

Assessing Spinal Muscular Atrophy Across the Patient Journey

A SUPPLEMENT TO

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Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal recessive, progressive neuromuscular disease, affecting about 1 in 10,000 live births.^{1,2} Recent advances in the management of SMA may improve outcomes in this disease that historically has had few treatment options. As a means to increase SMA awareness, two SMA experts, Perry Shieh, MD, PhD, and Sally Dunaway Young, PT, DPT, conducted an industry-sponsored symposium on SMA, providing the audience with an overview of the disease. The faculty also presented patient cases designed to demonstrate the broad phenotypic spectrum of SMA. "We want to give you an idea of how we see SMA, and what you might want to look for when you are assessing a patient who might have a neuromuscular disease like SMA," Dr. Shieh explained to the audience.

The Genetic Basis and Clinical Manifestations of SMA

Clinical manifestations of SMA are the result of deficiency of survival motor neuron (SMN) protein, which is primarily expressed from the *SMN1* gene.^{3,4} In SMA, deletions and/or point mutations in the *SMN1* gene disrupt the production of SMN protein: 95% of SMA is caused by a homozygous deletion of exon 7 of the *SMN1* gene; the remaining 5% arises from a combination of a deletion and point mutations.⁵ Humans also carry anywhere from 1 to 8 copies of a second homologous gene, *SMN2* (sometimes referred to as the "backup gene"), which differs from *SMN1* by 5 base pairs, but most importantly a C-to-T substitution within exon 7 that interferes with *SMN2* messenger RNA splicing.^{3,6,7} As a result, the majority of mature transcripts from the *SMN2* gene lack exon 7 and do not result in the expression of functional SMN protein.^{5,6} The *SMN2* gene does, however, produce a low level of full-length SMN transcript, including exon 7, resulting in a functional SMN protein. The expression of SMN protein from *SMN2* is lower than when derived from an *SMN1* gene.^{5,8} "SMA is not a complete absence of SMN," Dr. Shieh noted, "but rather a relative deficiency of SMN. The greater the deficiency, the more severe the disease." SMA patients with a higher *SMN2* copy number (eg, 3-4 copies) generally (but not always) produce more SMN protein compared to those with a lower copy number (eg, 1-2 copies), and tend to have milder disease.⁸

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SMN protein plays an important role in motor neuron survival, and many of the clinical symptoms of SMA are related to motor neuron degeneration. “What we see in SMA is progressive skeletal muscle denervation, which leads to skeletal muscle atrophy, which leads to weakness, and then patients begin to lose function,” explained Dr. Shieh.¹ Muscle weakness in SMA is usually more common in the lower extremities than the upper extremities and typically more proximal than distal.⁹ Orthopedic complications result from muscle weakness: scoliosis develops because of axial muscle weakness and contractures develop because of imbalanced muscle strength across joints.¹⁰⁻¹² Respiratory accessory muscles are also affected, so patients are at risk for recurrent pneumonia and hypoventilation.¹¹ Likewise, feeding and nutritional difficulties can arise secondary to loss of bulbar function or decreased gastrointestinal motility related to immobility.^{11,12}

SMA Diagnosis: Timely Recognition of a Heterogeneous Disease

Newborn screening to detect homozygous deletion of exon 7 in the *SMN1* gene is an effective way to identify SMA and allows for intervention at the earliest stages of the disease.¹³ While the US Department of Health and Human Services added SMA to the Recommended Uniform Screening Panel (RUSP) for newborns in July 2018, adoption and implementation of this recommendation is on a state-by-state basis.¹⁴ Nationwide implementation is slow; as of mid-2020, routine newborn screening has been implemented in only 23 states.¹⁴ Additionally, genetic testing does not detect the 5% of SMA that results from heterozygous point mutations.¹³ Thus, clinical recognition of SMA signs and symptoms remains a critical first step in

the diagnostic process. Primary care clinicians and general neurologists will still need to understand when to suspect SMA, and be comfortable referring those patients to neuromuscular specialists to help confirm the diagnosis.

Dr. Shieh pointed out that, “When you see a patient with symmetric proximal muscle weakness that is greater in the legs than in the arms, with absent or reduced tendon reflexes, and preserved sensation, you have a good reason to suspect SMA.”

Dr. Shieh also explained that despite the typical pattern of muscle weakness, SMA has a broad range of phenotypes spanning from infants who can barely move to adults who are able to walk independently.¹ “You may wonder if these individuals, in fact, have the same disease,” he noted. While mutations in *SMN1* are found in most types of SMA, the phenotype is determined by the amount of SMN an individual produces, which correlates to the *SMN2* copy number. **Table 1** describes the 3 most common presentations of SMA.

Measuring Motor Function Changes in SMA

The natural history of motor function in SMA also differs by phenotype, and is represented in **Figure 1**. In patients without SMA, motor function develops steadily until early adolescence and then plateaus.¹⁶ In patients with SMA, you see a slower rate of motor function development and in most patients a period of decline in motor function after development. Later in the disease, there seems to be a plateau phase.¹⁶ The rate of decline in later stages of Type 2 and Type 3 SMA can be very slow.¹⁶

Table 1. Clinical Classification of SMA

Type	Age of Onset ¹	Typical <i>SMN2</i> Copy Number ^{1,15}	Impact	Life Expectancy ^{15,16}
1	<6 months	2-3	<ul style="list-style-type: none"> • Never sit¹⁵ • Respiratory insufficiency, feeding complications, failure to thrive¹ 	<2 years ¹⁵
2	7-18 months	3	<ul style="list-style-type: none"> • Never walk¹⁵ • May be able to stand with assistance¹⁵ • Scoliosis and contractures are common¹ 	Up to early adulthood or longer ¹⁵
3	>18 months	3-4 ¹	<ul style="list-style-type: none"> • Walk independently, but may lose the ability over time¹⁵ 	Normal ¹⁵

Healthcare professionals use a number of validated scales to assess motor function in patients with SMA. These assessments are commonly administered by a physical therapist, and Dr. Dunaway Young explained that the results not only provide insight into the degree of muscle weakness and motor impairment, but also help guide the rehabilitation management plan. For example, assessments can help physical therapists pinpoint muscles that need to be stretched, determine which devices or braces might help with positioning or mobility, and develop targeted plans for strengthening and exercise. Regular administration of motor assessments are also helpful to measure disease progression and changes over time,¹² which allows healthcare providers to understand when a patient is benefitting from prescribed interventions. Examples of commonly used motor function assessment scales are presented in **Table 2**.

Figure 1. The Natural History of Motor Function in SMA by Phenotype¹⁶

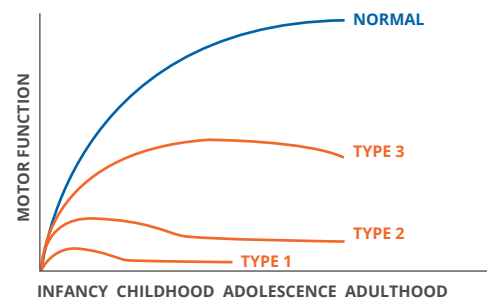


Figure used with permission from: Sumner CJ, Crawford TO. *J Clin Invest.* 2018;128(8):3219-3227.

Table 2. Motor Function Assessment Scales Used in Patients With SMA

Scale	Population	Description
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	Infants aged 4 months to >4 years ¹⁷	<ul style="list-style-type: none"> • 16-item scale assessing motor function¹⁸ • Total score ranges from 0-64; higher scores indicate better function¹⁸
Bayley Scales of Infant and Toddler Development (Bayley-III)	Infants and toddlers aged 1-42 months ¹⁹	<ul style="list-style-type: none"> • Assesses developmental function using a series of developmental play tasks to determine need for further assessment and intervention¹⁹ • Scores compared to norms from typically developing children¹⁹
Test of Infant Motor Performance Screening Items (TIMPSI)	Infants aged <5 months ²⁰	<ul style="list-style-type: none"> • 29-item scale assessing clinically relevant motor function typically affected by weakness in infants with SMA; 3 item sets (screening set, easy set, hard set)²⁰ • Total score is the sum of subset scores²⁰
Hammersmith Infant Neurological Examination (HINE) Section 2	Infants aged 2-24 months ²¹	<ul style="list-style-type: none"> • 8-item scale assessing motor milestones²¹ • Total score ranges from 0-26; higher scores indicate better function²¹ • Note that patients with type 1 SMA may not achieve any motor milestones, resulting in a score of zero²¹
Hammersmith Functional Motor Scale-Expanded (HFMSSE)	Children aged >2 years and adults with SMA (sitters and walkers) ²²	<ul style="list-style-type: none"> • 33-item scale of gross motor assessments^{22,23} • Total score ranges from 0-66; higher scores indicate better function^{22,23}
Revised Upper Limb Module (RULM)	Children aged ≥30 months and adults with SMA ²⁴	<ul style="list-style-type: none"> • 20-item scale (19 scored) measuring upper limb function²⁴ • Total score ranges from 0-37; higher scores indicate better function²⁴
Motor Function Measure (MFM)	Ambulatory and nonambulatory children and adults with neuromuscular disease ^{25,26}	<ul style="list-style-type: none"> • Assesses function in 3 domains: standing position and transfers, axial and proximal motor function, and distal motor function^{25,26} • Total score is expressed as a percentage of 100; higher scores indicate better function²⁶
6-Minute Walk Test (6MWT)	Ambulatory children and adults ²⁷	<ul style="list-style-type: none"> • Assesses walking ability and functional exercise capacity in patients with neuromuscular disorders²⁷ • Measures distance walked in 6 minutes and may help to quantify fatigue²⁷

Case Study: An Infant With Type 1 SMA

To illustrate what to look for in an infant with suspected or diagnosed Type 1 SMA, Dr. Shieh and Dr. Dunaway Young presented images of an infant with Type 1 SMA undergoing motor function assessment via the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale. Dr. Dunaway Young noted that CHOP INTEND was developed specifically to assess motor function in severely weak infants; it minimizes changes in position, requires no additional equipment, and usually takes 15 to 40 minutes to administer. It has been validated in infants with Type 1 SMA.¹⁷ Items assessed include spontaneous movement, handgrip, head and neck movement, upper and lower body strength, facilitated rolling, and reflexive movements in prone suspension.¹⁸

From a supine position (**Figure 2**), an infant with Type 1 SMA frequently has a “frog-legged posture” and limited antigravity movement—“arms, hands, feet, and knees rarely come off the mat, though you may see distal movement of the ankles, fingers, and wrists,”²⁸ Dr. Dunaway Young explained. Weakness in the neck muscles may be evident: if the head is positioned in midline without support, it may fall to one side. From this position, examiners can also try to facilitate a roll or address handgrip strength.

Also from supine, infants with Type 1 SMA may appear to have a bell-shaped chest, which Dr. Shieh explained is caused by weakness of the intercostal muscles with relative sparing of the diaphragm. When the patient breathes in, the diaphragm contracts and the belly moves outward, but the chest collapses, resulting in a belly-breathing presentation. “Bell-shaped chest is a prominent symptom of SMA and can assist in differential diagnosis,” Dr. Shieh commented. “It is not seen in some of the other neuromuscular diseases that present in this young age group.”

Figure 2. Supine²⁸



Photo used with permission from: Oskoui M et al. Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ et al, eds. *Spinal Muscular Atrophy. Disease Mechanisms and Therapy*. London, United Kingdom: Academic Press; 2017:3-19.

Dr. Dunaway Young noted that when a Type 1 infant is held in supported standing (**Figure 3**), the examiner will notice a generally floppy appearance. The infant cannot take weight or bear weight through the legs, and there is little active movement in the legs. Because of trunk and shoulder girdle weakness, it may appear as if the child is slipping through the examiner’s hands.²⁸

Figure 3. Supported Standing²⁸



Photo used with permission from: Oskoui M et al. Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ et al, eds. *Spinal Muscular Atrophy. Disease Mechanisms and Therapy*. London, United Kingdom: Academic Press; 2017:3-19.

Figure 4. Pull to Sit²⁸



Photos used with permission from: Oskoui M et al. Spinal muscular atrophy: 125 years later and on the verge of a cure. In: Sumner CJ et al, eds. *Spinal Muscular Atrophy. Disease Mechanisms and Therapy*. London, United Kingdom: Academic Press; 2017:3-19.

In the CHOP INTEND assessment, examiners attempt to pull the child from a supine to a sitting position (**Figure 4**). Dr. Dunaway Young noted, “When you attempt to raise a typically developing infant from supine to sitting, you observe flexion in the elbows and a chin tuck to help lift the head off of the mat. You won’t necessarily see that with Type 1 SMA. You may not see any type of active arm movement, and head lag may be observed.”

Figure 5. Prone Suspension²⁹



Photo used with permission from: PNCN Network for SMA. CHOP INTEND Manual of Procedures. <http://columbiasma.org/docs/cme-2010/CHOP-INTEND-for-SMA-Type-I-Manual-of-Procedures.pdf>.

When held in prone suspension (**Figure 5**), an infant with Type 1 SMA will appear to flop over the examiner’s hands. Dr. Dunaway Young explained that when a typically developing infant is suspended in a prone position, an examiner will observe neck extension or wiggling when the back of the neck or spine is stroked, and that this will likely be absent in an infant with Type 1 SMA.

Additional assessments are performed in a supported sitting position. Dr. Dunaway Young noted that, occasionally, the infant might find some head/neck balance when placed in a stacked sitting position. This may only be for a moment, and if moved outside the stacked position, the infant's head can immediately drop down.

In Type 1 SMA, facial muscles are relatively spared and cognitive development is not affected. "What I have noticed is that, despite the fact that these children have significant muscle weakness, if you look at their faces they are very engaged and very bright. Cognition is very good."

-Perry Shieh, MD, PhD

The faculty agreed that CHOP INTEND is very helpful in assessing the Type 1 patient. Infants with Type 1 SMA usually do not score above 40 on the CHOP INTEND.³⁰ "We may see scores in the 20- to 25-point range," Dr. Dunaway Young noted. The interval between 6 and 12 months of age seems to be the period of most rapid decline, with a plateau in score occurring after that time point.³⁰

As with all SMA patients, infants with type 1 SMA require a multidisciplinary approach.¹² In Type 1, however, the following areas of care may require special attention:

- Nutrition and Swallowing: Infants may require nutritional support, including insertion of a feeding tube.¹²
- Respiratory Support: Infants may require assistance with airway clearance as well as invasive or noninvasive ventilator support.³¹
- Orthopedic Needs: Infants may require bracing, support for trunk and head posture, and in some cases scoliosis surgery when the child is older (at least 4 years of age).¹²

Case Study: A 16-Month-Old Child With Type 2 SMA

Dr. Shieh shared the case of a 16-month-old child with Type 2 SMA that he sees in practice. In addition to providing an overview of the clinical presentation of Type 2 SMA, this case provided insight into the challenges many families face in obtaining an SMA diagnosis. "When this boy was about 1 year old, his parents began to notice that he was not moving his

legs very much, and not trying to stand. His pediatrician labeled him a 'lazy baby.' In speaking with the parents after he was referred to our clinic, I noted that this child had presented with several symptoms in infancy which could suggest SMA, including failure to lift his head while prone, inability to crawl or get on his hands and knees, curvature of the spine, and significant constipation."

In the clinic, this child was assessed via the CHOP INTEND scale. Dr. Shieh shared several video clips of the assessment and Dr. Dunaway Young described his presentation.

Figure 6. Supine



This child could raise his arms off the mat to reach overhead, but demonstrated little movement in the legs and was unable to lift his feet or knees off the bed (**Figure 6**). Movement in the arms but not the legs is consistent with SMA in general, where weakness in the lower extremities is typically greater compared with the upper extremities.¹⁵ The child could initiate a roll to his side, but could not completely roll over. "You may see a bit more trunk strength in patients with Type 2 as compared to Type 1 SMA," Dr. Dunaway Young noted. Head lag was also noted when the child was pulled to a sitting position.

Dr. Dunaway Young explained that in supported sitting (**Figure 7**), the child could move his legs slightly, but there was no active knee extension as would typically be seen in a child without SMA. She also remarked that the child would not be able to hold this position without support and lacked head control, indicating weakness of the trunk and neck muscles.

Figure 7. Supported Sitting



Unlike patients with Type 1 SMA, those with Type 2 SMA can sit independently¹ (**Figure 8**), though Dr. Dunaway Young pointed out that this patient required a wide base of support to maintain a sitting position and that he was unlikely to be able to transition to sitting from supine or easily return to supine without falling over. “Curvature of the spine is common in Type 2 SMA,” Dr. Dunaway Young noted. “This particular patient exhibits a rounded spinal posture with some kyphosis.”

This child is able to balance his head on top of his spine, with his head tipped into some extension. This is difficult to maintain and he could fall over at any point when he finds himself out of balance. He probably fatigues very easily in this position.

-Sally Dunaway Young, PT, DPT

Figure 8.
Independent Sitting



From supported standing (**Figure 10**), the examiner can tell that the child is unable to fully bear weight in his legs. Similar to the patient with Type 1 SMA, the child appears to be slipping through the hands of the examiner, which Dr. Dunaway Young indicated is a sign of shoulder girdle and trunk weakness.

The faculty explained that management of Type 2 SMA requires careful attention to orthopedic needs. Scoliosis commonly develops secondary to axial muscle weakness.¹⁰ Scoliosis, in turn, can compromise the patient’s respiratory function, and many patients require bracing or surgical intervention.¹² Contractures are also common, and physical therapists need to determine which muscles would benefit from stretching or bracing to prevent contractures and maintain flexibility and function for as long as possible.^{1,12}

Figure 10.
Supported Standing



Figure 9. Upper Body Strength



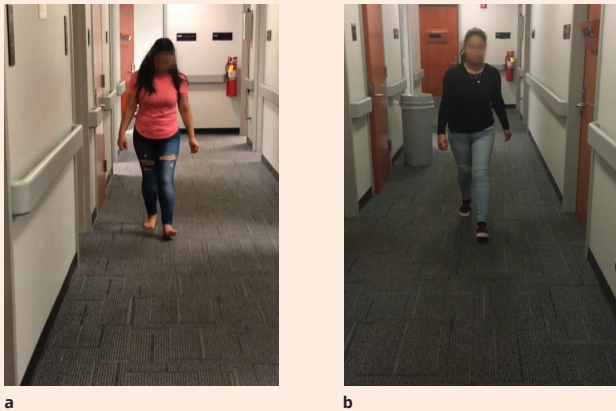
Video footage in which this child attempts to reach for a toy demonstrated the proximal muscle weakness seen in patients with SMA.¹¹ While the child was able to use his arms and hands, he could not raise his hand higher than chin or nose level (**Figure 9**). The toy needed to be lowered to chin level in order for him to reach it.

Case Study: A Young Adult With Type 3 SMA

For the last case, Dr. Shieh shared a video of an 18-year-old female living with what he described as “a milder presentation of Type 3 SMA.” He noted that the phenotypic spectrum for type 3 SMA is particularly broad, with some patients losing the ability to walk early on and others remaining ambulatory well into adulthood.^{1,15} This case illustrates how, at first glance, it might be difficult to recognize SMA in patients with milder symptoms, and how motor function assessments can assist healthcare practitioners in establishing a diagnosis.

The patient reported that when she was around 4 years of age, her parents suspected that something might be wrong because she was falling frequently and struggling when she climbed the stairs. She described herself as nonathletic, being the slowest child in gym class and other sports. Over the years, she saw multiple specialists and was diagnosed with lower-extremity weakness. One neurologist suggested that she might have muscular dystrophy. At age 14, she underwent an electromyogram, which demonstrated neurogenic changes. Subsequently, she underwent genetic testing, which confirmed her diagnosis of SMA. Because she was able to walk, she was diagnosed with Type 3 SMA.

Figure 11. Walking



Dr. Dunaway Young explained it is difficult to identify symptoms of SMA by watching this patient walk. In the first video, taken at age 17, the patient's gait appeared normal with a typical heel-to-toe pattern and no major trunk sway (**Figure 11a**). One year later, Dr. Dunaway Young noted the patient had a more pronounced hip drop, but overall her gait still appeared normal (**Figure 11b**).

"Even though her gait looks normal, she fatigues very easily when walking long distances. For example, she typically uses a wheelchair when she visits a theme park," Dr. Shieh noted.

This patient appeared to transition from sitting to standing without difficulty, however Dr. Dunaway Young pointed out some signs that indicate muscle weakness (**Figure 12**). "During the transition, [the patient] leans a little more forward; that is typical in a person with SMA. She also needs to use the arms of the chair to get up. If her arms were folded while she transitioned, there would likely be more of a forward trunk lean. She might have more difficulty getting up from a lower chair due to proximal hip weakness."

The patient's muscle weakness becomes more evident when she is asked to squat (**Figure 13**), as is typical for a patient with Type 3 SMA. She can perform about 40% of a total squat. Dr. Dunaway

Figure 12. Transition From Sitting to Standing



Figure 13. Squatting



Young suggested that if the patient tried to go lower, she would likely collapse to the floor as a result of proximal muscle weakness in her legs. Note that the patient also needs to grab the handrail for stability.

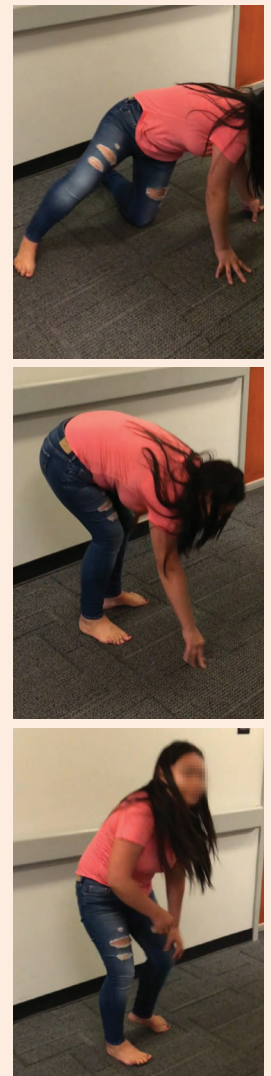
"As the patient gets closer to the floor, her bottom falls quickly due to proximal muscle weakness. We see this with most Type 3 patients," Dr. Dunaway Young pointed out. Additionally, when getting up from the floor, the patient demonstrates the Gowers' maneuver, requiring her hands on the floor and on her thighs to "walk" herself upright (**Figure 14**).

Assessment via the Hammersmith Functional Motor Scale-Expanded (HFMS-E) provides a clearer picture of this patient's motor weakness. The HFMS-E is designed to assess motor function in patients with Types 2 and 3 SMA.²³ Unlike CHOP INTEND, it assesses a wide range of functional skills such as sitting, rolling, transitions (including crawling and kneeling), standing, stepping, squatting, jumping, and stair climbing.²³ The HFMS-E has been validated in patients with SMA and correlates with select measures of strength, pulmonary function, and SMN2 copy number.^{23,32} Dr. Dunaway Young noted that it imposes minimal patient burden, takes about 10 to 15 minutes to complete, and requires little equipment.

The Motor Function Measure-32 (MFM-32) could also be used to assess this patient. Dr. Dunaway Young noted that, similar to the HFMS-E, the MFM-32 assesses a wide range of functional abilities, looking at overall mobility, fine motor control, core muscles, and postural concept. It contains 32 items that are separated into 3 domains³²:

- Domain 1: Standing and transfers
- Domain 2: Axial and proximal motor function
- Domain 3: Distal motor function

Figure 14. Transition From Standing, Down to Floor, and Back to Standing



The MFM-32 has been validated in patients with SMA and has been shown to correlate with other functional measures.³³ Dr. Dunaway Young pointed out that the scale requires some equipment and can take anywhere from 15 to 45 minutes to complete, depending on the patient's functional impairment.

Both the MFM-32 and HFMSE have been tied to meaningful clinical outcomes in patients with SMA. For example, HFMSE item 28 assesses squatting. In a 2017 study from Pera et al, caregivers of children with SMA report that the ability to squat allows children to sit down independently, pick up an object off the floor, tie their shoes, or pull up their pants.³⁴ Similarly, changes in the MFM-32 score have been linked to meaningful functional changes across a wide range of patient ages and functional abilities. Dr. Dunaway Young presented a 2019 Rasch analysis from Trundell et al, which described the estimated total MFM thresholds that corresponded to a gain or loss of specific daily functions.³⁵ She explained that a highly functioning patient may have a score of 59 and be able to sit up independently, however, a 2-point increase to a score of 61 would mean that the patient could stand. A patient with more severe SMA may have a score of 13 and be able to reach for an item at arm's length (such as a toy), but a 3-point increase to a score of 16 would mean the patient has the ability to feed independently.

Conclusion

"It is an exciting time for healthcare providers who see SMA patients," Dr. Shieh concluded. "Newborn screening, evolving care guidelines, and disease-modifying therapies will change the way we look at SMA, allowing us to approach management of the disease differently in the future." Applying motor function assessments to evaluate for muscle weakness characteristic of SMA is an important part of the process for management and treatment strategies. Early identification of SMA symptoms, with appropriate referral, allows patients to benefit from the latest care advances at the earliest stages of disease. Ongoing assessment allows healthcare providers to evaluate the benefit of their interventions and modify care plans accordingly.

The healthcare system will likely need more providers familiar with SMA recognition and management. Now is the time for all healthcare providers to gain an understanding of SMA so that this population of children and adults can access timely and appropriate care.

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