A longitudinal study of CMT1A using Rasch analysis based CMT neuropathy and examination scores

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Abstract

Objective

To evaluate the sensitivity of Rasch analysis-based, weighted Charcot-Marie-Tooth Neuropathy and Examination Scores (CMTNS-R and CMTES-R) to clinical progression in patients with Charcot-Marie-Tooth disease type 1A (CMT1A).

Methods

Patients with CMT1A from 18 sites of the Inherited Neuropathies Consortium were evaluated between 2009 and 2018. Weighted CMTNS and CMTES modified category responses were developed with Rasch analysis of the standard scores. Change from baseline for CMTNS-R and CMTES-R was estimated with longitudinal regression models.

Results

Baseline CMTNS-R and CMTES-R scores were available for 517 and 1,177 participants, respectively. Mean $\pm$ SD age of participants with available CMTES-R scores was 41 ± 18 (range 4–87) years, and 56% were female. Follow-up CMTES-R assessments at 1, 2, and 3 years were available for 377, 321, and 244 patients. A mixed regression model showed significant change in CMTES-R score at years 2 through 6 compared to baseline (mean change from baseline 0.59 points at 2 years, $p = 0.0004$, $n = 321$). Compared to the original CMTES, the CMTES-R revealed a 55% improvement in the standardized response mean (mean change/SD change) at 2 years (0.17 vs 0.11). Change in CMTES-R at 2 years was greatest in mildly to moderately affected patients (1.48-point mean change, 95% confidence interval 0.99–1.97, $p < 0.0001$, for baseline CMTES-R score 0–9).

Conclusion

The CMTES-R demonstrates change over time in patients with CMT1A and is more sensitive than the original CMTES. The CMTES-R was most sensitive to change in patients with mild to moderate baseline disease severity and failed to capture progression in patients with severe CMT1A.

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Inherited Neuropathies Consortium—Rare Diseases Clinical Research Network (INC-RDCRN) members are listed in the Appendix 2 at the end of the article.

Glossary

CI = confidence interval; CMT = Charcot-Marie-Tooth; CMTES = CMT Examination Score; CMTES-R = Rasch-modified CMTES; CMTNS = Charcot-Marie-Tooth Neuropathy Score; CMTNS-R = Rasch-modified CMTNS; CMTNSv2 = CMTNS version 2; COA = clinical outcome assessment; CMT1A = Charcot-Marie-Tooth disease type 1A; INC = Inherited Neuropathies Consortium; RDCRN = Rare Diseases Clinical Research Network; SRM = standardized response mean.

Charcot-Marie-Tooth (CMT) disease type 1A (CMT1A) is the most common form of hereditary neuropathy, accounting for >50% of all cases.¹ CMT1A is caused by a duplication encompassing the *PMP22* gene and most commonly manifests in the first 2 decades of life with foot deformities, length-dependent sensory loss, varying degrees of distal extremity weakness, and gait difficulty. No treatment for CMT1A is currently available; however, an increasing number of candidate therapies that reduce *PMP22* expression have emerged from preclinical studies, paving the way for clinical trials.²

The paucity of clinical outcome assessments (COAs) that are sensitive enough to capture the slow clinical progression has been a major impediment to previous clinical trials in CMT1A. The most commonly used outcome measure in CMT1A studies to date has been the Charcot-Marie-Tooth Neuropathy Score (CMTNS), which was developed to quantify clinical severity and measure disease progression in patients with CMT.³ The CMTNS is a validated, composite score that is based on patients' symptoms, physical findings, and electrophysiology. The CMT Examination Score (CMTES) is a subscore of the total CMTNS and is based only on patients' symptoms and physical findings, excluding electrophysiology. Two randomized controlled trials of ascorbic acid in CMT1A have underscored the limitations of the CMTNS; no meaningful clinical progression was detected in the placebo groups in either of these studies over a 2-year period.^{4,5} To minimize floor and ceiling effects, the CMTNS was revised, yielding the CMTNS version 2 (CMTNSv2).⁶ A follow-up Rasch analysis of the CMTNSv2, however, revealed that the revised score continued to cluster impairment scores from patients with CMT1A in the middle range of severity, thus failing to adequately discriminate mildly and severely affected patients from those in the middle.⁷ To make the CMTNS more linear and thereby ensure that smaller differences in clinical change could be detected, Rasch-modified CMTNS (CMTNS-R) scores were developed.⁷

The Rasch model is a mathematical framework developed to analyze rating scales with the goal of determining how well individual items of the scale contribute to the measurement of a derived trait (in the case of the CMTNS, the severity of neuropathy). In contrast to the original CMTNSv2, in which all items contribute identically to the overall score, the CMTNS-R variably weights category responses to provide a more accurate estimate of disease severity, as we have previously published.⁷ For example, the

Rasch model predicted that motor items would be more representative of increased disability and therefore deserve higher scores compared to sensory items. Reapplying Rasch analysis using the weighted scale showed significant improvement in psychometric properties of the outcome measure, mainly less noise (fitting), better reliability, and reduced floor/ceiling effect.⁷ The CMTNS-R is therefore predicted to be more sensitive in detecting change in patients with CMT1A, but it has not yet been evaluated in longitudinal studies.

The Inherited Neuropathies Consortium (INC) was created in part to perform natural history studies in the varied forms of CMT. The INC has included up to 20 sites, currently including 16 actively enrolling sites in the United States, Europe, and Australia, and has been evaluating patients since 2009. In the current study, we have performed a longitudinal study of CMT1A in patients enrolled at 18 centers of the INC over a 6-year period using the CMTNS-R and CMTES-R (table 1). Because repeated nerve conduction studies are uncomfortable and often costly for patients, the CMTES is increasingly used in place of the CMTNS in our clinics. We have therefore focused our analysis on the CMTES-R and evaluated its potential use as an independent outcome measure in CMT1A.

Methods

Standard protocol approvals, registrations, and patient consents

All sites participating in the INC natural history study (protocol 6601) received Institutional Review Board/Ethics Board approval for the study. All patients or their guardian signed consent forms. This trial was registered at ClinicalTrials.gov (NCT01193075).

Patients

Patients with CMT1A were recruited from the INC, which is a member of the NIH Rare Diseases Clinical Research Network (RDCRN; rarediseasesnetwork.org/). Data were collected as part of the INC natural history study (protocol 6601) between February 2009 and September 2018 from a total of 18 sites within the INC (table 1). Patients were examined by clinical investigators who had received training and were certified in the proper use of the CMTNSv2, a validated 9-item, 36-point composite score based on patients' symptoms (3 items), examination findings (4 items), and electrophysiology (2 items), with scores of 0 to 10, 11 to 20,

Table 1 Sites of the INC

INC site	Subjects contributed, n
National Hospital for Neurology and Neurosurgery	398
University of Iowa	251
Carlo Besta Neurologic Institute	197
Johns Hopkins University	90
University of Pennsylvania	87
University of Rochester	48
Wayne State University	33
Children's Hospital of Philadelphia	23
Stanford University	21
Harvard/Massachusetts General Hospital	12
Cedars Sinai Medical Center	11
University of Michigan	8
University of Minnesota	8
Vanderbilt University Medical Center	7
University of Miami	5
The Children's Hospital at Westmead	4
University of Washington Medical Center	3
Nemours	3

Abbreviation: INC = Inherited Neuropathies Consortium.

and >21 indicating mild, moderate, and severe disease, respectively.^{3,6} The CMTES is a subscore of the total CMTNSv2 that includes 7 items based on patients' symptoms and examination findings and excludes the electrophysiology, with a maximum total score of 28 points. Patients were evaluated at yearly intervals, and the CMTNSv2 and CMTES scores were recorded at each visit. If patients did not undergo nerve conduction studies during a particular visit, only the CMTES score was obtained. CMTNSv2 and CMTES scores were then converted into their Rasch-modified scores (CMTNS-R and CMTES-R), with total scores of 40 and 32, respectively.

Patients were diagnosed with CMT1A on the basis of clinical evidence of sensory and/or motor peripheral neuropathy (including length-dependent sensory loss, weakness, and atrophy of the distal musculature and decreased deep tendon reflexes), nerve conduction studies, and confirmatory genetic testing for a *PMP22* duplication. Standard methods were used for all electrophysiology. A Clinical Laboratory Improvement Amendments-certified laboratory in the United States or an equivalent certified testing facility outside of the United States performed all

genetic testing. Participants were required to have a duplication in the *PMP22* gene to be enrolled in the INC database with a diagnosis of CMT1A. However, detailed descriptions of duplication length were not available for all participants.

Statistical methods

Only patients with a *PMP22* duplication were included. Data were analyzed mostly on an available case basis. When longitudinal models were fitted, the number of follow-up times was limited so there would be adequate sample size for all groups and all times. Because the model incorporates longitudinal correlation between repeated measures on a subject, every subject with at least 1 measurement contributed information to estimating the model parameters. We assumed data missingness is not "not at random" and kept the covariance structures of the longitudinal models as free as possible, so the longitudinal model fit to available case data should be valid. Most results were obtained from the model parameter estimates, unless otherwise stated. The value of α was set to 0.05 by default.

Summary statistics for CMTES, CMTNS, CMTES-R, and CMTNS-R scores were obtained by time point, along with baseline demographic data. Change over time was estimated with longitudinal mixed model regression. Interaction effects for variables including sex, age, and baseline category of severity status were studied.

Severity categories for CMTES-R were determined by use of the established categories for CMTNS (mild, moderate, and severe) and CMTES-R as a discriminator variable. A standard discriminant analysis was applied and evaluated with cross-validation. The classification ranges in CMTES-R were then categorized as mild, moderate, and severe. The effects of baseline CMTES-R category on longitudinal change were then analyzed with mixed model regression. Change scores from baseline were the response, so to be included in the model, it was necessary for a subject to have a measurement at baseline and at a minimum of 1 follow-up time.

The performance of the CMTES-R vs CMTES and the CMTNS-R vs CMTNS was evaluated by comparing mean change from baseline to 2 years to the SD of the change, the standardized response mean (SRM = mean change/SD change), for the first 2-year change. SRM values of 0.20 to 0.49, 0.50 to 0.79, and ≥ 0.80 reflect low, moderate, and high responsiveness, respectively.⁸ Estimated annual mean score and changes and their SDs were obtained from the model parameters.

SRMs were also obtained on the 2-year change scores for the components of the scales. The components were not modeled with regression, so it was necessary for each observation to have data at baseline and at 2 years of follow-up.

Data availability

Data not provided in the article because of space limitations, the study protocol, and the statistical analysis will be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Results

The INC evaluated patients with CMT1A between February 2009 and September 2018. Baseline CMTNS-R and CMTES-R scores were available for 517 and 1,177 patients, respectively (CMTNS-R and CMTES-R baseline data were missing for 754 and 94 patients) (table 2). Among the 1,209 patients who had at least 1 CMTES-R observation, either at baseline or during the first 6 years of follow-up, the mean $\pm$ SD age was 41 ± 18 years (range 4–87 years), and 233 (19%) were <21 years of age. Six hundred seventy-eight (56%) were female, and 530 (44%) were male (sex data were missing for 1 subject). Follow-up assessments at 1, 2, and 3 years were available for 377, 321, and 244 patients, respectively (table 2). A mixed regression model, fitted with the sample described in table 2, showed significant change in CMTES-R at years 2 through 6 compared to baseline (mean change from baseline 0.59 points at 2 years, $p = 0.0004$, $n = 321$) (figure 1). Consistent increases in CMTES-R were found at 2-year intervals (mean change 0.59 points, 95% confidence interval [CI] 0.27–0.92, $p = 0.0004$ from 0 [baseline] to 2 years, 0.72 points, 95% CI 0.35–1.09, $p = 0.0002$ from 1–3 years, and 0.84 points, 95% CI 0.46–1.22, $p < 0.0001$ from 2–4 years). Figure 1 also compares the categorical time model to a simplified linear time model and shows that the deviation of the 2 was marginally statistically nonsignificant (likelihood ratio test p value = 0.07). Goodness-of-fit tests suggest that the tradeoff between model fit and parsimony is about equal. The linear model estimates a change in mean CMTES-R score of 0.59 (95% CI 0.44–0.74, $p < 0.0001$) per 2 years. Comparing the CMTES-R to the original CMTES on the same dataset

revealed a 55% improvement in the SRM (mean change/SD change) for the CMTES-R score at 2 years (0.17 vs 0.11) (figure 2).

Of particular interest for future clinical trials for CMT1A was the subgroup analysis evaluating sensitivity to change of the CMTES-R in patients with varying baseline disease severity. This evaluation required us to define mild, moderate, and severe disease categories for the CMTES-R as was previously done with the CMTNS.³ On the basis of this analysis, CMTES-R subgroups were defined as follows: mild 0 to 9, moderate 10 to 18, and severe >19. Change in CMTES-R at 2 years was numerically greater in mildly affected compared to moderately affected patients: 1.48-point mean change (95% CI 0.99–1.97, $p < 0.0001$) for participants with baseline CMTES-R scores of 0 to 9 vs 0.79-point mean change (95% CI 0.28–1.29, $p = 0.002$) for those with baseline scores of 10 to 18 (figure 3). The difference between the 2 changes did not reach statistical significance (-0.70 , 95% CI -1.40 to 0.00 , $p = 0.05$); however, the SRM in the CMTES-R at 2 years was higher in mildly than in moderately affected patients (0.55 vs 0.22), suggesting that CMTES-R scores may be more sensitive in detecting clinical progression in those with milder disease.

Severely affected patients (CMTES-R score >19) demonstrated a decrease in CMTES-R score at 1 year (-0.83 point, 95% CI -1.34 to -0.32 , $p = 0.002$) and at 2 years (-0.77 point, 95% CI -1.50 to -0.05 , $p = 0.037$). There was a small estimated decrease for moderately affected patients at 1 year, but it was not statistically significant (-0.11 , CI -0.49 to 0.27 , $p = 0.56$). The baseline data in the severe group ranged from 19 to 32, with 22 as the median and 27 as the 95% percentile. The trajectories of individual participants were examined and were quite varied, with some increasing and some decreasing during the initial follow-up years, and a slow drift toward higher values over the 6-year follow-up period. The maximum possible value of the CMTES-R scale (total 32 points) was not

Table 2 Demographics and CMT scores

	CMTES-R					CMTNS-R	
Age, mean $\pm$ SD, y	41.1 $\pm$ 18.0					43.1 $\pm$ 16.7	
M/F, n (%)	530 (44)/678 (56)					316 (58)/231 (42)	
Race, white yes/no, n (%)	1,100 (91)/109 (9)					480 (88)/68 (12)	
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
CMTES	9.8 $\pm$ 4.9 (1,177)	9.8 $\pm$ 4.6 (377)	10.2 $\pm$ 4.8 (321)	10.5 $\pm$ 5.2 (244)	10.6 $\pm$ 4.9 (208)	10.7 $\pm$ 5.3 (160)	11.4 $\pm$ 5.0 (119)
CMTES-R	13.3 $\pm$ 6.4 (1,177)	13.4 $\pm$ 6.9 (377)	14.1 $\pm$ 6.2 (321)	14.4 $\pm$ 6.7 (244)	14.5 $\pm$ 6.3 (208)	14.7 $\pm$ 6.8 (160)	15.6 $\pm$ 6.4 (119)
CMTNS	15.4 $\pm$ 5.7 (517)	15.5 $\pm$ 5.6 (54)	17.6 $\pm$ 5.9 (32)	17.4 $\pm$ 6.6 (18)	17.2 $\pm$ 5.4 (17)	21.5 $\pm$ 7.0 (15)	18.2 $\pm$ 5.1 (11)
CMTNS-R	19.1 $\pm$ 7.1 (517)	19.0 $\pm$ 7.0 (54)	22.1 $\pm$ 7.5 (32)	21.8 $\pm$ 8.3 (18)	21.1 $\pm$ 6.9 (17)	26.4 $\pm$ 8.4 (15)	22.2 $\pm$ 6.7 (11)

Abbreviations: CMT = Charcot-Marie-Tooth; CMTES = Charcot-Marie-Tooth Examination Score; CMTES-R = Rasch-modified Charcot-Marie-Tooth Examination Score; CMTNS = Charcot-Marie-Tooth Neuropathy Score version 2; CMTNS-R = Rasch-modified Charcot-Marie-Tooth Neuropathy Score version 2. Data in the bottom part of the table are mean $\pm$ SD (number).

Figure 1 Change in CMTES-R score over 6 years

	Change from baseline	95% Confidence interval	p value
Year 1	0.20	-0.23, 0.28	0.85
Year 2	0.59	0.27, 0.92	0.0004
Year 3	0.74	0.37, 1.12	0.0001
Year 4	1.43	1.03, 1.83	<0.0001
Year 5	1.20	0.71, 1.68	<0.0001
Year 6	1.79	1.22, 2.63	<0.0001

Change in Rasch analysis-adjusted Charcot-Marie-Tooth Examination Scores (CMTES-R) from baseline over a 6-year period. CMTES-R scores increase gradually over subsequent years with relatively linear progression. Linear model estimates a change in mean CMTES-R score of 0.59 (95% confidence interval [CI] 0.44–0.74, $p < 0.0001$) over 2 years.

reached by the vast majority of participants, suggesting that there was not a true ceiling effect. Participants with milder disease severity in our cohort were younger (mean age 30 years in the mild group, 43 years in the moderate group, and 54 years in the severe group, $p < 0.0001$). Adjusting for age at baseline revealed the same patterns of progression in CMTES-R score in the 3 groups, with the mild group progressing by 2.82 points more than the severe group in the first 2 years ($p < 0.0001$).

Sample sizes limited the analysis of the CMTNS-R scores, and change over time was therefore evaluated only over a 4-year time frame. Baseline CMTNS-R scores were available for 517 participants, and 548 had at least 1 CMTNS-R observation at baseline or between 1 and 4 years of follow-up (table 2). A significant change in the scores (compared to year 0/baseline) was present at years 2 through 4 (mean change 2.3 points, 95% CI 0.92–3.74, $p = 0.002$ at 2 years, $n = 27$). A mixed model found a mean CMTNS-R score change of 1.61 points from baseline to 2 years (95% CI 0.54–2.67, $p = 0.004$), 1.36 points from 1 to 3 years (95% CI -0.25 to 2.96, $p = 0.0959$), and 0.50 point from 2 to 4 years (95% CI -1.08 to 2.08, $p = 0.53$) (figure 4). Similar to the CMTES, comparing CMTNS-R to original CMTNS scores revealed an improvement in the SRM for the CMTNS-R score at 2 years (0.51 vs 0.43).

The individual items on the CMTES that showed the most progression at 2 years included leg motor symptoms (change 0.14 points, $p < 0.0001$), and arm motor symptoms (change 0.09 points, $p = 0.023$). These 2 items also demonstrated the highest SRM (0.25 and 0.13, respectively). The remaining items showed a trend toward progression with the exception of pinprick sensitivity and arm strength (figure 5). Evaluation of the 2 electrophysiologic items on the complete CMTNS showed the most change in the ulnar compound muscle action potential (change 0.3 points, $p = 0.04$). However, this finding must be interpreted with caution given the small sample size ($n = 27$).

We also analyzed the potential effects of age and sex. As expected, participants <26 years of age had lower CMTES-R scores at baseline than those ≥ 26 years of age (8.3 for age <26 years, $n = 292$ participants; and 14.8 for age ≥ 26 years, $n = 916$ participants, $p < 0.0001$). However, there was no age group effect on rate of change at any individual time point ($p = 0.75$ for baseline–2 years). There was also no evidence of a mean baseline difference in CMTES-R score between the sexes ($p = 0.32$) or that sex affected the rate of change in CMTES-R score ($p = 0.54$ for baseline–2 years, $p = 0.70$ for all times).

Figure 2 Change in CMTES score over 6 years

Discussion

This is the largest longitudinal study of patients with CMT1A to date and the first longitudinal study to evaluate the CMTNS-R and CMTES-R. Our results show that the CMTES-R demonstrates change over time in patients with CMT1A and that Rasch-modified scores show improved sensitivity to change compared to the raw CMTES scores (55% improvement in the SRM at 2 years). We found no evidence that the responsiveness of the CMTES-R differs according to age or sex. In regard to individual items on the CMTNS, our findings corroborate prior observations that pinprick sensitivity is the least responsive.^{9,10}

Of particular interest for future clinical trials for CMT1A was the subgroup analysis evaluating sensitivity to change of the CMTES-R score in patients with varying baseline disease severity. This evaluation required us to define mild, moderate, and severe disease categories on the CMTES-R. Subgroup analysis using the new severity categories (scores of 0–9, 10–18, >19) on the CMTES-R revealed that change in CMTES-R score at 2 years was numerically greater in mildly than in moderately affected patients and that the SRM for change in CMTES-R score at 2 years was 150% higher in mildly compared to moderately affected patients. While the difference in change on the CMTES-R between the mild and moderately affected patients did not reach statistical significance ($p = 0.05$), these findings suggest that the CMTES-R

may be more sensitive in detecting clinical progression in mildly affected patients with CMT1A. In contrast, severely affected patients (CMTES-R score >19) demonstrated a small improvement in the CMTES-R over the first 2 years of the study, even when controlling for age, and are therefore not good candidates for clinical trials using the instrument. Our findings contrast with prior findings showing that items on both the CMTNS and CMTNSv2 are most appropriate for assessing patients with moderate and severe neuropathy.^{7,11} Additional studies using the CMTES-R in conjunction with other COAs and biomarkers are needed to confirm that the severity categories we have defined accurately reflect disease severity and disability and that mildly affected patients are indeed the optimal candidates for emerging treatment trials.

Our data underscore the limitations of using the CMTES-R as the sole clinical outcome measure in CMT1A. While the CMTES-R significantly changed over a 2-year time frame, the numeric change (0.59 on a 32-point scale) is small and commensurate with the slow clinical progression experienced by patients. Even for the mildly affected patients with CMT1A, the group who changed the most, a 2-year randomized, double-blind clinical trial evaluating a disease-arresting treatment would require ≈ 235 participants per group to achieve a 75% effect size ($\alpha = 0.05$). Therefore, it seems appealing to combine the CMTES-R score with biomarkers that correlate to it but that are themselves more

Figure 3 Influence of baseline disease severity on change in CMTES-R score (mixed model regression)

Weighted CMTES	Mean change from baseline at 2 years (CI)	p value	SRM
0-9 (n = 89)	1.48 (0.99, 1.97)	<0.0001	0.55
10-18 (n = 154)	0.79 (0.28, 1.29)	0.002	0.22
>19 (n = 68)	-0.77 (-1.50, -0.05)	0.037	0.22

Categorical model showing change in Rasch-modified Charcot-Marie-Tooth Examination Score (CMTES-R) based on disease severity at baseline over a 6-year period. Red indicates mild (CMTES-R score 0–9); green, moderate (CMTES-R score 10–18); and blue, severe (CMTES-R score >19). Bars are 95% confidence intervals (CIs). Mildly and moderately affected patients show more disease progression than severely affected patients. SRM = standardized response mean.

sensitive to change and can serve as primary outcome measures for emerging clinical trials in CMT1A. Fat fraction in the calf muscle on MRI is particularly promising in this regard; it has an SRM of 1.04 over 12 months and correlates well with the CMTES.¹² The fat fraction, however, has higher responsiveness in patients with moderate to severe CMT1A, and correlating this with the CMTES-R will require additional work.¹³

The small number of participants who underwent electrophysiology prevented us from adequately evaluating the responsiveness of the CMTNS-R in CMT1A. Electrophysiology is an objective test and indirectly measures axonal loss, but it is not routinely done as part of annual visits for

CMT. The INC has therefore increasingly moved toward using the CMTES to maximize the number of participants contributing to our natural history data. It has previously been suggested that the CMTES may be preferable to the CMTNS in clinical trials because it was demonstrated to show more deterioration over time with a higher SRM than the CMTNS.⁸ Post hoc analysis of an ascorbic acid trial in CMT1A also demonstrated a better outcome as measured by the CMTES.⁸ Another limitation of our study is that not all patients returned every year and that some patients had missing baseline CMTES-R scores. We have addressed this by using longitudinal regression models to evaluate change in CMTES-R score, allowing for missing years between visits.

Figure 4 Change in CMTNS-R score over 4 years

Categorical model showing change in Rasch-modified Charcot-Marie-Tooth Examination Scores (CMTNS-R) from baseline over a 4-year period. CMTNS-R scores increase over subsequent years.

The INC continues to evaluate novel outcome measures for CMT in an effort to develop optimal tools that capture disease severity and progression for emerging clinical trials. These

include the recently developed functional outcome measure for CMT and the patient-reported CMT Health Index.^{14,15} Emerging COAs and biomarkers for CMT1A have to be

Figure 5 Responsiveness to change of individual CMTES items at 2 years

Change in individual Charcot-Marie-Tooth Examination Score (CMTES) items over a 2-year period. Pinprick sensibility and arm strength were least responsive.

correlated with clinical assessments that have been used in natural history studies to ensure clinical relevance. In addition to serving as a measure of clinical progression, the CMTES-R will therefore have an important role in the evaluation of these novel measures and biomarkers in patients with CMT1A. It is worth noting that while our study included younger patients with CMT1A (233 patients <21 years of age, range 4–83 years), outcome measures designed specifically for children and infants with CMT have been developed within the INC and remain optimal measures for clinical trials in pediatric patients with CMT.^{16,17}

The Rasch analysis-based CMTES-R demonstrates change over time in patients with CMT1A and is more sensitive than the original, unweighted CMTES. We found that the CMTES-R was most sensitive to change in patients with mild to moderate baseline disease severity and failed to capture progression in patients with severe CMT1A. While significant, the actual degree of change in CMTES-R remains small, underscoring the importance of its use in conjunction with other objective and patient-reported outcome measures in future clinical trials.

Disclosure

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