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Clinical Outcome Measures in Spinal Muscular Atrophy

Jacqueline Montes, PT, MA, NCS, Andrew M. Gordon, PhD, Shree Pandya, PT, MS, Darryl C. De Vivo, MD, and Petra Kaufmann, MD, MSc

Spinal muscular atrophy is one of the most devastating neurological diseases of childhood. Affected infants and children suffer from often severe muscle weakness caused by degeneration of lower motor neurons in the spinal cord and brainstem. Identification of the causative genetic mutation in most cases has resulted in development of potential treatment strategies. To test these new drugs, clinically feasible outcomes are needed. Several different assessments, validated in spinal muscular atrophy or similar disorders, are being used by national and international research groups; however, their sensitivity to detect change is unknown. Acceptance of a few standardized, easily administered, and functionally meaningful outcomes, applicable to the phenotypic spectrum of spinal muscular atrophy, is needed. Consensus is imperative to facilitate collaboration and explore the ability of these measures to identify the therapeutic effect of disease-modifying agents. Following is an evidence-based review of available clinical outcome measures in spinal muscular atrophy.

Keywords: spinal muscular atrophy; outcome measures; clinical trials

Spinal muscular atrophy is a genetically determined motor neuron disease that often presents in infancy or childhood. The most severe form of the disease, occurring in infancy and first described in the late 19th century by Werdnig and Hoffman, remains the leading genetic cause of infant death today.[1] More than 50 years later, Kugelberg and Welander described a milder form of the disease that presents later in childhood.

Spinal muscular atrophy affects motor neurons and the motor units associated with them, causing muscle atrophy and weakness. It is an autosomal recessive disorder genetically characterized by homozygous deletion of the survival motor neuron 1 gene located on chromosome 5q13.[2] A clinical classification of spinal muscular atrophy, based on maximum motor function achieved, is used to help describe the different phenotypes, with the most severe form, spinal muscular atrophy type 1, beginning in early infancy and the least severe form, spinal muscular atrophy type 3, later in childhood and adulthood.[3] Although the phenotypic heterogeneity is in part because of the copy number of survival motor neuron 2, a disease-modifying homologue gene,[4] there is phenotypic variability within participants carrying the same number of survival motor neuron 2 copies.

Identification of the causative genetic mutation occurring in most patients with spinal muscular atrophy has led to advances in diagnosis and has facilitated research into the mechanisms underlying spinal muscular atrophy. Several new drug treatments are now on the horizon and the first clinical trials are ongoing. However, there are no validated biomarkers, so researchers must rely on clinical benefit. Suitable outcome measures must be sensitive, reliable, easy to interpret, and not burdensome to patients.

At a time when disease-modifying therapies are approaching the clinical community, it is imperative to identify a few standardized, reliable, and functionally meaningful outcome measures. Selection should be based on ease of administration, burden imposed on the patient, and relevance to the largest possible phenotypic spectrum. Consensus is important to allow for collaboration. This review will summarize the available evidence for outcomes investigators can choose from.

Background

The overall incidence of all types of spinal muscular atrophy is 1 per 6700 live births in the United States.[5] Life

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From the Department of Neurology, Columbia University Medical Center, New York, (JM, DCD, PK); Department of Biobehavioral Sciences Teachers College, Columbia University, New York (AMG); and School of Medicine and Dentistry, University of Rochester, Rochester, New York (SP).

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Address correspondence to: Jacqueline Montes, PT, MA, NCS, SMA Clinical Research Center, Columbia University, 180 Ft Washington Avenue, 5th Floor, New York, NY 10032; e-mail: jm598@columbia.edu.

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Table 1. Clinical Outcome Measures for Spinal Muscular Atrophy Type I

Outcome Measure	Age	Disease Specific	Type of Measure	ICF Classification[18]	Published Clinical Trials
Survival/ventilation >16 hours/day	Any age	No	End point	Impairment	Riluzole[18]
Alberta Infant Motor Scale	0-18 months	No	Functional motor assessment	Activity limitation	
Test of Infant Motor Performance	<4 months	No	Functional motor assessment	Activity limitation	
CHOP Toss/Intend	<2 years	Yes	Functional motor assessment	Activity limitation	

Note: CHOP, Children's Hospital of Philadelphia, ICF, International Classification of Functioning, Disability and Health.

expectancy is strongly correlated with age of onset[6] with the most severe cases often not living into adulthood[7] and the least severe cases with survival rates not significantly different from the normal population.[8] Spinal muscular atrophy has been divided into 3 clinical groups defined by maximum function achieved.[3] In all spinal muscular atrophy types, the disease typically enters a stable course with little if any decline. Especially in the early-onset forms, there can be a more rapid rate of decline early in the course of the disease with a stabilization over time, which is modified by influences such as growth and complications of weakness.[9]

Within each clinical group exists a spectrum of disease severity and functional ability. Type I spinal muscular atrophy includes infants diagnosed before 6 months of age and, by definition, never achieving the ability to sit unsupported. This group could be further classified into 3 subtypes.[10] Patients with the most severe form are usually diagnosed in the neonatal period, suffer a paucity of movement, and require neonatal ventilatory support. Less severe type I infants have poor head control, difficulty handling secretions, feeding problems, and eventually require noninvasive respiratory support. Infants who achieve head control or can sit with support have the best prognosis among patients with spinal muscular atrophy type I. Recent, more proactive, clinical management is likely changing the natural course of type I patients.[11]

Patients with spinal muscular atrophy type II are typically diagnosed between 6 and 18 months and achieve unsupported sitting at some point but never walk. Pulmonary and orthopedic complications are common in this group and often require respiratory interventions such as noninvasive ventilatory support and scoliosis management.[12]

Patients with spinal muscular atrophy type III have the mildest form of the disease and usually a normal life expectancy.[8] Diagnosed after the age of 18 months, people with spinal muscular atrophy type III are able to walk unaided at some point, but some loose the ability to walk. Symptom onset after 3 years of age has a greater association with remaining ambulatory later in life.[8,13]

Spinal muscular atrophy is limited to the motor system, affecting the motor unit from the anterior horn cell to the muscle, leaving cognitive function intact. Anecdotally, clinicians believe children with spinal muscular atrophy may be brighter than their peers but there is limited evidence to substantiate this observation. One published study compared intellectual ability in spinal muscular atrophy to age-matched controls and found that the older children and adolescents with spinal muscular atrophy had significantly higher verbal IQ scores than their peers.[14]

Motor and Pulmonary Measures

Recent preclinical research has identified potential therapeutics agents that have shown beneficial effects in animal models or in vitro.[15] Clinical studies must select a few meaningful outcome measures to evaluate a treatment effect. These measures must be valid, reliable, sensitive to change, and assess disability at both the impairment and performance level.[16] It will be difficult to assess the sensitivity of an outcome measure for spinal muscular atrophy, a mostly stable disease, until there is an effective agent that influences the disease course.

National and international clinical research networks collaborate in multicenter projects to reach more patients with this relatively rare disease. Ideal measures for multicenter clinical trials are easily administered, require minimal training and equipment, and minimize patient burden.[17] Selecting the same outcome measures will permit meta-analysis and facilitate comparable trials data that can accelerate research. To facilitate research collaborations and to allow for future meta-analyses between trials, a consensus on outcome measures for spinal muscular atrophy is needed. This review aims to provide an overview on the outcomes to choose from.

Type I

Available standardized functional motor exams for this age group are primarily designed to track motor development in preterm infants. These exams often include both observed and elicited movements. In spinal muscular atrophy type I, survival has been suggested as a primary outcome. However, families make a range of choices in the extent of aggressive medical care resulting in a variation of outcomes for spinal muscular atrophy type I, making survival a less robust outcome.[11] Concurrent controls are recommended as available historical data may falsely indicate a treatment effect because of progress in supportive treatment. Available clinical outcomes, suitable for type I patients, are described in detail below (Table 1).

Alberta Infant Motor Scale. The Alberta Infant Motor Scale is a norm referenced measure of motor development for preterm infants. It is a gross motor scale assessing weight bearing, posture, and antigravity movement, validated in a large sample of children from 0 to 18 months.[19] The scale has both discriminate and predictive validity as well as excellent interrater and intrarater reliability.[20] The Alberta Infant Motor Scale has been used as a primary outcome measure in infants with metabolic myopathy[21,22] and preterm infants[23] and has been used as a standard for the development of new measures.[24] A comprehensive manual is available and test administration does not require any special equipment.

Test of Infant Motor Performance. The Test of Infant Motor Performance is a functional scale validated in preterm infants under 4 months of age, which includes both observed and elicited movements.[25] The Test of Infant Motor Performance is sensitive to age-related development,[25] discriminates between those at low and high risk for motor problems,[26] and predicts delayed motor development in preterm infants.[27] The Test of Infant Motor Performance has excellent intrarater and interrater reliability in preterm infants.[28] In spinal muscular atrophy, a screening version of the Test of Infant Motor Performance also demonstrated excellent interrater and test-retest reliability.[29] However, to date, no published clinical trial used the Test of Infant Motor Performance or the screening version of the Test of Infant Motor Performance as a primary outcome measure in spinal muscular atrophy.

Children's Hospital of Philadelphia (CHOP) Test of Strength in spinal muscular atrophy and Infant Test for Neuromuscular Disease. Children's Hospital of Philadelphia Test of Strength in spinal muscular atrophy and Infant Test for Neuromuscular Disease were developed specifically for weak infants with neuromuscular disease including spinal muscular atrophy. The tests include assessments of neck, trunk, proximal and distal limb strength using both observational and elicited movements. Initially, the Children's Hospital of Philadelphia Test of Strength in spinal muscular atrophy was compared to the Test of Infant Motor Performance in 7 patients with spinal muscular atrophy and then later revised and called the Children's Hospital of Philadelphia Infant Test For Neuromuscular Disease, which includes the initial assessments plus 4 items from the Test of Infant Motor Performance. Excellent interrater and intrarater reliability were shown in a small sample of participants with spinal muscular atrophy.[30] Instructional videos in test administration and written procedural and scoring directions are available.

The Alberta Infant Motor Scale and Test of Infant Motor Performance both assess function at the performance level and have demonstrated sensitivity to developmental motor delay. Although spinal muscular atrophy is sometimes considered a developmental disorder,[24] these measures may have a ceiling effect and possibly not capture the unique patterns of weakness.[31-35] Designed specifically for neuromuscular disease, the Children's Hospital of Philadelphia Test of Strength in spinal muscular atrophy and infant test for neuromuscular disease may be more sensitive but more evidence is needed.

Type II/III

The phenotypic spectrum of spinal muscular atrophy types II and III is continuous. There is overlap in the age at disease onset and in functional status as many patients with spinal muscular atrophy type III lose the ability to walk independently. The wide age range of people affected, from early childhood through adulthood, is an additional challenge. To facilitate recruitment into trials, outcome measures that assess a continuum of ability are necessary and would avoid a floor and ceiling effect. Functional assessments are feasible in patients 2 years and older. Strength measures such as quantitative and manual muscle testing are possible in types II and III patients 5 years and older. Quantifiable muscle strength testing does not directly correlate with function[36] and is therefore considered less clinically meaningful. Clinical outcome measures used in spinal muscular atrophy types II and III but not specifically designed for the disease as well as disease-specific assessments are outlined in detail below (Table 2).

Gross Motor Function Measure. The Gross Motor Function Measure, developed as an outcome measure for children with cerebral palsy,[45-47] is a comprehensive functional exam that was shown to be a valid and reliable measure in patients with spinal muscular atrophy.[48-50] The Gross Motor Function Measure contains 88 items in 5 dimensions: (a) lying and rolling, (b) sitting, (c) crawling and kneeling, (d) standing, and (e) walking, running, and jumping and takes approximately 45 to 60 minutes to complete. This hierarchical organization permits patients to progress through each dimension according to their ability without a ceiling effect.

Although some items and postures are not possible in the setting of contractures and scoliosis, the Gross Motor Function Measure discriminates between walkers and nonwalkers and correlates with quantitative muscle strength in patients with spinal muscular atrophy.[48] The Gross Motor Function Measure has high interrater reliability[49] and is a feasible outcome measure in clinical trials in spinal muscular atrophy.[51,52] A revised version with 22 less items was later developed, removing items that did not fit the construct using a standardized statistical model.[53] A detailed published manual for the Gross Motor Function Measure is available including video instruction.

Table 2. Clinical Outcome Measures for Spinal Muscular Atrophy Type II/III

Outcome Measure	Age	Disease Specific	Type of Measure	ICF Classification[18]	Published Clinical Trials
Gross Motor Functional Measure	2-18 years (Spinal Muscular Atrophy)	No	Functional motor assessment	Activity limitation	Hydroxyurea[37]
Hammersmith	2-13 years	Yes	Functional motor assessment	Activity limitation	Phenylbutyrate,[38,39] albuterol[40]
Modified Hammersmith	2-12 years	Yes	Functional motor assessment	Activity limitation	L-Carnitine and valproic acid[41]
Expanded Hammersmith	2-45 years	Yes	Functional motor assessment	Activity limitation	
Motor Function Measure	1-adults >25 years	No	Functional motor assessment	Activity limitation	
Egen Klassifikation Scale	Teens-adults	No	Functional, evaluator-administered questionnaire	Activity limitation	
Spinal Muscular Atrophy Functional Rating Scale	Adults	yes	Functional, evaluator-administered questionnaire	Activity limitation	Gabapentin[42]
Wee Functional Independence Measure	6 months-6 years	No	Functional, evaluator-administered questionnaire	Activity limitation	
Handheld dynamometry	>5 years	No	Muscle strength	Impairment	Phenylbutyrate,[38,39] albuterol,[43] gabapentin,[44] L-carnitine, and valproic acid[41]
Quantitative Muscle Strength	>9 years-adults	No	Muscle strength	Impairment	
Forced vital capacity	>5 years	No	Pulmonary function, diaphragm muscle strength	Impairment	Albuterol,[43] gabapentin,[42,44] phenylbutyrate,[38,39] L-carnitine, and valproic acid[41]

Note: ICF, International Classification of Functioning, Disability and Health.

Hammersmith Functional Motor Scale. The Hammersmith Functional Motor Scale, devised specifically for use in patients with spinal muscular atrophy type II and nonambulatory type III patients, is a 20-item functional assessment arranged in an order of progressive difficulty.[54] This disease-specific scale was designed for ease of use and minimal patient burden. Good interrater reliability has been demonstrated.[54,55] The Hammersmith Functional Motor Scale is sensitive to change resulting from intercurrent illness or surgery,[55] correlates with biomarkers of disease severity,[56] and has been used in single center, phase I and multicenter center, phase II clinical trials in patients with spinal muscular atrophy type II.[38-40]

To further enhance the scale's usability in multicenter collaborative settings, the scale was modified to include concrete operational definitions and instructions for scoring.[57] Additionally, the items on the scale were reordered to minimize position changes and associated fatigue, forgoing the original functional hierarchy of activities. High intrarater reliability in live patients and interrater reliability from videotaped assessments were achieved in nonambulatory type II and III patients from 2 to 12 years of age. They also showed good test-retest reliability with no significant difference in scores within 6 months. In a multicenter, phase II clinical trial, the Modified Hammersmith Functional Motor Scale showed excellent intrarater reliability in the nonambulant patients but lower reliability in the ambulatory cohort because of significant ceiling effects of the scale.[58]

The Hammersmith Functional Motor Scale has also been augmented by 13 relevant items from the Gross Motor Function Measure to eliminate the ceiling effect of the original scale with patients having ambulant spinal muscular atrophy.[59] The items chosen from the Gross Motor Function Measure for the Expanded Hammersmith Functional Motor Scale were deemed statistically most sensitive, without a ceiling effect, and most clinically meaningful by expert consensus. The Expanded Hammersmith Functional Motor Scale shows good test-retest reliability, is highly correlated with the Gross Motor Function Measure, and discriminates between walkers and nonwalkers.[59] It correlates with other clinical and physiological measures such as forced vital capacity and isometric muscle strength assessed using handheld dynamometry as well as survival motor neuron 2 copy number.[60] The scale retained its original properties of ease of use and minimal patient burden requiring only standard equipment and taking less than 15 minutes on average.

Motor Function Measure. The Motor Function Measure was developed for people with neuromuscular disease,

including spinal muscular atrophy, to assess motor function. It is made up of 32 items organized in 3 domains; standing position and transfers, axial and proximal motor function, and distal motor function. Test items include a continuum of functional ability, ranging from simple motor skills in a supine position to a 10-m run. Also included in the Motor Function Measure is a fine motor assessment of hand function.

The Motor Function Measure was validated in a large sample of neuromuscular patients, aged 6 to 62 years, less than 12% of which were patients with spinal muscular atrophy.[61] Interrater and intrarater reliability was excellent for the total score and subscores of the 3 domains. High correlations were found with the Functional Independence Measure as well as specific scales that assess only lower and upper extremity function. It takes an average of 36 minutes to complete and has been shown to be sensitive to change in Duchenne muscular dystrophy.[62]

Wee Functional Independence Measure. The Wee Functional Independence Measure is an evaluator administered, questionnaire designed to assess disability, based on the framework proposed by the World Health Organization,[16] and validated for children between 6 months and 6 years with developmental disabilities[63] and Down Syndrome.[64] It is organized in 3 main domains: self care, mobility, and cognition, and it is scored on a 7-point scale ranging from total assistance to complete independence. In a cross-sectional study of patients recruited from a spinal muscular atrophy patient registry, the Wee Functional Independence Measure was able to discern between type I and type II participants and weak and strong type III patients; however, it was unable to distinguish type II from type III patients as they often overlap in functional and disability level.[65] As expected, all patients with spinal muscular atrophy performed best in the cognition domain. However, because the scale is designed for children up to 6 years of age, this assessment has limited applicability to patients with spinal muscular atrophy type II and III.

Spinal Muscular Atrophy Functional Rating Scale. The Spinal Muscular Atrophy Functional Rating Scale is an evaluator-administered questionnaire adapted from the Amyotrophic Lateral Sclerosis Functional Rating Scale.[66] Modeled after already validated scales in other adult neurodegenerative diseases,[67] the Amyotrophic Lateral Sclerosis Functional Rating Scale is used as a primary outcome measure in phases II[68,69] and III[70] clinical trials in Amyotrophic Lateral Sclerosis.

The Spinal Muscular Atrophy Functional Rating Scale measures 4 components of physical functioning: bulbar function, arm function and ability to perform activities of daily living, leg function, and respiratory function. The scale was used as a secondary outcome measure in a clinical trial of gabapentin in adult patients with spinal muscular atrophy[42] and is currently an outcome in a trial assessing valproic acid in ambulant, adult patients with spinal muscular atrophy.

Egen Klassifikation Scale. The Egen Klassifikation Scale was developed to assess motor function in patients with later stage Duchenne muscular dystrophy and nonambulant spinal muscular atrophy.[71] This interview-based questionnaire, designed for older children, teens, and adults, has 10 questions encompassing performance of functional tasks scored on a 4-point ordinal scale. Activities of daily living assessments such as wheelchair use, ability to transfer, arm function and feeding, turning in bed, coughing, speaking, and health-related quality of life are included in the Egen Klassifikation Scale but not all items are relevant to spinal muscular atrophy conditions. Scores on the Egen Klassifikation Scale did not correlate with or change similarly over time with manual muscle testing and forced vital capacity in patients with spinal muscular atrophy.[72] The Egen Klassifikation Scale has a user's manual with detailed directions for scoring. A revised version, designed specifically for patients of any age with spinal muscular atrophy, is currently being evaluated (personal communication).

Quantitative Muscle Testing. Quantitative Muscle Testing is used to assess strength using maximal voluntary isometric contraction in neuromuscular disease and has been used as a primary outcome measure in adult motor neuron disease trials.[73-75] It was found to be more sensitive than manual muscle testing in Amyotrophic Lateral Sclerosis, but because it requires special equipment, extensive evaluator training, and can be burdensome to patients, it may no longer be considered an ideal outcome for multicenter trials by many.[76]

Good intrarater and interrater reliability of quantitative muscle testing has been demonstrated in children with Duchenne muscular dystrophy and spinal muscular atrophy[50,77] but did not correlate with functional changes in spinal muscular atrophy.[78,79] Because patient cooperation is essential, the test is not applicable to young children. In an adult spinal muscular atrophy clinical trial, where quantitative muscle testing was the primary outcome measure, some patients had to be excluded because of weakness sufficient to preclude registering strength by this method.[42]

Handheld dynamometry is another method of quantifying strength. The examiner fixes a handheld device against a limb or body part while the patient performs a maximal voluntary isometric contraction. Similar to quantitative muscle testing, it is not practical in children under 5 years old, and requires evaluator training, but is less expensive and portable.

Table 3. Clinical Outcome Measures for Ambulant Patients With Spinal Muscular Atrophy

Outcome Measure	Age	Disease Specific	Type of Measure	ICF Classification[18]	Published Clinical Trials
Time to rise from floor	>5 years	No	Functional motor assessment	Activity limitation	Gabapentin,[44] hydroxyurea[37]
10-m walk test	>5 years	No	Functional walking assessment	Activity limitation	Gabapentin,[44] hydroxyurea[37]
Time to climb steps	>5 years	No	Functional motor assessment	Activity limitation	Gabapentin,[44] hydroxyurea[37]
Six minute walk test	>4 years	No	Functional walking assessment	Activity limitation	
Accelerometers		No	Quantitative assessment of activity	Activity limitation	

Note: ICF, International Classification of Functioning, Disability and Health.

In spinal muscular atrophy, good interrater reliability and test-retest reproducibility has been shown in all muscle groups except ankle dorsiflexors.[36] In a study of gabapentin in spinal muscular atrophy, leg megascores from handheld dynamometry improved significantly but this improvement did not correlate with functional assessments.[44] In a separate observational study, handheld dynamometry scores correlated with timed function tests and could discern between walkers and nonwalkers.[80]

Performance-based measures such as the Gross Motor Function Measure, Hammersmith Functional Motor Scale, Expanded Hammersmith Functional Motor Scale, Motor Function Measure, and Egen Klassifikation Scale assess functionally meaningful abilities that one would want to affect in a treatment trial. Outcome measures designed to evaluate impairment such as manual muscle testing and quantitative muscle testing may detect change that does not necessarily correlate with noticeable changes for the patient. For observational studies, or studies that aim to describe the natural course of spinal muscular atrophy, impairment based measures are useful. Treatment trial outcomes must demonstrate clinically meaningful differences to evaluate the benefit of the intervention. The Spinal Muscular Atrophy Functional Rating Scale and Wee Functional Independence Measure, also function-based evaluations, and the Egen Klassifikation Scale are easily administered but do not encompass a large age range of patients with spinal muscular atrophy. The Gross Motor Function Measure, although shown to be reliable in spinal muscular atrophy, is not disease specific and can be burdensome to patients. The Expanded Hammersmith Functional Motor Scale carries little patient burden and assesses a large spectrum of disease severity without a ceiling effect.

Gait Assessments

Proximal muscle weakness, common in spinal muscular atrophy, affects a person's ability to stand, rise from a seated position, walk, and negotiate stairs. Limited endurance and fatigue may also impair functional mobility and performance in activities of daily living but measures sensitive enough to quantify fatigue have not been identified.[81] In clinical practice, neurologists and rehabilitation therapists routinely assess functional mobility and gait. In clinical trials, tests that quantify functional mobility are commonly used in similar pediatric (PTC 124 Duchenne muscular dystrophy) and adult[82] neuromuscular disorders.

The Six-Minute Walk Test is an objective evaluation of functional exercise capacity, which measures the distance a person can walk quickly in 6 minutes.[83] It is a global measure of multiple body systems including cardiopulmonary, vascular, and neuromuscular systems. It is easily administered and requires no special equipment or training. Of functional measures used in cardiopulmonary care, the Six-Minute Walk Test is best tolerated, most representative, and meaningful of a person's ability to perform activities of daily living because the intensity of the test is self-selected.[84] Although most commonly used in cardiorespiratory disorders, the Six-Minute Walk Test has been used to assess function in neurological disorders such as Parkinson disease,[85] stroke,[86,87] cerebral palsy,[88] and Kennedy disease.[89] Currently, the Six-Minute Walk Test is the primary outcome measure in an international clinical trial in Duchenne muscular dystrophy and is currently being assessed in a spinal muscular atrophy natural history study.

Gait observation and descriptive gait assessments are routinely part of a neuromuscular evaluation and are the areas where improvements or deteriorations are noted during clinic visits. Timed walking is a quantitative measure used to evaluate mobility in similar pediatric and adult neurological conditions. In clinical management, timed walking tests predict falls in neurological disorders other than spinal muscular atrophy,[82,90] and fall risk and assessments are part of recently defined practice guidelines for neurological conditions.[91]

In clinical trials, objective gait assessments are easy to administer and clinically relevant but to date in spinal muscular atrophy are limited. As an adjunct to gross motor function measures, quantifying walking ability may be more sensitive to changes in the ambulatory cohort of patients with spinal muscular atrophy. A pediatric neuromuscular clinical network in the United Kingdom compiled a battery of timed functional tests including time to rise from the floor, ascend and descend stairs, jump, hop, and run, but no published data are available. Assessments used in ambulatory patients in spinal muscular atrophy are described below (Table 3).

10-m walk test. The 10-m walk test quantifies the time it takes to walk 10 m as fast as possible. It has been shown to be a valid and reliable measure in assessing walking ability in spinal cord injury[92,93] and sensitive to change in Duchenne muscular dystrophy.[94] In spinal muscular atrophy, the 10-m walk test correlated with knee extensor and flexor strength and discriminated between young and older ambulant patients.[80]

Time to ascend/descend stairs–Time to rise from floor. Timed tests of mobility such as ascending and descending stairs and rising from the floor are used in the clinical management of patients with Duchenne muscular dystrophy to assess functional leg strength. In addition to the quantitative assessment, these tests allow qualitative assessment of mobility. Similar to the 10-m walk test, time to ascend/descend stairs and rise from floor correlated with leg strength in patients with spinal muscular atrophy.[80]

Respiratory Assessments

Pulmonary function tests, such as forced vital capacity, measure respiratory muscle strength and are commonly used to monitor pulmonary status and determine clinical respiratory interventions in neuromuscular diseases[95-97] including spinal muscular atrophy.[12] Typically, children must be at least 5 years old because cooperation is essential in the performance of this effort dependent test. Forced vital capacity scores are expressed in percentage predicted determined by height and age. Contractures and scoliosis, common in spinal muscular atrophy, make accurate height measurements difficult and may influence the test results and deem them less reliable.

Despite its limitations, forced vital capacity is a common secondary outcome measure in spinal muscular atrophy clinical trials[39,42,44] and good interrater reliability can be achieved.[50] Forced vital capacity can discriminate between ambulant and nonambulatory participants,[80,98,99] but does not change significantly over time[100] and may not be a sensitive indicator of the need for mechanical ventilation in spinal muscular atrophy.[101,102]

Alternative volitional pulmonary function tests that are simple and unlike forced vital capacity, do not require aptitude and coordination, are available. Maximal sniff pressure[103,104] is a simple maneuver used to assess inspiratory muscle strength. Calculated by performing repetitive, short, maximal sniffs, maximal sniff pressure is the best predictor respiratory failure in adult motor neuron disease.[105] Additionally, cough peak cough flow and peak expiratory flow are clinically meaningful and feasible measures of respiratory muscle strength in adults and children with neuromuscular disease.[106]

Other respiratory function tests such as measuring gastric cough pressure[107] and magnetic stimulation of the phrenic nerve[108,109] have been shown to correlate with nonvolitional tests and forced vital capacity in neuromuscular disease including spinal muscular atrophy.[110] Assessing the ventilatory response to carbon dioxide is a nonvolitional assessment of respiratory function, which distinguishes between ventilated and nonventilated children with neuromuscular disease[111] and predicts nocturnal hypercapnia in Duchenne muscular dystrophy.[112] These alternatives to forced vital capacity are useful clinical tools but to date, their utility and responsiveness in clinical trials have not been explored.

Quality of Life Measures

Evaluating quality of life is important if a change had an association with a change detected by a clinical or biological measure. Therefore, assessments of quality of life should be included as a secondary outcome measure in clinical trials.[113] Additionally, the effects of the disease on the family's as well as the individual's burden should be quantified. In families with chronically ill children, the Pediatric Evaluation of Disability Inventory, Parts II and III has been validated as an objective measure of caregiver burden,[114,115] and the Impact on Family Scale offers a measure of perceived burden.[116,117] Standardized instructions for administration and scoring are available for the Pediatric Evaluation of Disability Inventory but neither have been used in spinal muscular atrophy.

To date, no published spinal muscular atrophy clinical trial has included a validated quality of life or caregiver burden measure as an outcome. However, a Likert-type survey has been used to compare caregiver and clinician perception of quality of life in patients with spinal muscular atrophy type I.[118] In adult neuromuscular disease, caregiver burden measures were highly correlated with function.[119,120] Assessments used to assess quality of life in spinal muscular atrophy are outlined below.

PedsQL Pediatric Quality of Life Inventory

The PedsQL Pediatric Quality of Life Inventory instrument, a proprietary test, to measure quality of life, is a validated measure for use with healthy school and community populations as well as with pediatric populations with acute and chronic health conditions.[121,122] The validity of the PedsQL Pediatric Quality of Life Inventory was demonstrated through known group comparisons and correlations with other measures of disease burden. Age-specific forms for children 5 to 18 years old, parent/caregiver forms for children 2 to 18 years old as well as a neuromuscular disease-specific module are available. In spinal muscular atrophy, both the generic module[49] and neuromuscular module[50] have been shown to be reliable.

Conclusion

Spinal muscular atrophy is a genetically determined motor neuron disease typically presenting in infants and young children but affecting people across the life span. Because of recent advances in preclinical research, spinal muscular atrophy was selected by the National Institutes of Health as the prototype for their accelerated drug discovery efforts and, of many neurological diseases, is deemed the disease closest to treatment.[123,124]

At present, there are no biomarkers to measure disease progression in spinal muscular atrophy. Physiologic measures such as motor unit number estimation and compound motor action potential,[125,126] magnetic resonance imaging,[127-129] and dual-energy x-ray absorptiometry[43] have been considered in spinal muscular atrophy but to be used as a surrogate outcome must correlate with a functionally meaningful measure. Investigators must rely on clinical outcomes as measures of disease progression.

Currently, investigators from national and international research networks use several different assessments, validated in similar disorders or disease-specific measures, in natural history studies and clinical trials in spinal muscular atrophy. Performance-based measures are more desirable than assessments of impairment for clinical treatment trials. Quality of life measures should be used in conjunction with motor function assessments. Timed tasks should be considered outcomes in patients with ambulatory spinal muscular atrophy. Clinical outcomes should be chosen based on their ease of administration, patient burden, application to a wide range of patients with spinal muscular atrophy, reliability, and sensitivity to change. Consensus on a few standardized, objective measures is imperative as disease-modifying therapies approach the clinical community. Without such collaboration, the ability to define the impact of therapeutic agents will be delayed and comparison among trials nearly impossible.

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