Published in final edited form as:

J Peripher Nerv Syst. 2013 June ; 18(2): 177–180. doi:10.1111/jns5.12024.

Transitioning outcome measures: relationship between the CMTPedS and CMTNSv2 in children, adolescents and young adults with Charcot-Marie-Tooth disease

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Abstract

Long term studies of Charcot-Marie-Tooth disease (CMT) across the entire lifespan require stable endpoints that measure the same underlying construct (e.g., disability). The aim of this study was to assess the relationship between the CMT Pediatric Scale (CMTPedS) and the adult CMT Neuropathy Score (CMTNSv2) in 203 children, adolescents and young adults with CMT. There was a moderate curvilinear correlation between the CMTPedS and the CMTNSv2 (Spearman's rho $\rho=0.716$, $p<0.0001$), although there appears to be a floor effect of the CMTNSv2 in patients with a milder CMT phenotype. Univariate analyses indicate that the relationship between the CMTPedS and CMTNSv2 scores improves with worsening disease severity and advancing age. Although one universal scale throughout life would be ideal, our data supports the transition from the CMTPedS in childhood to the CMTNSv2 in adulthood as a continuum of measuring lifelong disability in patients with CMT.

Introduction

Charcot-Marie-Tooth disease (CMT) is the most common inherited neuromuscular disorder affecting 1:2500 individuals (*Skre, 1974*). Mutations in more than 50 genes cause CMT and

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clinical phenotypes range from slowly progressive to rapidly progressing neuropathies depending on the particular gene and mutation (*Reilly and Shy, 2009*). Many phenotypes begin in childhood and progress through the adult years. Therefore, long-term natural history studies and therapeutic trials of CMT need to evaluate patients across the entire lifespan and require stable outcome measures all quantifying the same underlying construct, such as disability.

At present, the CMT Pediatric Scale (CMTPedS) is a reliable, valid and sensitive global measure of disability for patients aged 3-20 years (*Burns et al., 2012*), while the CMT Neuropathy Score (CMTNS) has been implemented as the primary outcome measure in adult clinical trials (*Micallef et al., 2009; Pareyson et al., 2011*), with recent modifications to improve reliability and sensitivity (CMTNSv2) (*Murphy et al., 2011*). However, it is not known whether the CMTPedS and CMTNSv2 measure the same aspects of the disease, and whether it is appropriate in long-term studies to use the CMTPedS during childhood and transition to the CMTNSv2 into adulthood. Therefore, the aim of this study was to assess the relationship between the CMTPedS and the CMTNSv2 in a large sample of children, adolescents and young adults with CMT.

Patients and Methods Participants

The sample comprised 203 patients (105 girls and 98 boys) with CMT aged 3-20 years (median 11, IQR 7 years) who attended one of the Inherited Neuropathies Consortium centers (88 The Children's Hospital at Westmead, Sydney Australia; 49 Wayne State University, Detroit, MI & University of Iowa, Iowa City IA; 22 Children's Hospital of Philadelphia; 21 Carlo Besta Neurological Institute, Milan, Italy; 19 UCL Institute of Child Health & Great Ormond Street Hospital, London, UK; 4 University of Rochester, NY). CMT subtypes were: 50% Type 1A; 10% Type 1B-E; 5% Type 2A-L; 4% Type 4A-J; 3% X1-5; 28% Unidentified gene.

CMTPedS and CMTNSv2

All patients were assessed with the CMTPedS and the CMTNSv2. The CMTPedS is an 11-item composite scale which evaluates seven aspects of disease severity (strength, dexterity, sensation, gait, balance, power and endurance) with a range of scores from 0-44 based on norm-derived z-scores (*Burns et al., 2012*). The CMTPedS is a well-tolerated outcome measure that can be completed in 25 minutes and takes into account the influence of growth and development that normally occurs during childhood. It is a reliable, valid, and sensitive global measure of disability for patients with CMT aged 3-20 years. The CMTNSv2 is a 9-item adult composite score based on patient history, neurological examination, activity limitations and electrophysiology (*Murphy et al., 2011*). Since most of our sample (68%) did not have electrophysiological testing performed within 3 months of CMTNSv2 completion, a subscale which excludes electrophysiology with a range of scores from 0-28 was used for analysis. Inter- and intra-rater reliability is excellent (ICC 0.96) for the subscale (*Murphy et al., 2011*).

Data analysis

Descriptive statistics were calculated to characterize the study sample in SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Normality of data distribution was assessed using the Kolmogorov-Smirnov test with Lilliefors significance correction, and the appropriate parametric or non-parametric tests subsequently employed. The relationship between CMTPedS and CMTNSv2 scores was evaluated with Spearman's rho. Two subgroup univariate analyses were also performed. First, the CMTPedS and CMTNSv2 scores were divided into three severity groups: mild disability (CMTPedS 0-14,

CMTNSv2 0-9), moderate disability (CMTPedS 15-29, CMTNSv2 10-19) or severe disability (CMTPedS 30-44, CMTNSv2 20-28), to evaluate the relationship between the CMTPedS and CMTNSv2 with worsening disease severity. Second, the sample was divided into three 6-year age groups (early childhood 3-8 years, middle childhood 9-14 years, adolescence/young adulthood 15-20 years) to evaluate the relationship between the CMTPedS and CMTNSv2 with advancing age.

Results

CMTPedS scores ranged from 1-41 (median 20, IQR 13) on the 0-44 point scale. CMTNSv2 scores ranged from 0-21 (median 5, IQR 5) on the 0-28 point subscale. The percentages of patients falling into the different CMT categories were: mild (CMTPedS 27%; CMTNSv2 87%), moderate (CMTPedS 53%; CMTNSv2 12%) and severe (CMTPedS 20%; CMTNSv2 1%), indicating a floor effect of the CMTNSv2 in patients with a milder CMT phenotype.

Both the CMTPedS and CMTNSv2 significantly distinguished CMT Type (Independent Samples Kruskal-Wallis Test $p < 0.009$), particularly between CMT1A (CMTPedS median 17, IQR 11; CMTNSv2 median 4, IQR 4) and CMT Type 2 (CMTPedS median 32, IQR 21; CMTNSv2 median 10, IQR 8) and CMT Type 4 (CMTPedS median 35, IQR 11; CMTNSv2 median 11, IQR 13). Gender had no influence on any of the scores ($p > 0.396$).

There was a moderate curvilinear correlation between the CMTPedS and the CMTNSv2 (Spearman's rho $\rho = 0.716$, $p < 0.0001$) (Fig. 1), suggesting the association strengthens with worsening disease severity. CMTPedS worsened with advancing age (Spearman's rho $\rho = 0.527$, $p < 0.0001$) as did the CMTNSv2 (Spearman's rho $\rho = 0.337$, $p < 0.0001$). Subgroup analysis of age showed that the relationship between CMTPedS and CMTNSv2 scores strengthened with advancing age from early childhood ($n = 53$) (Spearman's rho $\rho = 0.555$, $p < 0.0001$) and middle childhood ($n = 97$) (Spearman's rho $\rho = 0.648$, $p < 0.0001$) to adolescence/young adulthood ($n = 53$) (Spearman's rho $\rho = 0.829$, $p < 0.0001$).

Discussion

The broad spectrum of disease severity in our large sample of children, adolescents and young adults with CMT was adequately captured by the range of scores available on the CMTPedS and CMTNSv2. However, there was an overrepresentation of mildly affected patients on the CMTNSv2 (87%) compared to the CMTPedS (27%), indicating a floor effect of the CMTNSv2 in patients with a milder CMT phenotype. Indeed, almost half of the entire sample ($n = 100$) scored only 0-4 points on the CMTNSv2, highlighting the insensitivity of the CMTNSv2 for milder pediatric patients.

To improve sensitivity, the CMTPedS was constructed to rate performance across age and gender with items measured in different units (degrees, seconds, newtons, meters) by converting items to z-scores based on age/gender-matched normative reference values collected by the Inherited Neuropathies Consortium and cross-checked with published data (Burns et al., 2012). Z-scores provide a dimensionless rating approach to the challenge of growth and development, offset by deterioration of strength and function, in children with CMT. To improve interpretation and generate a total score, z-scores were categorized along a continuum of five disability levels: normal, very mild, mild, moderate and severe. This approach mirrors the CMTNSv2 which was originally modified from the Total Neuropathy Score (Cornblath et al., 1999) by collapsing to a 5-point Likert response format (Shy et al., 2005). However, the CMTPedS categories are based on age and gender derived z-scores.

The original CMTNS was thought to have limited sensitivity in children to differentiate levels of disease severity, and the influence of growth and development that normally occurs

during childhood on the CMTNS was unknown. The original CMTNS has shown limited application in 20 children aged 3–10 years because only four of nine items were regarded as sensitive (*Haberlova and Seeman, 2010*). Further, the CMTNS has demonstrated limited potential to measure disability and severity in 21 children with CMT1A aged 6–17 years (*Pagliano et al., 2011*). However, our data demonstrated that the relationship between the CMTPedS and the new CMTNSv2 increases with worsening disease severity (Fig. 1), and given that age was a significant correlate of disease severity, indicates that the utility of the CMTNSv2 improves with advancing age.

A correlation coefficient of 0.83 between the CMTPedS and the CMTNSv2 in the 53 adolescents and young adults suggests both scales are measuring the same underlying construct (disability). Although one universal scale throughout life would be ideal, our data supports the transition from the CMTPedS in childhood to the CMTNSv2 in adulthood as a continuum of measuring lifelong disability in CMT.

Acknowledgments

We are grateful for the assistance of site co-investigators and project coordinators: Allan Glanzman, PT (Children's Hospital of Philadelphia, PA, USA), Karla Laubenthal, PT (University of Iowa, Iowa City, IA, USA), Andy Hiscock, PT (UCL Institute of Child Health & Great Ormond Street Hospital, London, UK), Janet Sowden BSc (University of Rochester, Rochester, NY, USA). Part of this work was undertaken at University College London Hospitals/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. We also wish to thank the patients and their families for their participation in the study. This research was supported by grants from the NHMRC (National Health and Medical Research Council of Australia, Fellowship #1007569 and Centre of Research Excellence #1031893), NIH (National Institutes of Neurological Disorders and Stroke and Office of Rare Diseases, #U54NS065712), Muscular Dystrophy Association, Charcot Marie Tooth Association and the CMT Association of Australia.

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Figure 1.
Relationship between CMTPedS and CMTNSv2 scores.