inquiry would be to compare the frequency of these variants in patients with other neuropathic disease states. Populations such as those with large fiber neuropathy, or with AN only, should be explored for frequency of *TTR* VUS, and this should be compared with frequencies of these variants in patients with concurrent AN and SFN. This would further elucidate the potential association of these VUS with specific pathologies. In addition, further work should be undertaken to elucidate the functional relevance of these VUS in the pathogenesis of SFN with an autonomic component. Fat pad biopsies should be performed in those patients with SFN and AN who have a VUS in the TTR gene to assess for the presence of amyloid deposits; we hypothesize that the mechanism for this predisposition is nonamyloidogenic. It is also possible that the finding of these VUS in patients with SFN and AN represents simply the identification of 1 gene mutation in a multi-genic process.

We acknowledge medical writing assistance provided by AXON Communications for the development of this manuscript.

Ethical Publication Statement: We (the authors) confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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MOTOR MILESTONE ASSESSMENT OF INFANTS WITH SPINAL MUSCULAR ATROPHY USING THE HAMMERSMITH INFANT NEUROLOGICAL EXAM—PART 2: EXPERIENCE FROM A NUSINERSEN CLINICAL STUDY

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Accepted 23 May 2017

ABSTRACT: *Introduction:* In this study we examined the feasibility of assessing motor milestone performance of infants with spinal muscular atrophy (SMA) using the Hammersmith Infant Neurological Exam—Part 2 (HINE-2) in a phase 2 study of nusinersen. *Methods:* Nineteen SMA infants were assessed using the HINE-2 at baseline (≤7 months of age), and periodically up to 39 months of age. We evaluated whether the HINE-2 was feasible, reliable, and sensitive to change. *Results:* Motor milestone assessments in SMA infants were feasible using the HINE-2. Baseline test–retest reliability was excellent (R = 0.987; $P < 0.0001$). SMA infants were extremely low functioning at baseline and the HINE-2 was able to detect changes over time in 16 of 19 infants within all 8 domains. HINE-2 improvements were correlated with changes in other neuromuscular outcome measures. *Discussion:* Results support the use of the HINE-2 motor milestone assessment in clinical trials of SMA infants.

Muscle Nerve **57**: 142–146, 2018

Spinal muscular atrophy (SMA; OMIM 253300) is an autosomal recessive disease caused by deletions/mutations in the *SMN1* gene[1,2] and characterized by motor neuron degeneration and progressive muscle weakness.[3] Infantile-onset SMA (equivalent to type 1) is the most common, severe form in which infants develop profound limb and trunk

weakness within the first few months and never achieve motor milestones such as rolling or independent sitting.[4–6] Clinical trials are ongoing to test the efficacy of potential SMA therapeutics; thus, tools for assessing motor function changes are needed. Motor milestones are important as they provide a contextualized assessment that is relatable to everyday function and capabilities.[7] The Hammersmith Infant Neurological Exam (HINE) was originally developed to assess development of global neurological function in normal infants.[8,9] and has been evaluated in several infant populations.[10–12] The HINE-2 contains a standardized tool for assessing motor milestone achievement, consisting of structured, developmentally appropriate items that assess incremental changes in head control, sitting, voluntary grasp, ability to grasp, ability to kick, rolling, crawling, standing, and walking. A recent retrospective natural history study using the HINE-2 indicated that SMA infants do not achieve motor milestones and seldom make even incremental improvements with development.[13] Herein, we report the first use of the HINE-2, a standardized tool for assessing motor milestone achievement, in a prospective treatment trial with SMA infants.

METHODS

Assessments were performed during an open-label, phase 2 clinical study (NCT01839656) of nusinersen, an antisense oligonucleotide.[14–16] Full study details and results of an interim analysis on January 26, 2016 have been published elsewhere.[17] Briefly, participants included 19 male and female infants from 3 weeks to $\leq$7 months old with SMA symptom onset between 3 weeks and 6 months of age, who had an *SMN1* homozygous gene deletion or mutation, and who met additional eligibility criteria.[17] Participants were enrolled after institutional review board approvals and written informed consent of the parents. Infants were 1–7 months old at baseline evaluation and 5–39 months at last assessment. Seventeen SMA infants had 2 copies of the *SMN2* gene, and 2 had 3 copies of the *SMN2* gene.

The HINE,[8] including the motor milestones portion (Part 2), was performed by pediatric neurologists. A second motor function assessment, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND),[18] a validated 16-item scale (0–64 points) designed specifically to capture motor function in SMA infants, was administered by trained physical therapist evaluators. Compound muscle action potentials (CMAPs) for the ulnar nerve[19] stimulated at the elbow and recorded from the abductor digiti minimi were measured by electrophysiologists following the motor function assessments. Assessments were performed at screening (within a 14-day period), day 1 (baseline), and periodically throughout the study (days 15, 29, 85, 92, 169, 254, 337, and 442, and then every 4 months). Relationships between outcomes were analyzed using Pearson correlations.

RESULTS

A total of 580 HINE-2 assessments were performed during the study by 4 evaluators at the 4 clinical centers. No assessments and only a few items (7 of 4,640) were missed (primarily missing assessment of rolling due to the presence of a feeding tube). Testing was well tolerated in infants with SMA across the age range and there were no adverse events related to its use. Screening and baseline assessments showed excellent test–retest reliability ($R = 0.987$; $P < 0.0001$). At baseline, SMA infants with 2 copies of *SMN2* were largely nonfunctional on motor milestones, with only a few performing at the first increment on grasping, ability to kick, and head control (Fig. 1, top panel) and low CHOP-INTEND scores (range 17–38, median 26) and CMAP amplitudes (range 0–0.60 mV, median 0.2 mV). One infant with 3 copies of *SMN2* had similar HINE-2 functioning to infants with 2 *SMN2* copies (see Fig. 1, top panel) and higher CHOP-INTEND score (42) and CMAP amplitude (2.2 mV), whereas the other 3-copy infant had much higher milestone functioning (see Fig. 1, top panel) and higher CHOP-INTEND score (64) and CMAP amplitude (3.2 mV).

At the last assessment, most infants (16 of 19) exhibited incremental improvements on motor milestone items (Fig. 1, bottom panel) compared with baseline. Improvements were observed in all 8 motor function domains: head control (10 infants); sitting (10 infants); grasping (14 infants); ability to

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale—Expanded; HINE, Hammersmith Infant Neurological Exam; HINE-2, Hammersmith Infant Neurological Exam—Part 2; SMA, spinal muscular atrophy; WHO, World Health Organization

Disclosures: K.M.B. is currently the chief scientific officer of Otonomy; from 2009 to 2015, she was a full-time employee of Ionis Pharmaceuticals. She serves in an advisory capacity to nonprofit organizations, including the SMA Foundation and the Myotonic Dystrophy Foundation. J.M. reports serving as a consultant from Ionis Pharmaceuticals, and serving on advisory boards for Roche Pharmaceuticals and Biogen. R.S.F. reports grants and personal fees from Ionis Pharmaceuticals and Biogen during the conduct of this study, He has also received grants from Cytokinetics outside the submitted work, and advisor fees from AveXis, Roche, and Novartis. R.S.F. serves in an advisory capacity to nonprofit organizations, including the SMA Foundation, Cure SMA, SMA Reach (UK), and SMA Europe, and has also served on the DSMB for the AveXis Gene Transfer and Roche RG7800 studies.

Supported by a grant from the Eunice Kennedy Shriver National Institute for Child Health and Human Development (1K01HD084690-01A1 to J.M.).

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Published online 26 May 2017 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/mus.25705

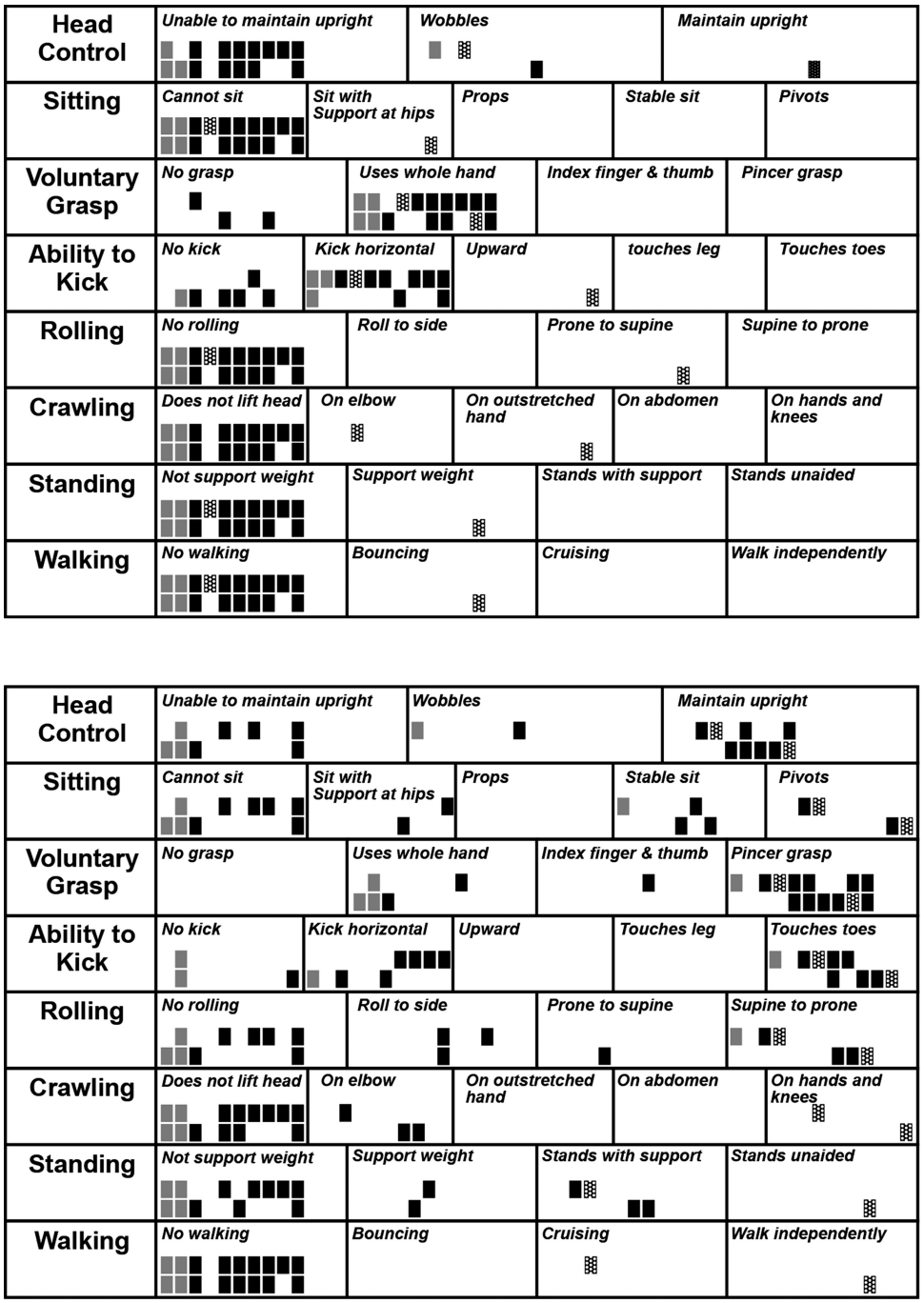

FIGURE 1. Motor milestones as assessed by the Hammersmith Infant Neurological Exam—Part 2. Baseline assessment (top panel) and assessment at last visit after treatment with nusinersen (bottom panel) for individual SMA infants. Gray boxes: infants given a lower dose of nusinersen (6 mg loading and then 12 mg maintenance); black boxes: infants given a higher dose (12 mg loading and maintenance). Solid boxes: infants with 2 copies of the *SMN2* gene; hatched boxes: infants with 3 *SMN2* copies. Assessments are listed consistent with the published HINE-2, with the exception of "Rolling," in which directions were assessed separately (prone to supine and supine to prone).

kick (12 infants); rolling (10 infants); crawling (5 infants); standing (7 infants); and walking (2 infants). Milestone progression generally occurred in the same stepwise progression as in normal development (i.e., from left to right across HINE-2 increments) and without skipping of increments. Statistically significant, moderate correlations were noted between improvement in HINE-2 and CHOP-INTEND scores and CMAP amplitude (see Fig. 2).

DISCUSSION

In this study, motor milestone assessment using the HINE-2 was feasible and practical in symptomatic, fragile infants with type 1 SMA. SMA infants were extremely low functioning at baseline, but

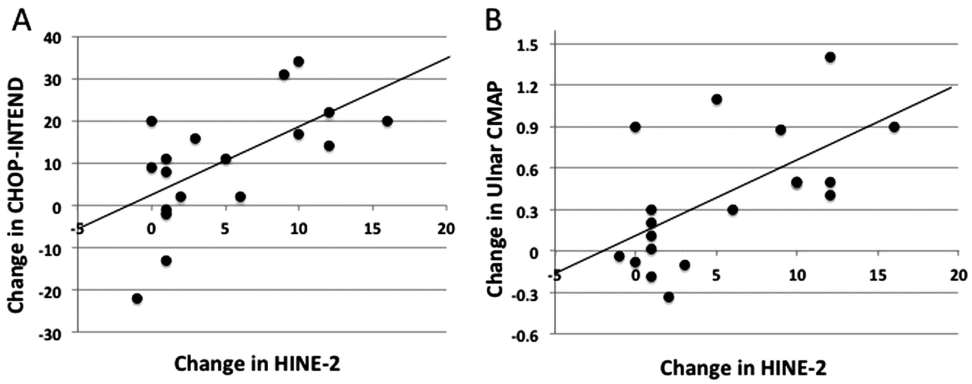

FIGURE 2. Change from baseline for individual SMA infants. **(A)** Change from baseline in HINE-2 vs. change from baseline in CHOP-INTEND (R = 0.691; P = 0.001). **(B)** Change from baseline in HINE-2 vs. change from baseline in ulnar CMAP amplitude (R = 0.511; P = 0.025).

the incremental nature of the HINE-2 allowed capture of status. Changes in the HINE-2 were detected in infants given nusinersen, and these HINE-2 changes were associated with changes in other clinical outcome measures (CHOP-INTEND and CMAP), providing construct validity. In contrast, SMA infants receiving standards of care retrospectively evaluated in a historical case series scored 0 on most items and low scores on 3 items (head control, grasp, kicking) that never advanced beyond partial achievement.[13]

The HINE-2 is a standardized evaluation of motor function, supporting its value as an important outcome measure in clinical studies. Although disease-specific scales such as the CHOP-INTEND are necessary, the addition of the HINE-2 captures the incremental progression of motor milestones and permits comparison to typically developing infants. Partial attainment of a skill can be reliably captured and full acquisition of a skill can be readily related to normal infant development. The World Health Organization (WHO) motor milestone benchmarks capture dichotomous yes/no motor skills without the partial achievement subscores that are addressed in the HINE-2.[20] WHO milestones address infant motor function at a most fundamental and intuitive level, whereas the disease-specific and sensitive CHOP-INTEND scale fails to link to functional skills. The HINE-2 bridges this gap. In this study, comparison of change from baseline in HINE-2 versus change from baseline in CHOP-INTEND suggested that the CHOP-INTEND may be more sensitive to change in lower functioning infants (Fig. 2A). Another advantage of the HINE-2 is that it involves only 8 items, which capture all of the salient aspects of infant motor development, to the point of independent ambulation, and can be readily, reliably, and safely administered. There is no floor effect with the HINE-2. Conversely, there is conceivably a ceiling effect for infants who attain independent ambulation. These factors favor the HINE-2 over other infant motor scales that are less well tolerated and therefore less reliably administered, but are without the ceiling effect: the Alberta Infant Motor Scale[21]; the Test of Infant Motor Performance[22]; and the Bayley III Scale.[23]

Although in this study the HINE-2 was performed by a neurologist as part of the overall HINE exam, the HINE-2 could easily be adopted by trained clinical therapist evaluators and included in the typical battery of motor function assessments of SMA infants. Implementation may be improved with clear administration criteria, a defined testing environment, and assessment of how behavioral state affects capture of the optimal score. Beyond type 1 SMA, examination of motor function in type 2 SMA using the HINE-2 as an adjunctive test to the Hammersmith Motor Function Scale—Expanded (HFMSE)[24] would also be of interest. The HINE-2 may provide a useful continuum bridging the assessment gap between the CHOP-INTEND used in type 1 and the HMFSE used in type 2 SMA.

Overall, results from this study strongly support the use of HINE-2 motor milestones as a major outcome measure in clinical trials of SMA infants. These data were also the basis for the selection of the HINE-2 as a primary endpoint in the first successful therapeutic phase 3 trial in infants with SMA,[25] where a significant difference in the proportion of SMA infants who exhibited improvement in HINE-2 motor milestones was observed between those treated with nusinersen and sham controls, and resulted in regulatory approval by the U.S. Food and Drug Administration in December 2016.[26] Thus, the HINE-2 represents an important outcome measure for clinical trials in SMA infants and should be considered in ongoing and future drug development programs.

The authors sincerely thank the parents/guardians of the participants in this study. We greatly appreciate the dedication of the personnel at the study sites who contributed: Nemours Children's Hospital, Orlando, FL (Dawn Cook, Julie Duke, Marla Kasper, Jenna Turner); Columbia University Medical Center, New York, NY (Claudia Chiriboga, Darryl De Vivo, Rosángel Cruz, Sally Dunaway Young, Nicole LaMarca, Jonathan Marra, Molly Popolizzio, Rachel Salazar, Louis Weimer); The Hospital for Sick Kids, Toronto, ON, Canada (Juri Vajsar, Jennifer Boyd, Renee Haldenby, Lynn MacMillan); Stanford University Medical Center, Palo Alto, CA (John Day, Richard Gee, Shirley Paulose, Carolina Tesi-Rocha, Karolina Watson); and Ionis Pharmaceuticals, Carlsbad, CA (Katie Alexander, Katherine Kwoh, Margaret Whitely, Shuting Xia, Frank Bennett).

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QUANTITATIVE SONOGRAPHIC ASSESSMENT OF MYOTONIA

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Accepted 23 May 2017

ABSTRACT: *Introduction*: This study explores ultrasound imaging for qualitative and quantitative assessment of myotonia. *Methods*: Sixteen patients with myotonia and 16 controls underwent sonographic evaluation of the thenar eminence muscles to assess the relaxation time after muscle percussion. *Results*: The mean time for complete muscle relaxation in patients with myotonia was longer than that of controls. A cutoff of >0.9 s for myotonia detection had a sensitivity of 88% and a specificity of 100%. The interrater reliability was moderate for qualitative assessment but was high for quantitative assessment. The relaxation time did not correlate with the number of trinucleotide repeats in patients with myotonic dystrophy. *Discussion*: Sonographic evaluation for the presence of myotonia is feasible, sensitive, and specific but does not correlate with disease severity in myotonic dystrophy.

Muscle Nerve **57**: 146–149, 2018

Additional supporting information may be found in the online version of this article.

Abbreviations: ICC, intraclass correlation coefficient; MD1, myotonic dystrophy type 1

Key words: hyperkalemic periodic paralysis; myotonia; myotonia congenita; myotonic dystrophy; ultrasound

Funding: No funding was received for the publication of this article.

Conflicts of Interest: The authors have no conflicts of interest to report.

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Published online 31 May 2017 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.25714