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Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era

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Abstract

Spinal muscular atrophy (SMA) describes a group of disorders associated with spinal motor neuron loss. In this review we provide an update regarding the most common form of SMA, proximal or 5q SMA, and discuss the contemporary approach to diagnosis and treatment. Electromyography and muscle biopsy features of denervation were once the basis for diagnosis, but molecular testing for homozygous deletion or mutation of the *SMN1* gene allows efficient and specific diagnosis. In combination with loss of *SMN1*, patients retain variable numbers of copies of a second similar gene, *SMN2*, which produce reduced levels of the survival motor neuron (SMN) protein that are insufficient for normal motor neuron function. Despite the fact that the understanding of how ubiquitous reduction of SMN protein leads to motor neuron loss remains incomplete, several promising therapeutics are now being tested in early phase clinical trials.

Keywords

spinal muscular atrophy; electromyography; SMN1; gene therapy; antisense

Introduction

The term spinal muscular atrophy (SMA) is applied to a diverse group of genetic disorders that all affect the spinal motor neuron. The different forms of SMA are associated with numerous gene mutations and significant phenotypic variability. SMA is usually categorized by pattern of weakness (i.e. whether predominantly proximal or distal) and mode of inheritance. The emphasis of this review will be autosomal recessive proximal SMA or 5q-SMA, the most common form that accounts in most series for up to 95% of cases. This form of SMA is due to a homozygous deletion or mutation of the *Survival Motor Neuron 1* (*SMN1)* gene and has a frequency of 1/11,000 births.[1–3] It is the most common genetic cause of death in infants.[4]

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Cause and Pathogenesis of Proximal SMA

Humans have 2 nearly identical inverted *SMN* genes on chromosome 5q13, and homozygous deletion of the *SMN1* gene was identified as the cause of SMA in 1995.[3] *SMN1*, the telomeric copy of the *SMN* gene, and *SMN2*, the centromeric copy, differ by only 5 base pairs, and the coding sequence differs by a single nucleotide. This C>T change within the coding sequence in exon7 of *SMN2* does not alter an amino acid but does affect splicing and causes ~90% of transcripts from *SMN2* to lack exon7.[5–8] As a consequence, in contrast to *SMN1*, which predominantly produces full length SMN protein, the *SMN2* gene produces predominantly a shortened, unstable, and rapidly degraded isoform.[9–12] Alternative splicing events in the *SMN2* gene however, cause ~10% of *SMN2* transcripts to include exon7 and therefore produce some full length SMN protein.[5,6] The combined effects of homozygous loss of *SMN1* and retention of *SMN2* are low levels, not absence, of full length, stable SMN protein (Figure 1).

Full length SMN protein is a ubiquitously expressed 294 amino acid polypeptide. It is found within the nucleus and cytoplasm in self-associating multimeric structures as part of the SMN complex.[13] Shortly after loss of the *SMN1* gene was determined to cause SMA, complete elimination of SMN function in the mouse was shown to be lethal, resulting in massive cell loss and demise *in utero*.[14] This is not surprising, since there is a single *Smn* gene in the mouse (i.e. there is no *Smn2*), and SMN protein is now known to have a critical role in the assembly of Sm proteins onto small nuclear RNA and RNA metabolism.[15] While it has been established that SMN plays a key role in RNA splicing in all cells, the cellular populations where high levels of SMN are required are not known. Expression levels of SMN are known to normally be higher in motor neurons compared with other tissues, and current work suggests that there are requirements for high levels of SMN protein in the motor neuron, and likely other neurons.[16–21]

The role of SMN in RNA splicing suggests that a disease-pertinent transcript or transcripts (isoform specific to motor neuron function) could be disrupted by splicing defects. This theoretical specificity could explain why motor neurons alone seem to be affected in SMA despite the ubiquitous nature of SMN; i.e. it is expressed in all tissues of the body. Supporting this concept is the fact that biochemical assays of the ability of SMN to assemble Sm proteins onto small nuclear RNA correlate closely with phenotype severity in mouse models of SMA.[22,23]

Altered transcripts (in the setting of SMN deficiency) have been identified, but a definite link to the disease pathogenesis has not been confirmed.[20,21,24] For example, the protein Stasimon was identified recently as a potential disease-related target of altered splicing caused by SMN deficiency.[21,25] It is known that there is a homolog of the Stasimon gene in humans, and investigators have demonstrated aberrant splicing of Stasimon in SMA mice.[21] Whether restoration of Stasimon corrects a mammalian model of SMA or whether knockdown leads to a SMA-relevant phenotype has yet to be determined.[26]

SMN deficient disruption of other cellular processes may also be important in the pathogenesis of SMA, and impairment of axonal mRNA transport may also have a role in

SMA.[26,27] Animal models have also demonstrated early or selective vulnerability of the neuromuscular junction.[28–31] These findings could suggest a primary requirement for high levels of SMN for synaptic maturation and maintenance, but they could also simply represent loss of motor neuron function and associated secondary failure of the terminal motor axons.

Variability of Clinical Features and Severity

The predominant clinical features of SMA are muscle weakness and atrophy attributed to motor neuron dysfunction and loss. Weakness is usually symmetric and proximally predominant. The spectrum of severity may range from mild proximal limb weakness noticed in adulthood to severe generalized weakness with respiratory failure in the neonatal period. Lower limbs are more involved than upper limbs, and bulbar and respiratory weakness usually occurs in cases with more severe limb weakness. The onset and progression of weakness is distinct from many other motor neuron disorders in that there is usually a presymptomatic period in all but the most severe cases (type 0), followed by rapidly progressive functional loss and a later relatively static phase with slow progression. Occasionally, some families will even report periods of transient improvement after a period of progression. The reason for this pattern of progression is not understood, nor is the natural history in the earliest stage of disease well defined. During periods of stress such as infection or pregnancy, some patients experience worsening weakness.[32]

Long before identification of the causative gene, clinicians recognized a continuum of severity in SMA patients that eventually resulted in a disease classification.[33–35] SMA has been classified traditionally into types 1–3, but some experts suggest an expanded classification that includes additional subtypes. Table 1 includes a classification strategy that may be used. Onset and severity of disease, and therefore type, correlate mainly with *SMN2* copy number (and theoretically with SMN protein level) providing a molecular basis for the classification of the different subtypes of SMA.[36–40] At least 1 copy of *SMN2* is required for the development of SMA, and infants with the most severe form of disease (type 0) usually have only 1 copy. Infants with type 1 SMA usually have 2 or 3 copies of *SMN2*. Type 2 SMA is usually associated with 3 copies. Type 3 patients have 3–4 copies, and patients with type 4 usually have 4 copies or more. In addition to variations of copy number of the *SMN2* gene, variants within the *SMN2* gene can increase full length SMN protein and therefore impact phenotypic variability. An example includes 859G>C in exon7 of *SMN2* that increases exon7 inclusion by 20%.[41–43] Reports of discordant phenotypic severity in siblings with the same copy number of *SMN2* suggest other genetic modifiers outside of *SMN2*.[37,44–46] Plastin 3 has been reported to be a modifier of severity in females with *SMN1* deletions, but high expression of plastin 3 has also been reported in severely affected female siblings.[47,48]

Using the traditional classification strategy, type 1 SMA is the most common and severe form, representing 45% of cases; it is associated with onset after birth but before age 6 months.[49] Infants may appear entirely normal prior to developing limb weakness, respiratory distress, weak cry, and poor feeding. Because of severe hypotonic weakness in the lower limbs, affected babies develop a splayed-leg or “frog-leg” lower limb posture. A

bell-shaped deformity of the chest may also be evident resulting from poor expansion of the ribcage with relative preservation of diaphragm strength.[50,51] Paradoxical breathing is a characteristic feature with flattening of the chest wall (rather than expansion) and protrusion of the abdomen during inspiration. Examination demonstrates are flexic proximal-predominant weakness with sparing of the eye muscles and relative sparing of facial muscles. Tongue fasciculations are common. Cognition is spared, and higher than average intelligence has been noted.[52,53] By definition, the ability to sit independently is never achieved, and in the majority of cases the natural history includes death prior to age 2. Implementation of aggressive supportive care, including respiratory support, can markedly improve survival. An uncommon and unusually severe clinical phenotype has been recognized in some infants, and the classification of type 0 SMA is sometimes used.[54,55] Clinical features of type 0 include hypotonia, respiratory distress, weak cry, and poor feeding with onset is usually prior to birth, and diminished intrauterine movement may lead to joint contractures. Respiratory insufficiency is present at birth, and death typically occurs within weeks of birth. As an alternative to using the classification of SMA type 0, some prefer to subdivide SMA type 1 into a, b, and c, with type 1a being the most severe form overlapping with type 0.

Type 2 SMA, representing about 20% of cases, typically has onset between ages 6 and 18 months. The ability to sit is usually achieved by 9 months, although this milestone may be delayed.[49] By definition these children never stand or walk independently, but some patients will be able to stand with the assistance of bracing or a standing frame. Examination demonstrates proximal predominant weakness that is most severe in the lower limbs. Reflexes are usually absent. A fine tremor (minipolymyoclonus) is often apparent mainly in the distal limbs and has long been associated with intermediate forms of the disease.[56,57] Tongue atrophy with fasciculations is also characteristic. Similar to type 1, facial and eye muscles are spared. Impaired swallowing and ventilatory insufficiency are frequent in type 2, particularly in patients at the severe end of the type 2 spectrum. Scoliosis occurs universally in this group and is a significant contributing factor to restrictive ventilation defects. The majority of patients with SMA type 2 survive to age 25, and many patients live much longer due to improved natural history related to more aggressive supportive care.

About 30% of patients have type 3 SMA, which is associated with onset between ages 18 months and adulthood. By definition standing or walking without support is achieved, although many patients lose these abilities later with disease progression.[49] Type 3 patients are further classified into type 3a with onset between ages 18 months and 3 years and 3b with onset between ages 3 and 30 years. Patients usually present with symptoms of falls, difficulty climbing stairs, and other features of proximal weakness. Abnormal gait characteristics are common in order to compensate for weakness, and many patients are able to continue ambulation despite severe weakness. Foot deformity may be seen in ambulatory patients.[57] Lifespan is normal in SMA type 3. Some classifications of SMA include an additional disease subtype at the mild end of the continuum. In this case, patients may be classified as having type 4 SMA. Patients with type 4, representing less than 5% of SMA, are ambulatory and have the mildest form of SMA. The presentation is very similar to type 3 and is distinguished solely on later onset during adulthood.[49,55,58] Though onset of type 4 is not clearly defined, it is often considered to be at age 30 or later.

In addition to the features of SMA related to motor unit loss, peculiar findings in preclinical animal models and rare case series of patients have suggested that non-motor features may occur on occasion. These may include sensory involvement, cardiac defects, gastrointestinal and autonomic dysfunction, and endocrine abnormalities.[59–67] The possibility of non-motor aspects of SMA is not surprising due to the ubiquitous nature of the SMN protein and the universal requirement of SMN for cellular function, but the true frequency and impact of these atypical features are not well defined.[68] These features are typically reported in more severe cases, and this trend could be related to a threshold effect of susceptibility of other tissues to very low levels of SMN protein associated with type 0 SMA and a single *SMN2* copy.

Diagnostic Testing

Molecular genetic testing is the standard tool for diagnosis of SMA. Due to the efficiency of molecular testing and high frequency of SMA in the hypotonic or “floppy” infant, it should be an early consideration in any infant with weakness or hypotonia.[69] The differential diagnosis of severe forms of SMA includes all other causes of hypotonic weakness in the infant. At one time, muscle biopsy and electrodiagnostic testing were standard procedures for evaluation, but since molecular testing is readily available, these and other diagnostic investigations (e.g. MRI) are usually unnecessary. In patients with intermediate forms of the disease the differential includes other disorders of the peripheral nervous system including myopathy (dystrophinopathies, limb girdle muscular dystrophy, metabolic myopathies, or inflammatory myopathies), neuropathy (inflammatory neuropathies), neuromuscular junction disorders (myasthenia gravis or congenital myasthenic syndromes), and other motor neuron disorders (non-5q form of SMA or late onset hexosaminidase A deficiency). In patients with adult onset disease the differential overlaps with that of the intermediate forms of the disease but also includes later onset disorders such as amyotrophic lateral sclerosis and Kennedy disease (X-linked spinobulbar muscular atrophy).

Molecular Diagnosis

Importantly, patients with SMA have homozygous loss of function of both *SMN1* copies; genetic testing for homozygous deletion will confirm the disease in 95% of patients irrespective of disease severity.[3] Essentially all other patients with SMN-related SMA will be compound heterozygotes with a single *SMN1* deletion and a frameshift, nonsense, or missense mutation in the other *SMN1* copy.[70] Therefore, if homozygous *SMN1* deletion is not evident in a patient with suspected SMA, *SMN1* dosage analysis (to look for deletion of 1 copy) and sequencing of the remaining *SMN1* gene (to look for a mutation) should be performed (Figure 2). Only a single patient has been reported with SMA and an associated homozygous double mutation in the *SMN1* gene.[71]

The homozygous deletion of *SMN1* is essentially 100% specific for the diagnosis of SMA, and disease severity is modified by *SMN2* copy number. Most healthy individuals in the population will have 0–3 copies of *SMN2*, but *SMN2* is absent in about 10% of humans in the healthy population.[70] Consistent with the fact that SMA is related to low levels (not absence) of SMN protein, no patients have been reported with loss of both the *SMN1* and *SMN2* genes. An important issue of molecular diagnosis arises with presymptomatic or

prenatal diagnosis. *SMN2* copy number is available clinically, and this number correlates with severity in groups of patients.[36–39] For reasons mentioned previously and other unknown factors, the severity of disease in a particular individual cannot be predicted precisely using copy number alone. Therefore caution should be exercised when utilizing copy number to predict clinical severity and prognosis in an individual. Appropriate genetic counseling should be provided to patients and families for all individuals undergoing testing, particularly in presymptomatic individuals and in situations involving possibly affected siblings.

Carrier testing is available, and carrier frequencies range from 1 in 47 to 1 in 72 depending on the population studied.[72,73] *SMN1* dosage testing will identify 95% of carriers, but the remaining 5% of carriers can have a deletion of *SMN1* on 1 chromosome with a duplication of *SMN1* on the other chromosome, or in other cases a deletion on 1 chromosome with an *SMN1* mutation on the other. These situations will not be identified with standard *SMN1* dosage testing and highlight again the need for accurate genetic counseling in these individuals.[70] In about 2% of cases of SMA, a *de novo* mutation may occur in which an *SMN1* deletion is only inherited from 1 parent.[74] Prenatal screening by chorionic villus sampling or amniocentesis to obtain fetal DNA is also available. Additionally, pre-implantation embryonic testing during *in vitro* fertilization can be performed.[75]

Other Testing Modalities

Prior to the availability of molecular testing, other diagnostic studies to demonstrate the presence of denervation, such as electrodiagnostic studies and muscle biopsy, were important tools for evaluating suspected SMA. In general, electrodiagnosis should now be reserved only for evaluation of atypical patients or patients who are negative for both *SMN1* deletion and *SMN1* mutation testing (Figure 2).[69] Muscle biopsy is no longer indicated, as features of denervation can be demonstrated more readily demonstrated with electrodiagnosis. Because of the frequency of SMA and efficiency of genetic testing, it is very important to avoid testing that is both unnecessary and invasive. Nevertheless, we will review the findings of these studies, since they are still obtained on occasion and are also relevant to findings in preclinical animal SMA models.

Electrodiagnostic studies show variable features of motor neuron/axon loss consistent with loss of motor neuron function.[76–78] Sensory involvement is usually lacking, but exceptional cases have been reported with association sensory neuropathy or sensory ganglionopathy.[79] Electrodiagnosis remains an important diagnostic tool in atypical cases and non-5q related SMA to demonstrate the neurogenic nature of the illness. In later onset disease, where proximal predominant limb weakness produces a broad differential diagnosis, electrodiagnostic testing can be helpful and is more often utilized early in the workup. Electromyography (EMG) reveals features of motor neuron or motor axonal loss in the form of active denervation and chronic compensatory changes of reinnervation and motor unit action potential enlargement. Abnormal spontaneous activity in the form of fibrillation potentials is typically evident. Voluntary EMG assessment shows drop out and compensatory enlargement of motor unit action potentials (MUAPs). In very severely affected patients and very weak or end-stage individual muscles, MUAPs may lack clear

neurogenic features of long duration and large amplitude and instead have reduced amplitude and duration. An unusual form of spontaneous activity has been reported in which motor unit action potentials are noted to be firing at rates of 5–15 Hz. These potentials have rarely been reported, but in some series have been noted in 75% of patients.[76] This continuous spontaneous motor unit action potential activity is distinguished from fasciculation potentials by regular firing rhythm, ability to be activated by voluntary control, persistence for long periods and occurrence during sleep.[76] Interestingly, the source and significance of these findings have not been defined.

Nerve conduction studies typically show features of chronic motor axonal loss and preservation of sensory nerve action potentials. Compound muscle action potential (CMAP) amplitudes are the predominantly affected parameter with relatively preserved conduction velocities. CMAP amplitudes correlate with clinical severity, age, and function, and patients with milder disease often have normal CMAPs.[78,80,81] Correlation of CMAP size and function in patients with SMA highlights the potential to use CMAP as a biomarker for prognosis. Motor unit number estimation (MUNE) is an estimation of the number of motor neurons/axons innervating a muscle or group of muscles.[82] Several variations of MUNE have been applied to SMA patient populations, and they all have shown similar features of motor unit loss.[78,81,83,84] In addition to motor unit loss, features of failed neuromuscular transmission may also be seen in patients with SMA, but it is uncertain if these changes are related to primary defects in NMJ transmission or secondary effects related to denervation and reinnervation. Repetitive nerve stimulation studies have shown CMAP amplitude decrement at low frequencies of stimulation without facilitation at more rapid rates.[85] Similarly, single fiber EMG may show increased jitter and blocking.[86] These features are typically less prominent than in other motor neuron disorders that have more rapid, ongoing denervation and reinnervation, such as amyotrophic lateral sclerosis.

Electrophysiological measures of EMG, CMAP, and MUNE have shown good correlation with clinical severity, age, and functional status, but most patients included in these studies have been assessed later in the course of disease. Importantly the few patients studied prior to overt disease have shown relatively preserved electrophysiological measures of motor unit function.[78,87] The timing and rate of motor unit loss during different disease phases continues to remain uncertain. Investigation of CMAP and MUNE in the Delta 7 mouse model, the most commonly utilized mouse model of SMA, shows similar features of motor unit loss, and studies done prior to overt motor phenotype show preserved CMAP amplitudes and MUNE.[88] Similarly, preliminary findings suggest that there are features of motor unit loss in milder mouse models of SMA, and these findings are less severe and occur later than in delta 7 mice (Unpublished personal observation and communication with C. DiDonato). These findings suggest that similar electrophysiological findings are seen in patients with SMA and in animal models of the disease, and the timing of onset and severity of motor neuron loss correlate with disease severity.

Muscle biopsy is no longer performed to diagnose SMA. Even in atypical patients or patients with negative testing for *SMN1* deletion or mutation, features of denervation should be sought with less invasive testing, such as EMG, which offers the ability to screen several muscle groups. Muscle biopsy cannot distinguish clearly between SMA subtypes, but certain

histological features are associated with disease severity. Muscle biopsy in infants with types 1 and 2 shows large groups of atrophic fibers interspersed with fascicles of hypertrophied and normal fibers. The atrophic fibers are of both type 1 and 2 and are typically round rather than angular in shape. The hypertrophied fibers are usually type 1.[89,90] In milder cases of type 2 and type 3 SMA, there are typically groups of uniformly atrophic fibers between groups of non-atrophic muscle fibers. Both the atrophic and non-atrophic groups may be of either type 1 or 2 muscle fibers. The groups of atrophic fibers vary in size. The non-atrophic fibers are arranged in large groups of 30 to 200 fibers of a single type and are most commonly composed of type I rather than type II fibers. Muscle biopsy features in type 4 SMA are similar to type 3.[91]

Management

At present there are no effective disease-modifying treatments for SMA. Regardless, precisely designed supportive, rehabilitative, and palliative care can partly reduce the disease burden and alter the natural history.[92] Treatment is designed to address the primary and secondary effects of muscle weakness and should include management of pulmonary complications, nutritional and gastrointestinal support, orthopedic care, rehabilitative interventions, and end-of-life care. Standards of care for SMA are established, but there is need for improved and more specific directives in this regard.[50] A multidisciplinary team with experience in the care of SMA patients is usually most effective for delivery of care. Disease burden is somewhat specific to type of SMA, with more severe subtypes requiring more aggressive management. It is important to understand the expected natural history of SMA to anticipate and stratify risk, to monitor function with appropriate measures, to determine the appropriate treatment options, and to delivery timely intervention. Proactive care and treatment decision-making by the treatment team and family are of utmost importance.

Pulmonary Care

Establishing a therapeutic relationship with an experienced pulmonary specialist familiar with management of SMA is critical and should occur at the time of initial diagnosis, because pulmonary-related complications are a major source of morbidity and mortality in SMA. Respiratory issues include weak cough with poor clearance of lower airway secretions and hypoventilation. Pulmonary complications are related to severity of disease, and more severe disease burden requires closer monitoring and more frequent intervention. All children with SMA type 1 and about a third with type 2 will have respiratory insufficiency or failure during childhood. There is early involvement of the expiratory muscles of ventilation with relative sparing of the diaphragm.[93,94] This can lead to difficulties with secretion management prior to failure of ventilation.[95]

Anticipatory planning is much more satisfactory and effective as compared with treatment during a bout of respiratory failure. Parents should be informed about care options and the role of noninvasive ventilation. They should also be educated about the illness course and complications (e.g. the risk of aspiration, how to manage secretions, etc.). Other general health preventive measures such as routine immunizations against influenza, pneumococcus,

and respiratory syncytial virus are recommended. With disease progression, noninvasive ventilation with bi-level positive pressure can be initiated at night in children with sleep-disordered breathing and later on during the day if daytime hypercapnia becomes an issue. Overnight noninvasive ventilation has been shown to increase chemosensitivity and improve daytime hypercapneic ventilatory drive.[96] For airway clearance and management, caregivers should learn to assist coughing when needed, through use of a cough-assist device. Chest physiotherapy and postural drainage might be used as secretion mobilization techniques. Oral suctioning can help in secretion management. Intubation with ventilation might be warranted in acute illnesses.

In patients with recurrent pulmonary infection and frequent hospitalizations, tracheostomy with mechanical ventilation might be required. The decision to pursue invasive ventilatory support needs to be discussed carefully with parents, taking into consideration the quality of life and the parents' desires. During acute illness, intubation with mechanical ventilation may be needed with failure of the non-invasive approach, but with recovery, transitioning back to noninvasive ventilation should be the goal. There is no consensus on long-term mechanical assisted ventilation through tracheostomy when non-invasive ventilation is insufficient. In a retrospective study, it was suggested that tracheostomy helped in clearance of secretions, given the nonfunctional cough and weakness of abdominal muscles. This regimen improved spontaneous ventilation during wakefulness and allowed some patients in this series to attend school, college, and be a parent.[97] Tracheostomy for chronic ventilation should be discussed carefully with the parents. In general most experts recommend avoidance of tracheostomy and management with noninvasive ventilation if possible, but all options should be considered carefully, and treatment must be individualized for each patient and family.

Gastrointestinal and Nutrition

Gastrointestinal complications are very common in SMA patients but they have received surprisingly little formal research attention.[66,67] These complications can cause primary and secondary morbidity and can increase the risk of aspiration and pneumonia. Gastrointestinal dysfunction includes difficulty feeding and swallowing due to bulbar dysfunction, which is typical in patients with severe generalized weakness, tongue weakness, difficulty opening the mouth, and poor head control. Other problems include gastroesophageal reflux, delayed gastric emptying, and constipation. These complications are common in patients who cannot sit or stand and is seen less commonly in ambulatory patients.

To manage aspiration associated with feeding and swallowing difficulties, changing food consistency can help in optimizing food intake. A semisolid diet and thickened liquids can compensate for poor chewing and protect against aspiration, respectively. There is no consensus as to when to refer a patient for gastrostomy tube placement. This approach should be considered when oral intake is insufficient due to prolonged mealtimes, fatigue, and when unsafe oral feeding is a concern. Gastrostomy tube placement can be performed via percutaneous insertion with endoscopic guidance or via an open or laparoscopic surgical approach with an anti-reflux procedure such as Nissen fundoplication. Gastrostomy tube placement does not protect from aspiration of oropharyngeal secretions, but a very small

study suggested there was modest benefit to this approach.[98] Gastroesophageal reflux can be treated by acid neutralizers such as calcium or magnesium carbonate, and/or inhibitors of acid secretion such as histamine blockers and proton pump inhibitors. For severe cases, a laparoscopic anti-reflux procedure can be performed during gastrostomy tube placement, if general anesthesia is tolerated.

Secondary to decreased oral intake, malnutrition can be an issue in SMA. Malnutrition is commonly seen in SMA type 1 and some more severely affected patients with type 2. Malnutrition and periods of fasting should be avoided in this group of patients, as it can contribute to reduction of muscle mass and subsequent impaired function and worsening weakness. In clinical practice, height and weight plots in patients with SMA can be deceiving due to reduced lean body mass.[99] Obesity can be a problem, more commonly in patients with the ability to sit and ambulate. To manage these complications, each child should be evaluated individually during routine visits by a dietitian with a goal to maintain each child on his or her own growth curve and to avoid inadequate or excessive intake.[50] Because of a tendency for decreasing bone mineral density with increasing age in SMA patients, adequate intake of vitamin D and calcium should be provided.[100] Families, caregivers, and primary physicians often inquire about specific dietary interventions or recommendations for treatment of SMA, but there has been surprisingly little research in this area. A recent survey indicated that dietary changes implemented by caregivers were frequently made independent of medical provider or dietician input, and in this study a majority of caregivers reported using elemental or semi-elemental formula.[101] Fatty acid oxidation abnormalities have been noted in patients with SMA, but the significance and mechanism of these findings remain undefined.[102]

Musculoskeletal

Weakness and impaired mobility, the central features of SMA, predispose to numerous musculoskeletal issues. Early recognition and appropriate management is helpful in maintaining function, preventing deterioration in vital capacity, and improving quality of life. Similar to other aspects of the disease, a multidisciplinary approach is best suited to implement efficient and effective treatment. This team approach should aim to understand the patient's functional level and limitation and to improve the quality of life and offer independent mobility and activities of daily living. In non-ambulatory patients, contractures are common, and regular stretching and bracing programs to preserve flexibility and prevent contractures are the main focus of therapy.[103,104] For independent mobility, manual or power wheelchair use can be initiated as early as 18 to 24 months. For patients who are able to bear some weight on their legs and have some trunk control, a standing frame or mobile-stander with ankle-foot orthoses should be considered. Physical therapy can help to maximize endurance and safety. Patients should be encouraged to be involved in physical activities such as swimming, aquatic therapy, and adaptive sports to increase stamina and fitness. In addition to weakness, neuromuscular fatigue appears to contribute to functional limitation. [105] A wheelchair can be used for long distance mobility and independence. Modifications in the environment and at home should be considered to allow safe accessibility and to optimize independence. Strategies to provide long-term joint protection should be encouraged.

Scoliosis is a major musculoskeletal issue that mostly impacts patients with intermediate forms of the disease, and it is almost universally present in non-ambulatory patients with types 2 and 3 SMA.[106] In type 1 SMA, scoliosis is not a major issue because of severe muscle weakness and inability to sit independently upright. In SMA type 4, scoliosis is typically mild and does not require surgical intervention. Untreated, scoliosis causes chest-cage deformities with subsequent respiratory restriction. Therefore, anticipatory observation is very important. The rate of scoliosis progression is faster in patients who lose ambulation at or before puberty. This suggests that preserved ability to stand and/or walk can help delay scoliosis progression. Therefore, physical therapy and other interventions to help maintain ambulation should be employed.

Surgery is the treatment of choice for scoliosis. Spinal bracing does not prevent scoliosis, but it may slow down the rate of progression in some patients for a limited time. Spinal bracing may provide stability during the seated position, which may temporarily delay the need for surgical intervention. In some individuals bracing may be the only option if they are unable to undergo surgery or when surgery must be delayed. Spinal bracing might not be tolerated and can cause restriction of the vital capacity.[107] In ambulatory patients, bracing is often contraindicated due to gait impairment. In patients who require surgery, there is no clear data that clearly define the best timing for surgical intervention, and early anticipatory involvement of an experienced orthopedic specialist is vital. The goal should be to safely delay surgery enough to allow for optimum growth while taking into account progression of the disease and optimizing surgical outcome. Usually surgery is delayed until at least age 10–12 in non-ambulatory patients.[107,108] Scoliosis surgery in the ambulatory patient must have a strong indication, because there is a risk of losing ambulation.[109]

Therapeutic Development and Clinical Testing

Preclinical progress in the SMA field has been rapid since the identification of *SMN1* as the responsible gene in 1995 and by the creation of the first mouse model in 2000.[110,111] Preclinical work using this and subsequent animal models has led to the development of many promising preclinical SMN-restoring therapies. Several clinical therapeutic trials have been performed in SMA without success. Prior studies investigating gabapentin and riluzole with a rationale of possible neuroprotection showed no effect.[112,113] Prior controlled trials with small molecules, including phenylbutyrate, hydroxyurea, and valproic acid in an attempt to upregulate full-length SMN production, have also been unsuccessful.[114–119] Potential factors that could be related to this lack of efficacy include inadequate induction of SMN protein from *SMN2*, incorrect timing of treatment after loss of motor neuron function, or inability to identify a minor effect in patients with slowly progressive clinical deficits. It is becoming increasingly clear that there are phases in the SMA disease (presymptomatic, rapid disease progression, and later plateau/slow progression).[78,87] Furthermore, preclinical studies have repeatedly shown the importance of early SMN restoration, and the diminishing returns of late rescue in mouse models.[120–123] Whether very late restoration of SMN protein has any clear effect on motor neuron function remains to be established, and whether the therapeutic timing will be similar in different severities of SMA remains unknown, largely because of a paucity of milder animal models.

Preclinical Development and Future Directions

In 2010-2011 the first very successful therapies in murine models of SMA were published using gene therapy to replace the *SMN1* gene.[120,124–126] Subsequent development of antisense oligonucleotide therapies that can modify *SMN2* splicing to include exon7 and produce increased amounts of full length SMN protein has shown similar promising results.[127] Additionally, newer small molecule compounds with improved ability to alter *SMN2* splicing have shown impressive results in animal models; these approaches have recently been reviewed in detail.[26] There are currently early phase clinical trials under way investigating intrathecal delivery of antisense oligonucleotide therapy in patients with SMA, and the results suggest that these therapies are safe and possibly effective.[128] Additionally, a phase 1 trial using systemic delivered AAV9 gene therapy to replace *SMN1* in infants with SMA type 1 is currently recruiting patients.

Conclusions

SMA is the most common genetic disease of the spinal motor neuron. It can manifest any time from prior to birth to adulthood with varying severity and disease impact, and it is the most common genetic cause of death in infants. Though discovery of the causative gene occurred almost 20 years ago, no disease modifying treatments are yet available. Nevertheless, effectively designed supportive care can reduce disease burden and improve quality of life significantly, but continued refinement of supportive care is needed. Despite major progress in our understanding of the biological consequences of SMN reduction, the pathogenic mechanism of SMA by which low levels of SMN protein lead to selective loss of motor neurons remains undefined. Regardless, preclinical development has led to several SMN-restoring therapies that have shown dramatic success in animal models of the disease, and several of these candidates are currently being testing in early phase clinical trials.

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Abbreviations

SMA	spinal muscular atrophy
SMN	survival motor neuron
RNA	ribonucleic acid
EMG	electromyography
MUAPs	motor unit action potentials
CMAP	compound muscle action potential
MUNE	motor unit number estimation

NMJ neuromuscular junction

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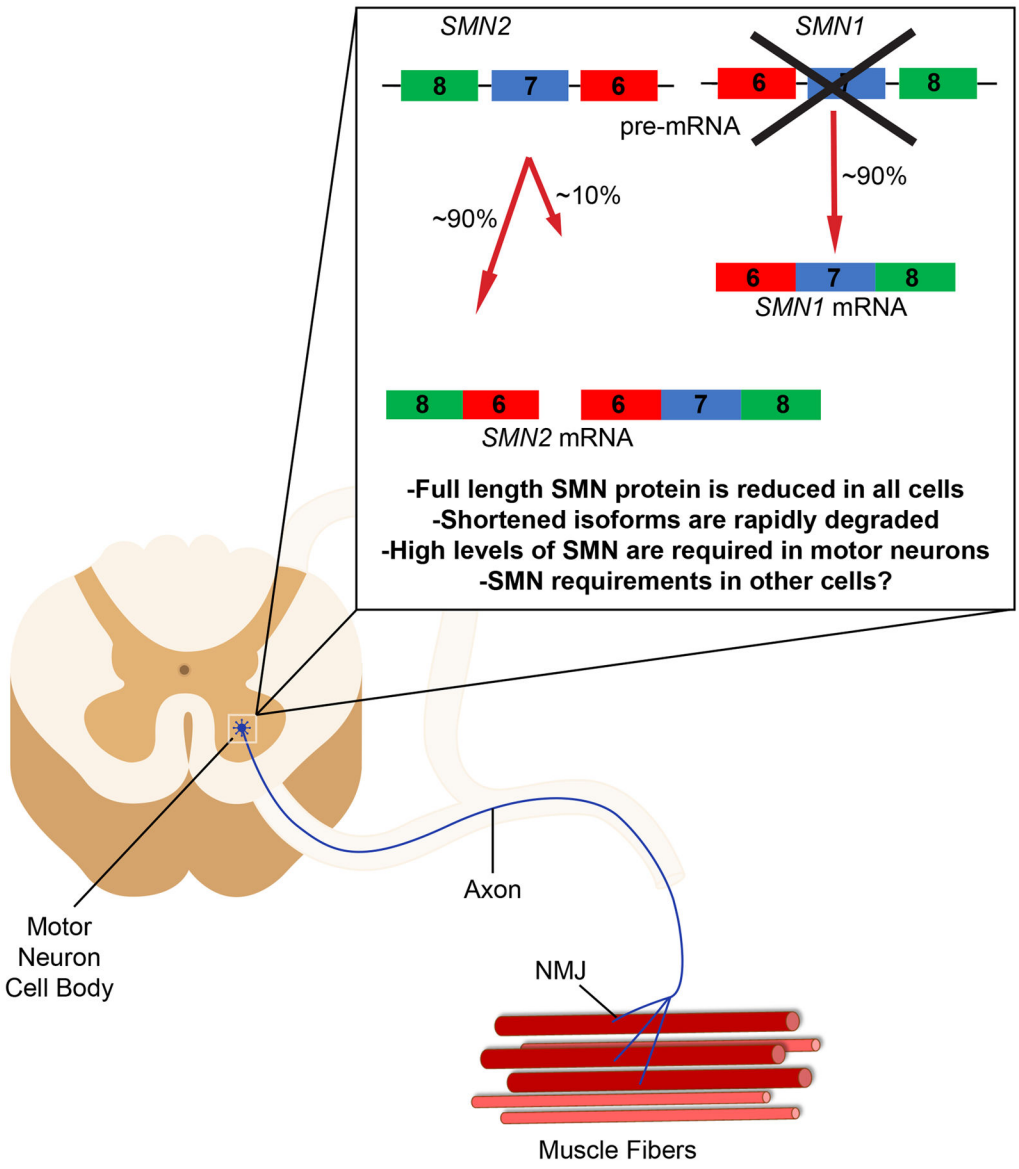

Figure 1.

Spinal muscular atrophy is caused by caused loss of the *SMN1* gene and retention of the *SMN2* gene, leading to low levels of full length SMN protein in all cell types. High levels of full length SMN protein are required in motor neurons, but the other cell types and tissues that require high levels of SMN remain to be determined.

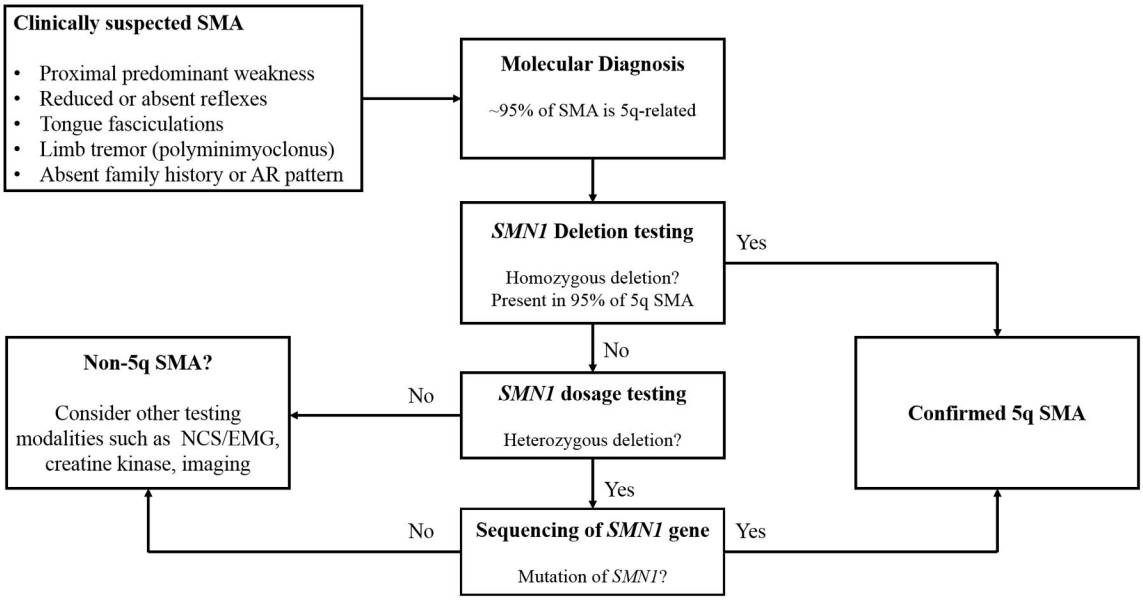

Figure 2.
Approach to molecular diagnosis of SMA.

Table 1

TYPE	ONSET	FUNCTION	MEDIAN SURVIVAL*
0	Prenatal	Respiratory failure at birth	Weeks
1	0–6 months	Never sit	< 1 years
2	< 18 months	Sit	>25 years
3	> 18 months	Stand or ambulatory	Adult
4	30 years	Ambulatory	Adult