Rare Opportunities IN PEDIATRICS

Collaborating in the Care of Spinal Muscular Atrophy: A Multidisciplinary Approach to Timely Screening, Diagnosis, and Management

A SUPPLEMENT TO Pediatric News

Introduction to Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a progressive, recessively inherited neuromuscular disease characterized by proximal muscle weakness, atrophy, and paralysis. SMA results from a mutation of the survival motor neuron 1 (*SMN1*) gene, which affects production of SMN protein, resulting in degeneration of alpha motor neurons in the spinal cord[1,2] (see **Genetics of SMA: Role of *SMN1* and *SMN2* Genes** on page 3). While SMA is classified as a rare disease, it is one of the more common rare diseases, with an incidence rate of about 1 in 10,000 to 12,000 live births and a carrier rate of about 1 in 50 adults.[3,4] SMA has a heterogeneous presentation, and while the most severe form of SMA is considered to be the leading genetic cause of infant mortality,[4,5] it is estimated that there are approximately 10,000 patients living with SMA in the United States.[6] Individuals with less severe forms of SMA may live into adulthood, with some patients having a normal or near-normal life expectancy.

With advances in management and the development of standards of care, the landscape of SMA is changing. Experts believe that early diagnosis with appropriate management could allow patients to live longer and healthier lives. With that in mind, a wide range of healthcare providers (HCPs) should be prepared to encounter patients with SMA in their practices, recognize SMA symptoms, facilitate referrals to specialists when appropriate, and collaborate with specialists in ongoing SMA management.[1,7]

I worry about SMA patients transitioning from pediatric to adult care. Patients are living longer, and there are not enough HCPs familiar with SMA who can care for them.

– **Diana P. Castro, MD**

SMA Classification and Clinical Presentation

SMA is currently classified into 5 clinical subtypes on the basis of the age of symptom onset and the highest level of motor function achieved[8] (see **Table 1**[9-12]). This may change as our understanding of SMA progresses. Genetic markers, specifically the number of copies of the *SMN2* gene an individual patient carries, may eventually play a

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Genentech, a member of the Roche Group, sponsored an expert roundtable on SMA in May 2019. The meeting brought together expert clinicians and researchers specializing in neuromuscular disorders, representing a variety of academic institutions, teaching hospitals, and advocacy groups. Objectives of the meeting were to discuss the evolving landscape of SMA management and the role that the broader healthcare community can play in the diagnosis and care of patients with SMA. The faculty present this educational supplement to increase awareness of SMA among general neurologists and primary care practitioners.

Table 1. Clinical Classification of SMA

Type[9]	Age of Onset[9-11]	Motor Function Achieved[10]			Life Expectancy[11,12]
		Sitting	Standing	Walking	
0	Prenatal	✖	✖	✖	Weeks
1	0-6 months	✖	✖	✖	<2 years
2	<18 months	✓	✖ (some may stand with support)	✖	>2 years (often early adulthood)
3	>18 months	✓	✓	✓ (may need assistance)	Normal
4	Typically 20-30 years	✓	✓	✓	Normal

role in disease classification (see **Genetics of SMA: Role of *SMN1* and *SMN2* Genes**).

Muscle weakness and atrophy are the common presenting symptoms of SMA,[12] with feeding/nutritional, respiratory, and orthopedic issues occurring as a result of muscle degeneration.[12] Patients typically have a presymptomatic period, followed by rapid functional loss. Some patients may then experience a plateau phase where disease progression is very slow.[12,13] The clinical presentation varies by subtype, and in general, early onset of symptoms is associated with a more severe phenotype.[14,15] Note that patients with SMA have normal cognition.[16]

Type 0 SMA is characterized by prenatal onset, severe hypotonia, respiratory distress, and contractures. This form of SMA is associated with a survival time of less than 6 months and respiratory and feeding support is required from birth.[17]

Type 1 SMA is the most common SMA subtype, accounting for approximately 60% of reported cases.[3] Patients with type 1 SMA may be asymptomatic at birth, but onset of hypotonia and proximal muscle weakness occurs within 6 months of birth and are profound—patients are unable to sit without assistance, lack head control, and have poor spontaneous movement. Weakness is usually symmetrical and begins in the lower extremities. Facial muscles are not affected early in the disease, and deep tendon reflexes are typically absent.[10]

Muscle weakness in the neck, jaw, and tongue fasciculations are prevalent in type 1 patients, resulting in difficulty feeding and swallowing, failure to thrive, and increased aspiration risk.[10,14] Nutritional intervention is commonly needed; one study demonstrated that the median time to feeding tube placement in an infant with untreated type 1 SMA is 8 months.[18] Weakness of the intercostal muscles with sparing of the diaphragm leads to paradoxical breathing, bell-shaped chest, and the need for respiratory support.[1,10,14] Median time to initiation of noninvasive ventilation or tracheostomy in untreated patients has been reported as 11 months.[18] Without treatment, life expectancy for an infant with type 1 SMA is typically less than 2 years,[2] and death is usually related to respiratory complications.[15,18] Proactive initiation of noninvasive ventilation, cough-assist, and nutritional support has been shown to improve survival in patients with type 1 SMA, underscoring the need for early diagnosis.[19,20]

Type 2 SMA accounts for about 20% of SMA cases.[3] In type 2 disease, symptom onset occurs between 7 and 18 months of age, and the spectrum of symptom severity ranges from very weak children to children with stronger trunk, limb, and respiratory muscles. Weakness is predominantly proximal and most severe in the lower limbs. These patients can sit, but cannot stand without support or walk. Fine tremors of the upper extremities are common, and deep tendon reflexes are absent. Impaired swallowing and respiratory insufficiency may also be present, particularly in patients with a more severe disease course. Scoliosis occurs in almost all patients with type 2 SMA and contributes to respiratory difficulties.[10,12]

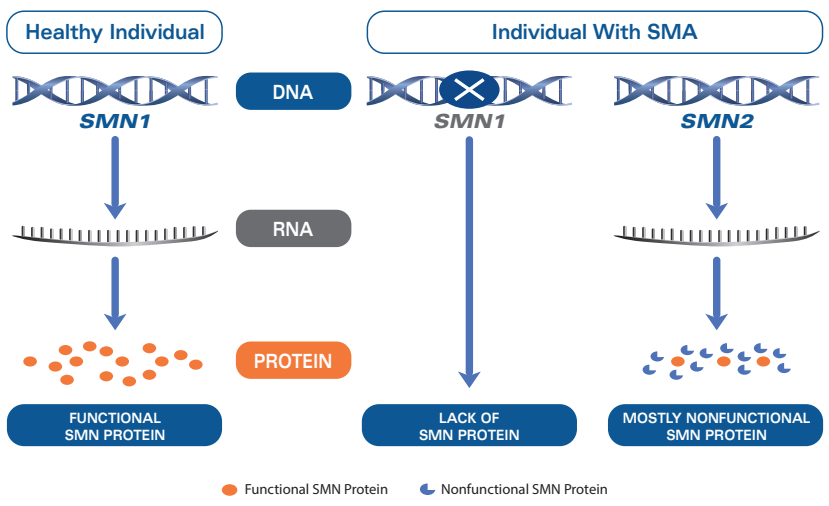
Motor and respiratory function in patients with type 2 SMA declines slowly over time.[15,21,22] Lifespan varies, but most patients live into early adulthood or longer.[12]

Genetics of SMA: Role of *SMN1* and *SMN2* Genes

SMA occurs as the result of decreased expression of the SMN protein and the loss of lower motor neurons.[1] The physiological role of SMN is not completely understood; however, SMN is known to play a critical role in ribonucleic acid (RNA) metabolism, including transcription, precursor messenger RNA (pre-mRNA) splicing, assembly of spliceosomal small nuclear ribonucleoproteins (snRNPs), translation, and mRNA trafficking.[2] While SMN protein is found in all cell types,[2] motor neurons in particular are highly susceptible to SMN deficiency, resulting in the clinical signs and symptoms of SMA. It is not completely understood why motor neurons exhibit this susceptibility to SMN depletion or why some pools of motor neurons are more affected than others.[1] However, evidence does suggest that SMN deficiency affects several components of the motor unit, including the motor neuron,[1] motor axon,[3] neuromuscular junction,[4] and the muscle.[5]

SMA is caused by loss-of-function mutations or deletions of the *SMN1* gene, which codes for full-length SMN protein, and is the principal gene regulating SMN production in individuals without disease.[6] Approximately 96% of cases of SMA are caused by homozygous deletion of *SMN1* exon 7 (and in most cases exon 8). The remaining cases are caused by compound heterozygosity, with a point mutation within the SMN1 gene on one allele and a deletion of exon 7 (and exon 8) on the other. SMA is rarely the result of homozygous mutations.[7]

Figure. SMN Protein Production in Individuals With and Without SMA



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A nearly identical gene, *SMN2*, also codes for SMN protein, although a single base pair difference between the *SMN1* and *SMN2* genes results in reduced efficiency of exon 7 inclusion into mature transcripts from *SMN2*.[8] Skipping of exon 7 results in production of a predominantly truncated and unstable SMN protein. *SMN2* also produces a low level of full-length functional SMN protein, but the amount is insufficient to fully compensate for the decreased levels of SMN production resulting from the loss of *SMN1* activity[6] (see **Figure**). Humans carry anywhere from 1 to 6 copies of the *SMN2* gene, and the number of *SMN2* copies is inversely correlated with the severity and clinical subtype of SMA. Individuals with fewer *SMN2* copies tend to produce lower levels of functional SMN protein and exhibit greater SMA severity.[9] There are, however, exceptions to this rule—more severe phenotypes may have a high *SMN2* copy number and less severe phenotypes may have a lower *SMN2* copy number. The typical *SMN2* copy numbers associated with the various SMA phenotypes are shown in the **Table**.[10,11] Note that patients are currently classified and managed based on age and motor function as opposed to genotype.[7,12]

Table. Most Common *SMN2* Copy Number by SMA Phenotype[10,11]

Type	Typical *SMN2* Copy Number
0	1
1	2
2	3
3	3-4
4	>3-4

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Type 3 SMA accounts for about 20% of SMA cases.[3] Patients with type 3 SMA generally achieve all major developmental motor milestones, but at some point after infancy, they begin to exhibit proximal muscle weakness.[10] Patients may initially present with symptoms of falls, difficulty climbing stairs, or gait abnormalities.[12] Fatigue is common.[5] The spectrum of motor disability is broad: all patients initially develop the ability to walk, but some patients may lose the ability in early childhood while others may be able to walk throughout adulthood.[10] The rate of pulmonary and motor function decline is slow, and patients may have long periods of clinical stability.[21,23] Patients experiencing onset of symptoms after age 3 typically have a less severe disease course.[24] Type 3 patients have a normal lifespan.[12]

Type 4 SMA describes patients with onset of muscle weakness after 18 years of age. Clinical presentation is similar to type 3 SMA, but motor weakness is less severe. Waddling gait is common, and finger trembling and calf hypertrophy may occur.[10,25,26]

Beyond the Motor Neuron: Additional Complications of SMA

Studies have suggested that the role of SMN protein extends beyond the central nervous system[27-32] and that SMN deficiency may be linked to nonmotor symptoms of SMA. There are reports of structural cardiac pathology in severely affected patients (ie, SMA with one copy of *SMN2*) and less frequently, cardiac rhythm disorders have been reported in patients with milder SMA types (eg, SMA type 3).[28,33] Bone health is a concern in SMA. A retrospective study of 85 patients with SMA (age 12 months to 18 years) demonstrated that 85% had osteopenia, and 38% had experienced a fracture.[34] While immobility and low muscle mass may contribute to poor bone health, preclinical data also suggest that SMN protein may play a role in bone remodeling.[29,34] Additionally, vascular necrosis,[35,36] pancreatic abnormalities,[30] and abnormal kidney structure and function[37] have been reported in patients with SMA; changes in liver function[31] and gastrointestinal pathology[32] have been reported in preclinical models of SMA.

Early Recognition and Neonatal Screening

Studies in SMA type 1 have demonstrated that functional motor neuron loss is greatest in the first 3 months of life.[38] Likewise, progression of motor weakness is greatest at the onset of SMA, and slows during the long-term course of the disease.[38-40] The natural history of SMA demonstrates the critical importance of early recognition and intervention, which has been succinctly articulated by the observation that "time is motor neurons."[40] Early diagnosis allows for timely initiation of disease management.

It is important for the healthcare team to aggressively pursue a differential diagnosis when they see hypotonia in an infant or child. This may be counter to the "watch and wait" philosophy that some physicians have been trained on. Time is motor neurons.

– **Claudia A. Chiriboga, MD, MPH**

Despite the importance of early diagnosis and management, diagnostic delays are common in SMA. Cure SMA, a leading SMA advocacy organization, reports that the average infant with type 1 SMA is not diagnosed until 5 months of age.[41] A 2011 survey of 28 families of children with SMA found that the mean time between symptom onset and diagnosis was 2.9 months for type 1, 9.8 months for type 2, and 8.3 months for type 3.[42] A 2014 survey of individuals with SMA, parents of individuals with SMA, and clinicians specializing in SMA attributed diagnostic delay to 3 factors: 1) lack of SMA awareness among primary care clinicians and some neurologists; 2) difficulty distinguishing normal from abnormal development in infants; and 3) mistaking SMA for a different condition.[43]

To facilitate early diagnosis and management, the US Department of Health and Human Services added SMA to the Recommended Uniform Screening Panel for Newborns in July 2018.[44] Each individual state is responsible for adopting and implementing this recommendation, and as of March 2019, 5 states were routinely screening newborns for SMA and another 13 were enacting laws requiring screening.[45] While newborn screening will undoubtedly facilitate SMA diagnosis, screening is not universal and healthcare providers must still be vigilant in recognizing SMA symptoms in

Healthcare providers must be aware of the status of newborn SMA screening in their state, but should also recognize that there will still be individuals diagnosed with SMA after the neonatal period. Recognizing the symptoms of SMA is key.

– **Charlotte J. Sumner, MD**

their patients. **Table 2** presents examples of clinical scenarios that authors agree are suggestive of an SMA diagnosis and would warrant further testing.

Table 2. Roundtable Discussion: Clinical Scenarios That Should Prompt SMA Evaluation

- Hypotonic infants or children who appear otherwise healthy and have normal cognition and social development
- Infants who move very little
- Infants with absent reflexes
- Older infants who are unable to sit unassisted
- Toddlers who are late to walking or frequently falling
- Older children who have trouble climbing stairs or fatigue easily
- Adults with unexplained proximal weakness or fine tremor

Confirming the SMA Diagnosis and Establishing a Management Plan

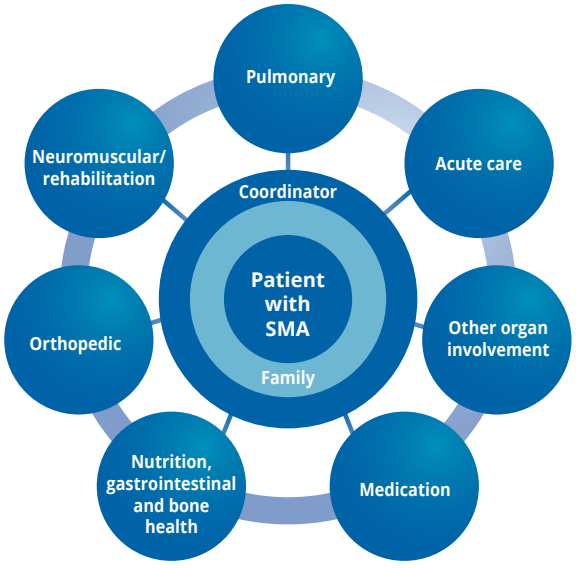
Confirming the Diagnosis

If SMA is suspected based on clinical presentation, genetic testing is required to confirm the diagnosis. This should include a quantitative analysis of both *SMN1* and *SMN2*.[1] If the *SMN1* testing demonstrates one copy of *SMN1* and there is high clinical suspicion, further testing for *SMN1* gene sequencing should be pursued as up to 5% of individuals with SMA have a point mutation not picked up on *SMN1* gene testing.[1] Authors agree that, when possible, patients be referred to an experienced multidisciplinary neuromuscular center for confirmation of the diagnosis as these centers are familiar with test interpretation and typically have resources available to support the newly diagnosed patient and provide management options.[1] The organization Cure SMA can assist healthcare practitioners in locating an SMA care center. Note that these centers are often willing to consult with community-based physicians to help determine if a referral is necessary.

Management of SMA

Ideally, patients with SMA are managed by a multidisciplinary team, with the neurologist or pediatric neurologist often serving as the coordinator[1] (see **Figure 1**). During the roundtable discussion, authors described how, at their neuromuscular centers, multidisciplinary care teams evaluate the patient, develop an appropriate care plan, and monitor the patient over time. During the evaluation, patients will undergo a motor function assessment using a validated scale. Several scales have been developed (see **Table 3**), so the care team must determine the appropriate motor function scale and make sure staff are trained on proper administration. Motor function assessment is repeated at routine intervals to assess patient status.[1]

Figure 1. The Multidisciplinary Care Team in SMA[1]



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Guidelines for the management of patients with SMA have been published, and suggest that ongoing care of SMA patients address physical therapy,[1] orthopedic management (scoliosis, rib deformity, hip instability, contractures),[1] nutrition (feeding/ swallowing, weight and growth, fluid and fiber intake, bone health),[1] pulmonary function (including ability to cough and clear secretions, hypoventilation, and sleep apnea),[33] and medication needs.[33] While these evaluations may be performed at a specialized neuromuscular center, community-based healthcare providers play an important role in providing general care and immunizations, and providing support and guidance within the local community. Authors encourage general neurologists, pediatricians, and other providers to utilize resources available from the neuromuscular care center or SMA advocacy organizations to stay updated on SMA management guidelines. Additionally, authors stressed that

Table 3. Examples of Functional Assessment Scales Used in SMA

Scale	Population	Description
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	Infants age 4 months to >4 years[46]	• 16-item scale assessing motor function[47] • Total score ranges from 0-64; higher scores indicate better function[47]
Bayley Scales of Infant Development (BSID)	Infants and toddlers age 1-42 months[48]	• Series of developmental play tasks used to determine need for further assessment and intervention[48] • Scores compared to norms from typically developing children[48]
Test of Infant Motor Performance Screening Items (TIMPSI)	Weak infants with type 1 SMA[49]	• 29-item scale assessing clinically relevant motor function typically affected by weakness in infants with SMA; 3 item sets (screening set, easy set, and hard set)[49] • Total score is the sum of subset scores[49]
Hammersmith Infant Neurological Examination (HINE) Section 2	Infants age 2-24 months[50]	• 8-item scale assessing motor milestones[50] • Total score ranges from 0-26; higher scores indicate improvement[50] • Note that patients with type 1 SMA may not achieve any motor milestones, resulting in a score of zero[50]
Hammersmith Functional Motor Scale-Expanded (HFMSE)	Patients with type 2 or 3 SMA age >2 years[51,52]	• 33-item scale of gross motor assessments[53] • Total score ranges from 0-66; higher scores indicate better function[22]
Revised Upper Limb Module (RULM)	Children and adults with SMA[54]	• 19-item scale measuring upper limb function[54] • Total score ranges from 0-37; higher scores indicate better function[54]
Motor Function Measure (MFM)	Ambulatory and nonambulatory children and adults with neuromuscular disease[55-57]	• Assesses measures in 3 domains: standing/transfer/walking; motor function in head, trunk, and upper part of arms and legs; motor function in lower arms, legs, hands, and feet[55] • Total score is expressed as a percentage of 100; higher scores indicate better motor function[55,58]
6-Minute Walk Test (6MWT)	Ambulatory children ≥5 years and adults[48]	• Assesses walking abnormalities in neuromuscular disorders[48] • Measures distance walked in 6 minutes[59]

community-based providers should be prepared to collaborate with the neuromuscular specialist in the event of an acute illness in an SMA patient.[33]

Addressing Barriers to SMA Management

Authors expressed concern that patients with SMA may not have access to healthcare providers experienced in SMA. The group pointed out that children with SMA may now be surviving into adolescence and adulthood, requiring lifelong multidisciplinary care. Additionally, adults living with milder forms of SMA who have disengaged from the healthcare system may start to seek out information on new management options. It was noted that today, there are not enough healthcare providers familiar with SMA management to provide this care, particularly in the adult population.

[Patients with SMA] and their families report frustration when they need to explain SMA to every new HCP that they see, or when HCPs say they don't know how to help.

– **Mary Schroth, MD**

Multidisciplinary neuromuscular centers and patient advocacy organizations such as Cure SMA can help the non-SMA specialist learn more about caring for patients with SMA. They offer web-based and live education for HCPs (https://www.curesma.org/current-educational-programs/). Additionally, they

maintain a database of care centers that provides therapies approved for SMA by the US Food and Drug Administration and can help healthcare providers with referrals if needed.

Not surprisingly, challenges with payers were identified as a barrier to SMA management.[60] Authors described collaborating with community neurologists and pediatricians familiar with the local payer landscape to help initiate care for patients with SMA. In some cases, authors called upon local providers to write prescriptions for ancillary therapies, formula, supplies, and equipment.

Education and Support Services

During the roundtable discussion, authors stressed that organizations supporting rare diseases serve as valuable resources for families living with SMA. Not only do these groups fund SMA research and provide education to families and caregivers, but they also provide vital support services. For example, Cure SMA maintains a pool of assistive equipment (eg, car beds, bath chairs, lightweight manual wheelchairs, therapy chairs, strollers) that is available to patients free of charge. The group described regularly interacting with these types of organizations and encouraging their patients with SMA to do the same.

Conclusion

This SMA roundtable revealed that while SMA may rarely be seen in general practice today, progress in SMA management has escalated the need for SMA education and awareness among general neurologists, pediatricians, and other HCPs. Untreated SMA can have devastating consequences and the experts agreed that timely identification of the symptoms of SMA by a community-based provider with prompt referral to a neuromuscular specialist is critical. After diagnosis, patients and their families face a complex array of medical needs. Collaboration among SMA experts, general neurologists, primary care physicians, patients, and caregivers will ensure that all patients can access evidence-based care and derive the maximum benefit from new advances in SMA management.

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