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The Charcot Marie Tooth Health Index: Evaluation of a Patient Reported Outcome

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Abstract

Objective—The development of a disease specific patient reported outcome for Charcot Marie Tooth disease is an important step in the preparation for therapeutic trials. This study describes the development of the Charcot Marie Tooth Health Index (CMTHI).

Methods—Inherited Neuropathy Consortium Contact Registry participants were queried on the symptoms that most impacted their lives. The CMTHI was developed based on these responses. Factor analysis, assessment of test-retest reliability, known groups validity, and patient interviews were utilized to refine the instrument.

Results—The final CMTHI contains 18 themes that capture CMT disease burden. The CMTHI has a high internal consistency and test-retest reliability. The CMTHI was able to discriminate between patient groups expected to have different disease burden. The CMTHI was able to discriminate levels of disability as measured by the CMT exam score and the mobility-Disability Severity Index.

Interpretation—The CMTHI represents a valid and reliable outcome to assess patient reported disease burden in CMT.

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Potential conflicts of interest: The CMTHI is a copyrighted instrument of the University of Rochester. Drs. Johnson, Heatwole, and Herrmann are co-inventors of the CMTHI and receive royalties from the University of Rochester.

Search terms

Charcot Marie Tooth disease; patient reported outcome measure; peripheral neuropathy

Introduction

Charcot Marie Tooth disease (CMT) is the most common form of peripheral neuropathy.¹ Most individuals with CMT are characterized by progressive distal weakness, atrophy, and numbness.¹ However, there may be significant variation in symptoms based on the CMT subtype. The variation in symptoms, severity, and disease progression create challenges when conducting and designing therapeutic trials in CMT.

Recent Food and Drug Administration (FDA) guidance has provided a structure for creating patient reported outcomes designed to measure the burden of a disease.² This type of patient input is critical for development of therapies as it provides an important window into the patient's perspective. While prior research has identified difficulty with ambulation, leg weakness, and muscle cramps as affecting quality of life, many of these studies were performed with generic patient reported outcomes (e.g., the Short Form-36) which may lack the sensitivity to detect changes in all of the areas important to CMT patients.^{3–6}

We previously identified 214 symptoms of importance to individuals with CMT in a cross-sectional survey and developed a model to understand how the functional limitations affect the disease burden in this population.^{7,8} From the survey data we have created the Charcot Marie Tooth Health Index (CMTHI), a disease-specific patient reported outcome measure. This patient reported outcome measure is designed to capture the overall disease burden associated with CMT. The CMTHI and its subscales are designed to be used in therapeutic trials, based on written guidance from the FDA.⁹ Here we detail the construction of the instrument, including its content validation, test-retest reliability, and ability to discriminate between groups thought to have different disease burden.

Methods

Eligibility Criteria

Participants were over the age of 18 and had a diagnosis of any form of CMT by genetic or clinical criteria.¹⁰ Participants were recruited from the Inherited Neuropathies Consortium Rare Diseases Clinical Research Network (RDCRN 1U54NS0657) Contact Registry for Group 1. Groups 2 and 3 were recruited from Investigator clinics (Utah, Rochester, and Iowa) and enrolled at either University of Utah (Group 2) or University of Rochester (Group 3). Three different samples were utilized for different aspects of this research. The first group (Group 1, n = 407) are those participants who initially completed the survey, as reported.⁸ The second group (Group 2, n = 15) are those participants who completed the cognitive interviews. The final group (Group 3, n = 45) are those participants who performed repeat assessments for the evaluation of test-retest reliability. All research activities were approved by the Institutional Review Boards at the University of Rochester and the University of Utah. All participants provided informed consent.

Charcot Marie Tooth Health Index Creation

Question Selection and Content Validity

We have previously reported on qualitative interviews that were used to comprehensively identify the symptom burden of CMT.⁷ These 214 symptoms were then included on a questionnaire that was given to 407 participants so that they could rate the impact of each symptom on a six point Likert scale, as previously reported.⁸ A population impact score was assigned to each question based on its prevalence in the individuals responding to the survey and relative impact (scale 0–4 with 4 representing the highest level of burden).⁸ To create the initial CMTHI, we utilized questions with a population impact score > 0.5. CMTHI questions that met this criterion were excluded if there was consensus amongst investigators that the question was: 1) redundant; 2) not amenable to therapeutic intervention; or 3) if it had vague wording.

Factor Analysis

The initial survey grouped questions into content-similar subscales. We subsequently used exploratory factor analysis to determine if questions within each subscale measured a similar concept. The exploratory factor analysis was performed using SPSS, with principal axis factoring as the extraction method and Oblimin with Kaiser Normalization as the rotation method. The response data from Group 1 were used for this analysis. Questions with factor loadings > 0.30 were determined to load on a particular factor. Questions with cross-loadings on different factors, and those with factor loadings < 0.30 on the primary factor were considered for transfer, depending on content, to a more appropriate subscale. Cronbach's alpha was used to evaluate the internal consistency of the whole scale. Additional questions were removed if there was low internal consistency within a factor. Confirmatory factor analysis (CFA) was performed using MPlus 7.4 to determine factor validity of the subscales. Estimation of parameters were carried out using weighted least squares with mean and variance adjustment (WLSMV) with delta parameterization over polychoric correlations. This method is robust to item skewness and kurtosis.

Cognitive interviews

Once the exploratory factor analysis was complete, we arranged questions in the CMTHI by subscale. This questionnaire represented version 1 of the CMTHI. Semi-structured interviews were then performed with 15 participants with CMT (Group 2). These interviews assessed the overall comprehension of the instrument, feasibility of use, scoring, and period of time by which participants assessed the symptom severity. Participants were provided version 1 of the CMTHI and asked to complete it. Following completion, participants described the theme behind each subscale, assessed whether the provided Likert responses accurately depicted their choices, provided feedback on wording, and identified symptoms that were not assessed. They also provided an assessment of the time frame they used to recall the individual symptom. These interviews were recorded and analyzed. CMTHI questions were discarded or re-worded based on participant input to create version 2 of the instrument.

Test-retest reliability

Test-retest reliability of the CMTHI version 2 was assessed in 45 participants with CMT (Group 3). Participants were provided the survey online, along with the SF-36. Participants completed the initial survey and received the exact same survey four weeks later. Reliability was assessed using the total score across the entire instrument, each subscale score, and individual question Likert responses. Intraclass correlation coefficients (ICCs) were used to quantify the reliability of the instrument. Questions with an ICC<0.70 were discarded. Once unreliable items were discarded, we performed another confirmatory factor analysis to confirm the continued construct validity of the instrument.

Scoring of the CMTHI

The overall instrument is weighted, with a possible score ranging between 0–100. Individual question weights were derived from the mean Likert response of each symptom using the survey responses from Group 1. The weighted sum of responses was transformed to a 0–100 scale by expressing it as a percentage of the maximum possible value with a score of 100 representing the most severe disease burden and a score of zero representing no disease burden. A similar algorithm was developed to compute individual scores (range: 0–100) for each subscale.

Known Group Validity

The average CMTHI total score and subscale scores were determined for predefined subgroups that may have different disease severity. Groups were defined by employment (employed vs. unemployed), disease duration (greater than or equal to 20 years vs. less than 20 years), and CMT subtype. Data from Group 1 were used for this analysis. Questions added after the original survey were treated as missing data. Group comparisons of the mean total scores were performed using Wilcoxon rank sum scores. To assess convergent validity, participants in Group 3 were provided the SF-36 at the same time as the CMTHI. The total CMTHI score was correlated with SF-36 scale scores using Pearson correlations. In addition, participants in Group 3 were evaluated using the CMT examination score (CMTES), a validated impairment assessment of the symptoms and signs associated with CMT.¹¹ Participants were grouped into those whose CMTES was less than 10 and those whose CMTES was greater than 10, to differentiate those individuals with less or more disability, respectively. Wilcoxon Rank-sum test was used to compare the CMTHI scores between these groups. The mobility-Disability Severity Index (mDSI) is a four-point scale that assesses the disability associated with CMT.¹² Participants scoring between 0–2 on the mDSI have no to mild disability, while those participants scoring 3–4 on the mDSI have moderate to severe disability. A Wilcoxon Rank-sum test was used to compare the CMTHI scores between these groups.

Results

Patients

The demographic and clinical characteristics for participants in Groups 1–3 are provided in Table 1.⁸

Initial Question Selection

The initial survey included 214 symptoms in 20 themes. We eliminated 58 questions based on low impact (17), redundancy (18), lack of perceived responsiveness to intervention (14), potential abrasiveness to respondents (1), and vague wording (8) (Figure 1).

Factor Analysis

The initial survey results from Group 1 were used for exploratory factor analysis. Eighteen different factors were identified from the exploratory analysis. As a result of the initial factor analysis, 39 questions were removed as they had low internal consistency within a factor (Cronbach's $\alpha < 0.40$) (Figure 1). Eight questions were moved to achieve a better internal consistency with the subscale. Finally, five subscales were removed because they had an overall low internal consistency or the questions were moved to another subscale to reduce the burden of the test. For example, the subscale "Decreased satisfaction in social situations" was merged with "Decreased performance in social situations." Four questions formed new single-item subscales (e.g., Breathing problems) because they had low internal consistency within other factors but remained relevant questions to understand the burden of CMT on a patient.

The instrument was subjected to a confirmatory factor analysis at the completion of patient interviews and test-retest reliability assessment. The internal consistency of each subscale is provided in Table 2.

Patient Assessment with Qualitative Interviews

Fifteen patients with CMT of different ages and subtypes provided feedback regarding the ease of completion and clarity of the instrument (Group 2). All participants were asked to identify the theme represented by each subscale, and all provided correct responses. Three questions were removed because participants could not understand what the question was asking (Figure 1). Participants provided disparate interpretations of the questions on "visual spatial difficulties," "difficulty doing laundry," and "sense that walking is uneven."

Overall, the participants provided positive feedback about the instructions, ease of use, and whether the CMTHI accurately captured all of the symptoms that may result from CMT. On average, the instrument required 15 minutes to complete (range 5–25 minutes).

Test-retest reliability

Forty-five participants (Group 3) completed the CMTHI twice over a one-month period (Supplemental Figure 1). The scores ranged from 0 to 95.88. Five questions were eliminated for an ICC less than 0.70 (Figure 1). The remainder of the questions had a test-retest reliability higher than this standard threshold.¹³ The five questions were (ICC): "Difficulty running" (ICC 0.55); "Having to look at feet when walking" (ICC 0.65); "Frustration" (ICC 0.66); "Impaired body image" (ICC 0.68); "Impaired interaction with family members" (ICC 0.64). Removal of these items yielded the final version of the CMTHI. The final version of the CMTHI consists of 18 subscales that measure 109 symptomatic themes of importance to patients with CMT. There are 127 total questions in the CMTHI. Participant response to each question using a 6-point Likert scale to identify the current impact that each

individual symptom has on their lives. The format of the questions and Likert scale has been previously tested and validated through extensive qualitative testing in multinational neuromuscular populations.^{14–17} The exact subscales measured using the CMT-HI and the number of questions in each subscale are detailed in Table 2.

Table 2 lists the ICC values for the CMTHI total score and each subscale. A plot of the CMTHI total scores at the first vs. second (repeat) assessments is provided in Figure 2.

Known Groups validity and Concurrent Validity

The CMTHI total score and subscale scores were able to differentiate between groups with different disease burden (Table 3; Supplemental Table 1). Four theme questions were added to the final instrument that were not present in the initial survey (figure 1). These were treated as missing data as part of this analysis. There were higher mean CMTHI total scores in patients who were not employed and had longer disease duration. Most of the subscales had a higher mean score in participants with a longer disease duration; the exceptions were for subscales that measured emotional issues, cognitive problems and constipation. There were no significant differences in mean CMTHI subscale scores between different CMT types with the exception of mean numbness scores, which were higher in CMT1B and CMT4, and lower in CMTX. There were some differences between male and female participants. Mean shoulder or arm weakness, pain, fatigue, and constipation scores were all higher in women. Six participants completed study visits remotely, and therefore did not have a CMTES score. There were differences in the CMTHI total score between those who are less impaired on the CMTES score and those who are more impaired (Table 3). There were also significant differences comparing the CMTHI total score between those with minimal to more severe disability (Table 3). Finally, the CMTHI total score and subscale scores had good correlation with the SF-36 scores (Table 4).

Discussion

The Charcot Marie Tooth Health Index (CMTHI) is a disease-specific, patient reported outcome measure designed for this broad category of inherited neuropathies. This instrument is specifically designed to capture the disease burden of these disorders in the context of a clinical trial.

These results highlight the disease burden associated with CMT and demonstrate that patient-perceived disease burden as measured by the CMTHI increases with disease duration and is strongly associated with the ability to work. The CMTHI was able to differentiate between different neurologic impairment and disability levels within CMT, as measured by the CMTES and mDSI.

The CMTHI, as a disease specific instrument, has advantages over generic instruments. Disease-specific instruments are able to focus on the questions most relevant to the disease population, excluding those questions that are less relevant. Disease specific instruments have been shown to have a reduced burden on the participant and improved sensitivity to change in a clinical trial.^{18–20} Disease states, such as CMT, prove a unique challenge as

there is heterogeneity between the different subtypes. The known group comparison demonstrated minimal variation in scores between the CMT subtypes assessed.

The FDA has provided specific guidance on the creation of patient-reported outcomes, such as this one.^{2,21} The creation of this instrument was extensively based directly on patient input. Patients identified the initial survey items de novo, and then subsequently validated the final set of items. The methodology described was designed to comply with the FDA's recommendations to demonstrate the reliability and validity of a patient-reported outcome measure. The CMTHI provides a mechanism to estimate disease burden in clinical trials. We have shown that the CMTHI is reliable and has a diverse range of subscales that have been psychometrically validated and shown to be important to the CMT population.

There are some limitations to our approach. The instrument was constructed based on input from CMT patients. These patients were recruited based on their involvement with the Inherited Neuropathies Consortium Rare Diseases Clinical Research Network. While we believe this to be an adequate representation of the CMT patients that may participate in future clinical trials, we cannot definitely state that this sample represents the greater CMT community. There were limited differences on the instrument when comparing CMT subtypes. It is possible that there was an insufficient sample size for rare CMT mutations to detect subtype differences. Six participants did not complete the CMTES, so it is possible that this analysis was skewed by severity. However relationships between the CMTHI and CMTES were concordant with those observed between the CMTHI and mDSI, which was completed by all participants. In addition, the responsiveness of this instrument has yet to be determined. While known groups testing is one way to crudely examine this, true responsiveness to disease progression must be confirmed using a longitudinal study.

These results describe the creation of the CMTHI, a disease specific patient reported outcome for use in Charcot Marie Tooth disease. The instrument is reliable and able to discriminate between different levels of disease burden. While these results provide initial reliability and validity testing, the instrument will benefit from additional longitudinal study to define the sensitivity of the instrument prior to use in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Development of the CMTHI

This flow diagram describes the development of the CMTHI, including the number of items removed during each step in the creation of the instrument.

1. 17 questions removed from low impact, 18 questions for redundancy, 14 questions for responsiveness, 1 for abrasiveness, 8 questions for vagueness

Figure 2.

The test-retest reliability of the CMTHI

Participants in cohort 3 received the CMTHI at baseline and 4 weeks later, along with the SF-36. The test-retest reliability for the overall instrument was high (ICC=0.96).

Table 1

Demographic and Clinical Characteristics of Participants

Group	Group 1 ^a	Group 2	Group 3
Number of Patients	407	15	45
Gender (% female)	64	60	51
Age (mean, SD)	52.3 (15.1)	38.8 (16.8)	54.8 (13.1)
CMT type (%)			
CMT1	0.0	0.0	8.9
CMT1A	36.1	46.6	35.6
CMT1B	3.4	0.0	4.4
CMT2	0.0	0.0	35.6
CMT2A	7.1	53.3	0
CMT4	1.5	0.0	2.2
CMTX	3.2	0.0	4.4
Unknown	48.7	0.0	8.9

Table 2

Internal consistency and test-retest reliability of CMTHI subscales

Subscale	Number of questions	Internal consistency (Cronbach alpha) ^I	Intraclass correlation coefficient (ICC)
Mobility	15	0.96	0.92
Foot/ankle weakness	4	0.91	0.85
Impaired balance	4	0.91	0.88
Activity limitations	13	0.93	0.95
Hand and finger weakness	13	0.96	0.90
Shoulder or arm weakness	3	0.91	0.90
Numbness	5	0.91	0.91
Pain	9	0.93	0.94
Fatigue	3	0.89	0.88
Impaired sleep	3	0.83	0.90
Emotional issues	7	0.92	0.93
Social performance	6	0.87	0.83
Difficulty thinking	2	0.82	0.92
Heartburn	1	N/A	0.90
Constipation	1	N/A	0.85
Hearing impairment	1	N/A	0.79
Breathing problems	1	N/A	0.85
Problems choking	1	N/A	0.87
CMTHI total score			0.96

^I Cronbach's alpha cannot be calculated for a single question subscale.

Table 3**Known Group Validity of the CMTHI**

CMTHI Subscales	Em-employed (n= 146)	Not Em-employed (n= 220)	Disease duration <20 years (n= 116)	Disease duration >20 years (n= 244)	CMTES score <10 (n=19)	CMTES score >10 (n=20)	mDSI score 0–2 (n=23)	mDSI score 3–4 (n=22)
Mobility	45.7 ¹	64.8	46.8	62.1	15.9	23.8	18.6	27.6
Foot/ankle weakness	58.8	71.7	57.7	70.8	17.1	22.8	16.9	29.4
Impaired balance	45.1	65.1	49.4	60.6	15.9	23.9	18.2	28.1
Activity limitations	32.3	49.9	35.8	46.3	16.4	23.3	20.7	25.4
Hand and finger weakness	32.8	49.8	31.4	48.5	15.1	24.7	19.2	26.9
Shoulder or arm weakness	23.6	38.6	23.3	37.5	16.0	23.8	19.7	26.5
Numbness	36.1	47.6	39.1	45.1	18.9	21.2	22.9	23.1
Pain	31.2	44.7	35.2	42.1	19.2	20.8	21.4	24.6
Fatigue	46.6	65.9	53.9	60.7	17.9	22.0	22.4	23.6
Impaired sleep	26.4	37.5	31.2	34.4	19.1	21.0	24.1	21.8
Emotional issues	22.8	31.5	27.2	28.8	19.7	20.2	22.1	24.0
Social performance	26.9	43.7	32.9	38.9	18.0	21.9	20.6	25.5
Difficulty thinking	10.2	15.8	13.2	14.1	19.4	20.6	22.7	23.2
Heartburn	20.9	26.7	18.1	27.0	17.3	22.6	22.0	24.0
Constipation	14.9	29.3	18.8	26.1	19.6	20.4	21.7	24.3
Hearing impairment	16.1	23.5	12.9	24.2	18.9	21.1	22.0	24.0
Breathing problems	16.9	24.8	14.0	26.0	17.5	22.4	21.4	24.7
Problems choking	8.0	13.6	7.1	13.8	19.9	20.1	25.0	21.0
Total score	34.6	49.1	36.9	46.5	16.8	23.0	20.0	26.1

¹ Bolded items indicate p<0.05² The CMTES and mDSI were performed in Group 3

Table 4

Correlations between CMTHI and SF-36 scores

SF-36 Scales									
CMTHI Scales	Physical component scale	Mental component scale	Physical functioning	Physical role	Bodily pain	General health	Vitality	Emotional Role	Mental health
Mobility	-0.64 [/]	-0.48	-0.81	-0.59	-0.34	-0.43	-0.57	-0.49	-0.70
Foot/ankle weakness	-0.47	-0.39	-0.61	-0.36	-0.34	-0.35	-0.48	-0.36	-0.47
Impaired balance	-0.57	-0.47	-0.69	-0.57	-0.28	-0.44	-0.52	-0.45	-0.56
Activity limitations	-0.57	-0.47	-0.69	-0.57	-0.28	-0.44	-0.52	-0.45	-0.56
Hand and finger weakness	-0.45	-0.47	-0.55	-0.39	-0.49	-0.32	-0.47	-0.45	-0.53
Shoulder or arm weakness	-0.61	-0.56	-0.68	-0.48	-0.49	-0.57	-0.63	-0.49	-0.62
Numbness	-0.39	-0.59	-0.38	-0.43	-0.59	-0.39	-0.45	-0.61	-0.56
Pain	-0.63	-0.68	-0.49	-0.65	-0.81	-0.47	-0.70	-0.60	-0.62
Fatigue	-0.72	-0.58	-0.61	-0.74	-0.58	-0.51	-0.75	-0.55	-0.48
Impaired sleep	-0.57	-0.74	-0.44	-0.61	-0.72	-0.62	-0.76	-0.68	-0.65
Emotional issues	-0.46	-0.84	-0.44	-0.53	-0.59	-0.64	-0.76	-0.66	-0.81
Social performance	-0.59	-0.64	-0.53	-0.66	-0.57	-0.50	-0.66	-0.65	-0.54
Difficulty thinking	-0.37	-0.71	-0.39	-0.52	-0.43	-0.47	-0.60	-0.62	-0.67
Heartburn	-0.41	-0.39	-0.27	-0.41	-0.40	-0.46	-0.50	-0.31	-0.39
Hearing impairment	-0.20	-0.51	-0.27	-0.36	-0.26	-0.23	-0.40	-0.51	-0.44
Breathing problems	-0.22	-0.45	-0.33	-0.23	-0.30	-0.23	-0.42	-0.37	-0.46
Problems choking	-0.33	-0.46	-0.33	-0.29	-0.45	-0.26	-0.49	-0.38	-0.38
Total score	-0.71	-0.72	-0.74	-0.70	-0.63	-0.58	-0.76	-0.68	-0.73

[/] Bolded items indicate p<0.05