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The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM)

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Abstract

Objective

The purpose of this study was to examine the feasibility, reliability, and convergent validity of the Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM), a new performance-based measure assessing functional ability in adults with CMT disease.

Methods

Adults with CMT type 1A (CMT1A) were recruited at the Universities of Rochester and Iowa. Participants were assessed using the CMT-FOM, CMT Exam Score (CMTES), and a symptom report. Test-retest reliability was examined using intraclass correlation coefficients, internal consistency using Cronbach α, and convergent and known-groups validity using Spearman rank analysis and the Mann-Whitney test.

Results

Forty-three individuals (70% women; mean age 41, SD 14.9 years) participated. The CMT-FOM (mean 25.3 ± 8.7, range 12–44/52) was moderately correlated with the CMTES (ρ = 0.62; $p < 0.0001$) and exhibited acceptable reliability (intraclass correlation coefficient = 0.92) and internal consistency (Cronbach α = 0.81). The CMT-FOM discriminated between participants with clinically mild vs moderate-severe CMT1A. Participants with the mildest CMT1A who demonstrated a floor effect on the CMTES showed functional limitations on the CMT-FOM.

Conclusions

The CMT-FOM is well tolerated and showed no floor/ceiling effects in an adult CMT1A cohort matching those likely to enter upcoming clinical trials. It appears to be reliable, and our data support convergent and known-groups validity in adults with CMT1A. Longitudinal studies further examining the psychometric properties of the CMT-FOM and its responsiveness to change before its application in therapeutic trials are necessary.

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Glossary

CMT = Charcot-Marie-Tooth; **CMT1A** = Charcot-Marie-Tooth type 1A; **CMTES** = Charcot-Marie-Tooth Exam Score; **CMT-FOM** = Charcot-Marie-Tooth Functional Outcome Measure; **CMTNS** = Charcot-Marie-Tooth Neuropathy Score; **CMTPedS** = Charcot-Marie-Tooth Pediatric Scale; **ICC** = intraclass correlation coefficient.

Charcot-Marie-Tooth neuropathy (CMT) is a collective name for inherited peripheral neuropathies, which affect 1 in 2,500 individuals and result from mutations in more than 90 genes. CMT type 1A (CMT1A), due to a duplication in the gene encoding PMP22, represents 50% of all CMT.[1] CMT1A manifests with slowly progressive distal motor and sensory loss resulting in limitations involving gait, balance, and hand function. There have been advances in understanding the pathomechanisms and natural history of CMT, with emerging therapeutic candidates, in particular for CMT1A. Clinical trials in CMT1A have been challenging because of the slow progression and lack of responsive, clinically meaningful outcome measures. The CMT Neuropathy Score (CMTNS), a validated measure of disease impairment, was unable to detect progression in the placebo-treated arm over 2 years in trials of ascorbic acid in CMT1A.[2] The CMTNS has since been modified—CMTNS version 2 and a Rasch weighted version, with efforts directed toward making it more amenable to detecting change in disease severity.[3,4] Notwithstanding, its responsiveness to change remains limited,[1] and it lacks a functional domain, an important element for Food and Drug Administration regulatory approval. Recently, the CMT Pediatric Scale (CMTPedS), a measure of functional disability, was validated and demonstrated responsiveness to change over 2 years in children with different CMT types, including CMT1A.[5,6] Future CMT1A trials will likely be conducted in adults initially, given its insidious course and variable age of symptom onset. Therefore, it is essential to have valid, responsive, and meaningful measures of function for adults with CMT. We report the development and initial evaluation of an adult CMT Functional Outcome Measure (CMT-FOM).

The CMT-FOM is modeled on the CMTPedS[6] and has been designed to meet Food and Drug Administration guidance of a valid, responsive, and meaningful measure of function for application in trials in CMT.

Methods

Standard protocol approvals, registrations, and patient consents

Individuals aged 18 to 70 years with genetically confirmed CMT1A were recruited from the University of Rochester and the University of Iowa under an institutional review board–approved protocol and provided informed consent. Participants at the University of Rochester who were able to return at 4 weeks completed a second visit to establish reliability.

Measures

The CMT-FOM is a performance-based assessment that measures the construct functional ability in adults with CMT1A (table 1). It was based on the CMTPedS and further developed using literature review, patient interviews, a survey of 407 adults with CMT,[7] and expert opinion, all supporting content validity. Items were selected based on CMT1A disease-specificity, functional/patient-relevance, reliability/validity, responsiveness to change, availability of published norms, and ease of administration and interpretation. The CMT-FOM includes items administered using standardized instructions[6] from the CMTPedS that are relevant to adults. CMTPedS items omitted from CMT-FOM include the long jump (safety and lack of relevance to adults), vibration and pinprick sensation testing (included in the CMTNS and its subscore, the CMT Exam Score [CMTES]), and a qualitative assessment of gait. The balance assessment was modified to include those items relevant and safe for adults, omitting balance beam items. Four items from the common data elements from the National Institute of Neurological Disorders and Stroke (sit to stand, 10-m walk/run, stair climb, and timed up and go test) that reflect patient-identified functional limitations were added. These items have previously been used in CMT1A trials,[2] natural history studies, or other neuromuscular conditions and have shown potential responsiveness. Lastly, the items were peer reviewed by experts in the field for quality and suitability.

The CMT-FOM is scored similarly to the CMTPedS.[6] To generate a total score ranging from 0 to 52, the raw score of each item is converted to a z score, based on available age- and sex-matched norms, and categorized to a 0 to 4 Likert along a continuum of impairment levels: normal (0), very mild (1), mild (2), moderate (3), and severe (4). The conversion of item scores to z scores is based on the 1000 Norms Project,[8,9] controls for sex differences and age-related changes.

The CMTES version 2 is a subscore of the CMTNSv2.[3] It is a composite score that assesses symptoms, and sensory and motor impairment; however, unlike the CMTNSv2, it does not include nerve conduction studies.

Participants were also asked about the presence of foot pain, leg cramps, unsteady ankles, daily tripping/falls, hand weakness, hand tremor, and sensory symptoms.

Analyses

Spearman rank analysis was used to examine the relationships between the CMT-FOM and the CMTES and between individual scored items and reported symptoms. Intraclass correlation coefficient (ICC) was used to examine test-retest reliability (n = 8). Internal consistency was assessed with

Table 1 The Charcot-Marie-Tooth functional outcome measure

Domain	Test item
Strength	Handgrip,[a] n Foot plantar flexion,[a] n Foot dorsiflexion,[a] n
Upper limb function	Functional dexterity test,[a] s 9-hole peg test,[a] s
Lower limb function	10-m walk/run, s Stair climb, s Sit to Stand, 30 s
Balance	Stance with eyes open,[a] s Stance with eyes closed,[a] s Single leg stance,[a] s
Mobility	Timed up and go, s 6-min walk test,[a] m

[a] Charcot-Marie-Tooth Pediatric Scale items.

Cronbach α. Convergent and known-groups validity was examined using the Mann-Whitney test to determine whether the CMT-FOM was able to discriminate according to disease severity (CMTES ≤8 and CMTES >8).

Data availability

The data used and analyzed for this report are available from the corresponding author upon reasonable request.

Results

Forty-three individuals (70% women; mean age of 41, SD 14.9 years; range 18–68 years) participated in the study. The mean CMT-FOM score was 25.3 (SD 8.7, range 12–44). The mean CMTES was 9.3 (SD 4.5, range 0–19). Participants completed all items without discomfort or burden in approximately 35 minutes. The CMT-FOM was moderately correlated with the CMTES ($\rho = 0.62$; $p < 0.0001$) (figure). Test-retest reliability (ICC) for the CMT-FOM was 0.92. Reliability of individual items was good (ICC >0.70) with the exception of single limb stance (ICC = 0.37), which exhibited large variation in one participant. The Cronbach α was 0.81. The item-total score correlation is summarized in table 2. The CMT-FOM discriminated between individuals with mild disease severity vs those with moderate-severe disease severity as reflected by the CMTES ($p = 0.003$). A report of more symptoms was associated with a higher CMT-FOM score ($\rho = 0.39$; $p = 0.01$). Sensory impairment on the CMTES was associated with balance tests of standing with feet apart on a line with eyes open ($\rho = -0.43$; $p = 0.004$) and with eyes closed ($\rho = -0.45$; $p = 0.003$).

Discussion

The CMT-FOM was developed as a measure of functional disability for adults with CMT, for application in clinical trials, particularly those involving CMT1A. It was modeled on the CMTPedS and 9 items are identical in both. Items lacking face validity in the adult population and that could be subject to floor/ceiling effects in adults were removed and replaced with items that measure areas that adults with CMT report, namely, reduced quality of life and mobility.[7] Slowing the functional decline or improvement in these areas would therefore be likely meaningful to patients.

The CMT-FOM was feasible, reliable, and internally consistent in this sample. Moderate correlations between scored items and the total score suggest no single item reflects global functional

Figure Association between the CMT-FOM and CMTES

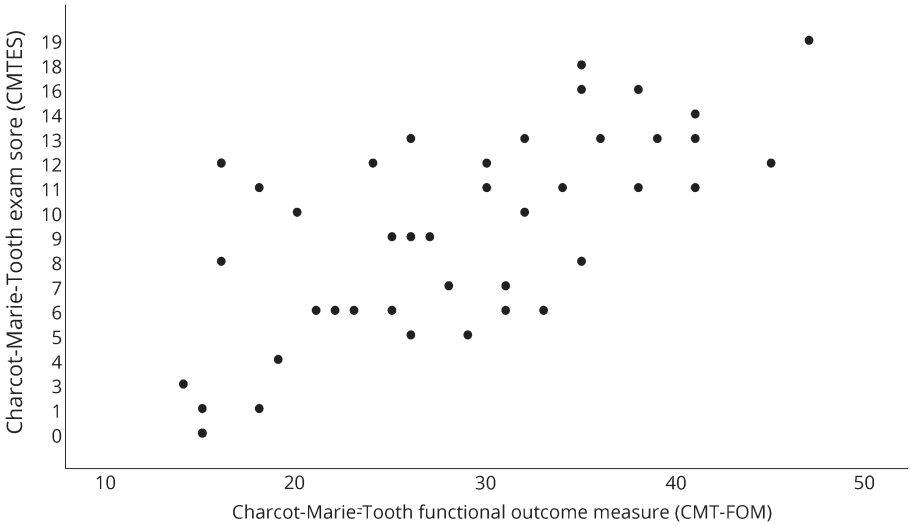

Table 2 Item-total score correlation

Item	Correlation	*p* Value
Functional dexterity test	0.52	<0.0001
9-Hole Peg Test	0.36	0.018
Grip	0.39	0.010
Plantar flexion	0.61	<0.0001
Dorsi flexion	0.54	<0.0001
Stance with eyes open	0.83	<0.0001
Stance with eyes closed	0.48	0.001
Single leg stance, eyes closed	0.51	<0.0001
6-min walk test	0.64	<0.0001
Timed up and go	0.63	<0.0001
30-s chair stand	0.36	0.019
30 foot go	0.59	<0.0001
Ascend stairs	0.61	<0.0001

impairment in CMT1A. The moderate correlation between the CMT-FOM and the CMTES indicated that while the scales are related, they also measure different aspects of the disease; the CMT-FOM assesses integrated sensorimotor function, whereas the CMTES emphasizes neurologic sensorimotor deficits. The CMT-FOM did not demonstrate floor or ceiling effects. Of note, in individuals with a very mild form of CMT1A who had a floor effect on the CMTES, decreased functional ability on the CMT-FOM was observed, suggesting that the CMT-FOM is less subject to a floor effect and that adults with the mildest severity of CMT1A may have functional limitations relative to the age- and sex-matched healthy population.

This initial study suggests that the CMT-FOM is reliable and supports content validity in CMT1A. It will be important to also examine the CMT-FOM in other CMT subtypes of differing disease severity. A larger validation study is required to further assess its psychometric properties including item redundancy, construct validity, multicenter intrarater and interrater reliability, and ability to detect change and the minimal clinically important change.[10]

Author contributions

Study design: K.E., J.B., D.N.H. Data collection, management, or analysis: C.B., M.L.S., J.M., J.S., D.N.H., K.C., M.E.S., R.S., K.E. Drafting the manuscript: K.C., J.B., M.E.S., D.N.H., K.E. All authors read and approved the final manuscript.

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