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Validation of the CMT Pediatric Scale as an outcome measure of disability

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Abstract

Objective—Charcot-Marie-Tooth disease (CMT) is a common heritable peripheral neuropathy. There is no treatment for any form of CMT although clinical trials are increasingly occurring. Patients usually develop symptoms during the first two decades of life but there are no established outcome measures of disease severity or response to treatment. We identified a set of items that represent a range of impairment levels and conducted a series of validation studies to build a patient-centered multi-item rating scale of disability for children with CMT.

Methods—As part of the Inherited Neuropathies Consortium, patients aged 3–20 years with a variety of CMT types were recruited from the USA, UK, Italy and Australia. Initial development stages involved: definition of the construct, item pool generation, peer review and pilot testing. Based on data from 172 patients, a series of validation studies were conducted, including: item and factor analysis, reliability testing, Rasch modeling and sensitivity analysis.

Results—Seven areas for measurement were identified (strength, dexterity, sensation, gait, balance, power, endurance), and a psychometrically robust 11-item scale constructed (Charcot-Marie-Tooth disease Pediatric Scale: CMTPedS). Rasch analysis supported the viability of the CMTPedS as a unidimensional measure of disability in children with CMT. It showed good

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overall model fit, no evidence of misfitting items, no person misfit and it was well targeted for children with CMT.

Interpretation—The CMTpedS is a well-tolerated outcome measure that can be completed in 25-minutes. It is a reliable, valid and sensitive global measure of disability for children with CMT from the age of 3 years.

Background

Charcot-Marie-Tooth disease (CMT) is named for the three neurologists who described it in the late 1800s.^{1,2} CMT affects ~1 in 2500 people and is among the most common inherited neurological disorders.³ The majority of patients with CMT have autosomal dominant inheritance, although X-linked dominant and autosomal recessive forms also exist. Most patients have a ‘typical’ CMT phenotype characterized by distal weakness, sensory loss, foot deformities (pes cavus and hammer toes) and absent ankle reflexes. Many patients develop severe disability in infancy or early childhood (congenital hypomyelinating neuropathy and Dejerine-Sottas neuropathy), while others develop few if any symptoms of neuropathy until adulthood.

At present, mutations in more than 50 genes have been identified that cause CMT. These genes and their proteins constitute a human ‘microarray’ of molecules that are necessary for the normal function of myelinated axons in the peripheral nervous system. These mutations have illuminated important intracellular pathways leading to demyelination or axonal degeneration, including intracellular protein trafficking, axonal transport, regulation of transcription and mitochondrial fusion/fission. As a result, rational hypothesis driven treatment approaches are underway and some clinical trials for CMT1A, the most common form of CMT, have been completed.^{4–7} However, clinical trials depend on carefully chosen outcome measures used in appropriately selected patients to have the best chance of success.

Outcome measures need to be clinically well validated and meet the demands of being well-tolerated, valid, reliable and sensitive.⁸ In adults with CMT, the CMT Neuropathy Score (CMTNS) has been implemented as the primary outcome measure in numerous drug trials.^{5,6} The CMTNS is a composite score based on patient history, neurological examination, activity limitations and clinical neurophysiology, and can detect an increase in impairment on a yearly basis.⁹ However, the CMTNS has limited sensitivity in children to differentiate levels of disease severity,¹⁰ and the influence of growth and development that normally occurs during childhood on the CMTNS is unknown.

Since most forms of CMT affect children there is a need for a clinical tool to measure impairment in children with CMT. For example, most patients with CMT1A¹¹ and CMT1X,^{12,13} the two most common forms of CMT, develop symptoms within the first two decades of life. Many patients with CMT2A, the most common form of CMT2, are wheelchair bound by 21 years.¹⁴ Moreover, childhood may be the ideal time to institute treatments for CMT before chronic changes of demyelination or axonal degeneration have occurred that make repair more difficult.¹⁵ In this article we describe efforts by our Inherited Neuropathies Consortium to develop a multidimensional pediatric scale for children with CMT.

The first crucial step in designing such a scale was to ensure its ability to measure outcomes that are relevant to neuropathy and disability, using test items that are sufficiently sensitive and responsive to change. This allows precise assessment of baseline performance and disease severity, monitoring of outcomes longitudinally in studies of natural history, and the determination of responses to existing and novel interventions. Our scale needed to be unambiguously constructed to represent only one of the outcome levels according to the

International Classification of Functioning, Disability and Health (ICF).¹⁶ Disability has been proposed as the preferential level for measuring therapeutic response in adults and children with CMT.⁸ The World Health Organization (WHO) defines disability as an umbrella term, covering impairments, activity limitations and participation restrictions.

Most disability scales used in the neuropathies have been validated using Classical Test Theory statistical techniques, such as inter-item correlations and factor analysis. Use of new psychometric methods such as the Rasch model, a modern technique that forms part of Item Response Theory, is regarded as a more clinically and scientifically meaningful scale development approach to measure disability.¹⁷ Rasch analysis is a probabilistic mathematical modeling technique used to assess properties of outcome measures including unidimensionality (extent to which items measure a single construct), item difficulty (relative difficulty of the items when compared to one another) and person separation (extent to which items distinguish between distinct levels of functioning). Rasch analysis has been widely used in the development and validation of outcome measures in neurology.^{18,19}

In this study, we identified a set of items that represent a range of impairment levels in childhood CMT and conducted a series of validation studies, including Rasch analysis, to build a linearly weighted disability scale for children with CMT, known as the Charcot-Marie-Tooth disease Pediatric Scale (CMTPedS).

Methods

We conducted two phases of research: development and validation of the CMTPedS. Ethics approval from all institutions for all studies, and written informed assent/consent from all children and their families was obtained.

The development stages of CMTPedS involved:

Definition of the construct

An extensive review of the literature on measurement of disability in children with CMT identified the need for a patient-centered multiple item rating scale with broad application to reflect all aspects of disability in children with all types of CMT from the age of 3 years.

Generation of the item pool

We searched MEDLINE (from January 1966), EMBASE (from January 1980), CINAHL (from January 1982), AMED (from January 1985), Cochrane Neuromuscular Disease Group Specialized Register and reference lists of articles. We contacted experts in the field to identify additional test items. A large pool of items was generated capturing: symptoms; foot and ankle involvement; hand dexterity; strength; sensation; balance; gait; motor function. The item pool included many tests all tapping the same underlying construct, and were selected based on disease-specificity, functional/patient-relevance, reliability/validity, responsiveness to change, availability of published norms, duration and ease of interpretation. Items were reduced based on being simple, safe to administer, well-tolerated, valid, reliable and sensitive.

Peer Review

Quality, suitability and coverage of potential items was peer-reviewed by 23 expert clinicians, scientists and patient representatives from Australia, Belgium, France, Germany, Italy, Netherlands, Spain, UK and USA at the 168th European NeuroMuscular Centre (ENMC) International Workshop.⁸ Based on experts' opinion, items with insufficient face/

content validity were removed to form the *preliminary* version of the CMTPedS containing 37 items.

Pilot testing

Following training of clinicians from USA, UK, Italy and Australia through a face-to-face workshop, online manual and video resources, the CMTPedS was pilot-tested with four affected children to check for administration problems, item instructions, order and duration. The *preliminary* CMTPedS could be completed in 45–60 minutes and was well accepted by the children. Feedback informed the *working* version of the CMTPedS containing 28 items (Table 1).

During a 14-month test period, the *working* version of the CMTPedS was prospectively administered to 172 children aged 3–20 years through the Inherited Neuropathies Consortium. A series of internal and external validation studies were conducted with these data in SPSS v18.0 and RUMM2030, as detailed in Table 2, in accordance with established methods.^{20–26} A glossary of statistical terminology to clarify the methods and results for the general readership is provided in Supplementary Table 1.

Results

Patient profile of the 172 cases was: 90 female (52%); mean age 10.8yrs (SD 4.2); mean height 1.44m (SD 0.22); mean weight 42.5kg (SD 18.9). Right limb was dominant in 90% of cases. The sample comprised a broad range of CMT types: 48% Type 1A; 9% Type 1B-E; 6% X-linked; 6% Type 2A-L; 5% Type 4A-J; 1% Dejerine-Sottas; <1% Type 5; 23% Unidentified gene.

1. **Item Analysis:** With regard to redundancies, all left and right limb paired items (Foot Posture Index, Ankle Flexibility, Functional Dexterity Test, Nine Hole Peg Test) were highly correlated ($r>0.76$ – 0.90 , $p<0.0001$), so to avoid a unit of analysis error²⁷ we retained one limb only (dominant) per item. Hand strength items (Grip, Thumb-Index Pinch, Three Point Pinch) were highly inter-correlated ($r=0.81$ – 0.92 , $p<0.0001$), so only Grip strength was retained because eight children could not produce a Thumb-Index Pinch or Three Point Pinch due to their inability to approximate the thumb to the digits because of poor thumb mobility or finger contracture (floor effect).

Foot strength items (Plantarflexion, Dorsiflexion, Inversion, Eversion) were highly inter-correlated ($r=0.71$ – 0.86 , $p<0.0001$), except Plantarflexion and Dorsiflexion ($r=0.65$), so only these were retained. Of the function items (Balance, Long Jump, 10m run/walk, Stair Ascend/Descend, Six-Minute Walk Test) there were high correlations ($r>0.76$ – 0.90 , $p<0.0001$) for 10m run/walk and Stair items. Since these items already correlate substantially with Balance, Long Jump, Six-Minute Walk Test, and were unlikely to detect differences between children with CMT because most cases were graded as normal (72–82%), only Balance, Long Jump and Six-minute Walk Test were retained.

With regard to uncorrelated items, the self-reported *Symptoms* item did not correlate substantially ($r>0.3$) with any other item and was retained only for patient profiling purposes.

2. **Scoring:** In order to rate performance across age and gender with the remaining 13 items measured in different units (degrees, seconds, newtons, meters), items were converted to z-scores based on age/gender-matched normative reference values collected by the Inherited Neuropathies Consortium and cross-checked with

published data.^{28–47} Z-scores provided a dimensionless rating approach to the challenge of growth and development, offset by deterioration of strength and function, in children with CMT. See Supplementary Table 2 for the z-score conversion process.

To improve interpretation and generate a total score, z-scores were categorized along a continuum of disability levels: normal, very mild, mild, moderate and severe. Our approach, outlined in Supplementary Table 2, mirrors the validated adult CMTNS which was originally modified from the Total Neuropathy Score⁴⁸ by collapsing to a 5-point Likert response format.⁴⁹ However, the CMTpedS categories are based on age/gender derived z-scores. This approach provides ease of interpretation and clinical utility by dovetailing the adult CMTNS.

Item analysis of the 13 categorized items showed scores ranging from a low of 0 (normal) to a high of 4 (severe). Mean scores ranged from a low of 0.6 (Vibration) to 3.2 (Dorsiflexion Strength) with all items varying across the full range from 0–4. In the inter-item and item-total correlation matrix, no pair was very highly correlated ($r > 0.7$) and all items correlated substantially (> 0.3) with at least one other item. Average inter-item correlation was 0.22 (range -0.09 – 0.54). The Item-Total correlation ranged from 0.14 (Ankle Flexibility) to 0.67 (Six-Minute Walk Test).

3. **Factor Analysis:** The 13 items were subjected to principal components analysis (PCA). The Kaiser-Meyer-Olkin value²² and the Bartlett's Test of Sphericity²³ supported the factorability of the correlation matrix. PCA revealed the presence of four components with eigenvalues exceeding 1, explaining 32%, 11%, 9% and 8% of the variance respectively for a total of 60%. An inspection of the scree plot revealed a clear break after the second component, supporting the retention of two components for further investigation.²⁴ This was further supported by the results of Parallel Analysis, which showed two components with eigenvalues exceeding the corresponding criterion values for a randomly generated data matrix of the same size (13 items $\times$ 172 cases).

The two component solution explained a total of 43% of the variance, with Component 1 contributing 32% and Component 2 contributing 11%. To aid in the interpretation of these two components, oblimin rotation was performed.²¹ The rotated solution revealed the presence of a simple structure, with both components showing a number of strong loadings and all, but two items (Foot Posture Index, Ankle Flexibility), loading substantially on only one component.

The interpretation of the two components suggested that the 11 items on Component 1 represent *Function* (Strength, Dexterity, Sensation, Balance, Gait, Power, Endurance), while the two items on Component 2 represented *Structure* (Deformity, Contracture). There was a weak correlation between the two factors ($r = 0.04$). The results of this analysis supported the use of the *Function* items in accordance with the WHO ICF framework, while the *Structure* items were retained only for patient profiling and clinical symmetry. The final 11-item solution explained a total of 49.4% of the variance.

4. **Reliability:** Internal consistency, or the degree to which the 11 items group together, was 'very good' with a Cronbach's coefficient alpha value of 0.82.²⁶ With regard to reproducibility, we conducted an inter-rater reliability study involving eight affected children (7 girls and 1 boy) aged 5–15yrs (mean 8.8, SD 3.2) with a variety of CMT subtypes (4 CMT1A, 2 CMT1B, 1 CMT1E, 1 CMT2A) all evaluated by eight clinicians (3 Physical Therapists, 1 Neurologist, 1 Pediatrician, 1

Podiatrist, 1 Occupational Therapist, 1 Medical Graduate) from four international sites. Each child was examined in the morning and afternoon across two days. To avoid fatigue there was a 2.5 hour time gap between assessments on each day. The CMTPedS total score exhibited 'excellent' inter-rater reliability ($ICC_{2,4,0.95}$) with narrow 95% confidence intervals (95% CI 0.84-0.99).²⁵

5. **Rasch Analysis:** Rasch analysis of the 172 patients supported the viability of the 11-item CMTPedS as a global measure of disability in children with CMT. It showed good overall model fit (chi-square probability 0.03, non-significant with Bonferroni correction $0.05/11=0.005$). There was no evidence of misfitting items (Fit residual mean 0.15, SD 1.18) with no fit residuals >2.5 and no significant chi-square probability values. There was no person misfit (mean -0.13 , SD 0.88) with no fit residuals >2.5 . There was acceptable person separation reliability to differentiate groups of patients (Cronbach's alpha 0.81). There were no items showing uniform/non-uniform differential item functioning (DIF). Residual correlations showed no evidence of serious response dependency. Formal dimensionality testing indicated that only 5 (3.8%) cases had statistically different scores ($p<0.05$) on the two sets of items identified from PCA of the residuals, suggesting the scale is unidimensional. Disordered thresholds were present; however there was excellent overall global fit so no action was taken. Person-Item distribution shows the CMTPedS is well targeted.

The item map showed a good spread across the full range of scores for this sample, with no gaps where there were insufficient items to assess specific levels of the trait (Supplementary Fig 1). Gait was the easiest item to score highly (i.e. commonly severely affected) and Vibration was the hardest item to score highly (i.e. rarely severely affected). There was no clustering at the low or high ends of the distribution (floor or ceiling effects). The *final* version of the CMTPedS shown in Fig 1 appeared well targeted for use with this group of patients.

6. **Sensitivity:** The 11-item CMTPedS score has a possible range of 0 to 44 and scores were normally distributed (Kolmogorov-Smirnov 0.068, $p=0.2$). Of the 172 cases, the mean was 19 (SD 8) with a range of 4–41 points. Sensitivity analysis identified no difference in mean CMTPedS score between boys (19, SD 8) and girls (mean 20, SD 8) ($t=-0.792$, $p=0.430$), although as expected there were gender differences for the 11 X-linked cases (boys 19, SD 9; girls 14, SD 8).

Older age was significantly associated with a higher CMTPedS total score ($r=0.44$, $p<0.001$) reflecting the progression of the disease with age. Fig 2 suggests a 16-point change from 3 to 20 years. Individual items did not correlate as highly with age ($r=0.15$ to 0.38). Dividing the sample into early childhood (3–8 years), middle childhood (9–14 years) and adolescence (15–20 years), as previously described,⁵⁰ showed that the CMTPedS score was significantly higher as the disease progressed through early childhood (14, SD 7), middle childhood (20, SD 8) and adolescence (25, SD 8) ($F=16.285$, $p<0.0001$). With regard to CMT type, children with CMT1A (17, SD 7) scored significantly better than other types of CMT (22, SD 9) ($t=-3.161$, $p=0.002$). Moreover, the demyelinating cases, confirmed with clinical neurophysiology, generally scored better (19, SD 8) than axonal (24, SD 9) cases.

Longitudinal data from 15 patients were analyzed to determine whether CMTPedS scores were sensitive to change over a one-year period, although we recognize that larger numbers of patients will be required to address this issue definitively. Their ages ranged from 4–17 years and included 11 patients with CMT1A, one each with CMT2A and CMT4A and two with unidentified genetic causes. Taken as an aggregate their scores demonstrated an increase (worsening) of the CMTPedS score

from baseline (mean 20, SD 10) to 1-year follow-up (mean 21, SD 11) (Table 3). However, scores from the two patients with CMT2A and CMT4A, more severe forms of CMT, progressed more than most patients with CMT1A and one outlier with more severe CMT1A was identified by an increase in 6 points over a one year period (Table 3).

A higher number of self-reported symptoms was modestly associated with higher CMTPedS score ($r=0.24$, $p=0.01$). In particular the presence of hand tremor (22, SD 7 vs. 18, SD 8; $t=-2.791$, $p=0.006$) and sensory symptoms (22, SD 9 vs. 18, SD 8; $t=-2.347$, $p=0.021$) significantly influenced the CMTPedS score. Presence of ankle contracture (lunge test) was also related to the CMTPedS score ($r=-0.209$, $p=0.029$), while foot deformity (Foot Posture Index) was not ($p>0.05$). Children that required Ankle-Foot-Orthoses (AFOs) to walk scored significantly worse on the CMTPedS (30, SD 9 vs. 18, SD 8; $t=3.702$, $p<0.0001$).

7. **Implementation:** A CMTPedS equipment and item instruction kit, available in Supplementary File 1, was compiled to facilitate worldwide training and implementation. Specialized scoring software was developed to automate the z-score conversion and categorization process and batch cases for total scoring based on age/gender-matched normative reference values (Supplementary Fig 2). This Windows software is available as a free internet download (<http://cmtpeds.org/>).

Discussion

Rating scales, based on modern psychometric validation, are increasingly used as primary outcome measures in natural history studies and clinical trials. The quality of the rating scale has the potential to influence the outcome of clinical trials and patient care.¹⁷ We performed a rigorous development and validation process to evaluate the CMTPedS. Based on the developmental phase of research, the CMTPedS is clinically meaningful, related to an explicit construct and easily interpretable. Based on the validation phase, the CMTPedS is a stable, reliable and psychometrically robust outcome measure for young children and adolescents with CMT to enable precise disease-relevant assessment. Based on the sensitivity analysis, the CMTPedS is highly sensitive to age and CMT type, generally not influenced by gender, and clearly reflects the severity of the disease.

There are no other measurement scales for children with CMT. The CMTNS, which has been validated in adults,⁴⁹ has limited application in children because only four of nine items are regarded as sensitive.¹⁰ There are few scales in the neuropathy field,^{18,51} and none in the inherited neuropathies, validated with modern psychometric methods. Rasch has become the preferential method of validation. The Rasch model focuses on the probability of individuals scoring on an item correctly given their responses to other items in the scale ('fit'). Within the framework of Rasch, the scale should work the same way, irrespective of the group being assessed (e.g. items should behave similarly independent of age, gender or diagnosis grouping).²⁰ Rasch analysis supported the viability of the 11-item CMTPedS as a unidimensional measure of disability in children with CMT. It showed good overall model fit, no evidence of misfitting items, no person misfit, ability to differentiate groups of patients, no differential item functioning and it was well targeted for children with CMT.

There is international support for the CMTPedS to be implemented as the primary outcome measure in studies of children with CMT.⁸ The CMTPedS was designed to supplement a thorough neurological examination and capture functionally relevant limitations caused by CMT in the pediatric population. It is intended to have broad application in natural history studies and clinical trials of rehabilitative (e.g. orthoses, stretching, strengthening), pharmacological (e.g. curcumin, anti-progesterone) and surgical (e.g. foot and hand tendon

transfer, arthodesis, hip dysplasia) interventions. At this stage, and by design, the CMTPedS is limited to children. However because it is based on activities that are relevant to daily life, there will be a demand to broaden the application of the CMTPedS to enable long term studies into adulthood to ensure consistent measurement across the lifespan of patient's with CMT.

This study is primarily based on a cross-sectional analysis. In the future, 5-year follow-up data will be available through the Inherited Neuropathies Consortium to determine the longitudinal responsiveness and minimal clinically important difference of the CMTPedS. These data will demonstrate how large a change in CMTPedS points would be regarded by patients, parents and clinicians as indicating a meaningful improvement in day-to-day function following an experimental intervention. Different subtypes of CMT vary in severity and rate of progression. For instance, CMT1A, the most common form of CMT, is thought to progress quite slowly during childhood while patients with CMT2A are wheelchair bound by 21 years. Therefore, as suggested by our preliminary longitudinal data, it is likely that the rate of change of CMTPedS will vary, depending on the CMT subtype. To determine this experimentally will undoubtedly require larger numbers of children with different subtypes assessed longitudinally for 2-5 years, as we propose to do within our Consortium. Furthermore, even within subtype, patient to patient variability will influence the rate of change of the CMTPedS. For instance, the preliminary longitudinal data revealed five cases of CMT1A that showed an improvement on the CMTPedS while the other six cases of CMT1A did not. This accurately reflects the well-known heterogeneity of the disease, particular during childhood where rapid periods of growth and development can produce a variable clinical presentation and rate of progression.

Indeed, results from our 1-year placebo-controlled clinical trial of ascorbic acid for 81 children with CMT1A showed some cases of marked improvement in strength and motor function equally in both the treatment and control group.⁴ While the CMTPedS was not utilized in this trial as an outcome measure, the fundamental components of strength and motor function are common elements and illustrate the point of variability in patient response during childhood growth and development. The implications of this phenotypic variability on future clinical trial design requires larger samples to increase power and longer follow-up duration to account for natural growth fluctuations.

In conclusion, the final 11-item CMTPedS is a well-tolerated outcome measure that can be completed in 25 minutes. It generates a normally distributed score ranging from 0 to 44 points which is a reliable, valid and sensitive measure of disability for children with CMT from the age of 3 years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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cmtpediatricscale

Initial Evaluation ☐ Re-Evaluation ☐ Date:

Patient Profile											
ID:			D.O.B:			Age (yrs):			Gender: Boy ☐ Girl ☐		
Height (m):		Weight (kg):		Dominant Hand: L ☐ R ☐		Dominant Foot: L ☐ R ☐		Diagnosis:			
Symptoms:		Foot pain ☐		Leg cramps ☐		Unsteady ankles ☐		Daily trips and/or falls ☐		Hand pain ☐	
		Hand weakness ☐		Hand tremor ☐		Sensory symptoms (e.g. pins and needles, tingling, numbness, prickling) ☐					
Lunge test (degrees)						Left:			Right:		
Foot Posture Index		Talar head palpation									
		Curves above and below lateral malleolus									
		Inversion/eversion of the calcaneus									
		Bulge in the region of the talonavicular joint									
		Congruence of the medial longitudinal arch									
		Abd/adduction of forefoot on rearfoot (too-many-toes)									
Total (-12 to 12)											

Hand Dexterity											
1. Functional Dexterity Test (sec)						2. Nine-hole peg test (sec)					
Strength		Trial 1		Trial 2		Trial 3		Average			
3. Hand grip (N)								x2:			
4. Foot plantarflexion (N)											
5. Foot dorsiflexion (N)											
Sensation		0	1	2	3	4	Score				
6. Pinprick		Normal	Decreased below or at ankle bones	Decreased at or below midline of calf	Decreased above calf midline up to and including knee	Decreased above knee (above top of patella)					
7. Vibration		Normal	Reduced at first metatarsal bone	Reduced at ankle	Reduced at knee (tibial tuberosity)	Absent at knee and ankle					

Balance		Assistive device required (e.g. AFO) Y/N. Describe device and footwear:									
8. Bruininks Oseretsky Test		Raw Score		Conduct second trial only if examinee does not earn the maximum score on the first trial						Point score	
		Trial 1	Trial 2								
Standing with feet apart on a line-eyes open		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Walking forward on a line		Raw	0	1-2	3-4	5	6				
		Point	0	1	2	3	4				
Standing on one leg on a line-eyes open		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Standing with feet apart on a line-eyes closed		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Walking forward heel-to-toe on a line		Raw	0	1-2	3-4	5	6				
		Point	0	1	2	3	4				
Standing on one leg on a line-eyes closed		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Standing on one leg on a beam-eyes open		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Standing heel-to-toe on a balance beam		Raw	0.0-0.9	1.0-2.9	3.0-5.9	6.0-9.9	10				
		Point	0	1	2	3	4				
Standing on one leg on a beam-eyes closed		Raw	0.0-0.9	1.0-2.9	3.0-4.9	5.0-7.9	8.0-9.9	10			
		Point	0	1	2	3	4	5			
Balance Subscale from the Bruininks Oseretsky Test of Motor Proficiency, Second Edition (BOT-2). Copyright© 2005 NCS Pearson, Inc. Adapted and reproduced with permission. All rights reserved.								Total			

Motor Function		Assistive device required (e.g. AFO) Y/N. Describe device and footwear:									
9. Gait		Foot drop: No ☐ Some ☐ Yes ☐		Difficulty heel walking: No ☐ Some ☐ Yes ☐		Difficulty toe walking: No ☐ Some ☐ Yes ☐					
10. Long jump (cm)						11. Six-minute walk test (m)					

Item Scores (0-4)											Total Score (0-44)
1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	

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Figure 1.
Final version of the 11-item CMTPedS data form.

Figure 2.

Relationship between the CMTPedS score and advancing age. Older age was significantly associated with a higher CMTPedS reflecting the progression of the disease with age.

Table 1

Draft items, associated equipment and trait, of the *working* version of the CMTPedS.

Item	Equipment	Trait
1. Symptoms ⁵⁰	Eight patient/parent questions	Symptoms: foot pain, cramps, unsteady ankles, daily trips/falls, hand pain/ weakness/tremor, sensory symptoms
2. Foot Posture Index, dominant ²⁸	FPI Score Sheet	Deformity: pes cavus
3. Foot Posture Index, non-dominant ²⁸	FPI Score Sheet	Deformity: pes cavus
4. Ankle Flexibility, dominant ³⁰	Lunge Test	Contracture: ankle
5. Ankle Flexibility, non-dominant ³⁰	Lunge Test	Contracture: ankle
6. Functional Dexterity Test, dominant ^{34 *}	Functional Dexterity Test	Dexterity: finger
7. Functional Dexterity Test, non-dominant ³⁴	Functional Dexterity Test	Dexterity: finger
8. Nine Hole Peg Test, dominant ^{35 *}	Rolyan® 9-Hole Peg Test	Dexterity: hand
9. Nine Hole Peg Test, non-dominant ³⁵	Rolyan® 9-Hole Peg Test	Dexterity: hand
10. Grip strength ^{38 *}	Citec Hand-held dynamometer	Strength: Grip
11. Thumb-Index strength ³⁸	Citec Hand-held dynamometer	Strength: Thumb-Index
12. Three Point Pinch strength ³⁸	Citec Hand-held dynamometer	Strength: Three Point Pinch
13. Plantarflexion strength ^{41 *}	Citec Hand-held dynamometer	Strength: Foot Plantarflexion
14. Dorsiflexion strength ^{41 *}	Citec Hand-held dynamometer	Strength: Foot Dorsiflexion
15. Inversion strength ⁴¹	Citec Hand-held dynamometer	Strength: Foot Inversion
16. Eversion strength ⁴¹	Citec Hand-held dynamometer	Strength: Foot Eversion
17. Pinprick ^{49 *}	Neurotips™	Sensation: Small fiber loss (A-delta fibers)
18. Vibration ^{49 *}	Rydel-Seiffer tuning fork	Sensation: Large fiber loss (Pacinian corpuscles, A-beta fibers)
19. Balance ^{47 *}	Bruininks Oseretsky Test of Motor Proficiency, 2 nd Ed	Balance
20. Gait ^{50 *}	Gait observation	Gait Sum Score: foot drop, difficulty heel walking, difficulty toe walking
21. Long Jump ^{45 *}	Tape Measure	Power
22. 10-meter run/walk, sec ⁵²	Stopwatch/Tape Measure	Speed
23. 10-meter run/walk, grade ⁵²	1–6 standardized scale	Speed
24. Stair ascent, sec ⁵²	Standard four 15 cm steps	Speed
25. Stair ascent, grade ⁵²	1–6 standardized scale	Speed
26. Stair descent, sec ⁵²	Standard four 15 cm steps	Speed
27. Stair descent, grade ⁵²	1–6 standardized scale	Speed
28. Six-minute walk test ^{46 *}	Stopwatch, Lap counter, Cones	Speed and Endurance

* Retained in final version of the CMTPedS

Table 2

Method for the internal and external validation studies of the CMTPedS.

Validity Approach	Method
1. Item analysis	In SPSS Version 18.0 the CMTPedS was refined by removing very highly inter-correlated items (>0.7) which can cause scale redundancy and local dependency issues in Rasch modeling. ²⁰ Uncorrelated items ($r<0.3$) were also removed because low item inter-correlations undermine internal consistency of a measurement scale.
2. Item scoring	For generalizability, a total score was constructed with items that were converted to a dimensionless variable, z-score, and then categorized to a 0–4 Likert scale. A z-score indicates how many standard deviations an item is above or below the mean. Z-scores are a dimensionless quantity derived by subtracting the population mean from an individual raw score and then dividing the difference by the population standard deviation. The advantage and challenge of using a z-score is that it transforms raw data into a relative expression of distance of that data point from the mean, based upon age and gender matched normative data. In this way a small improvement in the raw data over two time points can actually turn out to be a relative decline when compared to changes in age/gender matched norms. Conversion of raw scores to z-scores was based on age/gender-matched normative reference values collected by the Inherited Neuropathies Consortium and cross-checked with extensive published data. ^{28–47}
3. Factor analysis	The CMTPedS was subjected to principal components analysis (PCA) using SPSS Version 18.0 in accordance with an established protocol. ²¹
4. Reliability	In order for the CMTPedS to be a useful research or clinical tool, it must be reliable. The higher the reliability, the smaller the error. Both internal consistency and test reproducibility were assessed. Internal consistency is the homogeneity of items that make up the scale <i>i.e.</i> the degree to which items hang together and was calculated with Cronbach's coefficient alpha. For reproducibility, an intraclass correlation coefficient ($ICC_{2,4}$) was calculated using the two-way random-effects model with absolute agreement, single-measures option.
5. Rasch analysis	In RUMM2030 software all aspects of the CMTPedS including the response format, fit of the items, item bias, unidimensionality and the spread of items across the construct being measured were subjected to Rasch analysis following the procedures recommended by Pallant and Tennant. ²⁰
6. Sensitivity	The ability of the CMTPedS to differentiate age, gender, CMT type, neurophysiological features, severity of the disease and physical characteristics between children was performed using SPSS Version 18.0.
7. Implementation	Worldwide access to CMTPedS resources, equipment, training, computerized scale administration and online customised scoring software was developed.

Table 3

One year longitudinal data from the CMTPedS for 15 children with CMT.

Patient	Age years	Gender	CMT Subtype	CMTPedS Baseline	CMTPedS 1 year	CMTPedS Difference*
SYD-76997-0100	4	M	Type 1A	6	3	-3
WSU-75608-0001	4	M	Type 4A	29	34	5
CHP-76460-0001	7	F	Type 1A	11	11	0
SYD-76960-0001	7	M	Type 1A	10	11	1
WSU-75595-0001	7	M	Type 2A	35	38	3
SYD-76997-0001	7	F	Type 1A	11	17	6
SYD-76956-0101	9	F	Type 1A	18	15	-3
SYD-76955-0101	9	F	Type 1A	11	12	1
WSU-75545-9004	9	M	Type 1A	19	20	1
WSU-75600-0001	9	M	Unidentified gene	36	38	2
NHN_76156_0001	10	F	Type 1A	34	32	-2
SYD-76956-0001	11	M	Type 1A	23	22	-1
SYD-76955-0001	12	F	Type 1A	10	9	-1
SYD-76962-0001	15	F	Unidentified gene	18	18	0
WSU-75511-9000	16	M	Type 1A	28	28	0

* Positive values denotes a worsening of disease severity