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Title: Validation of the Parent-Proxy Pediatric Charcot-Marie-Tooth Disease Quality of Life

Outcome Measure

Running Title: Parent-proxy pCMT-QOL outcome measure

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ABSTRACT AND KEYWORDS

Objective: Charcot-Marie-Tooth disease (CMT) reduces health-related quality of life (QOL) in children. We have previously developed and validated the English and Italian versions of the pediatric CMT-specific QOL outcome measure (pCMT-QOL) for children aged 8-18. There is currently no parent-proxy CMT QOL outcome measure for use in clinical trials, which could provide complementary information in these children and adolescents. This study describes the validation studies conducted to develop the parent-proxy version of the pCMT-QOL outcome measure for children aged 8-18 years old.

Methods: Development and validation of the parent-proxy version of the pCMT-QOL outcome measure for children aged 8-18 years old was iterative, involving identifying relevant domains, item pool generation, prospective pilot testing and clinical assessments, structured focus-group interviews, and psychometric testing, conducted on parents of children with CMT seen at participating sites from the USA, United Kingdom, and Australia.

Results: We utilized previously described methods to develop a working parent-proxy version of the pCMT-QOL measure. From 2010-2016, the parent-proxy pCMT-QOL working version was administered to 358 parents of children with CMT aged 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 parent-proxy version of the pCMT-QOL outcome measure for children aged 8-18 years old.

Interpretation: The parent-proxy version of the pCMT-QOL outcome measure is a reliable, valid, and sensitive proxy measure of health-related QOL for children aged 8-18 with CMT.

KEYWORDS: Charcot-Marie-Tooth disease (CMT); Pediatric; Quality of life (QOL); Outcome Measure Validation; Clinical Trial Endpoint

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INTRODUCTION

Recent scientific advances in Charcot-Marie-Tooth disease (CMT), the most common inherited neurodegenerative disorder,¹ including antisense oligonucleotides² and gene replacement strategies^{3,4} are paving the way for clinical trials in CMT. Pediatric CMT trials with validated trial endpoints are especially needed as disease burden can increase through childhood to adulthood.⁵⁻⁸ As part of an international collaboration engaged in the critical effort to develop and validate CMT trial endpoints,⁹⁻¹² we have shown that health-related Quality of Life (QOL) is significantly reduced in children with CMT,¹³ and developed and validated the English and Italian version of the pediatric CMT QOL (pCMT-QOL) patient-reported outcome (PRO) measure for use in international CMT trials.^{14,15} While child self-report is considered the gold standard in QOL assessment, parent-proxy reports can provide complementary information on health-related QOL^{16,17} and can at times be the only source of QOL information in young children.¹⁸ There is no parent-proxy QOL outcome measure for pediatric CMT. The objective of this study was to build and rigorously validate the parent-proxy version of the pCMT-QOL outcome measure for use in pediatric CMT 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. Samples used for pilot testing have been previously described.¹⁴ The parents of 358 children with CMT seen in the prospective, natural history study in children with CMT were recruited for the parent-proxy version development and validation (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- Regional Ethics Committee and UCL Institutes of Child Health and Neurology, London, and associated hospital trusts, UK; Australia- University of Sydney & Children's Hospital, Sydney, Australia. In addition, 13 parent-child dyads were recruited from the University of Iowa for test-retest validation and assessment of parent-child concordance. Ethics approval from all institutions for all studies and written informed consent from all participants were obtained.

Statistical Analysis

The iterative process to define the construct, generate the item pool, and pilot testing has been previously described; the pilot testing was done on the parents of the 31 children with CMT ages 4-17 referenced in the original paper.¹⁴ The resulting parent-proxy working version of the pCMT-QOL outcome measure for children aged 8-18 was administered prospectively to one parent or primary caregiver (both henceforth referred to as parents) of children seen at the participating sites of the Inherited Neuropathies Consortium. The version underwent psychometric testing, including internal

consistency, convergent validity, and IRT modeling, to develop the final parent-proxy version of the pCMT-QOL outcome measure for children aged 8-18. 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.

Test-retest reliability: Parent-child dyads were administered the working version of the pCMT-QOL outcome measure for children aged 8-18 twice. Intraclass correlation coefficients (ICCs) were used to quantify the test-retest reliability of the pCMT-QOL.

Internal consistency: The exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) undertaken to identify domains and assess their content validity, and item response theory (IRT) analysis to verify the unidimensionality of each domain, has been previously described.¹⁴ The internal consistency of the redistributed items per domain were assessed with standardized Cronbach's alpha.

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

Convergent 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 parent-proxy version's and the child version's Total score, Physical Composite Domain Score, and Mental Composite Domain Score.

Known group comparisons: Two-sample t tests were used to compare groups defined by the child's gender, disease severity characterized by child's CMTES score ≥ 10 correlating with moderate/severe disease,¹² and child's CMT genetic subtype (CMT1A vs. all others).

Longitudinal analysis: Longitudinal responsiveness was assessed by calculating the Pearson correlation coefficient for the 1-year change in the parent-proxy version Total Score with the 1-year change in CMTES score, and comparing with the observed change to the 7-point Parent-Proxy Global Impression of Change (PPGIC) 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 parent-proxy version’s Total Score over time was also calculated by dividing the mean change in scores over time with the standard deviation of change over time.

Prediction models: The relationship between parent-proxy version scores and child version scores was evaluated using multiple linear regression models, controlling for the effects of other variables, including the child’s age, gender, race, ethnicity, BMI status, CMT subtype, and disease severity characterized by child’s CMTES score. Except for parent-proxy scores and age, all other variables were binary.

RESULTS

The parent-proxy working version of the pCMT-QOL for children with CMT aged 8-18 was identical to the Child version with the exception of containing a “do not know” scoring option for each item based on focus group input; these selections were treated as missing values in the analysis. From 2010-2016, the parent-proxy working version of the pCMT-QOL outcome measure for children aged 8-18 was administered prospectively to parents of 358 children with confirmed CMT aged 8-18, seen at the participating sites of the Inherited Neuropathies Consortium.

Test-retest reliability: Thirteen parent-child dyads were administered the working version of the pCMT-QOL outcome measure for children aged 8-18 twice within a 7-week period, the first provided in clinic, and the second mailed to home. Test-retest reliability for the parent-proxy version was high (ICC = 0.99). All 60 items also had an ICC higher than 0.5; we retained the same 57 items in the parent-proxy version that had been previously validated in the child version of the pCMT-QOL measure.

Internal consistency: To have the parent-proxy version retain consistency with the child version of the pCMT-QOL measure, the factor analysis from the original paper¹⁴ was used to assign the items to the previously identified six unidimensional domains. Standardized Cronbach alpha coefficients for the items per domain were high, reflecting good internal consistency, see Table 1.

Final version and scoring: The final 57-item parent-proxy version of the pCMT-QOL outcome measure for children aged 8-18 is shown in the Appendix. The ‘do not know’ scoring option, which

did not show any trends indicating irrelevance of particular items to parents, were removed from the final version. Similar to the child version, all parent-proxy pCMT-QOL items were reverse scored such that lower scores indicated higher QOL and higher scores indicated worse QOL. Individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score, and Total Score for the parent-proxy version were calculated and standardized similar to the child version: 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 (including those with ‘do not know’ responses), 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 (see Appendix 2 for a scoring example). 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. Differences in the mean individual domain scores, Physical Composite Domain Score, Mental Composite Domain Score, and Total Score between the parent-proxy version and Child version of the pCMT-QOL using t-test are provided in Table 2.

Convergent validity: Spearman’s Rank Correlations, as shown in Table 3, were high between parent-proxy version scores and child version scores for Total, Physical Composite Domain, and Mental Composite Domain Scores, indicating significant convergent validity. We further assessed for variability in QOL score correlations based on the child’s age (adolescents vs. younger) to see if

changing age impacted the agreement between parent-proxy scoring vs. the child's scoring; no impact of age was seen on the agreement.

Known group comparisons: Differences in the parent-proxy pCMT-QOL scores based on the child's gender, child's CMT genetic subtype, and child's CMT disease severity using t-test are shown in Table 4. There was a significant difference based on disease severity status, with worse QOL scores seen with more severe disease in the mean parent-proxy Total Scores (31.5 for mild disease and 41.9 for moderate/severe disease) and Physical Composite Domain Scores (35.1 for mild disease and 50.8 for moderate/severe disease). The parent-proxy Mental Composite Domain Score was not affected by the child's disease severity. A significant difference was also seen only in the Physical Composite Domain Score by gender (worse scores in females). There was no significant impact of the child's CMT genetic subtype on the parent-proxy scores.

Longitudinal analysis: Over a five-year period, out of the 358 parents of children aged 8-18 with confirmed CMT, 57 parents had assessments at both baseline and year 1; over the next 5 years these numbers decreased to five parents having repeat assessments from baseline to year 5. Longitudinal responsiveness, assessed by calculating the Pearson correlation coefficient for the 1-year change in parent-proxy Total Score with the 1-year change in CMTES score, was 0.28 ($p = 0.13$). The average PPGIC score at year 1 was 3.2 with a SD of 0.9, which is closest to the "no change" (score = 3) value on the PPGIC scale. Correspondingly, the parent-proxy Total Score was fairly stable over 1 year, with a mean difference of -1.69 in raw scores with SD of 9.0 and an overall SRM of -0.188.

Prediction models: Using multiple linear regression models, controlling for the effects of variables including the child's age, gender, race, ethnicity, BMI status, CMT subtype, and disease severity

characterized by child's CMTES score, relationships were characterized between the parent-proxy version scores and child version scores of the pCMT-QOL. Overall, there was a positive correlation between the parent-proxy scores and the child scores, with parents slightly overestimating the impact of CMT on their child compared to the child themselves. Individual equations to derive the child's pCMT-QOL scores from parent-proxy scores are shown in Table 5.

DISCUSSION

We have developed and rigorously validated a disease-specific, parent-proxy version of the pCMT-QOL PRO measure in this longitudinal study. As seen with the pCMT-QOL PRO measure,¹⁴ the mean scores of the parent-proxy version also indicate that parents perceive there is an impact of CMT on their child's QOL. The most common genotype was CMT1A, and the overall parent-proxy version QOL Total score was 34, suggesting that even in the genotype considered to have the mildest phenotype, parents concur with the children that there is room for QOL improvement. Further, the Composite Domain scores and Total Scores of the parent-proxy version of the pCMT-QOL PRO measure showed good agreement with the child's direct-report scores regardless of whether the child was young (ages 8-12) or an adolescent (ages 13-18), suggesting that even as the child with CMT ages and is presumably less dependent on their parents, the parents continue to have a good grasp of the impact of the disease on their child's QOL.

Similar to what we reported with pCMT-QOL PRO measure scores,¹⁴ parent-proxies scored female children with worse Physical Composite Domain scores, but no significant difference was seen in the Total or Mental Composite Domain scores. Quality of life instruments in other neurological diseases have demonstrated poorer QOL in females compared to males. For example, poor physical functioning and socioemotional health related quality of life has been reported in female patients with Parkinson Disease,¹⁹ and poorer quality of life has been reported in female patients with Myasthenia Gravis.²⁰ However, to our knowledge, this is the first study to show that parent-proxy QOL scores also reflect this assessment by female participants. As studies have not shown more severe disease in females compared to males with CMT, or in those other chronic diseases, there

must be factors other than severity that causes both female children and their parents to score their physical QOL worse than males.

There were some differences in the scoring of two Physical Domains, the Physical Composite Domain and the Total Score, between the parent-proxy version and the child version of the pCMT-QOL PRO measure. Parent-proxies had slightly higher scores in Physical Function, Physical Social Activities, and Physical Composite Domains than their children; this is consistent with findings in other proxy-QOL PRO measures where parents overestimate the physical impact of the disease on their child's QOL compared to the child's self-reported assessment.^{21,22} However, both parents and children are fairly similar in their assessment of the mental impact of CMT. Overall, this translates to a Parent-proxy Total Score that is slightly higher than the child's self-reported Total Score on the pCMT-QOL PRO measure. We developed individual equations through multiple linear regression models that account for these differences and can be used to predict the child's pCMT-QOL scores when only parent-proxy scores are available.

It has become critically important in recent times to develop trial endpoints and clinical assessments for rare diseases that can be administered remotely. There are very few clinical centers that are specialized in the care of children with CMT and capable of conducting clinical trials in this patient population. Further, with a genetic disease, many parents are similarly affected which creates an added burden for families to travel to remote sites. The on-going COVID-19 pandemic is an additional reminder that random events can preclude travel to a clinical or trial site. The parent-proxy version of the pCMT-QOL outcome measure we have developed does not require in-clinic

visits and can be assessed remotely, with excellent test-retest reliability up to 7-weeks apart with remote administration.

There are some limitations to this study. The demographic distribution (age, gender, race) of our patient population was previously pointed out as a limitation that required further prospective studies to ensure applicability of these results in diverse populations with CMT.¹⁴ While there was no significant difference in parent-proxy 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 parental concordance with child scores remains high for all CMT types. We did not assess parental CMT status; personal perception may have an impact on their proxy-score. However, CMT can be due to *de novo* mutations and are not always inherited; no significant outliers were seen amongst the parent proxy scores to suggest that parental CMT status might impact their assessment of their child's CMT. As previously noted,¹⁴ there was significant attrition in the study group, limiting the number of parent-proxy repeat annual assessments from baseline to year 5. Similar to the child measure, the parent-proxy Total Score was fairly stable over 1 year, as was the 1-year Parent-Proxy Global Impression of Change (PPGIC) score, approximating 3 ("no change"). While the longitudinal responsiveness assessed by calculating the Pearson correlation coefficient for the 1-year change in parent-proxy Total Score with the 1-year change in CMTES score was not significant, the interpretation is limited by the fewer numbers of patients with longitudinal data. Based on the known-group comparisons showing strong correlation with disease severity as assessed by the CMTES ($p < 0.0001$), we anticipate the measure will be responsive to changes over time in disease severity; however, definitive studies on this issue will require larger numbers of patients evaluated longitudinally. Changes in the scores in intervention

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trials will also help determine how responsive to change the instrument will be. Finally, this parent-proxy version did not assess the QOL in very young children (ages < 8), who may have the greatest responsiveness to therapeutic interventions and thus are most in need of validated trial endpoints. Validation of items that may be pertinent to the QOL in this age group is currently underway.

The parent-proxy version of the pCMT-QOL PRO measure for children ages 8-18 demonstrates robust psychometric properties overall, and is complementary to the direct-report child pCMT-QOL PRO measure. The parent-proxy version can be used along with the recently validated pCMT-QOL PRO measure, either in a clinical setting or as a trial endpoint, to provide a holistic assessment of the disease burden experienced by the child with CMT, complementing the information obtained from the child version, and predicting when direct report data are unavailable.

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CONFLICT OF INTEREST

The authors have no commercial relationships that are of relevance to the current study. Funding sources for this study include NINDS K23-NS072279 (SR) and NINDS/ORD U54-NS065712 (MES, FM, MMR, CS). The Inherited Neuropathies Consortium (U54NS065712) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through collaboration between NCATS and NINDS.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

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TABLES

Table 1: Internal Consistency of the Domains of the Parent-Proxy Version of the pCMT-QOL Outcome Measure for Children Ages 8-18

Domain	Number of variables	Themes of Items pertaining to Domain	Standardized Cronbach alpha
Physical: Symptoms	12	Parent perception of the child's physical fatigue/weakness, pain, sleep, tremor, cramps	0.89
Physical: Function	10	Parent perception of the child's physical ADLs, upper extremity and lower extremity functions, balance	0.89
Physical: Social Activities	7	Parent perception of the child's physical activities with peers and adults	0.85
Mental: Feelings	10	Parent perception of the child's experiences of stigma, anxiety/fear, depression, stress	0.90
Mental: Cognition	10	Parent perception of the child's perceived cognitive function	0.92
Mental: Social Skills	8	Parent perception of the child's Self-esteem, emotional bonding with peers and adults	0.86

Table 2: Individual Domain Scores, Composite Domain Scores, and Total Score: Parent-proxy Version vs. Child Version

Variable	Mean Parent-Proxy Version Score (n, SD)	Mean Child Version Score (n, SD)	Two-sample t-test: Parent-Proxy vs Child Version
Physical Domain Symptoms	35.3 (328, 16.7)	33.5 (355, 17.2)	p = 0.08
Physical Domain Function	36.6 (330, 21.5)	29.5 (357, 19.5)	p < 0.0001*
Physical Domain Social Activities	45.4 (329, 21.3)	41.2 (355, 20.8)	p = 0.005*
Mental Domain Feelings	29.4 (330, 19.2)	28.4 (356, 22.7)	p = 0.27
Mental Domain Cognition	29.3 (326, 20.7)	29.2 (355, 18.4)	p = 0.47
Mental Domain Social Skills	19.9 (326, 14.8)	20.7 (355, 16.3)	p = 0.25
Physical Composite Domain Score	38.7 (330, 16.5)	34.6 (357, 15.1)	p = 0.0004*
Mental Composite Domain Score	27.3 (327, 14.7)	27.1 (356, 15.5)	p = 0.43
Total Score	33.6 (330, 13.9)	30.9 (357, 13.6)	p = 0.005*

*significant p; uncorrected for multiple testing

Table 3: Convergent Validity of Parent-proxy Version vs. Child Version: All ages and by Young Child vs. Adolescent

	Spearman Correlation Coefficient, all ages	Spearman Correlation Coefficient, young child: ages 8-12	Spearman Correlation Coefficient, adolescent: ages 13-18
Parent-proxy version vs Child pCMT-QOL Total Score	0.70, $p < 0.0001^*$	0.70, $p < 0.0001^*$	0.69, $p < 0.0001^*$
Parent-proxy version vs Child pCMT-QOL Physical Composite Domain Score	0.74, $p < 0.0001^*$	0.73, $p < 0.0001^*$	0.75, $p < 0.0001^*$
Parent-proxy version vs Child pCMT-QOL Mental Composite Domain Score	0.62, $p < 0.0001^*$	0.64, $p < 0.0001^*$	0.60, $p < 0.0001^*$

*significant p ; uncorrected for multiple testing

Table 4: Known Group Comparisons for Mean Parent-Proxy Scores by Child's Gender, Child's Disease Severity, and Child's CMT Genetic Diagnosis

		Mean Parent- Proxy Total Score, (SD)	p- value	Mean Parent- Proxy Physical Composite Domain Score, (SD)	p- value	Mean Parent- Proxy Mental Composite Domain Score, (SD)	p- value
Child's Gender	Male (n= 180)	33.2, (14.8)	0.24	37.0, (17.0)	0.04*	27.7, (15.6)	0.59
	Female (n =150)	34.9, (13.1)		40.7, (15.7)		26.8, (14.1)	
Child's CMT Subtypes	CMT1A (n =167)	33.3, (14.3)	0.49	36.9, (16.4)	0.05	28.1, (15.7)	0.07
	Non-CMT1A (n =82)	34.6, (12.6)		41.2, (15.8)		24.7, (12.7)	
Child's CMT disease severity	CMTES <10; Mild (n = 220)	31.5, (14.2)	<.0001*	35.1, (16.0)	<.0001*	26.5, (15.1)	0.22
	CMTES >/=10; Moderate/Severe (n =39)	41.9, (9.7)		50.8, (10.8)		29.7, (15.5)	

*significant p; uncorrected for multiple testing

Table 5: Equations to Derive Child's pCMT-QOL Scores from Parent-Proxy Scores

Score	Equation
Child pCMT-QOL Total Score	$= 0.28 + 0.71(\textit{parent-proxy Total score}) + 0.35(\textit{age}) + 5.06(\textit{gender}) - 2.56(\textit{race}) - 0.38(\textit{ethnicity}) + 3.05(\textit{BMI}) + 3.96(\textit{CMT subtype}) - 0.86(\textit{CMT severity})$
Child pCMT-QOL Physical Composite Domain Score	$= 2.20 + 0.68(\textit{parent-proxy Physical Composite Domain Score}) + 0.31(\textit{age}) + 5.60(\textit{gender}) - 2.10(\textit{race}) - 1.72(\textit{ethnicity}) + 2.24(\textit{BMI}) + 3.52(\textit{CMT subtype}) - 1.29(\textit{CMT severity})$
Child pCMT-QOL Mental Composite Domain Score	$= 0.19 + 0.71(\textit{parent-proxy Mental Composite Domain Score}) + 0.35(\textit{age}) + 4.65(\textit{gender}) - 3.00(\textit{race}) + 1.24(\textit{ethnicity}) + 4.17(\textit{BMI}) + 4.34(\textit{CMT subtype}) - 0.73(\textit{CMT severity})$

NB: parent-proxy scores = derived from survey responses as described in the paper; age = child's age from 8 to 18 years in whole numbers; gender female = 1, male = 0; race Caucasian =1, all other race = 0, ethnicity Hispanic =1, all other ethnicity = 0, BMI \geq 90th percentile = 1, all other percentiles =0; CMT subtype 1A =1, all other subtypes = 0; CMT severity mild (i.e. CMTES <10) =1, moderate/severe (i.e. CMTES \geq 10) = 0. Values were rounded up to two decimal points; significant variables ($p < 0.05$) are italicized.

APPENDIX

Appendix 1: Pediatric Charcot Marie Tooth Quality of Life Instrument (pCMT-QOL), Parent-Proxy
Version Ages 8-18

Appendix 2: Item weights for scoring the Parent-Proxy version of the pCMT-QOL with sample
calculation