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# Beyond the Clinical Trial: The Role of the Physical Therapist in Diagnosis and Management of a Patient with Spinal Muscular Atrophy Type II

Brandilynne Schierland  
*University of Iowa*

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# Beyond the Clinical Trial: The Role of the Physical Therapist in Diagnosis and Management of a Patient with Spinal Muscular Atrophy Type II

Brandilynne Schierland

DPT Class of 2017

Department of Physical Therapy & Rehabilitation Science  
The University of Iowa

## Abstract

**Background:** Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular condition characterized by progressive loss of muscle function. Mutation of the survival motor neuron (SMN1) protein results in degradation of motor neuronal pools. Despite variability in phenotypic expression, SMA is classified into subtypes based upon achievement of gross motor milestones. **Purpose:** The purpose of this case report is to highlight the physical therapist's role in reducing diagnostic delays and in the ongoing management of SMA while discussing the impact of medical advancements. **Case Description:** The patient was diagnosed with SMA Type II at 17 months of age following evaluation for delayed milestones. The child presented with significant hypotonia and decreased muscle strength with a Gross Motor Quotient of 61 on the Peabody Developmental Motor Scale (PDMS-2). The patient is currently 8 years old and utilizes a power mobility device. Breath support strategies have been implemented to improve control of respiratory muscles in addition to resistance exercise and postural control training. **Outcomes:** Forced Vital Capacity (FVC) is frequently used to monitor respiratory status, but Maximum Phonation Time (MPT) and rib cage excursion may provide alternative means of assessment. Additional measures included the Hammersmith Functional Motor Scale Expanded (HFMSSE), Sitting Balance Scale (SBS), and Canadian Occupational Performance Measure (COPM). **Discussion:** Diagnosis of neuromuscular diseases is complicated by variability in clinical presentation and lack of expertise by healthcare professionals. Increased awareness and knowledge of red flag warning signs will help decrease delays in diagnosis and improve access to medical services. Further, the progressive nature of SMA can make it difficult to show improvement using functional outcome measures. Participation-based measures provide a means to demonstrate meaningful change throughout habilitation.

## Background

Neuromuscular disease is a term used to describe a group of pathologies of impaired muscle function. The physiological mechanisms underlying neuromuscular disease include direct damage to the muscle, lesions of the motor neuronal pool or the nerves which supply muscle, and deficits within the neuromuscular junction. Many neuromuscular diseases are progressive in nature and often onset of symptoms occurs in childhood with muscular weakness, delayed motor milestones, and generalized fatigue. Spinal Muscular Atrophy (SMA) is one such example of a progressive neuromuscular disease which affects voluntary control of muscle movement. Delayed motor development and progressive loss of muscle strength are among the first signs and symptoms of this neuromuscular condition which often leads to referral for physical therapy and eventually consideration of diagnostic testing for SMA.

SMA is an autosomal recessive genetic disorder characterized by degeneration of the anterior horn cells of the spinal cord and motor nuclei of the lower brainstem. SMA is the most common inherited motor neuron disease with an incidence of 1/10,000 live births due to the high carrier frequency of the disease-causing mutation in the general population.<sup>1</sup> That is, one in every fifty people carry the mutation of the survival motor neuron (SMN1) gene. Under normal conditions, the SMN1 gene functions to generate viable proteins via mRNA synthesis needed to maintain motor neuronal pools. Additionally, the SMN1 gene aids in the formation of axons and dendrites which enable the transmission of nerve impulses to the muscle to produce voluntary movement.<sup>1</sup> Deletions or mutations in the SMN1 gene lead to deficiencies of the SMN protein resulting in progressive deterioration of the motor neurons, impaired transmission of impulses from the brain to the muscle, and loss of normal muscle function.

Traditionally SMA is classified into types I, II, and III based upon age of onset, clinical course, and achievement of motor milestones. Infantile onset (Type I), also known as Werdnig-Hoffmann disease, presents before six months of age, however, the infant may be born full-term with no medical complications or apparent signs of muscular weakness. Within the first few months of life the infant will develop bilateral flaccid paralysis never achieving the ability to sit unsupported. Life expectancy is generally less than 2 years of age.<sup>1,2</sup> SMA Type II, formally named Dubowitz disease, is considered the intermediate form with onset of symptoms between 3 to 15 months of age. These individuals demonstrate the ability to sit unsupported, but do not achieve the ability to stand or walk independently. Individuals with type II are expected to live into the second decade of life.<sup>1,2</sup> Clinical onset of SMA Type III or Kugelberg-Welander disease occurs after the age of 18 months, but before adulthood, thus is referred to as the juvenile form of SMA. A full lifespan into adulthood is expected.<sup>1,2</sup> Individuals diagnosed with SMA Type III achieve the ability to ambulate, however, with progression of the disease many lose this level of functional independence and eventually utilize a wheelchair for mobility.

All forms of SMA are associated with symmetric, proximal muscle weakness affecting the lower extremities more so than the upper extremities as well as diminished deep tendon reflexes and restrictive respiratory insufficiencies.<sup>1</sup> The extent to which these symptoms emerge and impact the individual, however, is highly dependent on the subtype of SMA and its unique clinical course. Further, phenotypic expression of SMA is variable and spans a spectrum despite a more concrete classification system which is primarily utilized for prognostic purposes. Moreover, it is thought that the loss of SMN1 protein is partially compensated for by SMN2 protein synthesis which explains the variability of phenotypic expression in individuals with SMA. It is important to note that over 94% of SMA cases occur due to a homozygous deletion of exon 7 within the SMN1 gene on chromosome 5q13.2. This is significant because the SMN1 and SMN2 genes have been found to be more than 99% identical in genetic configuration meaning 10-15% of the mRNA produced from SMN2 genes contain exon 7.<sup>1,3</sup> Therefore, copies of the SMN2 gene have the capacity to produce some full-length, functional SMN proteins which modify disease severity. Research shows that disease severity is inversely correlated with number of SMN2 gene copies; a greater number of copies predicts milder phenotypes.

Further, recent advancements in the medical management of SMA have increased recognition of this progressive neuromuscular disease which is the number one genetic cause of infantile death. On December 23<sup>rd</sup>, 2016 the U.S. Food and Drug Administration (FDA) approved SPINRAZA™

(Nusinersen) as the first FDA-approved drug for treatment of SMA. Nusinersen is an intrathecal injection in which the medication is circulated directly through the cerebrospinal fluid surrounding the brain and spinal cord. The drug is an antisense oligonucleotide which modifies splicing of the mRNA in the SMN2 gene promoting increased production of full-length SMN proteins.<sup>2,3</sup> Recent medical advances have the potential to change the course of this neuromuscular disease and have increased awareness amongst healthcare professionals. The purpose of this case report is to discuss the comprehensive role of the physical therapist in the diagnosis and ongoing management of SMA Type II.

## Case Description

### Referral and Care Coordination

The patient was born full-term with no medical complications, however, at her one year well-child physician visit concerns for delayed developmental milestones and generalized hypotonia were noted. She was initially referred to orthopedics by her pediatrician. Due to the patient's limited ability to weight-bear through bilateral lower extremities, diagnostic imaging was ordered. Radiographic images revealed no abnormalities of the hips, ruling out instability. A month later a second referral was made for her to be seen for further evaluation by an interdisciplinary healthcare team in a neurodevelopmental specialty clinic. Additional testing was completed at the time of this evaluation. Diagnostic testing revealed normal creatine kinase levels, normal FISH (Fluorescence in situ Hybridization) results, and normal brain MRI with no structural abnormalities. Following this array of negative diagnostic tests, physical therapy was initiated and the patient was promptly referred to pediatric neurology.

### Physical Therapy Examination and Evaluation

At the age of 15 months the patient was seen by physical therapy secondary to concerns of developmental delay. At the time of initial evaluation the patients' mother expressed concerns that her child was not able to stand independently and that her arms and legs felt weak. The patient was able to tolerate short periods of independent sitting, but did not like tummy time and was unable to crawl.

The patient did not express signs of pain or discomfort with hands on examination. Range of motion was found to be within normal limits throughout bilateral lower extremities with passive range of motion testing. The patient had a tendency to sit with the pelvis in a posteriorly tilted position and forward flexed posture of the spine despite support. When the patient was placed in a supported standing position, significant pronation of the feet was observed. Additionally, the patient stood with bilateral hip external rotation for increased base of support.

The patient presented with decreased functional muscle strength throughout the trunk and extremities as evidenced by a noticeable head lag with pull to sit and decreased weight bearing with supported standing. The patient relied on the use of her arms to maintain a prop sitting position for short periods when placed, but was unable to correct for loss of balance and did not demonstrate the ability to transition into or out of sitting positions. She was able to roll bi-directionally though coordination of this movement was effortful.

The Peabody Developmental Motor Scale, 2<sup>nd</sup> Edition (PDMS-2) was conducted by the physical therapist during this evaluation. The PDMS-2 is a standardized, norm-referenced outcome measure used to assess fine and gross motor skills of children from birth

**Table 1.** Scores on the PDMS-2 at initial evaluation. Standard scores of 8-12 are within normal limits for each category of gross motor skills.

	Skills	Standard Score	Age Equivalent
Stationary	Head control, sitting balance, standing balance	4	6 months
Locomotion	Walking, running, jumping	1	3 months
Object Manipulation	Kicking, catching, throwing	7	12 months

\* The patient had a Gross Motor Quotient of 61. Scores ranging from 85 to 110 are considered within normal range.

through five years of age. Three subcategories of this test comprise the overall Gross Motor Quotient and consist of stationary skills, locomotion, and object manipulation. Standard scores of 8-12 are within average range for each subtest.<sup>4</sup> This patient's standard scores were 4, 1, and 7 respectively indicating that her gross motor skills were significantly delayed compared to age-matched peers (Table 1).

### Clinical Impressions

The patient was assessed to have severe hypotonia of unknown etiology which was contributing to significant developmental delay with regards to gross motor skill acquisition. Low muscle tone can often impact gross motor development which becomes more evident as the child begins working on more dynamic movement patterns. These complex movements require greater activation of large stabilizing muscle groups to move against gravity and for transitioning between a variety of positions. Furthermore, at a chronological age of 15 months, this patient presented in clinic with motor skills equivalent to that of a 3-6 month old with regards to locomotor and stationary skills respectively (Table 1). It was recommended for the patient to continue with outpatient physical therapy in addition to receiving early intervention services through the local Area Education Agency in order to promote gross motor development including strength, balance, and coordination.

### Diagnosis Confirmed

Although the child was initially referred to neurology from the orthopedic specialist, the compilation of findings from the interdisciplinary healthcare team and the physical therapist, provided valuable information to the pediatric neurologist regarding the nature of this case. A comprehensive neurological evaluation was then performed by the neurologist one month later which provided additional clues such as absent deep tendon reflexes, mild tongue fasciculation, and slightly elevated lactic acid levels. It was at this time that blood samples were sent for genetic testing for SMA. A follow-up appointment was scheduled approximately one month later to review the results with the family. The genetic results confirmed the diagnosis of SMA at approximately 17 months of age. Thus, for this patient, the diagnosis took approximately 5 months from the time at which *delayed* symptoms were first noted at the one year well-child visit to the date of formal diagnosis.

### Delayed Diagnosis

Neuromotor deficits lead to the emergence of delayed developmental milestones. Often a child who presents with developmental delay is referred for evaluation by a pediatric physical therapist. It is the role of the physical therapist to further investigate the underlying cause of motor delay. A thorough assessment is completed which includes measures of tone, strength, alignment, postural control, and coordination in conjunction with subjective history and pertinent medical history. Although the physical therapist does not formally diagnose a medical condition such as SMA, their ability to detect red flag warning signs for neuromuscular disease is critical for prompt and appropriate referral. This highlights the importance of the physical therapist in helping to minimize the frequency of delayed diagnosis which leads to missed opportunities for life-saving medical interventions and early intervention services.

The clinical presentation of SMA is highly variable in onset and severity which contributes to delays in diagnosis along with limited recognition of this condition by healthcare professionals. A systematic literature review in the *Journal of Pediatric Neurology* captures the significance of diagnostic delay in children with SMA. The study analyzed a series of articles which reported information on the age of symptom onset and age of diagnosis as confirmed by genetic testing in order to further evaluate diagnostic delay. Overall, results indicated that the delayed timeframe of diagnosis inversely correlated to disease type and severity.<sup>2</sup>

Closer analysis of the data for children with SMA type II revealed a mean 12.4 month delay from clinical onset of symptoms to formal diagnosis. Average onset of symptoms was reported to be at  $8.3 \pm 1.6$  months with the average time of diagnosis at  $20.7 \pm 2.6$  months.<sup>2</sup> The patient discussed in this case report was diagnosed with SMA type II at approximately 17 months of age, but had shown significant delays in development much earlier. By standards of normal development, a child should demonstrate

independent sitting by 6 months of age whereas this patient was only able to achieve the ability to tolerate short periods of independent sitting by 9 months of age. Further, she was unable to weight bear in a supported standing position well past the age in which typically developing children are walking.

Increased awareness of SMA is one of the primary ways to close the gap in diagnosis to improve access to medically necessary interventions, improve quality of life, and decrease unnecessary stress on the patient and their families. The National Task Force for Early Identification of Childhood Neuromuscular Disorders was created in order to target improved recognition of red flag warning signs for neuromuscular diseases like SMA. Again, the pediatric physical therapist is in a prime position to evaluate for red flags which will help to guide clinical decision-making with regards to the nature of neuromotor deficits and the need for referral.

The Task Force outlines important indicators of neuromuscular weakness which may be indicative of more involved pathology. For instance, it is recommended to assess the breathing pattern of an infant with suspected neuromuscular disease for signs of sternal retraction, paradoxical breathing, and a bell-shaped chest. The presence of a noticeable head lag at 5 months of age also demonstrates need for further evaluation. The inability to sit independently by 7 months, transition into sitting by 9 months, or walk well by 18 months are considered major red flags and require immediate referral.<sup>5</sup> The patient in this case study was evaluated at 15 months of age by the physical therapist demonstrating each of these red flags. Additionally this patient presented with mild evidence of tongue fasciculation, poor feeding, and frequent fatigue which are means of concern. For more information regarding yellow flag warning signs of neuromuscular disease, developmental normative data, and information on other diagnostic testing and referral visit the following web page: [www.childweakness.org](http://www.childweakness.org).<sup>5</sup>

## Ongoing Management

The patient is now eight years old and utilizes a Permobil power mobility device secondary to loss of muscle function and limited postural control. She continues to be followed for management of SMA by pediatric neurology, but is also seen by a pulmonologist for restrictive lung disease and orthopedics for neuromuscular scoliosis. Additionally, the patient in this case study participates in episodes of physical therapy to promote strength, balance, motor control, and respiratory endurance as well as to prevent secondary complications of neuromuscular weakness related to SMA.

## Individualized Goals and Interventions

Traditional physical therapy interventions included resistance exercise, range of motion, and postural control training. In terms of the most recent episode of care, the patient and family identified two primary goals for therapy: improved sitting balance and ability for the patient to assist caregivers with positional transitions. Therefore, musculoskeletal and neuromuscular interventions were incorporated into the physical therapy plan of care to improve strength and postural awareness for decreased functional dependence with bed mobility and other activities of daily living.

Musculoskeletal interventions focused on multi-directional trunk activation, active-assisted range of motion of the extremities, and progression of partial transitions with manual assistance and tactile cueing. In order to work on functional strengthening and coordination of the trunk and extremities, the physical therapist provided manual resistance opposite the direction of movement while the child was asked to roll between supine and sidelying positions. Additionally, isometric trunk activation was frequently utilized to promote activation of abdominals and lumbar extensors while in a seated position. Due to significant weakness, active-assisted range of motion was indicated for more isolated strengthening of proximal muscle groups. Manual assistance was provided by the physical therapist for movement of the upper extremities in flexion, extension, and D2 movement patterns. Lower extremity strengthening was promoted with the patient in hooklying position so as to enable the therapist to guide the desired hip motions in a modified gravity-eliminated plane. Lastly, the patient worked on partial transitions between side prop on elbows to an upright sitting position to resemble tasks related to bed mobility. The therapist provided moderate assistance for safe transitions.

Neuromuscular interventions related to postural awareness and improved static and dynamic sitting balance. One of the primary neuromuscular interventions incorporated dynamic sitting with upper extremity reaching tasks. The patient worked to maintain sitting balance while seated on a semi-unstable surface such as an airex pad. Further, the patient was encouraged to engage in a variety of reaching tasks which required core stability, shoulder girdle activation, and initiation of balance reactions. For instance, the patient would be asked to reach with either the left or the right hand to obtain an item, such as a toy ladybug, which was then placed on a large tic-tac-toe board requiring her to reach outside her base of support to make her next move. It is important to note that her ability to maintain dynamic balance is limited and thus these activities were closely supervised by the physical therapist providing consistent assistance.

In addition to more traditional physical therapy interventions, breath control strategies were also implemented with this patient to target decreased respiratory sufficiency due to profound proximal muscle weakness. The International Classification of Functioning, Disability, and Health (ICF) Model and participation-based outcome measures were utilized in order to generate meaningful patient and family-centered goals. It was identified that the patient was having difficulty with sound production in terms of volume and her ability to maintain breath control throughout a conversation. Through the administration of the *Preferences for Activities of Children* (PAC) it was determined that the child was interested in music and more specifically that she wanted to learn to play the recorder. The PAC is a self-report participation measure designed to assess a child's participation or interest in recreation and leisure activities outside the context of the school curriculum. This information enables the therapist to derive individualized goals that are functional and meaningful to the patient. The goal became to increase the duration of exhalation from a baseline of 6 seconds to 8 seconds in order to be able to play a variety of songs on the recorder. This goal addresses the functional need to increase breath control and respiratory endurance while incorporating a participation level component of the ICF Model.

Cardiopulmonary interventions were incorporated into bimonthly physical therapy sessions during the most recent episode of care. In the past, the patient has also worked with Speech Language Pathology for hypophonia. Further, she continues to be followed by pulmonology for early onset of Interstitial Lung Disease secondary to neuromuscular weakness. Physical therapy-related cardiopulmonary interventions were designed to work on resisted expiration, inspiratory muscle strength, and breath control. Resisted expiration was achieved by having the patient blow through a narrow straw. This intervention was implemented in several creative ways in order to make the activity more age-appropriate and motivating to maximize the patient's engagement in the activity. For instance, the patient was asked to make different size bubbles in a glass of water by blowing through the straw with varying amounts of force and expiratory control. A similar activity required the patient to blow through the straw to move paint across a piece of paper to create a piece of artwork. Other related tasks included the use of a whistle or production of sustained vowel sounds. In order to promote inspiratory muscle strength the patient worked to pick up pom-poms with a straw; a task which required significant inspiratory force. This task also challenged the patients' motor planning for maximum expiration in preparation for sufficient inspiration to successfully obtain the pom-pom. Recorder activities were utilized to encourage breath control and sustained breath support. An emphasis was placed on a series of four notes while playing simple recorder songs; notes were between one and four seconds in duration. The patient initially worked to hold single notes on the recorder, but eventually was able to play songs which contained all four notes promoting improvements in respiratory endurance.

Another intervention to consider is thoracic proprioceptive neuromuscular facilitation (PNF) which was not formally implemented in this specific case. Deep breathing PNF involves a quick stretch at the end of maximal expiration in order to facilitate inspiratory muscle contraction and greater chest expansion. Additionally the application of the quick stretch is thought to provide increased afferent input to the intercostal muscles enhancing overall activity of the muscles of the thoracic region.<sup>6</sup> One study found that such interventions improved respiratory function in individuals with Myotonic Dystrophy, a form of muscular dystrophy resulting in progressive neuromuscular weakness much like SMA.

Increases in SpO2 and thoraco-abdominal motion were observed in addition to decreases in heart rate and respiratory rates following application of PNF deep breathing interventions.<sup>6</sup>

**Outcome Measures**

Functional outcome measures such as the Hammersmith Functional Motor Scale Expanded (HFMSE) and Sitting Balance Scale (SBS) are frequently utilized in the SMA patient population. Research has consistently shown the HFMSE to be a valid and reliable measure of motor function in children with SMA with previously established values indicative of clinically meaningful change reported as a 3-point difference in HFMSE score.<sup>7,8</sup> The HFMSE contains a total of 33 items which include simple motor tasks such as unsupported sitting and dynamic sitting with upper extremity movement progressing to more functional mobility tasks such as rolling, standing, and walking.<sup>7</sup> Each of these items are rated on a 3 point likert scale (0-2) for a maximum total HFMSE score of 66. The most recent HFMSE score for this case study patient was 15/66 which represents a 4-point increase from her previous score of 11/66 in a four month time span (Table 2). This increase indicates improvement in gross motor function secondary to the effects of Nusinersen and biweekly physical therapy which helps to promote gains in muscle function. The SBS functional outcome measure was also used to assess static and dynamic sitting balance related to her functional goals of improved independence with sitting. In this same four month time frame the patient showed a 2-point improvement in sitting balance, however, there is limited evidence to suggest this change is clinically meaningful. That being said, typically decreases in motor function are captured by functional outcome measures such as the HFMSE and SBS due to the progressive nature of this neuromuscular condition.

**Table 2.** HFMSE scores at two time points during recent episode of care. Scores for each subtest item rated on a 3-point likert scale as 0-2.

Item #	Score: 7.8 y/o	Score: 8 y/o	Item #	Score: 7.8 y/o	Score: 8 y/o
1	2	2	18	0	0
2	1	2	19	0	0
3	1	2	20	0	0
4	1	1	Subtotal	9/40	11/40
5	2	2	21	1	2
6	1	1	22	1	2
7	1	1	23	0	0
8	0	0	24	0	0
9	0	0	25	0	0
10	0	0	26	0	0
11	0	0	27	0	0
12	0	0	28	0	0
13	0	0	29	0	0
14	0	0	30	0	0
15	0	0	31	0	0
16	0	0	32	0	0
17	0	0	33	0	0
			Total	11/66	15/66

\* Subtotal derived from original Hammersmith Functional Motor Scale consisting of 20 items with a maximum total score of 40.

Further, the Canadian Occupational Performance Measure (COPM) was utilized in order to demonstrate improvements at the participation-level of the ICF Model. The COPM is a parent-report

**Table 3.** Parent-reported ratings of performance and satisfaction relating to child's functional balance at two time points during recent episode of care.

Functional Activity	Initial Rating Performance	Final Rating Performance	Initial Rating Satisfaction	Final Rating Satisfaction
Sitting at edge of bed for assisted upper body dressing with caregiver	4/10	7/10	6/10	7/10

\* Performance is defined as one's ability to complete the task, action, or activity. Satisfaction refers to how satisfied the individual is with their overall performance.

measure used to identify perceptions of activity performance and satisfaction over time and provides a basis for individualized goal setting and intervention.<sup>9</sup> In this case the COPM was used as an alternative measure of functional balance. Performance and satisfaction ratings were provided pertaining to the patients' ability to sit edge of bed for assisted upper body dressing (Table 3).

Spirometry is considered the gold-standard for valid and repeatable measures of pulmonary function in many patient populations including SMA. Forced Vital Capacity (FVC) is the volume of air forcibly exhaled after a maximum inspiratory breath. Predicted normal respiratory parameters have been reported in the literature based upon patient-specific factors including age, height, and sex. These norm-referenced values are used to calculate percent predicted FVC values. More specifically, the Utrecht dataset aimed to define reference values for pediatric pulmonary function testing with defined algorithms for predicted FVC in children ages 2-18.<sup>10</sup> At the patient's last follow up, FVC was 35% of predicted value indicative of restrictive lung disease, respiratory insufficiency, and decreased pulmonary function.

Though these values are important for monitoring changes in pulmonary status, there are several additional methods which may be implemented by the physical therapist on a more routine basis to screen for changes in lung capacity and respiratory function. One such method is Maximum Phonation Time (MPT) which is the maximum time in which a sound can be sustained during one breath. Typically MPT is measured using a sustained vowel sound such as "a" or "e" and provides an objective means of assessing respiratory support and capacity for phonation. MPT is directly related to FVC with variation based on the patient's age, weight, height, and neuromuscular control of respiratory muscles.<sup>11</sup> This is a tool which can be easily and reliably implemented in clinic by a physical therapist in order to monitor for changes in respiratory status. Normal values for MPT based upon age and gender can be found in the literature. One recent study aimed to define norm-referenced MPT values for children between the ages of 4-12 who did not present with signs or symptoms related to general vocalization or phonation. The average MPT for girls between the ages of seven and nine was found to be 7.90 ± 1.98 seconds for the vowel sound "a".<sup>11</sup> The patient was able to sustain this sound for an average of 6.33 (6,7,6) seconds which is below average as compared to age-matched peers.

Aside from MPT, rib cage excursion or chest wall expansion provides an indirect means of assessing lung capacity and is a measure of the difference in chest wall circumference during maximum inspiration as compared to maximum expiration. Chest expansion measurements (CEMs) are often recorded using the fourth intercostal space and xiphoid process as bony landmarks. A similar method was implemented in this clinical case study in which thoracic spinal levels T5 and T10 were utilized as the points of reference. The purpose was to more specifically assess rib cage excursion which is often limited as a result of impaired breathing mechanics, thus, could be used

**Table 4.** Rib cage excursion measured at thoracic levels T5 and T10 in supine and sitting positions.

	Supine Rest	Supine Max Inhale	Sitting Rest	Sitting Max Inhale
T5	66.2 cm	66.3 cm	67.6 cm	67.9 cm
T10	65.9 cm	65.4 cm	69.0 cm	68.0 cm

as an indirect measure of pulmonary function. Measurements were obtained at rest and with maximum inhalation in sitting and supine positions in order to monitor for positional changes in respiratory status (Table 4). Minimal differences in chest expansion were observed between positions and when comparing upper and lower rib cage excursion secondary to restrictive lung disease.

Limited research is available on the use of CEMs in children and even less is known about the psychometric properties of this measure in children with neuromuscular and related conditions. Despite the lack of current research in this area some studies have been conducted to investigate alternative measures of pulmonary function in other chronic diseases of childhood onset. For instance, one study aimed to examine the reliability of CEMs in children with Cystic Fibrosis as well as how these measurements correlated with pulmonary function. Although Cystic Fibrosis is an obstructive lung disease, as compared to SMA which often leads to restrictive lung disease, both genetic conditions

result in respiratory insufficiency requiring frequent monitoring of pulmonary function. This study found CEMs to be moderately correlated with pulmonary lung function and a reliable measure for longitudinal assessment. A partial correlation between CEMs and FVC was reported as .44 ( $p < .001$ ) when adjusted for height. It was also shown that 20% of the variation in CEMs relates directly to changes in lung function parameters.<sup>12</sup> That being said, it is important to be aware of additional factors such as spinal deformity which may contribute to fluctuation in these values. Therefore, CEMs should be used as a tool for monitoring and screening lung function with routine follow ups with pulmonary specialists.

## Discussion

SMA is a rare, genetic condition characterized by progressive loss of motor function which has the potential to significantly impact the individuals' quality of life and their families. Diagnosis of this condition is confirmed through genetic testing, however, there are many challenges that often result in diagnostic delay of SMA. Due to the spectrum of phenotypic expression, further dichotomized into three subclasses or types, onset of symptoms and clinical presentation vary significantly between individuals who may later be diagnosed with SMA.

Additional considerations for the frequency of diagnostic delay is the specialization of medical healthcare professionals in conjunction with a generalized lack of awareness of SMA and related classes of Muscular Dystrophy.<sup>2</sup> Initially, families are often referred to several specialty clinics such as orthopedics, neurology, and pulmonology as well as physical therapy and speech-language pathology due to the complexity and diversity of emerging symptoms.

Despite limited available data, a literature review conducted in 2016 aimed to review awareness and knowledge of SMA amongst clinicians and to identify attitudes towards the addition of SMA to newborn screening. This study concluded that clinicians had inadequate awareness of SMA and were not well-versed in related clinical genetics which had an impact on referrals for early diagnosis.<sup>13</sup> A related study surveyed 227 medical students and new physicians in Sri Lanka and found that only 59% had even been exposed to this neuromuscular disorder in their respective medical school programs.<sup>13</sup>

Moreover, increased awareness and knowledge of red flag warning signs will help to decrease delays in diagnosis and improve access to medical services. Early intervention is imperative to the health, quality of life, and potentially the life expectancy of a child with SMA. The recent FDA-approval of the drug Nusinersen is a prime example of a potential life-saving medical intervention in which critical access may be impeded by a delay in diagnosis.<sup>1,3,14</sup> CHERISH is a global multicenter, randomized, double-blind control trial which investigated the safety and clinical effectiveness of Nusinersen in children with symptomatic SMA between the ages of 2-12. The HFMSE was selected as the primary outcome measure for this study. An important secondary outcome measure was termed "HFMSE Responders," defined as the proportion of children who achieved  $\geq 3.0$  point increase in HFMSE score at 15 months from baseline. Overall, a 4.9-point treatment difference on the HFMSE was shown between those who received Nusinersen as compared to those who received the sham-procedure ( $p = .0000001$ ).<sup>14</sup> Additionally, it was shown that 58.6% of subjects who received Nusinersen met the criteria as a responder whereas decline in function was observed in those who were not administered this drug.<sup>14</sup> The patient in this case study participated in the original CHERISH study through the University of Colombia, New York and is now part of the SHINE open-label extension meaning all participants are given the drug due to its shown clinical effectiveness in the studied patient population.

In addition to the use of the HFMSE in clinical trials, this functional outcome measure is often used in clinic by the physical therapist to monitor for changes in motor function in children with SMA Types II and III.<sup>8</sup> One study conducted a qualitative investigation pertaining to perceptions of meaningful change in SMA which included individuals with SMA, parents of children with SMA, and clinicians. Those surveyed indicated that meaningful change related to functional ability and reported that even small changes make a substantial difference in quality of life and level of participation. Further, participants were in agreement that the HFMSE items assessed functional abilities which were relevant and pertinent to their everyday lives.<sup>15</sup> Many indicated that improvement on any one item resulted in some level of improved independence. That being said, they felt as though functional

measures were not always sensitive enough to capture these more subtle improvements.<sup>15</sup> Therefore, in this patient population, participation-based measures such as the COPM and Pediatric Quality of Life Inventory (PedsQL) may be better able to demonstrate meaningful change throughout habilitation.

SMA is a medically complex condition which presents with great variability in phenotypic expression. In addition to the progressive loss of muscle strength and function, gastrointestinal; pulmonary; and orthopedic complications are prevalent in this population.<sup>1,2,16</sup> With the exception of the recently FDA-approved drug Nusinersen, most treatments are supportive in nature. The goal of these support therapies is to provide nutrition and respiratory support as well as to prevent secondary complications of decreased mobility and muscle weakness. Interestingly, a survey used to assess the needs of the SMA population indicated that patients and their families as well as healthcare professionals rank breathing issues as the number one most important aspect of patient care.<sup>16</sup> This survey included responses from 77 patients or family members of an individual with SMA and 89 healthcare professionals representing a variety of medical fields such as pulmonologists, orthopedic surgeons, neurologists, and physical therapists.

Furthermore, pulmonary complications are a primary concern for individuals with SMA as a result of impaired respiratory mechanics and airway clearance. Though respiratory insufficiency is common among this patient population, limited data has been published regarding the expected digression of respiratory capacity in those individuals diagnosed with SMA types I, II, and III respectively. One retrospective study compiled data from across the spectrum of SMA patients in order to further describe the clinical and respiratory course of SMA. Overall, the study demonstrated the progressive nature of restrictive respiratory insufficiency in this patient population as well as the significant differences in the rate of infant mortality based upon SMA type and the onset of pulmonary complications.<sup>17</sup> Further, it was shown that an FVC of 30% predicted for SMA Types I and II is associated with significant increased risk for complications related to pulmonary function.<sup>17</sup> These complications include aspiration pneumonia, recurrent bronchopulmonary infections, atelectasis, and respiratory insufficiency. The potentially life threatening and severe consequences of respiratory complications is another reason to promote early diagnosis for access to early intervention.

In order to better understand the nature of the pulmonary complications associated with neuromuscular weakness, it is important to understand the basic principles of breathing. Dr. Mary Massery, PT, DPT, DSc, a physical therapist and researcher, highlights the dynamic and intricate interactions between impaired motor control and cardiopulmonary compromise in individuals with profound neuromuscular weakness. She proposes a multi-systems treatment approach based upon three principles: 1. Breathing is a three-dimensional motor task influenced by gravitational forces; 2. Normal breathing mechanics support respiration and postural control; and 3. Integration of properly functioning body systems optimizes health and human performance.<sup>18</sup>

Under normal conditions the chest wall has the ability to expand in three dimensions including anterior-posterior, inferior-superior, and lateral planes. Normal chest wall development is influenced by the balance of gravitational and muscular forces acting upon the thoracic spine and surrounding rib cage.<sup>18,19</sup> Typically developing infants are able to transition between a variety of postures which promotes normal development of the chest wall and efficient breathing mechanics. A child with neuromuscular weakness, on the other hand, will often develop a bell-shaped chest wall and a paradoxical breathing pattern due to muscle imbalances which limit the body's ability to counter gravity. Many children with SMA exhibit chest wall deformities in conjunction with this form of "belly breathing" due to weakness of the abdominal muscles and intercostal muscles relative to the diaphragm. During inspiration the contraction of the diaphragm draws the rib cage downward, however, the abdomen will rise due to the inability to maintain positive pressure. The chest often collapses inward upon inspiration due to the lack of stabilizing forces from the intercostal musculature of the rib cage.<sup>18,19</sup> Aside from the impaired mechanics of breathing, Massery purports the importance of breath support in postural control as well as the vocal folds in controlling positive thoracic pressures for phonation and stabilization of the shoulder girdle – these principles are also demonstrated by the patient in this case study.

Moreover, SMA is a growing area of interest for researchers in light of recent advancements in available interventions in combination with the high carrier-frequency of the SMA mutation. Although progress has been made in understanding the clinical course of SMA, further research should be conducted in order to determine the extent of disease progression and degree of functional loss which occurs between onset of symptoms and diagnosis. Future research should also aim to generate a core set of valid and reliable participation measures for children with neuromuscular disorders like SMA. Additionally, pediatric physical therapists ought to be encouraged to evaluate, monitor, and treat cardiopulmonary compromise with frequent communication with other members of the healthcare team as respiratory insufficiency is common in many progressive neuromuscular conditions.

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