disorders of the peripheral nerves</td>
</tr>
<tr>
<td>Diseases of the neuromuscular junction</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Drug intoxication during pregnancy or delivery</td>
</tr>
<tr>
<td><strong>After 6 months of age</strong></td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Spinal muscular atrophy, types II and III</td>
</tr>
<tr>
<td>Polyneuropathies</td>
</tr>
<tr>
<td>Childhood myasthenia gravis</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>Metabolic myopathy</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Rickets</td>
</tr>
<tr>
<td>Metabolic diseases</td>
</tr>
<tr>
<td>Nephropathies</td>
</tr>
<tr>
<td>Lung diseases</td>
</tr>
</tbody>
</table>

**Figure 2** - Genotypes of people affected and unaffected by SMA
Table 2 - Principal differences between spinal muscular atrophy and the muscular dystrophies

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Spinal muscular atrophy</th>
<th>Muscular dystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Weakness</td>
<td>Weakness</td>
</tr>
<tr>
<td>Signs</td>
<td>Muscle atrophy, lack of deep reflexes, fasciculations, rapid and discrete involuntary movements of muscles, such as trembling</td>
<td>Pseudo-hypertrophy of the calf, deep reflexes may be normal, reduced or absent, depending on the degree of muscle weakness</td>
</tr>
<tr>
<td>Test findings</td>
<td>Normal or reduced muscle enzymes, neurogenic electroneuromyography results, muscle biopsy with atrophic appearance</td>
<td>Very high muscle enzyme levels, myopathic electroneuromyography results, muscle biopsy with dystrophic appearance</td>
</tr>
<tr>
<td>Definitive diagnosis</td>
<td>Genetic test showing deletion of SMN&lt;sub&gt;1&lt;/sub&gt; gene from chromosome 5</td>
<td>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)</td>
</tr>
<tr>
<td>Disease mechanism</td>
<td>Degeneration of nerve cells in the spinal ventral horn</td>
<td>Degeneration of muscle cells</td>
</tr>
<tr>
<td>Genetic heredity</td>
<td>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)</td>
<td>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)</td>
</tr>
<tr>
<td>Treatment</td>
<td>First line treatment is physiotherapy (more details will be given later in the text)</td>
<td>First line treatment is physiotherapy (corticoids may be prescribed)</td>
</tr>
<tr>
<td>Most common complications</td>
<td>Respiratory problems, scoliosis, contractures</td>
<td>Respiratory and cardiac problems, scoliosis and contractures</td>
</tr>
<tr>
<td>Natural course of disease</td>
<td>SMA is a progressive disease; degeneration is faster or slower depending on type</td>
<td>Dystrophies are progressive diseases; degeneration is faster or slower depending on type (Duchenne, Becker, etc.)</td>
</tr>
</tbody>
</table>

SMA = spinal muscular atrophy; SMN = survival motor neuron.

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 SMN<sub>1</sub> 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.\(^3\)\(^2\)\(^3\)

**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 SMN\(_1\) gene is completely absent (with or without a deletion of exon 8).\(^3\)\(^8\) Since the SMN\(_1\) gene does not have this exon, its absence also demonstrates that the SMN\(_1\) gene is nullified.

If a patient suspected of having SMA does have a copy of the SMN\(_1\) 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.\(^8\)

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.\(^1\)

Alternatively, Kolb et al.\(^3\)\(^3\) 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 authors\(^3\)\(^3\) 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.

**Treatment**

Since it is a progressive neurodegenerative pathology, SMA patients require a range of special treatments that can halt the disease’s progress and prolong their lives. The majority of care revolves around supportive therapies because, unfortunately, there is not yet any pharmacological treatment.

**Supportive therapies**

A multidisciplinary team is responsible for prolonging and improving the quality of patients’ lives.\(^2\)\(^4\) Care covers respiratory and nutritional support in addition to orthopedic and physiotherapeutic care, to avert postural problems.

a) Respiratory care:

Pulmonary diseases are the principal cause of morbidity and mortality among patients with SMA types I and II and can affect a small number of patients with type III SMA.\(^8\)

The severity of muscle weakness and the fact that these patients are either always lying down or get up very little mean that they have a limited capacity to cough and remove secretions from the lower respiratory tract. As a result of this they are prone to recurrent infections which exacerbate the muscle weakness (particularly of the respiratory muscles),\(^8\) and can lead to atelectasis and pulmonary collapse.\(^2\)\(^4\) Additionally, these children may suffer from nocturnal hypoventilation and underdevelopment of the lungs and chest wall.\(^8\)\(^2\)\(^4\)

 Provision for these patients includes rapid access to special clinical intervention and respiratory support when necessary (ranging from noninvasive ventilation to tracheostomy and mechanical ventilation). Techniques for cleaning the Airways and moving secretions are very useful, including pulmonary physiotherapy and postural drainage. These patients also need rapid access to antibiotic therapy and should be on an immunization schedule including several vaccines against agents that can cause severe pulmonary infections.\(^8\)\(^2\)\(^4\)\(^3\)\(^4\)

Both atrophy and hypotonia of the muscles have a direct influence on the degree of compromise to respiratory and motor function. In these situations it is the physiotherapist who works to prevent and treat bone deformities and respiratory disorders, contributing to preventing the disease from progressing and to improving patients’ quality of life.\(^1\)

b) Nutritional care:

Children with SMA can suffer from a variety of gastrointestinal problems, such as gastroesophageal reflux, constipation, abdominal distension and retarded gastric emptying.\(^5\)\(^2\)\(^4\) Reflux is a determinant of mortality and morbidity, because it can be associated with silent aspiration, which can lead to aspiration pneumonia, worsening the situation even further. High fat foods should be avoided because they delay gastric emptying and increase the risk that reflux will occur.\(^8\)

 The origins of constipation are multifactorial and it may be the result of abnormal gastrointestinal tract motility, reduced intake of foods rich in fibers and of water and also hypotonicity of muscles in the abdominal wall.\(^8\)\(^3\)\(^4\) Furthermore, in these patients reduced intestinal movement can result in abdominal distension.\(^8\)

 Patient care includes pharmacological treatment for gastroesophageal reflux, involving gastric acid neutralizers and/or gastric secretion inhibitors, such as proton pump inhibitors and histamine blockers,\(^8\) in addition to prokinetic agents.\(^2\)\(^4\)

Diet can be assessed by a nutritionist. It should be remembered that SMA patients may have an acceptable fat mass for their body, but may be classified as below normal weight, on the weight/height criterion, because of their reduced body mass. This could lead to inappropriate dietary advice, which would in turn lead to obesity.\(^8\)

In severe cases, where children are unable to feed sufficiently enterally, parenteral calorie supplementation should be considered in order to avoid muscle catabolism in children with low fat reserves.\(^8\)
c) Orthopedic care:

The principal problem that results from the limited trunk and limb motor function caused by the muscle weakness include postural deformities (scoliosis), limitations to mobility and the ability to carry out daily activities, increased risk of pain, osteopenia and fractures.\textsuperscript{4,8,24} Iannaccone\textsuperscript{34} reports that scoliosis is rare before early childhood, and so is not normally seen in children with Type I SMA, but is common in patients with Type II SMA and less common in those with Type III. Weakness of the paraspinal muscles means that scoliosis progresses gradually and should be monitored regularly.\textsuperscript{24}

Patients with Type I SMA also have difficulties related to limited head control, posture and alignment. The principal problems among Type II patients are contractures, respiratory dysfunction and scoliosis. The combination of proximal muscle weakness and impaired balance means that patients with Type III SMA fall frequently and suffer abnormal fatigue during physical activity.\textsuperscript{8}

Interventions that can be employed to avoid worse consequences are postural control, pain control and contracture control, adaptation of daily activities, mobility with a wheelchair or walking frame, orthoses for limbs and therapies that encourage the development of mobility, prolonging these children's survival and alleviating the burden of the disease.\textsuperscript{8}

Regular exercise, such as swimming or other appropriate sports, is important to recover the self-esteem of these children, to introduce them into a social context and to help maintain physical fitness. Swoboda et al.\textsuperscript{13} report that regular physical exercise can be helpful to develop muscles and joints, increase bone density, improve intestinal mobility and promote a general sense of wellbeing.

Grondard et al.\textsuperscript{35} studied the benefits of regular exercise in mutant rats with Type II SMA and found positive results. They noted that mutant rats that were forced to run in a wheel exhibited an impressive increase in survival time, compared with non-exercised rats, and they also observed a reduction in medullary motor neuron death. These results suggest that regular physical exercises should be combined with pharmacological treatment in order to test the possibility of cumulative protective effects against disease progression.

Finally, Oskoui & Kaufmann\textsuperscript{24} point out that modifications need to be made to the homes of these children in order to guarantee their safety and allow them independence.

Pharmacological

Sadly, there is currently no pharmacological treatment available for SMA. However, on the basis of progress in understanding the genetic bases and the pathophysiology of SMA, potential candidates to attempt to treat it are emerging.\textsuperscript{36,37} Some drugs that are being tested for treatment of SMA patients have as their therapeutic targets the SMN\textsubscript{2} gene. Strategies that increase its transcription or that stabilize the protein it forms appear to be promising.\textsuperscript{37,38} Some drugs based on this therapeutic perspective are described below.

a) Histone deacetylase inhibitors:

This class of drugs has been investigated for treatment of SMA because of its ability to activate transcription of the SMN\textsubscript{2} gene, because when histone is acetylated (inhibited histone deacetylase), transcription factors become more accessible to several genes (including SMN\textsubscript{2}), encouraging their transcription.

Clinically known drugs, such as valproic acid, sodium butyrate and phenylbutyrate are examples of compounds that have an inhibitory action on the histone deacetylase enzyme. This property makes them potential candidates for treatment of SMA, particularly valproic acid\textsuperscript{17,38,39} and phenylbutyrate,\textsuperscript{40} which are better able to penetrate the CNS, in addition to the fact that their pharmacokinetics and safety profiles have already been described.

Valproic acid is the histone deacetylase inhibitor that has been most investigated in preclinical and clinical trials assessing its efficacy for treating SMA.\textsuperscript{17,38,39} The efficacy of valproic acid to induce an increase in the levels of the SMN protein has been demonstrated in cultures of fibroblasts from patients with SMA I,\textsuperscript{17,39} in hippocampus slices\textsuperscript{39} and in motor neuron cultures\textsuperscript{38} from an SMA I rat model. In vivo, administration of valproic acid in the drinking water of a mouse model of SMA III, increased SMN protein levels in spinal marrow and also improved motor function, with increased evoked motor potentials, reduced spinal marrow neuron degeneration and better innervation of the neuromuscular junction when compared with control SMA animals.\textsuperscript{41}

After these encouraging preclinical results, clinical trials were started. Non-randomized and non-placebo-controlled clinical studies by Tsai et al.\textsuperscript{42} and Weihl et al.\textsuperscript{43} with small numbers of patients demonstrated a modest improvement in muscle strength and subjective function. These studies used the same dosage of valproic acid that is recommended for the treatment of epilepsy (15 to 50 mg/kg/day). Recently, Swoboda et al.\textsuperscript{44} published the first phase II clinical trial of valproic acid (15 to 50 mg/kg/ day), given to 42 patients with Type I, II or III SMA aged from 2 to 31 years. The results are to a certain extent inconclusive, probably because of the heterogeneous nature of the sample, and it was not possible to detect a clear interference in disease progression caused by the drug. Some patients suffered weight gain and carnitine depletion. The authors themselves\textsuperscript{44} stressed the need for randomized, placebo-controlled and double-blind clinical trials that would be capable of a more accurate investigation of the efficacy of valproic acid for SMA treatment.
A study conducted by Rak et al.,\textsuperscript{38} that is still in prepublication for the journal Neurology of Disease, showed that cultures of motor neurons from mice with SMA I that were treated with valproic acid also increased SMN protein expression. However, unexpectedly, they observed a reduction in the excitability of axonal terminals, caused by an inhibitory effect of the drug on voltage dependent Ca\textsuperscript{2+} channels and, possibly in other channels that contribute to motor neuron excitability. On the basis of these findings, the authors warn that valproic acid could aggravate certain symptoms of the disease in SMA patients.

Other drugs that are in preclinical or clinical phases are hydroxyurea\textsuperscript{37,43} and the quinazolines,\textsuperscript{37} which have the capacity to activate SMN\textsubscript{2} gene transcription through mechanisms that do not interfere in histone deacetylase enzyme activity.

b) Drugs to stabilize the SMN\textsubscript{A7} protein:

This group includes indoprofen\textsuperscript{46} (non-steroidal anti-inflammatory) and some aminoglycosides antibiotics, such as amikacin and tobramycin.\textsuperscript{47} These drugs have the capacity to increase the efficiency of the translation process of the protein derived from the SMN\textsubscript{A7} gene, leading to a more stable protein. Unfortunately, both indoprofen and aminoglycosides penetrate the CNS poorly.\textsuperscript{37} The synthesis of compounds that retain the stabilizing property, but are able to pass the hematoencephalic barrier is awaited with great expectation.

**Future prospects for diagnosis and treatment of SMA**

There are still several unknowns relating to SMA that need to be elucidated. Wang et al.\textsuperscript{8} predicted that, based on recent therapeutic advances, it is possible that in the future SMA will be treated more effectively in presymptomatic patients, diagnosed as soon as the disease begins to develop, so that the clinical course is interrupted before muscle weakness becomes evident.

Preliminary data from electrophysiological studies that included estimation of motor units in children with SMA suggest that motor neuron loss is most significant during the postnatal period for the majority of patients.\textsuperscript{13} Therefore, exams should be implemented for neonatal diagnosis, or even for prenatal detection, in order to anticipate access to special medical care. Wirth et al.\textsuperscript{10} report that families at risk of having a child with SMA can be offered a prenatal diagnostic test based on analysis of chorionic villi (10th and 12th week) or amniotic fluid (14th and 16th week of pregnancy).

In Brazil, the Centro de Estudos do Genoma Humano, Universidade de São Paulo (CEGH-USP), offers prenatal diagnosis to couples who have already had one child with SMA, since at every pregnancy they run a 25% risk of having another child with the same disease. A positive diagnosis of genetic disease should not be interpreted as the determining factor for terminating a pregnancy, but as a signal to introduce treatment before the baby develops symptoms related to the condition.

Therefore, it is also worth commenting that prenatal diagnosis is worthless if there is no adequate treatment that offers a positive response without provoking deleterious side-effects whether for the expectant mother or for her child. However, this will only be possible once there is a universal plan for newborn infants, the necessary infrastructure to enroll them on clinical trials and approved ethical regulations for treatment of these presymptomatic children.\textsuperscript{24}

The use of stem cells is being studied as a promising cellular source for treatment of disorders related to the loss of these exclusive cells, as is the case of SMA.\textsuperscript{48} It is important to remember that there are many obstacles that researchers need to overcome in order to confirm effective use of stem cells. Among these are: the production of a large quantity of differentiated motor neurons from stem cells\textsuperscript{49}; survival of partially differentiated cells in the nervous system after implantation; cells must have the capacity to extend axons and create synapses; and, lastly, they must all lead to significant functional recovery.\textsuperscript{24} Thus, in the not so near future stem cells may be used for recuperation in neuromuscular diseases.

Finally, substances with a neuroprotective action, (such as cardiotrophin-1),\textsuperscript{50} and genetic conversion of the SMN\textsubscript{2} gene into SMN\textsubscript{A7},\textsuperscript{51} are also the subject of therapeutic proposals being studied.

**Final comments**

Both medical follow-up and palliative care are important throughout SMA patients’ entire lives. This care includes respiratory and nutritional support, and orthopedic and physiotherapeutic care to avoid postural disorders. In addition to this we can cite pharmacological treatments that are still being studied, both employing new drugs and drugs that are already well-known.

It cannot be expected that the pharmacological treatments currently being studied can recover motor neurons or muscle cells that have already been lost to atrophy. Rather, the objective is to retard the progress of the disease and improve residual muscle function. Sadly, paralysis can be halted, but it cannot be reversed. However, through a combination of medical care and rehabilitation, many patients with SMA can have fulfilling and productive lives and often have normal life expectancy.

Finally, there is one other point it is important to emphasize, which is that since SMA is a recessive genetic disorder, genetic counseling is an essential component for the families of these patients. Through genetic counseling,
parents, who are carriers of SMA, should be encouraged to be cautious when planning future pregnancies because the risk of having children with the same heritage does not go away.

References


Correspondence:
Celia Regina Ambiel
Rua Carlos Roberto Seghezzi 668
CEP 87140-000 - Paiçandu, PR - Brazil
E-mail: crasilva@uem.br