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ABSTRACT

Background: In spinal muscular atrophy (SMA), weakness, decreased endurance, and fatigue limit mobility. Scales have been developed to measure function across the wide spectrum of disease severity. However, these scales typically are observer dependent, and scores are based on sums across Likert-scaled items. The Six-Minute Walk Test (6MWT) is an objective, easily administered, and standardized evaluation of functional exercise capacity that has been proven reliable in other neurologic disorders and in children.

Methods: To study the performance of the 6MWT in SMA, 18 ambulatory participants were evaluated in a cross-sectional study. Clinical measures were 6MWT, 10-m walk/run, Hammersmith Functional Motor Scale-Expanded (HFMSE), forced vital capacity, and handheld dynamometry. Associations between the 6MWT total distance and other outcomes were analyzed using Spearman correlation coefficients. A paired t test was used to compare the mean distance walked in the first and sixth minutes.

Results: The 6MWT was associated with the HFMSE score ($r = 0.83, p < 0.0001$), 10-m walk/run ($r = -0.87, p < 0.0001$), and knee flexor strength ($r = 0.62, p = 0.01$). Gait velocity decreased during successive minutes in nearly all participants. The average first minute distance (57.5 m) was significantly more than the sixth minute distance (48 m) ($p = 0.0003$).

Conclusion: The Six-Minute Walk Test (6MWT) can be safely performed in ambulatory patients with spinal muscular atrophy (SMA), correlates with established outcome measures, and is sensitive to fatigue-related changes. The 6MWT is a promising candidate outcome measure for clinical trials in ambulatory subjects with SMA. *Neurology*® 2010;74:833-838

GLOSSARY

FVC = forced vital capacity; **HFMSE** = Hammersmith Functional Motor Scale-Expanded; **HHD** = handheld dynamometry; **6MWT** = Six-Minute Walk Test; **SMA** = spinal muscular atrophy.

Spinal muscular atrophy (SMA) is the second most common neuromuscular disease of childhood,¹ and in its mildest form, type 3, individuals have proximal weakness and impaired ambulation. In addition, fatigue is a common symptom^{2,3} and also may impair function and endurance. However, existing motor function measures do not capture fatigue.⁴

Identification of a common genetic mutation simplifies diagnosis and has led to the discovery of potentially effective treatments.⁵ The rapid assessment of the effectiveness of these compounds requires the development of validated outcome measures. Global assessments have the advantage that they can be used over a wide range of function.⁶ Assessments of walking ability and endurance are direct measures of functional mobility and are thus considered inherently clinically meaningful, and may be more sensitive to change.

The Six-Minute Walk Test (6MWT) is an objective evaluation of exercise capacity and is representative of a person's ability because the test intensity is self-selected.⁷ The 6MWT has been used to

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assess function^{8,9} and has been accepted by regulatory agencies as a clinically meaningful endpoint¹⁰ in other neurologic disorders. The 6MWT also has been shown in other pediatric disorders and in healthy children to be a valid and reliable measure,¹¹ demonstrates good test-retest reliability,^{12,13} and is sensitive to change.^{14,15} Normative standards for children,¹⁶ adolescents,^{16,17} and adults¹⁸ are available. The goals of this study were to evaluate the validity and feasibility of the 6MWT in patients with SMA and to determine whether it captures the clinical phenomenon of fatigue.

METHODS Subjects. Eighteen ambulatory participants (4–48 years old, 8 female and 10 male) from an ongoing multicenter natural history study of SMA were included in this cross-sectional study. The 6MWT evaluations were added to the protocol partway through the natural history study and were performed between July 2008 and July 2009 at the 3 participating sites (Columbia University, Children’s Hospital Boston, Children’s Hospital of Philadelphia). Each participant had genetic confirmation of SMA with a homozygous deletion of exon 7 in the SMN1 gene. Eleven of the 18 participants had clinical symptoms before age 3 years, also termed *type 3a*¹⁹; the others had clinical symptoms after age 3 years, termed *type 3b*. Informed consent for the institutional review board–approved study was obtained from all participants. Participants had to have been diagnosed with SMA before age 19 years, could not have unstable medical conditions that would preclude participation, had to live within reasonable driving distance from the clinical site, and had to be able to walk safely without assistance. To reduce selection bias, all patients seen in the neuromuscular clinics who fulfilled eligibility criteria were offered enrollment. Additional recruitment efforts included a study Web site and interactions with family groups. The use of assistive devices such as ankle foot orthoses, crutches, walkers, or canes was not permitted during any functional or gait assessments.

Standard protocol approvals, registrations, and patient consents. All participants or guardians of participants signed informed consent approved by the individual institutional review boards at the 3 sites. The study was registered with ClinicalTrials.gov (NCT00443066).

Outcome measures. Six-Minute Walk Test. Participants were instructed to walk as fast as possible along a 25-m linear marked course on a linoleum floor, turn around a marker cone, and then return in the opposite direction and to repeat this loop as often as possible for 6 minutes. The course had a start line, placed horizontally at the beginning, with smaller horizontal lines placed every 1 m. The participants were comfortably dressed with rubber-soled shoes appropriate for walking. Assistive devices were not permitted, such as ankle braces, walkers, crutches, or canes. Participants were permitted to rest, without sitting, if necessary. Running or jogging was not permitted. Distance walked each minute and time to complete each 25-m segment were recorded. Standard encouragement using even, neutral tones was used for each patient, adopted from American

Thoracic Society guidelines.⁷ Falls, if any, were recorded as adverse events.

10-m walk/run. This test measures the time it takes a participant to walk or run 10 m as fast as possible without compromising the participant’s safety. In SMA, the 10-m walk/run time correlated with knee extensor and flexor strength and discriminated between younger and older ambulant patients.²⁰ The 10-m walk/run test is a good measure of walking ability with minimal, if any, endurance demands.

Hammersmith Functional Motor Scale–Expanded. The Hammersmith Functional Motor Scale–Expanded (HFMSE), a 33-item scale designed to assess motor function in patients with SMA type 2 and type 3, is associated with minimal participant burden, requires only standard equipment, and is completed in less than 15 minutes on average.²¹ The HFMSE showed excellent test-retest reliability and is correlated with other clinical and physiologic measures in SMA.²²

Forced vital capacity. Pulmonary function was assessed by measuring forced vital capacity (FVC) as percent predicted for age and height.²³ Pulmonary measures have been validated for use as outcomes in SMA, and among these, FVC was the most reliable measure.²⁴ The best of 3 trials was recorded.

Handheld dynamometry. Handheld dynamometry (HHD) was used to quantify strength. In SMA, good interrater and intrarater reliability has been shown for measures of strength in elbow flexors, knee extensors, and knee flexors,²⁵ and composite leg scores have been shown to be sensitive to change.²⁶ HHD scores have also been shown to be correlated with timed function tests and to discriminate between walkers and nonwalkers.²⁰ Strength of the knee flexors and knee extensors was assessed on the participant’s preferred side. While seated, the participant was evaluated using the “break” method, where the participant was instructed to push as hard as possible on a stable myometer for 3 to 5 seconds before this effort was overcome by the evaluator. The best of 3 trials was recorded. The clinical evaluators were trained in HHD, and interrater reliability was established before collection of these data.

Data analysis. Walking distances and average velocities were summarized for each minute (1–6) separately and cumulatively, overall and by SMA type. Total distances for the 6MWT were compared with normative values (children <19 years old,¹⁶ adults ≥19 years old¹⁸) and predicted distances based on maintenance of the average velocity observed for the first 25 m. Associations between the 6MWT total distance and other outcomes were analyzed using Spearman correlation coefficients because of the presence of unusual values for some outcomes. A paired *t* test was used to compare the mean distances walked in the first and sixth minutes.

The sample size of 18 participants was determined by the number of ambulatory subjects with SMA type 3 who were enrolled in the ongoing natural history study and had a 6MWT assessment; it was not prospectively determined based on statistical considerations.

RESULTS Eighteen participants performed the 6MWT; their clinical characteristics, including 6MWT distances, are summarized in the table, overall and by SMA type. The 6MWT distance was significantly associated with HFMSE score ($r = 0.83$, $p < 0.0001$), 10-m walk/run time ($r = -0.87$, $p < 0.0001$), and knee flexion HHD ($r = 0.62$, $p = 0.01$). The associations with FVC ($r = 0.35$,

Table Clinical characteristics of participants by spinal muscular atrophy type^a

Variable	Overall (n = 18)	Type 3a (n = 11)	Type 3b (n = 7)
Age, y	15.3 (13.3)	9.2 (7.8)	24.9 (14.9)
Age at symptom onset, y	3.9 (4.0)	1.6 (1.0)	7.4 (4.5)
Male, %	55.6	54.6	57.1
SMN2 copy number, %			
3	31.3	33.3	28.6
4	62.5	55.6	71.4
5	6.3	11.1	0.0
HFMSE	52.8 (9.9)	51.4 (10.9)	55.1 (8.1)
FVC, % predicted	106.0 (14.0)	103.3 (12.7)	109.7 (15.9)
Median 10-m walk/run time (25th, 75th percentiles), s	8.4 (5.4, 10.7)	9.4 (5.4, 19.1)	8.4 (3.9, 10.3)
HHD-knee extensor, lb of force	5.6 (6.1)	3.7 (2.0)	8.8 (9.2)
HHD-knee flexor, lb of force	12.3 (7.3)	9.3 (4.9)	17.4 (8.3)
Distance walked in 6 min, m	288.9 (161.9)	239.2 (132.6)	367.1 (182.4)
Distance walked in first minute, m	57.5 (28.1)	49.3 (27.7)	70.4 (25.3)
Distance walked in sixth minute, m	48.0 (29.4)	39.5 (23.7)	61.4 (34.1)

Abbreviations: FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale-Expanded; HHD = handheld dynamometry.

^aValues are mean (SD) unless otherwise specified.

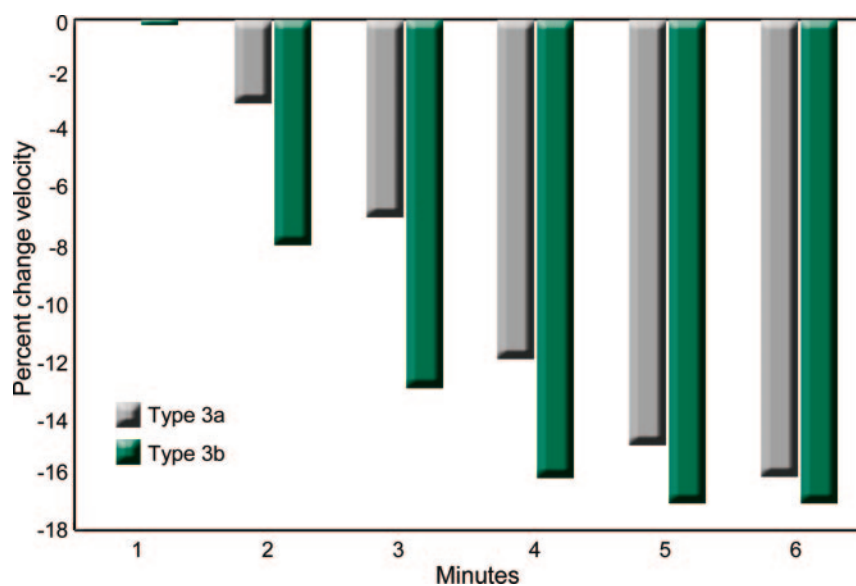
$p = 0.21$) and knee extension HHD ($r = 0.36$, $p = 0.17$) were considerably weaker. The mean distances walked during the first (57.5 m) and sixth (48.0 m) minutes were significantly different ($p = 0.0003$); this mean difference (9.5 m) was nearly the same for participants with type 3a (9.8 m) and type 3b (9.0

m). The mean velocity for each successive minute walked during the 6MWT decreased when compared with the mean velocity walked in the first minute for participants with type 3a and 3b (figure). Participants with type 3a had slower average velocities at each minute. In 17 (94%) of the 18 participants, the 6MWT distance was less than the predicted distance determined by the first 25-m velocity, and in all subjects, the 6MWT distance was less than that predicted for their age and gender. One participant fell while performing the 6MWT but was able to get up unassisted and complete the test, and no one sustained any injury.

DISCUSSION The 6MWT is a validated measure of exercise capacity and motor function that has been widely applied in the study of several other neuromuscular diseases and numerous other disease states. The ability to quantify functional endurance^{9,27} and the sensitivity to change²⁸ makes the 6MWT an attractive clinical outcome measure. It has been accepted by European (European Medicines Agency)^{10,29} and US (Food and Drug Administration) regulators^{10,30} as a primary endpoint in late phase clinical trials. It is easily administered and requires no special equipment or training. Future research is needed to determine the functional importance of changes in the 6MWT distance and in other measures of motor function (e.g., HFMSE).

In our sample, the 6MWT was highly correlated with the HFMSE but not with FVC (figure e-1 on

Figure Percent change in average velocity for each minute during the Six-Minute Walk Test



Percent change in average velocity for each minute compared with the average velocity walked in the first minute during the Six-Minute Walk Test (6MWT) for spinal muscular atrophy (SMA) types 3a and 3b. The average velocity for each minute walked during the 6MWT decreased when compared with the average velocity walked in the first minute for participants with type 3a and 3b. Participants with SMA type 3a had slower average velocities at each minute.

the *Neurology*[®] Web site at www.neurology.org). The 10-m walk/run test, an assessment of gait but not endurance, was also associated with the 6MWT (figure e-1). Subnormal performance on the 6MWT could be due to pulmonary or motor limitations. In SMA type 3, respiratory complications are uncommon, with the majority of patients having normal pulmonary function³¹; this was evident in our sample (mean FVC% 106, range 84–127). Therefore, the 6MWT in SMA is thought to reflect motor limitations, although poor cardiopulmonary fitness cannot be excluded as a component. We did not study concurrent heart rate change during the 6MWT to address this possibility. The 10-m walk/run test has been considered as an outcome measure because it is quick and less burdensome. However, although it correlates with the 6MWT, it does not measure endurance demands.

Interestingly, in this study, knee flexor but not knee extensor strength was moderately associated with distance walked during the 6MWT (figure e-1). Previous reports in SMA demonstrated correlations between HHD of both knee flexors and extensors with the 10-m walk/run test, timed rising from the floor, and time to climb stairs. However, none of these tests assessed exercise capacity or endurance.²⁰ Similar findings associating quadriceps strength and functional measures have been demonstrated in other neuromuscular disorders.³² Normal walking relies on only a few major muscle groups: hip and knee extensors, ankle plantar and dorsiflexors, and hip abductors.³³ The differences found in our study may reflect the unique requirements or compensatory strategies of functional ambulation in SMA and warrant further detailed, kinematic evaluation.

Fatigue is a typical symptom in some neurologic diseases³⁴ and a common physical symptom of patients with SMA. This symptom is more evident with patients with SMA type 3 than with patients with more severe forms of the disease.³ Severity of subjective fatigue can be evaluated using validated questionnaires,^{35,36} but this may not further our understanding of the pathophysiologic mechanisms underlying fatigue in SMA. Electrophysiologic fatigue is evaluated at the peripheral level using electromyography, and centrally with motor cortex stimulation or assessment of movement-related cortical EEG potentials.³⁷ In a large sample of patients with neuromuscular disease, including fascioscapulo-humeral dystrophy, myotonic dystrophy, and hereditary motor and sensory neuropathy, despite a significantly higher frequency of reports of subjective fatigue compared with age-matched controls, neither central nor peripheral electrophysiologic fatigue was

detectable by these laboratory means.³⁸ Similarly, quantitative strength testing using single maximal voluntary isometric contraction did not capture fatigue in patients with SMA.⁴ Other possible mechanisms of disease-related functional deficits and fatigue may occur at the neuromuscular junction as suggested by preclinical studies in transgenic models of SMA.³⁹ Indeed, in a mouse model of mild SMA, repetitive stimulation at high frequency resulted in intermittent neurotransmission failures.³⁹ Such failures would likely result in excessive fatigue, akin to the reduced endurance we observed in patients subjected to the 6MWT. Neuromuscular junction dysfunction, however, has not been evaluated directly in patients with SMA. Therapeutic strategies that successfully treat motor fatigue would be expected to improve daily function and quality of life in ambulatory patients with SMA. The 6MWT may be a useful outcome measure in clinical trials for such therapeutic interventions.

Unlike boys with Duchenne muscular dystrophy and healthy individuals,¹⁰ in our study, patients with SMA did not maintain consistent walking speed throughout the 6MWT, with a 17% decrement in performance from the first to the sixth minute. Furthermore, the walking speed assessed during the 10-m walk/run test does not capture deficits in endurance, as might be expected because it allows for running and may not be a good predictor of ability to function in the community.⁴⁰ The 6MWT may serve as valuable tool to quantify fatigue in this population. Furthermore, in addition to absolute distance and deviations from normative values, the change in walking speed during the 6MWT should be investigated as a useful measure of fatigue in clinical trials.

Our study indicates that the 6MWT can be safely performed in ambulatory patients with SMA. In this sample, only 1 fall occurred during the test, which did not result in injury, and the participant was able to rise unassisted and complete the test. The test correlates with standard measures of motor function, including another timed walking test. It is easily administered and could serve as a clinical outcome measure in clinical trials of ambulatory patients. Patients with SMA do not maintain consistent walking speeds throughout the 6MWT, indicating a clinically relevant aspect of motor fatigue; pathophysiologic correlates to this finding need to be explored. Although we attempted to minimize selection bias through recruitment efforts and the use of broad eligibility criteria, caution is needed regarding the generalizability of our results. It is essential that 6MWT methods be standardized for future international prospective studies across SMA centers. Larger studies are needed to confirm its reliability and sensitivity in this population.

AUTHOR CONTRIBUTIONS

Dr. McDermott performed the statistical analyses.

DISCLOSURE

Ms. Montes reports no disclosures. Dr. McDermott has received honoraria from the Michael J. Fox Foundation; has served as a consultant to the New York State Department of Health, the American Epilepsy Society, the Michael J. Fox Foundation, and Teva Pharmaceutical Industries Ltd.; has received research support from Medivation, Inc., Boehringer Ingelheim, NeuroSearch Sweden AB, and Forest Laboratories, Inc.; and receives research support from the NIH (NS42372 [Co-I], HD44430 [Co-I], DE16280 [Co-I], NS52619 [PI], NS45686 [Co-I], NS46487 [Co-I], NS50095 [Co-I], NS49639 [Co-I], AR52274 [Co-I], NS50573 [Co-I], HL80107 [Co-I], RR24160 [Co-I], NS58259 [Co-I], and NS48843 [Co-I]), the US Food and Drug Administration, the Michael J. Fox Foundation, the SMA Foundation, and the Muscular Dystrophy Association. Mr. Martens reports no disclosures. Dr. Dunaway reports no disclosures. Dr. Glanzman has received travel expenses for educational activities not funded by industry; and has received research support from PTC Therapeutics, Inc., the NIH (RO1 NS043264-04 A1 [clinical evaluator] and NIDRR 60662 [Site PI]) and from the SMA Foundation. Dr. Riley, Ms. Quigley, and Ms. Montgomery report no disclosures. Dr. Sproule has received funding for travel from UCB and for lectures or educational activities not funded by industry; his spouse is an employee of Pfizer Inc; receives research support from PTC Therapeutics, Inc. and the NIH/NINDS (K12NS01698) Neurological Science Academic Development Award; and holds stock and stock options in Pfizer Inc. Dr. Tawil receives research support from the NIH (N01-AR-50-227450 [role: co-PI]), the SMA Foundation, and from the Fields Family Foundation. Dr. Chung receives research support from the SMA Foundation, NHLBI U01 HL098163, NICHD HD057036, NIDDK DK52431, RC2 HD064525, NCI U01CA069398, DK-04-021, DK63608, US Department of Defense, and the Doris Duke Charitable Foundation. Dr. Darras receives royalties from publishing in UpToDate; serves as a consultant to and receives speaker honoraria from Genzyme Corporation; receives research support from PTC Therapeutics, Inc., the NIH (NIAMS 2P01 NS040828-6A11 [Co-PI] and NINDS HHSN265200423611C, [PI]), the SMA Foundation, the Muscular Dystrophy Foundation, the New England Research Institutes/SMA Foundation, and from the Slaney Family Fund for SMA. Dr. De Vivo serves on scientific advisory boards for the SMA Foundation, the Colleen Giblin Foundation, the Pediatric Neurotransmitter Disease Association, the International Reye Syndrome Foundation, and the Will Foundation; receives royalties from publishing *The Molecular Basis and Genetic Basis of Neurologic and Psychiatric Disease*, 4th ed. (Lippincott Williams & Wilkins, 2008); and receives research support from the NIH (1 UL1 RR024156-01 [investigator], NINDS 5K12NS01698 [program director] and 5R01NS37949 [PI]), and NICHD (5P01HD32062 [PI]), the SMA Foundation, the Colleen Giblin Foundation, the Will Foundation, and the Pediatric Neurotransmitter Disease Association. Dr. Kaufmann conducted the work reported here while she was a full-time employee of Columbia University. This report is not related to her current work at NINDS. Dr. Kaufmann has received consulting honoraria from the SMA Foundation. She has received travel reimbursement to investigator meetings from the NIH, SMA Foundation, the MDA, Santhera Pharmaceuticals and PTC Therapeutics, Inc.; she serves on the editorial board of *Neuromuscular Disorders*; has received travel expenses and/or honoraria for lectures or educational activities not funded by industry; has received research support from Santhera Pharmaceuticals, Penwest Pharmaceuticals Co., PTC Therapeutics, Inc., the NIH (RO1 NS48125 NINDS, PI); Department of Defense, and the SMA Foundation. Her spouse serves on the editorial board of *Pediatric Pulmonology*. Dr. Finkel serves on advisory boards for PTC Therapeutics, Inc., DuchenneConnect, Families of SMA, the National Fabry Disease Foundation, and TREAT-NMD; has received travel expenses for lectures not funded by industry; receives research support from PTC Therapeutics, Inc., Genzyme Corporation, Santhera Pharmaceuticals, the NIH (U54 AR0526446-03 [Co-I] and 1U54 NS0657-12-01 [Co-I]), the SMA Foundation, the Muscular Dystrophy Association, and the Foundation for the Eradication of Duchenne; and his spouse serves on the editorial

board of *Arthritis Research and Therapy*, holds and has received license fees for numerous patents related to T cell activation and HIV, and receives research support from Merck Serono and the NIH in the field of T cell activation, HIV and genomics of juvenile arthritis.

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