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Research Article

Development and Validation of the Pediatric CMT Quality of Life Outcome Measure

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ABSTRACT

Objective: Charcot-Marie-Tooth disease (CMT) reduces health-related quality of life (QOL), especially in children. Defining QOL in pediatric CMT can help physicians monitor disease burden clinically and in trials. We identified items pertaining to QOL in children with CMT and conducted validation studies to develop a pediatric CMT-specific QOL outcome measure (pCMT-QOL).

Methods: Development and validation of the pCMT-QOL patient-reported outcome measure was iterative, involving identifying relevant domains, item pool generation, prospective pilot testing and clinical assessments, structured focus-group interviews, and psychometric testing. Testing was conducted in children with CMT seen at participating sites from the USA, United Kingdom, and Australia.

Results: We conducted systematic literature reviews and analysis of generic QOL measures to identify six domains relevant to QOL in children with CMT. 60 items corresponding to those domains were developed de novo, or identified from literature review and CMT-specific modification of items from the pediatric Neuro-QOL measures. The draft version underwent prospective feasibility and face content validity assessments to develop a working version of the pCMT-QOL measure. From 2010-2016, the pCMT-QOL working version was administered to 398 children ages 8-18 seen at the participating study sites of the Inherited Neuropathies Consortium. The resulting data underwent rigorous psychometric analysis, including factor analysis, test-retest reliability, internal consistency, convergent validity, IRT analysis, and longitudinal analysis, to develop the final pCMT-QOL patient-reported outcome measure.

Interpretation: The pCMT-QOL patient-reported outcome measure is a reliable, valid, and sensitive measure of health-related QOL for children with CMT.

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common inherited neurodegenerative disorder, affecting 1 in 2500 individuals,[1] with no disease-modifying treatment. Previous therapeutic discoveries in CMT[2-4] led to several clinical trials;[5-7] though unsuccessful, these trials gave rise to an international collaboration to study the natural history of CMT[8] and validate new outcome measures for future trials.[9-12] Pediatric trials are especially in focus, as signs and symptoms can progress throughout childhood in CMT and many children become dependent on assistive devices by early adulthood.[13-16] Therefore, there is an urgent need for validated outcome measures for pediatric CMT trials, including patient-reported outcome (PRO) measures to assess disease burden. Health-related quality of life (QOL), a specific type of PRO, is an important outcome to assess in pediatric CMT trials as it is significantly reduced in children with CMT.[17,18] However, generic health-related QOL outcome measures are unsuitable for clinical trials as they lack specificity [19,20] and sensitivity[21,22] to disease-related changes, and there is no disease-specific health-related QOL outcome measure for children with CMT. The objective of this study was to build, and rigorously validate through prospective studies, a pediatric CMT health-related Quality of Life (pCMT-QOL) PRO measure for use in trials.

SUBJECTS AND METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved and monitored by the institutional ethics review board at Wayne State University and the University of Michigan. Three different samples were used for different aspects of the study: Group 1 (n = 31) participants were recruited from Wayne State University for the pilot testing of the pCMT-QOL PRO measure. Group 2 (n =398) participants were recruited through the prospective, natural history study in children with CMT (clinicaltrials.gov identifier NCT01193075) from 2010- 2016, at the following sites of the Inherited Neuropathies Consortium: USA- Wayne State University; University of Michigan; University of Iowa; Stanford University; Johns Hopkins University; University of Rochester; Children's Hospital of Philadelphia; Hospital of the University of Pennsylvania; and Nemours Children's Hospital; United Kingdom- UCL Institutes of Child Health and Neurology, London, UK; Australia- University of Sydney & Children's Hospital, Sydney, Australia. Group 3 (n=13) participants were recruited from the University of Iowa for test-re-test validation. Ethics approval from all institutions for all studies and written informed assent/consent from all children and their families were obtained.

Statistical Analysis

The development and validation of the pCMT-QOL PRO measure was an iterative process as recommended by FDA guidance.[23,24] The details of the conceptual framework (Figure 1) are provided below:

Defining the Construct: We identified domains that are pertinent to the health-related QOL of a CMT patient through (a) systematic literature review, and (b) analysis of common domains in existing pediatric QOL measures and the SF-36, a gold-standard adult generic QOL measure

Generation of the item pool: For the domains identified through the above process, a literature review was conducted to identify items pertaining to pediatric CMT health-related QOL; remaining items were developed de novo and through CMT-specific modification of select items from the pediatric Neuro-QOL measures, which in turn were developed and evaluated with National Institute of Health (NIH) funding.[25] The items were edited for clarity and then underwent patient and expert review[26] to develop a draft version of the pCMT-QOL PRO measure.

Pilot testing: We prospectively administered the draft version of the pCMT-QOL in 31 children with CMT ages 4-17 (Group 1), followed by structured focus-group interviews and clinical assessments to assess feasibility and face validity, and developed a working version of the pCMT-QOL PRO measure.

Psychometric Testing: From 2010 to 2016, the working version of the pCMT-QOL was also administered prospectively to 398 children seen at the participating sites of the Inherited Neuropathies Consortium (Group 2) for further psychometric testing, including internal consistency, convergent validity, and IRT modeling, to develop the final pCMT-QOL PRO measure. The working version of the pCMT-QOL PRO measure was also prospectively administered to 13 children with CMT (Group 3) to assess test-retest reliability. Validated assessments used for the analyses included the generic Child Health Questionnaire (CHQ), considered a gold standard in pediatric quality of life research,[27-30] and validated CMT Clinical Outcome Assessments (COAs), including the CMT Neuropathy Score (CMTNS) version 2, a validated composite outcome measure in CMT,[11] the CMT Exam Score (CMTES), a subset of the CMTNS without nerve conduction studies that has been validated as a stand-alone outcome measure in CMT,[12] and the CMTPedS,[10] the validated functional outcome measure in pediatric CMT. The statistical software used for the analyses were Stata-IC 12.1 (StataCorp, College Station, TX), SAS version 9.4 (SAS Institute Inc., Cary, NC) and Mplus version 8.4 (Muthén & Muthén, Los Angeles, CA). Specific analyses are detailed below.

Descriptive statistics: The study sample was characterized with descriptive statistics such as mean, standard deviations, median, and range.

Test-retest reliability: Thirteen children were administered the working version of the pCMT-QOL twice within a 7-week period, the first provided in clinic, and the second mailed to home. Intraclass correlation coefficients (ICCs) were used to quantify the test-retest reliability of the pCMT-QOL; individual items with low ICCs were discarded, depending on content analysis.

Factor analysis and IRT analysis: The construct validity of the 6-domain working version of the pCMT-QOL was assessed via exploratory factor analysis (EFA), with iterated principal axis factoring as the extraction method, and varimax as the rotation method. Questions with significant factor loadings (> 0.30) were assigned to a domain, while those with cross-loadings or factor loadings < 0.30 were considered for transfer to a more appropriate domain. Confirmatory factor analysis (CFA) was performed to determine construct validity of the domains. Item response theory (IRT) analysis using graded response models (GRM) was used to verify the unidimensionality of each domain.

Final version and scoring: The final version of the pCMT-QOL PRO measure was developed and domain, composite, and total scores were calculated and transformed to a 0-100 scale with a higher score indicating worse QOL.

Internal consistency and validity: Cronbach's alpha coefficient was calculated to evaluate the internal consistency within each domain. Convergent validity was determined by calculating the Spearman's Rank Correlation between the Total

pCMT-QOL score and validated outcome measures such as the CMTNS, CMTES, CHQ, and the CMTPeds, as well as the correlation between the pCMT-QOL Physical Composite Domain Score, the pCMT-QOL Mental Composite Domain Score, and the corresponding physical summary score and the psychosocial summary score of the CHQ.

Known group comparisons: Two-sample t tests were used to compare groups defined by gender, worse disease severity characterized by CMTES >/= 10,[12] and CMT genetic diagnosis.

Longitudinal analysis: Longitudinal responsiveness was assessed by correlating changes in Total pCMT-QOL Score over time with changes to the CMTES and the 7-point Patient's Global Impression of Change (PGIC) scores (the latter ranging from 6 = "very much worse," 3 = "no change," all the way to 0 = "very much better"). The standardized response mean (SRM) for the Total pCMT-QOL Score over time was also calculated: SRM = mean change in scores over time/ standard deviation of change over time.

RESULTS

Results from specific steps of the iterative process were as follows:

Defining the Construct:

(a) *Systematic literature review*: We identified the following domains impacting QOL from CMT literature: psychosocial stressors,[31] physical disability, depression, pain,[32] ability to ambulate independently, toe and heel walk, bodily pain, strength of forearm/hand intrinsic muscles,[33] lower limb weakness, and leg cramps.[34]

(b) *Analysis of existing QOL measures*: We compared three existing pediatric QOL scales: the pediatric quality of life inventory (PedsQL),[35,36] the TNO AZL Children's Quality of Life (TACQOL),[37] and the CHQ,[27-30] as well as one adult health status measure: the 36-item short-form (SF-36) survey.[38-40] Common domains identified in these scales included physical complaints and functioning, activities of daily living, bodily pain, cognitive complaints and functioning, and social play (physical) vs. social skills (mental). At the end of this process, six domains were identified as relevant to QOL in children with CMT, which could be further combined to two composite domains: physical and social (Table 1).

Generation of the Item Pool: For the six domains, literature review identified leg cramps, tremor, agility, endurance, and ankle flexibility as items pertinent to pediatric CMT health-related QOL.[41] Sleep and fatigue were additional items identified as relevant to CMT patients.[42] Remaining items for the previously identified six domains were developed de novo and through CMT-specific modification of select items from the pediatric Neuro-QOL measures,[25] for a total of 60 items (10 items per domain). The items were edited for clarity (ease of reading, present tense, active voice) and then underwent expert review by 21 researchers and 2 patient representatives from Australia, Belgium, France, Germany, Italy, Netherlands, Spain, UK and USA at the 168th European NeuroMuscular Centre (ENMC) International Workshop[26] to develop a draft version of the pCMT-QOL PRO measure.

Pilot testing: We administered the draft version of the pCMT-QOL prospectively to 31 children ages 4-17 with CMT, followed by structured focus-group interviews and CMTNS assessments, to assess feasibility and face content validity. Focus group characteristics and results are summarized in Table 2. The Physical Function domain and Social Activities domain of the pCMT-QOL PRO measure had an r of 0.70 and 0.51 with CMTNS scores respectively, providing early content validity. The contents of the draft version were also well accepted by children per their interview responses. Children under the age of 8 had trouble understanding and completing the surveys on their own and we therefore raised the minimum age for completing the pCMT-QOL PRO measure to age 8, and increased the upper age limit to 18 based

on patient input. Varying response categories to the items proved confusing to children, therefore all responses to questions were changed to a uniform 5-point Likert Scale: (0 = never, 1 = almost never, 2 = sometimes, 3 = almost always/ a lot of times, and 4 = always). Questions starting with "in the past 7 days" were problematic, especially if they referenced school activities and the child was being seen during holidays, these were changed to "lately." The final result was a working version of the pCMT-QOL PRO measure.

Psychometric testing: From 2010-2016, the pCMT-QOL working version was administered to 398 children seen at the participating study sites of the Inherited Neuropathies Consortium (Group 2). Of these, 358 had confirmed CMT; patient demographics and other characteristics are shown in Table 3.

Test-retest reliability: Test-retest reliability of the working version of the pCMT-QOL was assessed by prospective administration to 13 children (Group 3). The measure was administered twice within a 7-week period; the first administration was in clinic, and the second mailed to the child's home. Test-retest reliability for the overall measure was high (ICC = 0.92). Two items were eliminated for having an ICC less than 0.65: "My CMT makes it hard to plan spontaneous trips," (ICC 0.32), and "I have difficulty with my hobbies (ex. Playing video games) because of CMT" (ICC 0.17). One additional item, "I get easily frustrated with my reading or writing projects" (ICC 0.54) was retained as relevant to pediatric CMT after content review.

Factor Analysis and IRT analysis: EFA was used to determine whether the remaining questions within each of the six domains measured a similar concept. The Kaiser-Meyer-Olkin (KMO) value of 0.88 and the Tucker and Lewis's Reliability Coefficient of 0.945 indicated good reliability. Bartlett's test of sphericity showed a p-value <0.0001, supporting factorability.[43] The factor analysis revealed seven domains with eigenvalues greater than 1, explaining 83.5% of the total variance. After a careful examination of each question and loading values, the only item in the seventh domain (loading = 0.41) was transferred to the Symptoms Domain (loading = 0.34), resulting in the final six domains which overlapped well with our original domains. The item "I have trouble falling asleep at night" was removed after content review, since it was not pertinent to the Cognition domain assigned by EFA. CFA supported factor validity of the domains (χ^2/df ratio of 2.1 and root mean square error of approximation estimate of 0.0611 with 90% CI (0.0582, 0.0640)). IRT analysis using GRM for ordinal responses or rating scales supported the unidimensionality of each domain (first principal component explained >/= 50% of the variation).

Final version and scoring: The final version of the pCMT-QOL PRO measure is shown in Supplementary Table 1**.** All pCMT-QOL items are reverse scored such that lower scores indicate higher QOL and higher scores indicate worse QOL.

Individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score, and Total pCMT-QOL Score were calculated and standardized as follows: all scores were calculated for individuals with non-missing values for at least half of the items in each domain. For those with half or more missing values, the scores were set as missing. The score was calculated in two steps for those with more than half of the scores available. In step 1, the weighted sum of all items were calculated, with the weights derived from the mean Likert response of each question from the main dataset. At step 2, the weighted sum was transformed to a 0-100 scale as a percentage of the maximum possible value, with a score of 100 representing the most severe QOL and a score of 0 representing the best QOL (of note, this is the opposite of the CHQ, where the higher the score, the better the QOL). The same algorithm was employed for each domain score, physical and mental summary measures, and the overall score. If there were missing items and the number of missing items was smaller than half, then we only used the non-missing items in the calculations. The mean individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score, and Total pCMT-QOL Score in our study sample are provided in Table 4.

Internal consistency and validity: To assess internal consistency, we calculated Cronbach's alpha coefficients for the redistributed items per domain; this showed good internal consistency with Cronbach's alpha ranging from 0.78-0.90 for all six domains. Convergent validity as calculated by Spearman's Rank Correlations are shown in Table 5. All correlations were highly significant, except for the CMTNS and the Mental Composite Domain Score. The strongest correlations were seen between the Total pCMT-QOL Score and the CHQ Physical Summary Score (-0.61, $p < 0.0001$), the Physical Composite Domain Score and the CHQ Physical Summary Score (-0.67, $p < 0.0001$), and the Mental Composite Domain Score and the CHQ Psychosocial Summary Score (-0.51, $p < 0.0001$).

Known group comparisons: Differences in pCMT-QOL scores by gender, disease severity, and CMT genetic diagnoses using t-test are shown in Table 6. Significant differences in QOL scores were noted by disease severity (worse Total pCMT-QOL scores and Physical Composite Domain Scores in children with more severe disease as characterized by CMTES >/= 10; no difference between severity types in Mental Composite Domain Scores). Significant differences in QOL scores were also seen by gender (worse Total pCMT-QOL score and Physical Composite Domain Scores in females; no difference between genders in Mental Composite Domain Scores). No difference in QOL scores was seen by genetically confirmed CMT1A (most common genotype seen) vs. others. Further, the correlation between total pCMT-QOL score in genetically confirmed CMT1A and age was non-significant at 0.032 ($p = 0.67$).

Longitudinal analysis: Over 5 years, of the 358 children with CMT, 57 had assessments at baseline and year 1, but the numbers decreased to just five children having repeat assessments from baseline to year 5. Longitudinal responsiveness, assessed by calculating the Pearson correlation coefficient for the 1-year change in Total pCMT-QOL Score with the 1-year change in CMTES score, was high at 0.57 ($p = 0.0008$). The average PGIC score at year 1 was 2.5 with a SD of 1.4, which falls midway between the "no change" (score = 3) and "a little better" (score = 2) values on the PGIC scale. Correspondingly, the Total pCMT-QOL Score was fairly stable over 1 year, with a mean difference of -2.95 in raw scores with SD of 9 and an overall SRM of -0.327.

DISCUSSION

We have developed and rigorously validated a disease-specific, patient-reported health-related QOL outcome measure for children with CMT in this longitudinal study. The pCMT-QOL PRO measure can be used along with the recently validated adult CMT-specific QOL instrument, the CMT-Health Index,[44] to assess the QOL across all ages in patients with CMT.

It is important to note that our goal was not to merely show that QOL is impaired in CMT, but rather to systematically determine and quantify the factors that contribute to reduced QOL in children with CMT. The disease-specific pCMT-QOL PRO measure thus has important distinctions and advantages from generic QOL outcome measures; it includes items pertinent to pediatric CMT patients, which were modified and refined by prospective pilot testing prior to undergoing longitudinal validation. Further, the specificity of the pCMT-QOL PRO measure will complement other validated CMT-specific COAs such as the CMTPedS,[10] the Rasch-modified CMTNS version 2,[11] the CMTES,[12] and other measures in development such as the CMT Functional Outcome Measure,[45] to fully capture the disease burden experienced by the child with CMT. The pCMT-QOL PRO measure can thus be used in a clinical setting or as a trial outcome measure to obtain the child's views on the comprehensive effectiveness of an intervention on their CMT.

People with CMT often have physical limitations that limit their ability to travel to centers of excellence and be evaluated for clinical trials. In addition, recent events such as the COVID-19 pandemic have made even more clear that there is an urgent need for trial outcome measures that do not require in-clinic visits and can be assessed remotely. Fortuitously, our study had included remote assessments of test-retest reliability, and our results show test-retest reliability of the pCMT-QOL PRO measure up to 7-weeks apart with remote administration.

The known group comparisons in these children with CMT yielded several interesting results. Previous longitudinal studies have shown that the CMT Examination Score (CMTES) does worsen over time, as the patient ages.[12] To assess whether QOL scores also correlate with age, we calculated the Pearson's correlation between our total pCMT-QOL score in children with CMT1A and age; this was non-significant at 0.032 ($p = 0.67$). Of note, our longitudinal analysis showed a significant Pearson correlation coefficient of 0.57 ($p = 0.0008$) between the 1-year change in CMTES and total pCMT-

QOL score. Taken together, these findings seem to suggest that while QOL correlates well with examination findings in CMT, age alone may not account for how QOL, as assessed by the pCMT-QOL PRO measure, changes over time. Further longitudinal studies are needed given the significant attrition in numbers in our longitudinal group. Females had worse Total scores and Physical Composite Domain scores, but no significant difference was seen in the Mental Composite Doman scores. As studies have not shown more severe disease in females compared to males with CMT, there must be factors other than severity that causes females to score their physical signs worse than males. The pCMT-QOL PRO measure was able to statistically distinguish between mild and moderate/severe CMT, yet showed no significant difference in scores between CMT types, suggesting that QOL in pediatric CMT is not dependent on the underlying mechanism of the disease but rather the overall disease severity. This association in particular would be important to track in future pediatric CMT trials, especially those that target the molecular and genetic basis of the disease. Recent scientific advances such as the development of antisense oligonucleotides to decrease PMP22 expression in CMT1A,[46] or gene replacement strategies to treat CMT1X[47] or CMT4,[48] make clinical trials directed at reversing the genetic and molecular causes of CMT realistic. These novel treatments are not directed at axonal repair which causes much of the disability in patients, and are likely to be most effective when administered to children prior to the development of axonal degeneration and its consequences. However, since pediatric trials generally enroll children of varying ages and axonal loss, it would be pertinent to assess the impact of such root-cause treatments on the patient's overall QOL by disease severity.

There are some limitations in this study. While our sample size is robust, the age ranges and means for the overall study group is skewed to younger patients, which may affect the QOL scores. There was significant attrition in the overall study group, such that only five of the original 358 children had repeat annual assessments from baseline to year five. While the Total pCMT-QOL score stayed fairly stable over one year, we were able to show that the pCMT-QOL PRO measure was responsive to disease severity changes over time. This is important because it provides evidence that the pCMT-QOL-PRO measure is not limited by the disability paradox that can be seen in chronic illness, in which QOL scores improve despite disease progression due to closer alignment between functional expectations and functional limitations.[49] Further research, including the analysis of pCMT-QOL scores through a prospective longitudinal drug trial would allow for factor analysis to determine which items might be omitted to develop an abbreviated version of the pCMT-QOL, thus reducing patient burden in completing the measure, and making it more practical clinically. While

there was no significant difference in pCMT-QOL scores between the most common genotype (CMT1A) vs all others, given the higher prevalence of CMT1A in this study, genotype-specific correlative studies must be conducted to ensure the suitability of this outcome measure for all CMT types. Finally, since our analyses showed that gender and severity are related to the pCMT-QOL, future pediatric CMT studies should further evaluate the influence of demographic and disease severity variables in QOL outcomes.

The pCMT-QOL PRO measure demonstrates robust psychometric properties overall. Together with the recently developed and validated CMT COAs, the pCMT-QOL PRO measure can thus be used as a measure of disease burden in the clinical setting, as well as an outcome measure in future pediatric CMT clinical trials.

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AUTHOR CONTRIBUTIONS

SR, RSF, and MES contributed to the conception and design of the study; SR, TTW, RSF, CES, SMEF, JB, MMR, TE, and MES contributed to data acquisition, analysis and interpretation of the data, and to drafting the text and preparing the figures.

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POTENTIAL CONFLICTS OF INTEREST

The authors have no commercial relationships that are of relevance to the current study.

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FIGURE LEGEND

Figure 1. Conceptual Framework for pCMT-QOL Development and Validation

Abbreviations: CMT = Charcot-Marie-Tooth Disease; PRO = Patient-reported outcome; QOL = Quality of Life

TABLE LEGENDS

Table 1: Conceptual Domains of the Pediatric CMT QOL Outcome Measure

Table 2: Focus Group Characteristics and Results

Table 3: Patient Demographics and Characteristics

Table 4: Scores per Individual Domains, Composite Domains, and Total pCMT-QOL

Table 5: Spearman's Rank Correlations between pCMT-COL and other Standard CMT Assessments

Table 6: Known Group Comparisons by Gender, Disease Severity, and CMT genetic diagnosis for Total pCMT-QOL Score, and Physical and Mental Composite Domain Scores

Supplementary Table 1: Pediatric Charcot Marie Tooth Quality of Life Instrument (pCMT-QOL), Child Version Ages 8-18

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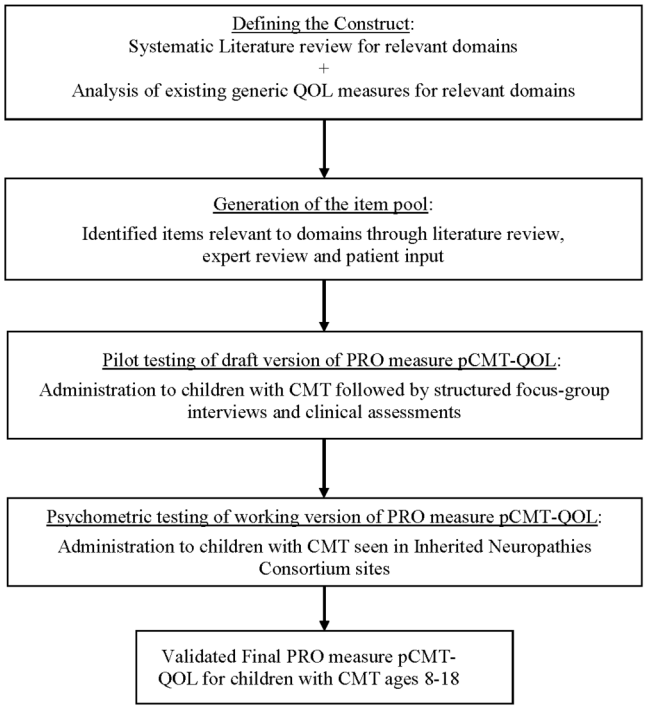

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Table 1: Conceptual Domains of the Pediatric CMT QOL Outcome Measure

Domain	Items pertaining to domain	Composite Domains	Complete Outcome Measure
Symptoms	Physical fatigue/weakness, pain, sleep, tremor, cramps	Physical Composite Domain	Pediatric CMT QOL Outcome Measure
Function	Physical Activities of Daily Living (ADLs), upper extremity and lower extremity functions, balance		
Social Activities	Physical activities with peers and adults		
Feelings	Stigma, anxiety/fear, depression, stress	Social Composite Domain	
Cognition	Perceived cognitive function		
Social Skills	Self-esteem, emotional bonding with peers and adults		

Table 2: Focus Group Characteristics and Results

N =31; 15 M and 16 F
84% Caucasian
Age range 4-17 years (mean age 10, SD 4)
Pearson Correlation Coefficients (r) between CMTNS and individual pCMT-QOL domain scores: – CMTNS and Symptoms Domain: r = 0.22 – CMTNS and Function Domain: r = 0.70 – CMTNS and Social Activities Domain: r = 0.51 – CMTNS and Feelings Domain: r = 0.23 – CMTNS and Cognition Domain: r =0.35 – CMTNS and Social Skills Domain: r = 0.05
Issues that needed immediate changes: – Age groups (5-17 changed to 8-18 years) – Recall period (“in past 7 days” to “lately”)

Table 3: Patient Demographics and Characteristics

N = 358 out of 398 with Charcot-Marie-Tooth Disease (CMT) Other diagnoses, excluded from analyses: – Hereditary Neuropathy with Liability to Pressure Palsies (HNPP): 4 (1%) – Hereditary Motor Neuropathy (HMN): 10 (2.5%) – Hereditary Sensory Neuropathy (HSN): 8 (2.0%) – Other: 5 (1.3%) – Unknown: 13 (3.3%)
Confirmed Genetic diagnosis: 272 of 358 (76%) Most frequently confirmed CMT genetic diagnoses (n, % of 358): – CMT1A: 183 (51.1%) – CMT2A: 17 (4.7%) – CMT1X: 12 (3.4%) – CMT1B: 9 (2.5%) – CMT4C: 9 (2.5%) – CMT1E: 6 (1.7%)
Age Range: 8-18 (Median 12) Age (mean, SD) of most frequent subtypes: – CMT1A (12, 3.1) – CMT2A (13, 3.9) – CMT1X (14, 3.1) – CMT1B (12, 3.6) – CMT4C (13, 2.9) – CMT1E (11, 3.8)
Gender: Male: 196 (54.8%)
Ethnicity: Not Hispanic, Latino or Spanish origin: 295 (82.4%)
Race: Caucasian: 298 of 358 (83.2%) Other races: – African American: 9 (2.5%) – Asian: 11 (3.1%) – Multiple: 11 (3.1%) – Unknown: 29 (8.1%)

Table 4: Scores per Individual Domains, Composite Domains, and Total pCMT-QOL

Domain	N	Mean	Standard Deviation	Minimum Score in Current Study Sample	Maximum Score in Current Study Sample
Symptoms	355	33.5	17.2	0	84.7
Function	357	29.5	19.5	0	92.8
Social Activities	355	41.2	20.8	0	100
Feeling	356	28.4	22.7	0	100
Cognition	355	29.2	18.4	0	90.4
Social Skills	355	20.7	16.3	0	100
Physical Composite Domain Score	357	34.6	15.1	0	83.1
Mental Composite Domain Score	356	27.1	15.5	0	81.6
Total pCMT-QOL Score	357	30.9	13.6	2.4	68.3

Table 5: Spearman's Rank Correlations between pCMT-COL and other Standard CMT Assessments

	Total pCMT-QOL Score	Physical Composite Domain Score	Mental Composite Domain Score
CMTES	0.36, $p < 0.0001$*	0.43, $p < 0.0001$*	0.19, $p = 0.0013$*
CMTNS	0.36, $p = 0.0001$*	0.39, $p < 0.0001$*	0.18, $p = 0.0624$
CHQ Physical Summary Score	-0.61, $p < 0.0001$*	-0.67, $p < 0.0001$*	-0.38, $p < 0.0001$*
CHQ Psychosocial Summary Score	-0.44, $p < 0.0001$*	-0.29, $p < 0.0001$*	-0.51, $p < 0.0001$*
CMTPedS	0.37, $p < 0.0001$*	0.47, $p < 0.0001$*	0.16, $p = 0.0036$*

*$p < 0.05$; uncorrected for multiple testing

Table 6: Known Group Comparisons by Gender, Disease Severity, and CMT genetic diagnosis for Total pCMT-QOL Score, and Physical and Mental Composite Domain Scores

Total pCMT-QOL Score			
Variable	N	Mean, SD	t Value, p
Male	195	29.4, 13.4	2.78, p = 0.0058*
Female	161	33.4, 13.5	
CMTES mild	231	29.1, 13.3	4.25, p < 0.0001*
CMTES moderate/severe	42	38.5, 12.3	
CMT1A	182	31.3, 14.1	-0.09, p = 0.9255
CMT other genetic types	88	31.1, 14.3	
pCMT-QOL Physical Composite Domain Score			
Variable	N	Mean, SD	t Value, p
Male	195	31.9, 14.6	-3.79, p = 0.0002*
Female	162	37.8, 15.2	
CMTES mild	232	31.6, 14.3	5.53, p < 0.0001*
CMTES moderate/severe	42	44.8, 13.4	
CMT1A	183	34.2, 15.3	1.05, p = 0.2927
CMT other genetic types	88	36.3, 16.3	
pCMT-QOL Mental Composite Domain Score			
Variable	N	Mean, SD	t Value, p
Male	195	26.4, 15.3	-0.92, p = 0.3571
Female	161	27.9, 15.7	
CMTES mild	231	26.1, 15.4	1.74, p = 0.0830
CMTES moderate/severe	42	30.6, 16.1	
CMT1A	182	27.7, 16.3	-1.5, p = 0.1343
CMT other genetic types	88	24.6, 15.2	

*p < 0.05; uncorrected for multiple testing

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