Spinal Muscular Atrophy: A Clinical and Research Update

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Abstract

Spinal muscular atrophy, a hereditary degenerative disorder of lower motor neurons associated with progressive muscle weakness and atrophy, is the most common genetic cause of infant mortality. It is caused by decreased levels of the “survival of motor neuron” (SMN) protein. Its inheritance pattern is autosomal recessive, resulting from mutations involving the SMN1 gene on chromosome 5q13. However, unlike many other autosomal recessive diseases, the SMN gene involves a unique structure (an inverted duplication) that presents potential therapeutic targets. Although no effective treatment for spinal muscular atrophy exists, the field of translational research in spinal muscular atrophy is active, and clinical trials are ongoing. Advances in the multidisciplinary supportive care of children with spinal muscular atrophy also offer hope for improved life expectancy and quality of life.

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Introduction

Spinal muscular atrophy is a genetic disorder clinically characterized by progressive muscle weakness and atrophy, associated with the degeneration of spinal and (in the most severely affected patients) lower bulbar motor neurons. Spinal muscular atrophy is the most common genetic cause of infant mortality, and seems to be present in practically all populations. In most patients, the disease results from homozygous deletions involving exon 7 of the "survival of motor neuron" (SMN) gene at locus 5q13. The SMN gene is present in two copies on each chromosome 5, designated SMN1 and SMN2, forming an inverted duplication (Fig 1). Five nucleotide changes that do not change amino acids differentiate SMN2 from SMN1. A single nucleotide change in an exonic splice enhancer in exon 7 of SMN2 is critical and leads to the exclusion of exon 7 in most transcripts [1]. Thus the duplicated (SMN2) gene produces less functional SMN protein. Most patients with spinal muscular atrophy harbor homozygous deletions involving the SMN1 gene, but maintain at least one copy of SMN2. A rough correlation exists between SMN2 gene copy number, which varies normally within the population, the level of SMN protein, and the severity of disease. The role of the SMN protein is still under active investigation. Modifying genes also appear to be present, serving other roles in motor neuron function. Spinal muscular atrophy may involve the dysfunction of more than lower motor neurons, with abnormalities of the neuromuscular junction observed in animal models, and abnormal muscle development in the most severely affected patients.

The development of therapies is aimed at devising pharmaceutical compounds that can upregulate the expression of SMN2 or affect other modifying genes to produce more functional SMN protein. Researchers are trying to achieve this goal with gene therapy or antisense oligonucleotides, and by using stem cells to replace degenerated motor neurons. A consensus statement for the multidisciplinary supportive care of patients with spinal muscular atrophy contains recommendations that have led to improved survival and quality of life for many patients during the past decade.

Epidemiology

The incidence of spinal muscular atrophy has been estimated at 1 in 6000-10,000 live births [2-4], or 7.8-10 per 100,000 live births [5-7] and 4.1 per 100,000 live births for spinal muscular atrophy type I [5]. A study from Cuba in 2005 found a reduced incidence of type I spinal muscular atrophy among the Cuban population overall (3.53 per 100,000 live births), and especially among those of African ancestry (0.89-0.93 per 100,000 live births) [8]. The carrier frequency for mutations in the SMN1 gene was estimated at 1:38-1:50, but lower frequencies were also reported. An epidemiologic study in 2009 sought to determine the carrier frequency in different ethnic groups in North America. The carrier frequency was highest in Caucasians (1 in 37, or 2.7%) and lowest in Hispanics (1 in 125, or 0.8%). Ashkenazi Jews (1 in 46, or 2.2%) and African Americans (1 in 56, or 1.8%) were of intermediate frequency [9]. Moreover, despite the high carrier frequency, the incidence of spinal muscular atrophy is lower than expected. This finding may

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reflect that some fetuses have a 0/0 SMN1/SMN2 genotype (i.e., no SMN protein is present at all), which is known in other species to be embryonic lethal [10].

Clinical Characteristics

Although most patients with spinal muscular atrophy manifest homozygous mutations involving the SMN1 gene, a range of phenotypic severity permits division into three broad clinical subtypes. The three main subtypes (I, II, and III) represent a phenotypic continuum, and a spectrum of severity exists within each of these groups (Table 1) [11,12]. For the purposes of clinical classification or of guidelines developed for standards of care, the “maximal functional status achieved” approach, which classifies type I patients as “nonsitters,” type II patients as “sitters,” and type III patients as “walkers,” has been used [13,14].

Type I spinal muscular atrophy

Patients with type I spinal muscular atrophy, also known as Werdnig-Hoffman disease, present between birth and age 6 months. Infants exhibit progressive proximal weakness that affects the legs more than the arms. They demonstrate poor head control, hypotonia that causes them to assume a “frogleg” posture when lying and to “slip through” on vertical suspension, and areflexia. They are unable to sit (“nonsitters”) (Table 1). Furthermore, weakness of the intercostal muscles, with relative sparing of the diaphragm, produces a bell-shaped chest and a pattern of paradoxical breathing or “belly-breathing.” Infants with type I spinal muscular

Table 1. Clinical classification of spinal muscular atrophy

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Other Names</th>
<th>Age of Onset</th>
<th>Life Span</th>
<th>Highest Motor Milestone Achieved</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>Prenatal, congenital SMA</td>
<td>Prenatal</td>
<td>&lt;6 months</td>
<td>Mostly unable to achieve motor milestones</td>
<td>Severe weakness at birth Profound hypotonia Facial diplegia Areflexia Early respiratory failure Joint contractures Weakness “Frogleg” posture, hypotonia Tongue fasciculations Hyporeflexia, areflexia Suck and swallow difficulties Respiratory failure</td>
</tr>
<tr>
<td>Type I</td>
<td>Werdnig-Hoffman disease, severe SMA (“nonsitters”)</td>
<td>0-6 months</td>
<td>&lt;2 years without respiratory support</td>
<td>Never sits supported</td>
<td>Proximal weakness, hypotonia Postural hand tremor Hyporeflexia Average or above average intellectual skills by adolescence Scoliosis</td>
</tr>
<tr>
<td>Type II</td>
<td>Intermediate SMA (“sitters”)</td>
<td>6-18 months</td>
<td>Approximately 70% alive at age 25 years</td>
<td>Sits independently, never stands or walks</td>
<td>May manifest hand tremor Resembles muscular dystrophy</td>
</tr>
<tr>
<td>Type III</td>
<td>Kugelberg-Welander disease, mild SMA (“walkers”)</td>
<td>&gt;18 months</td>
<td>Almost normal</td>
<td>Stands and walks</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>Adult SMA</td>
<td>&gt;21 years</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>
atrophies also classically exhibit tongue fasciculations, and eventually develop difficulty swallowing, with the risk of aspiration and failure to thrive. Other cranial nerves are not as affected, although facial weakness occurs at later stages. Cognition is normal, and patients are often observed at diagnosis to exhibit a bright, alert expression that contrasts with their generalized weakness. Infants with type I spinal muscular atrophy usually develop respiratory failure by age 2 years or much earlier, and in the past, most did not survive beyond age 2 years. However, some increase in survival has been evident in recent years with the use of assisted ventilation (to be described in more detail later) and other interventions [11,15-17].

Spinal muscular atrophy was previously regarded purely as a motor neuron disorder. However, recent studies indicate that severe type I spinal muscular atrophy can result in various organ manifestations, apart from the involvement of spinal cord motor neurons, e.g., brain, cardiac, vascular, and even sensory nerve. Recent autopsy studies demonstrated increasing evidence of congenital heart disorders in severe spinal muscular atrophy, of which the most common association is hypoplastic left heart syndrome [18]. In one study, three out of four (75%) patients with one copy of SMN2 manifested congenital spinal muscular atrophy (spinal muscular atrophy type 0), associated with hemodynamically significant atrial or ventricular septal defects, underscoring the relevance of the SMN protein for normal cardiac development [19]. Despite the reported cases, however, a chance association has not been definitively excluded in the noncongenital spinal muscular atrophy group of patients. Murine models of severe spinal muscular atrophy revealed autonomic disturbances, including bradyarrhythmia, progressive heart block, dilated cardiomyopathy, and decreased contractility [20-22]. In humans with molecularly proved spinal muscular atrophy, no evidence of dilative or congestive cardiomyopathy has appeared, nor have ativoventricular conduction anomalies or arrhythmias, aside from bradyarrhythmias, been reported. Studies of various murine models also demonstrated that severe SMN protein deficiency can present as vasculopathy. This finding was also described in case reports of two unrelated patients with severe spinal muscular atrophy type I. Both infants developed ulcerations and necroses of the fingers and toes. Sural nerve biopsy studies revealed a thrombotic occlusion of the small vessels without inflammation, resulting in perfusion abnormality and subsequent tissue necrosis in the absence of a significant peripheral neuropathy [23]. Autonomic dysfunction is thought to be the primary cause of this vasculopathy [24]. Although some reported patients manifested only one copy of SMN2, two infants with spinal muscular atrophy type I, in whom a distal necrosis developed, demonstrated two copies of SMN2 [24]. In a biopsy study by Rudnik-Schöneborn et al. [25] of 19 patients with infantile spinal muscular atrophy, significant sensory nerve pathology was evident in those with severe spinal muscular atrophy type I, whereas no sensory involvement was evident in patients with spinal muscular atrophy types II and III. Of these, axonal degeneration was noted in seven patients and abnormal sensory conduction in five patients with spinal muscular atrophy type I. The patients with abnormal results of nerve conduction studies were followed with biopsies that revealed a marked reduction of fiber density in four patients, indicating that patients with severe spinal muscular atrophy type I can manifest both clinical and morphologic involvement of their sensory nerves.

Type II spinal muscular atrophy

Patients with type II spinal muscular atrophy, or intermediate spinal muscular atrophy, can sit unsupported at some point (“sitters”), but are never able to walk (Table 1). They exhibit progressive proximal weakness affecting the legs more than the arms, hypotonia, and areflexia. They also develop progressive scoliosis that, in combination with intercostal muscle weakness, results in significant restrictive lung disease as they grow older. They develop joint contractures and, in some cases, ankylosis of the mandible. They exhibit tremor or polyminymyoclonus of the hands [11,17]. Although their body mass index may be low (at the third percentile or less, compared with normal children), the high-functioning, nonambulatory patients exhibit a higher relative fat mass index, and are at risk of becoming overweight [26]. Cognition is normal, and verbal intelligence may be above average [27]. In a study of 240 type II patients, survival rates were 98.5% at age 5 years, and 68.5% at age 25 years [28]. Patients may live into their third decade, but life expectancy is shortened because of the risk of respiratory compromise [11,17].

Type III spinal muscular atrophy

Patients with type III spinal muscular atrophy, also known as Kugelberg-Welander disease, are able to walk at some point (“walkers”). They manifest progressive proximal weakness affecting the legs more than the arms, and may ultimately need to use a wheelchair, but they develop little to no respiratory muscle weakness or scoliosis. They may demonstrate tremor or polyminymyoclonus of the hands. Their life expectancy is not significantly different compared with the normal population [11,17,28] (Table 1).

Much debate has arisen about the appropriate classification of patients into these three types of spinal muscular atrophy, because, as mentioned, patients within these categories exhibit phenotypes of differing severities. A classification system based on a continuous rather than discrete variable (e.g., spinal muscular atrophy “type 1.8” in the case of a less severely affected type I patient) was proposed to capture the clinical spectrum of these patients more accurately [12].

Outliers

Some patients represent outliers at either end of the phenotypic spectrum. A spinal muscular atrophy “type 0” is used to describe neonates who present with severe weakness and profound hypotonia, probably of prenatal onset, and with a history of decreased fetal movements. The majority do not attain any motor milestones. Other findings include areflexia, facial diplegia, atrial septal defects, and joint contractures. In spinal muscular atrophy type 0, respiratory failure constitutes an important cause of morbidity and mortality, requiring noninvasive ventilation and endotracheal intubation at birth. Life expectancy is reduced, and most are unable to survive beyond 6 months of age (Table 1) [29,30].

Furthermore, arthrogryposis multiplex congenita (congenital joint contractures involving at least two regions of the body) was observed in patients with spinal muscular atrophy and SMN1 gene deletions [31]. Congenital axonal neuropathy involving the motor and sensory nerves, in conjunction with facial weakness, joint contractures, ophthalmoplegia, and respiratory failure at birth, was reported in three newborn siblings with deletions in the spinal muscular atrophy chromosomal region [32]. A milder adult-onset spinal muscular atrophy, or type IV spinal muscular atrophy, was also described. Most patients with spinal muscular atrophy type 0 and IV phenotypes manifest homozygous deletions of exon 7 in SMN1 [11,33].

Other “spinal muscular atrophies”

Finally, outside the scope of this review are the non-5q13-associated spinal muscular atrophies, which comprise
a heterogeneous group of motor neuron diseases associated with mutations in a variety of different genes, e.g., X-linked and autosomal dominant or recessive spinal muscular atrophies, distal spinal muscular atrophies or distal hereditary motor neuropathies, spinal muscular atrophy with respiratory distress (“spinal muscular atrophy respiratory distress” or “diaphragmatic spinal muscular atrophy,” resulting from mutations in the \textit{ICHMBP2} gene on chromosome 11q), and pontocerebellar hypoplasia with infantile spinal muscular atrophy [11,33,34]. Patients with these disorders generally exhibit some clinical characteristics to help differentiate them from those with 5q13-associated or classic spinal muscular atrophy [35]. The differential diagnosis of spinal muscular atrophy is detailed in Table 2.

Genetics

The SMN gene

Linkage analysis studies indicate that all three forms of spinal muscular atrophy map to chromosome 5q11.1–13.3. In 1995, Lefebvre et al. [36] identified the \textit{SMN} (survival of motor neuron) gene within this region, which was absent or interrupted in 98.6% of patients in their group. The structure of this region is complex, with a large inverted duplication of a 500 kb element. This duplication contains the \textit{SMN1} gene, which is deleted or interrupted in patients with spinal muscular atrophy and is evolutionarily older, in the telomeric portion of the region, and the \textit{SMN2} gene, a duplication of \textit{SMN1} that differs by only five nucleotides, in the centromeric portion (Fig 1) [36]. The critical difference between \textit{SMN1} and \textit{SMN2} is a C-to-T transition in an exonic splicing enhancer located in exon 7 of \textit{SMN1}. Although this change is translationally silent (i.e., it does not change the amino acid sequence), it affects the alternative splicing of the gene, so that exon 7 is spliced out of or excluded from most \textit{SMN2} messenger RNA transcripts. This altered messenger RNA results in the production of a truncated version of the \textit{SMN2} protein, much of which is degraded. Because exon 7 is not always spliced out of all \textit{SMN2} premessenger RNA, a small amount of full-length transcript, and hence functional protein, is produced by \textit{SMN2}, but it yields only about 10% as much as that produced by \textit{SMN1} [37]. In patients with spinal muscular atrophy, both copies of the \textit{SMN1} gene are deleted or disrupted, leaving the individual with only the small amount of \textit{SMN} protein produced by the remaining copies of \textit{SMN2}. The amount of \textit{SMN} protein is inversely correlated with the severity of disease [38].

About 95-98% of patients with spinal muscular atrophy harbor deletions of the telomeric \textit{SMN1} gene (Table 3). The rest manifest small intragenic mutations, or have undergone gene conversions from \textit{SMN1} to \textit{SMN2}. In the latter case, a frameshift or point mutation of \textit{SMN1} results in the disruption of exon 7, effectively converting \textit{SMN1} to \textit{SMN2} [4]. De novo mutations occur at a rate of about 2% (which is relatively high) because this region of chromosome 5 is unstable, containing not only the inverted repeat of \textit{SMN1} and \textit{SMN2}, but other surrounding low copy number repeats. This instability leads to a high rate of unequal crossover and de novo mutations (especially paternally derived), which could explain the relatively high carrier frequency despite the mortality rate for the most severe forms of the disease [39]. More mildly affected patients seem more likely to undergo gene conversions of \textit{SMN1} to \textit{SMN2}, rather than a deletion of \textit{SMN1} [40-42].

The number of copies of \textit{SMN2} per chromosome 5 varies among normal individuals, and 10-15% of the population possess no copies of \textit{SMN2} [4,43]. Among patients with spinal muscular atrophy, a clear correlation was established between \textit{SMN2} copy number and phenotypic severity. In 2002, Feldkotter et al. reported that 80% of the patients in their series with type I spinal muscular atrophy manifested one or two copies of \textit{SMN2}, 82% of patients with type II manifested three copies of \textit{SMN2}, and 96% of patients with type III manifested three or four copies of \textit{SMN2} [43]. Mailman et al. in 2002 [7] and Arkblad et al. in 2009 [44] produced similar results (95-100% of type I patients manifested one or two copies of \textit{SMN2}, and all type III patients manifested at least three copies of \textit{SMN2}). However, this correlation is not so perfect as to permit absolute predictions of clinical severity based on \textit{SMN2} copy number, especially in intermediate forms of the disease where some overlap occurs (patients with three copies of \textit{SMN2} were described with all three phenotypes) [45,46]. In general, though, a patient with one copy of \textit{SMN2} is highly likely to present with severe spinal muscular atrophy type 0 or type I [7,43]. Interestingly, unaffected family members with homozygous deletions of \textit{SMN1} and five copies of \textit{SMN2} were described, which suggests that the \textit{SMN2} copy number cannot be the sole modifying factor in disease severity, because some patients with type III spinal muscular atrophy also exhibit five copies of \textit{SMN2} [7,47].

A positive modifier was identified in the \textit{SMN2} gene [48]. A single base substitution in exon 7 in the DNA of three unrelated patients (c.859G>C) creates a new exonic splicing enhancer that increases the inclusion of exon 7 and thus the amount of full-length protein. The phenotype in these patients was less severe and did not correlate with their \textit{SMN2} copy numbers, supporting the positive modifying effect of this sequence change and the notion that not all copies of \textit{SMN2} are equal. A higher expression of plastin 3 was also identified as a sex-specific protective modifier of spinal muscular atrophy in asymptomatic \textit{SMN1}-deleted females who carried the same number of \textit{SMN2} copies as their affected siblings [49]. A subsequent study, however, revealed that plastin 3 may be an age-specific, puberty-specific, or sex-specific modifier, because the expression of the gene was greatest in postpubertal females with spinal muscular atrophy type III, intermediate in spinal muscular atrophy type II, and lowest in spinal muscular atrophy type I, underscoring an association with disease severity [50].

Table 2. Differential diagnosis of 5q spinal muscular atrophy

| Spinal cord disorders |  |
|-----------------------|  |
| Neoplasms (SMA types I, II, and III) |  |
| Other myelopathies (SMA types I, II, and III) |  |
| Other motor neuron disorders |  |
| SMARD1 (SMA type I) |  |
| Other non-5q SMA (SMA types I, II, and III) |  |
| Neuroopathies |  |
| Congenital hypomyelinating or axonal neuropathies (SMA types I and II) |  |
| Hereditary motor and sensory neuropathies (SMA types I, II, and III) |  |
| CIDP (SMA types II and III) |  |
| Neuro muscular junction disorders |  |
| Botulism (SMA type I) |  |
| Congenital myasthenic syndromes (SMA types I, II, and III) |  |
| Lambert-Eaton myasthenic syndrome (SMA type II) |  |
| Autoimmune myasthenia gravis (SMA types II and III) |  |
| Myopathies |  |
| Congenital myopathies (SMA types I, II, and III) |  |
| Congenital myotonic dystrophy (SMA type I) |  |
| Congenital muscular dystrophies (SMA types I and II) |  |
| Muscular dystrophies (DMD/BMD or LGMD) (SMA type III) |  |
| Mitochondrial myopathies (SMA types I, II, and III) |  |
| Acid maltase/Pompe disease (SMA types I, II, and III) |  |
| Other metabolic myopathies (SMA types I, II, and III) |  |
| Inflammatory myopathies (SMA type III) |  |
| Channelopathies (SMA type III) |  |
| Abbreviations: |  |
| BMD = Becker muscular dystrophy |  |
| CIDP = Chronic inflammatory polyneuropathy |  |
| DMD = Duchenne muscular dystrophy |  |
| LGMD = Limb-girdle muscular dystrophy |  |
| SMA = Spinal muscular atrophy |  |
| SMARD1 = Spinal muscular atrophy with respiratory distress |  |

J.A. Markowitz et al. / Pediatric Neurology 46 (2012) 1–12
In a patient with a homozygous deletion of exon 7, the restriction fragment is absent. In a patient with two copies of the SMN1 gene on one chromosome (so-called “2 + 0 carriers”), the restriction fragments will be absent, the DNA will not be amplified, and a band will not be evident on the gel. If an individual is a carrier (i.e., a heterozygous deletion), a lighter band will be present (Fig 2). Multiplex ligation probe amplification has been applied in many DNA diagnostic laboratories for deletion analyses of exon 7 of the SMN1 gene in potential probands and carriers. This type of targeted mutation testing, in conjunction with sequence analyses, can also detect individuals who are compound heterozygotes [43] with a deletion of exon 7 in one SMN1 allele and an intragenic point mutation in the other allele. In such cases (in approximately 2-5% of patients), a sequence analysis of the SMN gene will detect the mutation. This sequence testing, however, will not detect exonic deletions or duplications [52], and will not determine whether the point mutation is located in the SMN1 gene or SMN2 gene (if one of these genes is not deleted). Fortunately, certain point mutations were described in more than one patient with spinal muscular atrophy, and thus the detection of a previously reported mutation supports its pathogenicity and its location in the SMN1 gene.

Carrier testing is feasible and accurate in parents of patients with homozygous deletions of exon 7 or compound heterozygosity, using a polymerase chain reaction-based dose assay, known as “SMN gene dose analysis” (Fig 3). Sequencing of the SMN gene will detect point mutations in nondeletion carriers. Rarely, carriers may exhibit two copies of SMN1 on one chromosome (so-called “2 + 0 carriers”). The incidence of this genotype involves about 4% of the general population. In “2 + 0 carriers,” the spinal muscular atrophy dose carrier test will produce falsely normal results, and thus one may need to pursue other methods, such as family linkage analysis, to identify the disease-associated genotype in families in which a deletion mutation was transmitted more than once from a parent with two copies of the SMN1 gene on gene dose testing [39,53-55]. Because of the occurrence of de novo mutations in 2% of patients with spinal muscular atrophy, one of the parents may not be a carrier [52].

As already mentioned, a general correlation was demonstrated between SMN2 copy number and disease severity, and the determination of SMN2 copy number is relatively straightforward in individual patients by means of quantitative polymerase chain reaction. However, this correlation is not so strict that the severity or type of disease can be reliably predicted according to copy number, and hence we do not advise offering families prognostic information based on SMN2 copy number assays.

### Newborn screening

The potential for newborn screening of spinal muscular atrophy has been of great interest because the ideal time to initiate therapy would precede the initial degeneration of motor neurons, and newborn screening may help identify presymptomatic individuals [10,39]. Swoboda et al. performed a prospective study in prenatally diagnosed infants with type 1 spinal muscular atrophy and found that, associated with the initial onset of signs or decline in function in these young infants, electrophysiologic evidence of precipitous denervation was detected (assessed with serial measurements of compound motor action potential amplitude and motor unit number estimation), suggesting that motor neuron loss occurs very early [56]. This finding provides further support for the potential usefulness of newborn screening to identify patients before their period of greatest motor neuron loss, should a therapeutic intervention become available.

Regarding the issue of routine preconception and prenatal screening for spinal muscular atrophy, the American College of Obstetricians and Gynecologists Committee on Genetics issued an opinion recommending against preconception and prenatal screening for spinal muscular atrophy in the general population, citing insufficient evidence of its cost-effectiveness and concerns regarding the education of the public and physicians about the complex issues raised by prenatal diagnoses of this disorder [57]. However, other professional medical societies have stressed the importance of screening. To address this issue and create a consensus, a meeting was organized by National Institutes of Health in late 2009. That meeting led to the conclusion that carrier screening is technically feasible, but its implementation calls for addressing broader issues of screening in general [10,58].

### Table 3. Genetic diagnostic testing in spinal muscular atrophy

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>Test Applied</th>
<th>Mutation Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous deletion of exon 7</td>
<td>SMN1 Targeted mutation analysis, PCR/restriction enzyme analysis or multiplex ligation probe amplification methodologies</td>
<td>Approximately 95-98%</td>
</tr>
<tr>
<td>Compound heterozygosity (deletion of SMN1 exon 7 [allele 1] and an intragenic mutation of SMN1 [allele 2])</td>
<td>SMN1 gene sequence analysis, Quantitative PCR analysis.</td>
<td>2-5%</td>
</tr>
<tr>
<td>SMN2 copy number</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations:

N/A = Not available

PCR = Polymerase chain reaction

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![Figure 2](image)

Figure 2. Polymerase chain reaction diagnosis of SMN1 deletion. Polymerase chain reaction-based targeted mutation analysis uses a restriction enzyme that digests exon 7. In a patient with a homozygous deletion of exon 7, the restriction fragment is absent (no copies of SMN1). In a carrier (heterozygous deletion), a lighter band of SMN1 will be present. Similar targeted mutation analysis can be performed with multiplex ligation probe amplification methodology. SMA = spinal muscular atrophy.
Other Diagnostic Tests

In patients with spinal muscular atrophy, the level of serum creatine kinase may be elevated twofold to fourfold, but not more than 10 times normal [17]. Nerve conduction studies demonstrate normal sensory potentials, but may indicate diminished compound motor action potential amplitudes [56]. Needle electromyograms in type II and III patients demonstrate a neurogenic pattern with high amplitude, and motor unit potentials of long duration with a reduced recruitment pattern. Needle electromyograms in type I patients indicate denervation changes, but may not provide evidence of reinnervation, because the amount of SMN protein or time for reinnervation to occur may have been insufficient. Muscle biopsies in all types of spinal muscular atrophy demonstrate a neurogenic pattern, with grouped atrophy. For the same reasons as previously stated, this pattern is less consistently observed in patients with type I [17]. Notably, a fetal appearance was evident in muscle biopsy specimens from patients with type I spinal muscular atrophy, leading to the question of whether type I spinal muscular atrophy may actually result from arrested development of the motor unit rather than degeneration of the motor neuron. Indeed, a morphometric analysis of fetuses with type I spinal muscular atrophy at 12-15 weeks of gestation revealed delayed maturation of the myotubes, compared with control subjects [59]. Although electromyograms continue to be used in the diagnosis of spinal muscular atrophy in selected atypical cases, the use of muscle biopsy has become essentially obsolete.

Molecular Function of SMN

The SMN protein is 38 kDa and is evident in all cells, located in both the cytoplasm and the nucleus, where it localizes to structures known as “gems” [60]. Therefore, its expression is ubiquitous.

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**Figure 3.** Spinal muscular atrophy (SMA) carrier testing. This algorithm depicts the diagnostic investigation of carrier status in potential carrier parents with SMN1 gene dose analysis ± sequencing of the SMN1 gene. Rarely, family linkage analysis may need to be used in informative families, particularly if a deletion mutation has been transmitted more than once from a parent with two copies of SMN1 according to gene dose testing.
It is also localized in motor neuron axons [61]. The SMN protein, in conjunction with several Gemin proteins, forms an SMN complex whose chaperone function facilitates the assembly of spliceosomal small nuclear ribonucleoprotein particles [62-64], essential components of the spliceosome complex, and hence plays a critical role in premessenger RNA splicing. The SMN protein may also be essential in assisting the arginine methylation of some splicing-related proteins [65], in transporting axonal messenger RNAs in motor neurons [66] and perhaps in other processes in muscles and neuromuscular junctions. The role of SMN protein in axonal messenger RNA trafficking and premessenger RNA splicing may explain the selective vulnerability of spinal cord motor neurons to decreased SMN protein. Although they are not the only ones, these neurons have long axons and many targets, and thus may be very dependent on axonal messenger RNA transport. Further, they may be extremely vulnerable to splicing defects in messenger RNA.

The complete absence of the SMN protein in cells appears to be embryonic lethal in mice and other organisms [64,67]. The reason that motor neurons are specifically vulnerable to partial SMN deficiency is unclear. Murine and zebrafish models were used to explore this question, but because the SMN2 gene is present only in humans, animal models were created via the knockout of SMN with the insertion of a human SMN2 transgene [64,67,68]. In addition to its role in spliceosome assembly, which is presumably important in all cells, SMN seems to associate with actin, which is involved in motor axon pathfinding and outgrowth during development. Two groups demonstrated aberrant motor axon outgrowth and pathfinding in zebrafish models of spinal muscular atrophy [69,70]. The protein plastin 3 was demonstrated to increase levels of F actin and to rescue the effects of SMN deletion on axon growth in murine and zebrafish models, and six asymptomatic females were described with higher levels of plastin 3 expression than their affected relatives, suggesting that SMN may be involved in the regulation of actin cytoskeletal dynamics [49,71].

Patients with spinal muscular atrophy also appear to manifest structural and physiologic abnormalities of the neuromuscular junction [72-76]. Kong et al. revealed that in mice severely affected with spinal muscular atrophy, before anterior horn cell death or axonal degeneration, synaptic dysfunction occurred at the neuromuscular junction, with decreased synaptic vesicle density at motor terminals, reduced quantal content, slowed maturation of the acetylcholine receptor, and prolonged retention of fetal characteristics [74]. Kariya et al. [77] also demonstrated structural and functional abnormalities at the level of the neuromuscular junction that preceded overt signs in mice, and structural abnormalities in the neuromuscular junctions of humans with spinal muscular atrophy. Hence they proposed that spinal muscular atrophy may be a “synaptopathy” [77]. Based on that concept, treatment approaches directed toward enhancing neuromuscular transmission may also be beneficial in patients with spinal muscular atrophy.

Treatment

No cure exists for spinal muscular atrophy. However, despite the presence of homozygous deletions of SMN1 in the majority of patients with spinal muscular atrophy, the unique structure of the 5q11.1-13.3 inverted duplication provides potential therapeutic targets. Great interest has focused on identifying agents that can increase the amount of full-length SMN protein by upregulating the expression of the SMN2 gene or promoting the inclusion of exon 7. Researchers are also actively exploring several other approaches to treatment.

Clinical trials in spinal muscular atrophy: Outcome measures

Several challenges face those designing and implementing clinical trials in spinal muscular atrophy. The natural history of the disease, especially in patients with the intermediate forms of the disease, consists of early decline and a prolonged plateau period. Hence to detect the effect of therapy on the rate of progression during a 12-month or 18-month period may be extremely difficult. Quantitative strength measures may be insensitive because the signs tend to stabilize over time, and may also be unsuitable for very young children. Functional status scales may be difficult to interpret as development progresses and children learn to compensate for their weakness. Contractures may also complicate the picture [13,78]. To illustrate these difficulties, in a prospective study of 73 patients with spinal muscular atrophy (age range, 4-57 years; mean age, 17 years) over the course of 4 years, Iannaccone et al. detected no loss of strength and a loss of function in only some patients [13]. However, several new outcome measures have produced encouraging results in different subsets of patients with spinal muscular atrophy. The usefulness of quantitative muscle ultrasound was assessed in an observational study of 25 patients with spinal muscular atrophy (15 with type II, and 10 with type III) and 21 normal subjects [79]. A luminosity ratio was calculated by dividing muscle by subcutaneous fat luminosity. The strength and luminosity ratio demonstrated a good negative correlation ($r = -0.711, P < 0.001$). This correlation was reflected in the results, because more severely affected individuals demonstrated higher luminosity ratios, i.e., $1.27 \pm 0.26$ S.D. for normal subjects, $2.43 \pm 0.78$ S.D. for type III spinal muscular atrophy, and $3.85 \pm 1.3$ S.D. for type II spinal muscular atrophy ($P < 0.001$). In terms of other measures, for ambulatory patients with spinal muscular atrophy, the Six-Minute Walk Test produced good correlations with other established outcome measures such as the Hammersmith Functional Motor Scale Expanded ($r = 0.83, P < 0.0001$), the 10 minute walk/run ($r = -0.87, P < 0.0001$), and knee flexor strength ($r = 0.62, P = 0.01$). The Six-Minute Walk Test is objective and easy to administer [80]. Studies of therapies for patients with type I spinal muscular atrophy were partly limited because the rigorous assessment of motor skills in infants is difficult. However, the Infant Test of Neuromotor Disorders was developed by the Children’s Hospital of Philadelphia for this purpose, and may constitute a reliable outcome measure in infants [81]. Several other outcome measures for clinical trials were established as reliable in spinal muscular atrophy populations, including the Test of Strength in Spinal Muscular Atrophy by the Children’s Hospital of Philadelphia, the Gross Motor Function Measure [82], the Hammersmith Functional Motor Scale [83], and the Modified [84] or Expanded [15] Hammersmith Functional Motor Scale. Montes et al. reviewed these and concluded that a consensus needs to be established regarding the most reliable outcome measures for clinical trials [80,85].

Electrophysiologic outcome measures include the estimation of motor unit numbers and maximum compound motor action potential amplitude. An increase in compound motor action potential amplitude captures both an increase in the number of motor units and the presence of collateral sprouting of axons from adjacent surviving motor neurons. In a study of these two parameters in patients with spinal muscular atrophy, Swoboda et al. [56] detected a statistically significant correlation between compound motor action potential amplitude during initial assessment and patients’ functional outcomes. Patients with type II spinal muscular atrophy exhibited a decline in maximum compound motor action potential amplitude over time, and patients with types I and II exhibited an age-dependent decline in estimated numbers of motor units and maximum compound motor action potential amplitude.
As already described, prospective studies using estimation of motor unit numbers and compound motor action potential amplitude in infants diagnosed prenatally with type I spinal muscular atrophy detected precipitous denervation associated with the onset of signs or decline in function, suggesting that these are useful parameters to follow in individual patients over time [56].

Lastly, serologic biomarkers in the form of SMN messenger RNA and protein levels can be reliably measured from peripheral blood leukocytes in patients, but they do not necessarily correlate with disease severity. One group reported that patients with type II and III spinal muscular atrophy demonstrated relatively normal levels of peripheral blood SMN protein [51]. Another group described a high correlation between murine leukocyte and spinal cord SMN expression, but only a moderate correlation between leukocyte SMN expression and age at disease onset in patients with spinal muscular atrophy. Thus, peripheral blood SMN messenger RNA levels or protein levels may be useful to follow in individual patients as a response to therapy, but they may not be useful when comparing messenger RNA and protein levels between patients [51,86,87].

The American Spinal Muscular Atrophy Randomized Trial is a clinical consortium that has sought to validate outcome measures for strength, lung function, and motor function in the population from ages 2-18 years. The Pediatric Quality of Life Inventory Measurement Module integrated the relative merits of generic and disease-specific approaches with disease-specific modules. The Pediatric Quality of Life Inventory 4.0 Generic Core Scales and Pediatric Quality of Life Inventory 3.0 Neuromuscular Module demonstrated feasibility, reliability, and validity in 176 children with spinal muscular atrophy and their parents [88], thus providing a reliable research tool.

Clinical trials in spinal muscular atrophy: Therapeutics

Agents that upregulate SMN2 gene expression and promote the inclusion of exon 7

A class of drugs known as histone deacetylase inhibitors was investigated extensively as potential therapeutic agents in spinal muscular atrophy [89]. Histones, which are core proteins in chromatin, play a role in the epigenetic regulation of gene expression via their acetylation status. Several compounds that function as histone deacetylase inhibitors were demonstrated to increase full-length SMN2 transcript levels in cell lines from patients [51,90,91].

Phenylbutyrate is a histone-deacetylase inhibitor that was demonstrated to increase the amount of full-length SMN messenger RNA, SMN protein levels, and the number of nuclear gems in fibroblast cultures from type I, II, and III patients in vitro [92]. Other pilot studies detected increased SMN gene expression in peripheral leukocytes [93] and improvements in the Hammersmith Functional Motor Scale [94] after treatment with oral phenylbutyrate. However, a randomized, placebo-controlled trial detected no significant improvement on the Hammersmith Functional Motor Scale with a phenylbutyrate regimen [95].

Valproic acid, which was approved by the United States Food and Drug Administration for the treatment of epilepsy, is another histone deacetylase inhibitor that increases the amount of full-length SMN messenger RNA, SMN protein, and number of nuclear gems in fibroblasts derived from patients with type I spinal muscular atrophy [96,97]. A phase II open-label study involved two patients with type I, 29 patients with type II, and 11 patients with type III, treated with doses of valproic acid sufficient to achieve overnight trough levels of 50-100 mg/dL for 12 months. These patients exhibited no evidence of hepatotoxicity, but a significant proportion of the first patients enrolled developed low free or total plasma carnitine levels, associated with increased weakness in two patients, which prompted a recommendation for carnitine supplementation in all patients. The fat mass increased by 38% between baseline and 12 months in patients with type II, as opposed to a 14% increase in patients with type III. Increased weight was associated with a decline in motor function in several patients, as measured by a modified Hammersmith Functional Motor Scale. A significantly increased mean score on a modified Hammersmith Functional Motor Scale was evident in 27 patients with type II, most of whom were under 5 years of age. However, the possibility of developmental gain in motor function cannot be excluded. Bone mineral density and maximum ulnar compound motor action potential scores also increased significantly. Although levels of full-length SMN did not significantly change in treated patients, the amount of SMN messenger RNA missing exon 7 in patients was reduced during two out of three visits [98]. The recent phase II randomized, double-blind, placebo-controlled L-Carnitine and Valproic Acid Trial reported no difference in modified Hammersmith Functional Motor Scale after 6 months of treatment with valproate compared with placebo in a nonambulatory cohort with type II spinal muscular atrophy. Moreover, adverse events such as weight gain were more common in the group treated for 6 months treated compared with those receiving placebo. Nevertheless, a post hoc analysis revealed that weight gain, age, and duration of treatment could pose significant confounding factors affecting the results of the study, and should be considered when designing future trials [99].

Another histone deacetylase inhibitor, LBHS89 (hydroxamic acid), is already widely used in cancer clinical trials, and could constitute a promising candidate for treating spinal muscular atrophy. It induces a 10-fold increase in SMN levels, a twofold to threefold increase in full-length SMN2, and a marked increase in the number of gems in fibroblast cultures from patients with spinal muscular atrophy. LBHS89 proved active even in spinal muscular atrophy fibroblasts unresponsive to valproate [100].

The drug hydroxyurea, approved by the United States Food and Drug Administration, was identified in the course of drug screens, using cell lines from patients with spinal muscular atrophy, to increase the amount of full-length SMN transcript and protein in vitro [101-103]. However, a small pilot study of hydroxyurea at three different doses for 8 weeks in 33 patients with types II and III demonstrated no statistically significant benefit [102]. A randomized, double-blind, placebo-controlled trial of hydroxyurea (20 mg/kg/day) in patients with types II and III failed to demonstrate any improvement over an 18-month period [104].

Albuterol, a β-adrenergic agonist, was evaluated in a pilot study of 13 patients with spinal muscular atrophy types II and III because of its reported positive effect on muscle strength in healthy individuals. After 6 months, significant improvement was evident in terms of myometry, forced vital capacity, and dual-energy x-ray absorptiometry scores, but no significant change occurred in strength according to the Medical Research Council score [105]. Another pilot study of 23 patients with spinal muscular atrophy type II treated with salbutamol (a form of albuterol) for 12 months reported improved functional scores on the Hammersmith Functional Motor Scale after 6 and 12 months, but this study was not placebo-controlled, and must be interpreted with caution [106]. In a study by Tiziano et al. [107], 12 patients with type II and III spinal muscular atrophy received salbutamol orally for 6 months. The full-length transcript levels of SMN2 increased at baseline and at 3 and 6 months of treatment. The response was directly proportional to the SMN2 gene copy number [107]. On an in vitro level, salbutamol was demonstrated to increase full-length SMN messenger RNA, SMN protein, and gem numbers by promoting the inclusion of exon 7 [108]. This finding prompts further interest in exploring the effects of β-agonists on spinal muscular atrophy with randomized, controlled trials.
Other approaches

Aminoglycosides appear to promote a read-through of the stop codon in exon 8, thereby stabilizing the SMN protein and providing another way to increase SMN protein levels in patients’ fibroblasts [109]. Heier and DiDonato treated mice exhibiting spinal muscular atrophy with the aminoglycoside geneticin (G418), resulting in increased levels of SMN protein and improved motor function, but unfortunately this agent caused significant toxicity in the mice [110].

Riluzole and gabapentin, “the neuroprotective agents,” were studied to examine their effect on motor performance in spinal muscular atrophy. Unfortunately, the results were not encouraging, or the studies were inadequate to prove efficacy [111–114].

The activation of the N-methyl-d-aspartate receptor was found to increase the expression of SMN2 in a dose-dependent manner [115]. In a murine model of spinal muscular atrophy, activation of the N-methyl-d-aspartate receptor increased motor unit postnatal maturation, decreased apoptosis in the spinal cord, induced a marked increase of SMN expression, and extended lifespans. Thus, this agent holds therapeutic promise.

Antisense oligonucleotides were developed to block an intronic splicing suppressor element, which in turn prevents the skipping of exon 7 [116]. Hua et al., in a study of transgenic mice, reported that these intronic splicing suppressors were located on intron 7 as tandem motifs, i.e., heterogeneous nuclear ribonucleoproteins A1/A2 [117]. Blocking these motifs with antisense oligonucleotides enhanced the inclusion of exon 7 in their murine model of spinal muscular atrophy. Similar work by Singh et al. demonstrated an enhanced production of full-length SMN messenger RNA in fibroblasts from patients treated with antisense oligonucleotides [118].

Periodic intracerebroventricular deliveries of antisense oligonucleotides in murine models of spinal muscular atrophy were demonstrated to improve the motor phenotype [119,120]. Another group developed bifunctional RNAs that inhibited an intronic repressor and recruited an serine/arginine-rich protein to the critical exonic splice enhancer in exon 7, thus increasing the amount of full-length SMN in patients’ fibroblasts. Injecting these RNAs into the central nervous system of mice with severe spinal muscular atrophy increased their lifespan [121,122]. Although these results are encouraging, mode of delivery remains a significant problem, but it can be addressed if a therapy is established as effective. Other methodologies are under development.

Interest in the use of stem cells also continues, both as a potential treatment for spinal muscular atrophy and for use in constructing model systems for developing therapies. Pluripotent stem cells with the capacity to differentiate into motor neurons that lacked the expression of SMN1 were induced from a patient with type I spinal muscular atrophy and his mother [123,124]. Those studies could serve as the basis of an important model system.

Among other therapeutic targets, gene therapy has demonstrated potential in animal models [125,126]. Foust et al. [125] revealed that self-complementary adeno-associated virus 9 could cross the blood-brain barrier and infect approximately 60% of motor neurons when injected intravenously into neonatal mice. It was more beneficial when administered on postnatal day 1, compared with postnatal days 5 and 10 [125].

Those involved in the care of patients with spinal muscular atrophy who seek further information regarding ongoing clinical trials should visit the website www.clinicaltrials.gov and search under “spinal muscular atrophy”.

Care of the Patient With Spinal Muscular Atrophy

Patients with spinal muscular atrophy and their families benefit greatly from a multidisciplinary approach to care. This approach involves practitioners from neurology/neuromuscular medicine, orthopedics, physical and occupational therapy, pulmonology, nutrition, and gastroenterology. For severely affected patients with type I spinal muscular atrophy, the early involvement of pediatric advanced care or a palliative care team can provide parents with support and assistance in making decisions consonant with their values, and help maximize their child’s quality of life. In 2007, a Consensus Statement for Standard of Care in Spinal Muscular Atrophy was released by a multidisciplinary team regarding the best recommendations for managing patients with spinal muscular atrophy [14].

Pulmonary

Respiratory failure is the major cause of mortality in patients with type I and II spinal muscular atrophy. Infants with type I spinal muscular atrophy exhibit weak intercostal muscles with relatively preserved diaphragm strength, resulting in a bell-shaped chest, pectus excavatum, and underdevelopment of the lungs in some cases. Patients with type II spinal muscular atrophy exhibit weak intercostal muscles with scoliosis, contributing to their progressive restrictive lung disease [127,128]. Restrictive lung disease results in an insidious onset of sleep hypoventilation. Sleep-disordered breathing is often the first sign of respiratory muscle weakness in neuromuscular disease [129]. Mellies et al. [129] discovered evidence of sleep hypoventilation on overnight polysomnography in seven of 12 patients with spinal muscular atrophy whose vital capacities were below 60%. These patients demonstrated improvement in their signs (of fatigue, headaches, or disturbed sleep) after the initiation of noninvasive ventilation (bilevel positive airway pressure) [129]. Regarding the use of noninvasive ventilation in patients with type I spinal muscular atrophy, O’Hagen et al. [15] reviewed 143 type I patients enrolled in the International Spinal Muscular Atrophy Registry, and reported significantly increased survival for those born between 1995 and 2006 vs those born between 1980 and 1994, with a 70% reduced risk of death during a mean follow-up of 49.9 months. Survival was significantly affected by the increased use of ventilation (noninvasive, i.e., bilevel positive airway pressure, and invasive), mechanical cough assist devices, and gastrostomy feeding [15]. The proper use of bilevel positive airway pressure, with correct pressure adjustments and mask placement, produces no significant side effects on patient hemodynamics [130]. Patients with spinal muscular atrophy and respiratory muscle weakness also manifest a weak cough, which impairs their ability to clear the airway of secretions. This weakness places them at risk for hypoxemia from mucus plugging (especially during times of acute illness) and for recurrent infections. Patients at risk for mucus plugging should be monitored with overnight oximetry during acute illnesses, and assisted airway clearance methods should be used. These methods may involve a mechanical insufflator/exsufflator device, manual assisted airway clearance, and postural drainage. A low threshold for the use of antibiotics should also be applied during acute illnesses in these patients, because of the risk of pneumonia [14,127,128]. Patients should be followed regularly by a pulmonologist experienced in caring for patients with neuromuscular diseases.

Gastrointestinal

Patients with type I spinal muscular atrophy tire during feedings, which can lead to failure to thrive and aspiration with
recurrent respiratory infections [127]. Patients with spinal muscular atrophy are also thought to demonstrate a high incidence of silent gastroesophageal reflux, which can contribute to aspiration [131]. In a small retrospective study, Durkin et al. reported that early laparoscopic Nissen fundoplication and gastrostomy in patients with type I spinal muscular atrophy was associated with improved nutritional status in these patients, and also perhaps with a trend toward fewer long-term aspiration events [131]. Yuan et al. also described positive outcomes in a series of type I and one severe type II patient who underwent laparoscopic Nissen fundoplication and gastrostomy tube placement, followed by post-operative noninvasive ventilation, insofar as no adverse events occurred, with fewer cases of pneumonias after the procedure in some patients [132]. Lastly, patients with spinal muscular atrophy are at risk of constipation, which can, if severe (especially in young patients with type I), worsen reflux or even respiratory signs [127].

Nutrition

Failure to thrive or growth failure are common in infants with type I spinal muscular atrophy, and in some severely affected patients with type II. However, though many patients with type II plot a “normal” body mass index (often as low as the third percentile for healthy children of their age), they may actually manifest excessive fat mass relative to their muscle mass. Clinically high-functioning, nonambulatory patients with spinal muscular atrophy (Hammersmith score ≥ 12) were more prone to adiposity, compared with both low-functioning nonambulatory (Hammersmith score < 12) and ambulatory patients (likely attributable to excess calories provided, despite their low resting energy expenditure); these patients are at risk of becoming overweight [26,133]. Hence close attention must be paid to nutritional status in patients with all types of spinal muscular atrophy, and consultation with a dietician who is aware of these special concerns is vital.

Orthopedic

Patients with spinal muscular atrophy require close orthopedic follow-up for the development of scoliosis and contractures. Surgical intervention for scoliosis is often required, and careful coordination of perioperative respiratory and nutritional support can help minimize complications [14]. Fractures are commonly observed in patients with type II and III spinal muscular atrophy. The distal femur is the commonest fracture site, followed by the lower leg, ankle, and upper arm. Most fractures can be treated conservatively [134].

Conclusion

Spinal muscular atrophy is a chronic, inherited motor neuron disease for which no established treatment exists. Yet there is cause for optimism because it is an area of active research, and knowledge about the molecular genetics and pathogenesis of spinal muscular atrophy is ever increasing. Several groups are actively exploring pharmacologic treatments, whether through the use of approved drugs, the identification of new agents via high-throughput screens, or the development of novel pharmaceutical compounds. Consortia of clinicians and researchers are working together to organize multicenter trials and identify the best outcome measures. The Spinal Muscular Atrophy Patient Registry has helped facilitate the inclusion of patients in these studies. Standards of care were also developed to optimize the long-term multidisciplinary management of patients with spinal muscular atrophy. Patient support and advocacy groups (e.g., the Spinal Muscular Atrophy Foundation, Families of Spinal Muscular Atrophy, Fight Spinal Muscular Atrophy, and Project Cure) play a vital role in supporting research efforts and providing a community for children and families affected by spinal muscular atrophy. Although at times a treatment for spinal muscular atrophy may seem far in the future, advances made since the gene was identified only 14 years ago permit a modicum of hope to those with the privilege of caring for these patients.

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