Original Investigation

Phenotypic Variability of Childhood Charcot-Marie-Tooth Disease

Kayla M.D. Cornett, BHK, MSc; Manoj P. Menezes, MBBS, FRACP, PhD; Paula Bray, PhD; Mark Halaki, PhD; Rosemary R. Shy, MD; Sabrina W. Yum, MD; Timothy Estilow, OTR/L; Isabella Moroni, MD; Maria Foscan, PT; Emanuela Pagliano, MD; Davide Pareyson, MD; Matilde Laurá, MD, PhD; Trupti Bhandari, PT; Francesco Muntoni, MD, FRCPCH, FMed Sci; Mary M. Reilly, MD, FRCP; Richard S. Finkel, MD; Janet Sowden; Katy J. Eichinger, PT, DPT, NCS; David N. Herrmann, MBBCh; Michael E. Shy, MD; Joshua Burns, PhD; for the Inherited Neuropathies Consortium

IMPORTANCE Disease severity of childhood Charcot-Marie-Tooth disease (CMT) has not been extensively characterized, either within or between types of CMT to date.

OBJECTIVE To assess the variability of disease severity in a large cohort of children and adolescents with CMT.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study was conducted among 520 children and adolescents aged 3 to 20 years at 8 universities and hospitals involved in the Inherited Neuropathies Consortium between August 6, 2009, and July 31, 2014, in Australia, Italy, the United Kingdom, and the United States. Data analysis was conducted from August 1, 2014, to December 1, 2015.

MAIN OUTCOMES AND MEASURES Scores on the Charcot-Marie-Tooth Disease Pediatric Scale (CMTPedS), a well-validated unidimensional clinical outcome measure to assess disease severity. This instrument includes 11 items assessing fine and gross motor function, sensation, and balance to produce a total score ranging from 0 (unaffected) to 44 (severely affected).

RESULTS Among the 520 participants (274 males) aged 3 to 20 years, CMT type 1A (CMT1A) was the most prevalent type (252 [48.5%]), followed by CMT2A (31 [6.0%]), CMT1B (15 [2.9%]), CMT4C (13 [2.5%]), and CMTX1 (10 [1.9%]). Disease severity ranged from 1 to 44 points on the CMTPedS (mean [SD], 21.5 [8.9]), with ankle dorsiflexion strength and functional hand dexterity test being most affected. Participants with CMT1B (mean [SD] CMTPedS score, 24.0 [7.4]), CMT2A (29.7 [7.1]), and CMT4C (29.8 [8.6]) were more severely affected than those with CMT1A (18.9 [7.7]) and CMTX1 (males: 15.3 [7.7]; females: 13.0 [3.6]) ($P < .05$). Scores on the CMTPedS tended to worsen principally during childhood (ages, 3-10 years) for participants with CMT4C and CMTX1 and predominantly during adolescence for those with CMT1B and CMT2A (ages, 11-20 years), while CMT1A worsened consistently throughout childhood and adolescence. For individual items, participants with CMT4C recorded more affected functional dexterity test scores than did those with all other types of CMT ($P < .05$). Participants with CMT1A and CMTX1 performed significantly better on the 9-hole peg test and balance test than did those with all other types of CMT ($P < .05$). Participants with CMT2A had the weakest grip strength ($P < .05$), while those with CMT2A and CMT4C exhibited the weakest ankle plantarflexion and dorsiflexion strength, as well as the lowest long jump and 6-minute walk test distances ($P < .05$). Multiple regression modeling identified increasing age ($r = 0.356$, $\beta = 0.617$, $P < .001$) height ($r = 0.251$, $\beta = 0.309$, $P = .002$), self-reported foot pain ($r = 0.162$, $\beta = .114$, $P = .009$), and self-reported hand weakness ($r = 0.243$, $\beta = 0.203$, $P < .001$) as independent predictors of disease severity.

CONCLUSIONS AND RELEVANCE These results highlight the phenotypic variability within CMT genotypes and mutation-specific manifestations between types. This study has identified distinct functional limitations and self-reported impairments to target in future therapeutic trials.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A full listing of the members of the Inherited Neuropathies Consortium can be found at the end of this article.

Corresponding Author: Kayla M.D. Cornett, BHK, MSc, University of Sydney, East Street, Lidcombe NSW, Australia (kayla.cornett@health.nsw.gov.au).

Characterizing the variability of disease severity within and between types of Charcot-Marie-Tooth disease (CMT) is important to increase knowledge of genotype-phenotype associations and improve our understanding of the prognosis of this disorder. Charcot-Marie-Tooth disease is the most common inherited neuropathy, with an estimated prevalence of 1 in 2500.[1] Next-generation sequencing has resulted in a rapid expansion of gene discovery in CMT, with more than 80 genes identified and many more still to be discovered.[2] Charcot-Marie-Tooth disease is often characterized by distal weakness, foot deformity, sensory loss, areflexia, and difficulties with gait[2,3]; however, the frequency of these disease manifestations and the variability within and between types of CMT are poorly understood. While the prevalence of each type of CMT is becoming clearer, less is known about the clinical characteristics of each of these genetic types in childhood.

Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common form of CMT, accounting for approximately 60% of those with a genetic diagnosis.[4] Although CMT1A has been reported to be slower in progression compared with other forms of CMT, and most participants remain ambulatory through their lifetime, variability exists in the severity and rate of progression.[4] Charcot-Marie-Tooth disease types X1 and CMT2A are generally the next most common forms[4,5]; however, some geographic variability exists. Although disease severity of some of the rarer forms of CMT has been described, to our knowledge, no study has directly compared CMT types in childhood.[4,6-8] The development of the Charcot-Marie-Tooth Disease Pediatric Scale (CMTPedS) has provided the opportunity to compare types of CMT objectively and reliably in children and young adults across multiple centers.[3] The CMTPedS was developed through the Inherited Neuropathies Consortium, which is a member of the National Institutes of Health Rare Disease Clinical Research Network (http://www.rarediseasesnetwork.org/). The Inherited Neuropathies Consortium was established to conduct international collaborative research and natural history studies on adults and children with CMT. The CMTPedS is a linearly weighted and responsive clinical outcome measure to assess disease severity, and includes measures of hand dexterity, strength, sensation, gait, balance, power, and endurance. It provides an overall age-adjusted disability score allowing comparison within and between participants with different CMT types. The aim of this study was to characterize the range of disease severity both within and between children and adolescents with different CMT types enrolled in the Inherited Neuropathies Consortium.

Key Points

Question How does disease severity differ within and between types of Charcot-Marie-Tooth disease (CMT) in children and adolescents?

Findings In this multicenter cross-sectional study of 520 children and adolescents with CMT, measured with the well-validated CMT Pediatric Scale, participants with CMT2A, CMT4C, and CMT1B were more affected than those with CMT1A and CMTX1, although a spectrum of disease severity was identified within and between types.

Meaning These data highlight the phenotypic variability within CMT genotypes and mutation-specific manifestations between CMT types.

Methods

A total of 520 children and adolescents aged 3 to 20 years were enrolled across 8 sites in the Inherited Neuropathies Consortium between August 6, 2009, and July 30, 2014. The 8 sites included Children's Hospital at Westmead, Sydney, Australia (n = 113); University of Iowa Health Care, Iowa City (n = 92); Wayne State University, Detroit, Michigan (n = 85); Children's Hospital of Philadelphia, Pennsylvania (n = 72); Carlo Besta Neurological Institute, Milan, Italy (n = 66); National Hospital of Neurology and Neurosurgery and Great Ormond Street Hospital, London, England (n = 56); Nemours Children's Hospital, Orlando, Florida (n = 20); and University of Rochester, Rochester, New York (n = 16). Ethics approval was obtained at all institutions and written informed consent was obtained from all participants and/or their parents or guardians as required.

Demographic and Physical Characteristics

Information on demographics, clinical features, and genetic diagnosis was collected from all participants. Demographic information included sex, age, height, weight, and body mass index percentile. A diagnosis of CMT was made using clinical features, nerve conduction studies, family history, and genetic testing. Self-reported symptoms of foot pain, leg cramps, unsteady ankles, daily trips and falls, hand pain, hand weakness, hand tremor, and sensory symptoms, including tingling, numbness, or burning, were obtained from all participants. Symptoms were reported as being present or absent. Foot deformity was assessed using the validated Foot Posture Index[9] and ankle flexibility was assessed using the highly reliable weight-bearing lunge test.[10] The angle was measured using a digital inclinometer.

Disease Severity

The CMTPedS was performed on all children and adolescents by trained evaluators at each site. The CMTPedS measures hand dexterity (functional dexterity test and 9-hole peg test), strength (hand grip and ankle plantarflexion and dorsiflexion), sensation of the lower limbs (pinprick and vibration), gait (difficulty with heel walking, difficulty with toe walking, and presence of foot drop), balance (*Bruininks-Oseretsky Test of Motor Proficiency*, 2nd Ed),[11] and function (long jump and 6-minute walk test).[3] All items were assessed and raw scores compared with age- and sex-matched normative reference values to obtain a *z* score. The *z* scores were then converted to CMTPedS category scores ranging from 0 (unaffected) to 4 (severely affected). A category score of 0 indicates a *z* score within 1 SD from the normative reference value mean. A category score of 1, 2, or 3 represents a *z* score of 1 to 2, 2 to 3, or 3 to 4 SDs below normal, respectively. A score of 4 represents

more than 4 SDs below normal. Participants unable to perform an item owing to disease severity received a score of 4. Participants unable to perform an item for other reasons (eg, acute injury, recent surgery, behavioral issues) were not scored and a total score was not calculated. The 11-item category scores were summed to obtain a disease severity score out of 44, with 0 being unaffected and 44 being severely affected.

Statistical Analysis

Data analysis was conducted from August 1, 2014, to December 1, 2015, using SPSS, version 22.0 (IBM Corp). All data were assessed for normality and the appropriate parametric or nonparametric test subsequently used. Frequency of CMT types and self-reported symptoms were calculated as percentages. A 1-sample *t* test was used to compare foot alignment between participants with CMT and normative reference values for unaffected children and adolescents.[12] A 2 × 17 × 5-way (sex × age [years] × CMT type [1A, 1B, 2A, 4C, X1]) analysis of variance was performed to evaluate differences in CMTPedS total scores as well as individual item *z* scores. Significant interactions were examined with Tukey post hoc tests. A bivariate correlation matrix was conducted to determine the influence of age, height, weight, body mass index percentile, symptoms, foot alignment, and ankle flexibility on CMTPedS total scores. Significantly correlated items were entered into a stepwise multiple regression model that was reduced to the most parsimonious model to determine if the CMTPedS total score could be explained by these factors. Only 1 factor from highly correlated variables (eg, height, weight, body mass index percentile) was included to avoid multicolinearity. Standardized β weights were calculated. An α level of .05 was used for statistical significance.

Results

This study included 520 children and adolescents (274 males) aged 3 to 20 years (**Table 1**). An extensive number of CMT types were represented, with the most prevalent types being CMT1A (252 [48.5%]), CMT2A (31 [6.0%]), CMT1B (15 [2.9%]), CMT4C (13 [2.5%]), and CMTX1 (10 [1.9]%) (eTable 1 in the Supplement). There were no significant differences in age between the participants with the 5 most common types of CMT ($P < .05$). Foot alignment of participants with CMT was more cavovarus than in unaffected children and young adults ($P < .001$); however, there was a wide range of pes planus and pes cavus features (eFigure 1 in the Supplement). Unsteady ankles (272 [52.3%]), daily trips and falls (220 [42.3%]), and hand weakness (216 [41.5%]) were the most frequently reported symptoms for the entire cohort; when symptoms were divided by CMT type, the frequencies varied significantly between types (eTable 2 in the Supplement). Participants with CMT2A reported a significantly higher frequency of unsteady ankles (21 [67.7%]), daily trips and falls (18 [58.1%]), and hand tremor (17 [54.8]%) than did those with CMT1A (128 [45.4%], 101 [35.8%], and 92 [32.6%], respectively) ($P < .05$), while participants with CMT1B (9 [60.0%]) reported significantly more hand weakness than did those with CMT1A (98 [34.8%]) ($P < .05$) (eTable 2 in the Supplement).

Table 1. Physical Characteristics of the Sample

Characteristic	Mean (SD) [Range]
Age, y	10.9 (4.4) [3 to 20]
Height, m	1.44 (0.24) [0.90 to 1.98]
Weight, kg	42.2 (19.7) [11.2 to 120.6]
BMI	19.1 (4.9) [11.0 to 58.2]
BMI percentile	53.2 (32.5) [0.0 to 99.9]
Foot posture index score	1.4 (4.4) [−12 to 12]
Ankle lunge test, deg	22.3 (8.3) [0.0 to 50.0]
CMTPedS total score	21.5 (8.9) [1 to 44]

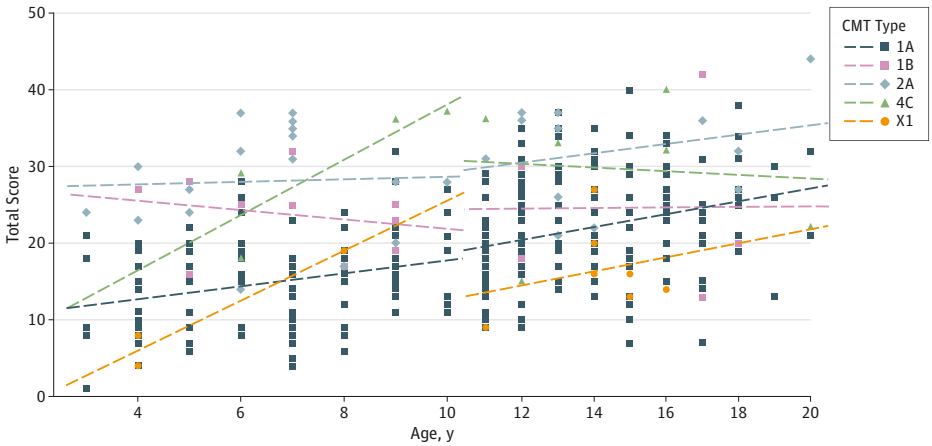
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMTPedS, Charcot-Marie-Tooth Disease Pediatric Scale.

A total of 474 children and adolescents were able to complete all 11 items of the CMTPedS to obtain a total disease severity score. The mean (SD) CMTPedS total score for the entire sample was 21.5 (8.9) (range, 1-44). The most affected items were dorsiflexion strength of the ankle and functional dexterity test of the hand with, respectively, 408 (82.3%) and 288 (56.5%) cases more than 3 SDs below normal (eFigure 2 in the Supplement). Analysis of variance indicated a significant interaction between age and CMT type on the CMTPedS score ($F_{33,245} = 1.836$, $P = .005$) whereby the CMTPedS score worsened with age ($F_{17,245} = 2.334$, $P = .003$). Scores on the CMTPedS tended to worsen principally during childhood (ages, 3-10 years) for participants with CMT4C and CMTX1 and predominantly during adolescence for those with CMT1B and CMT2A (ages, 11-20 years), while CMT1A worsened consistently throughout childhood and adolescence (**Figure 1**).

Type of CMT also significantly influenced the CMTPedS score ($F_{4,245} = 17.582$, $P < .001$) (**Figure 2**). Participants with CMT1A and CMTX1 demonstrated a significantly better CMTPedS score than did those with CMT1B ($P \leq .02$), CMT2A ($P < .001$), and CMT4C ($P < .001$), while participants with CMT1A had a significantly worse CMTPedS score than did those with CMTX1 (7 males and 3 females) ($P = .02$). Participants with CMT1B exhibited significantly better CMTPedS scores than did those with CMT2A ($P = .02$) and CMT4C ($P = .03$). There was no significant effect for sex for any CMT type ($P = .77$). Males with CMTX1 (mean [SD] CMTPedS total score, 15.3 [7.7]) were marginally more affected than females (13.0 [3.6]); however, this finding was not significant ($P = .65$).

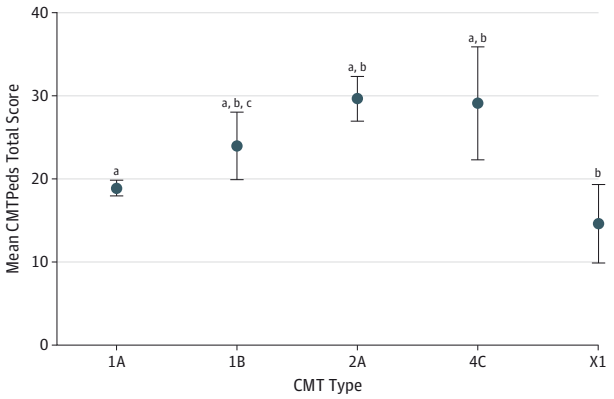
For individual CMTPedS item *z* scores, there was a significant effect for age ($P < .05$), whereby increasing age produced a worse score for each item. There was also a significant effect for sex on the 9-hole peg test ($F_{1,258} = 10.856$, $P = .001$), whereby females performed slower than males. No other items had a significant effect for sex ($P > .05$). Type of CMT had a significant effect on all CMTPedS item *z* scores ($P < .05$) (**Figure 3**). For the functional dexterity test, participants with CMT4C were significantly slower than those with all other CMT types ($P < .001$). For the 9-hole peg test, participants with CMT1A were significantly faster than those with CMT1B, CMT2A, and CMT4C ($P < .05$), while participants with CMTX1 were significantly faster than those with all other types

Figure 1. Charcot-Marie-Tooth Disease (CMT) Pediatric Scale Scores During Childhood and Adolescence for CMT Types



Individual data points are plotted with linear correlation best fit lines indicating change during childhood (ages, 3-10 years) and adolescence (ages, 11-20 years).

Figure 2. Charcot-Marie-Tooth Disease Pediatric Scale (CMTPedS) Total Score Differences Between Charcot-Marie-Tooth (CMT) Types



Values are given as mean (95% CI).

[a] Significantly different from CMTX1 ($P < .05$).

[b] Significantly different from CMT1A ($P < .05$).

[c] Significantly different from CMT2A ($P < .05$).

($P < .05$). Participants with CMT2A demonstrated significantly weaker grip strength than did those with CMT1A, CMT1B, and CMTX1 ($P < .05$) and participants with CMTX1 were significantly stronger than those with all other types ($P < .05$). Participants with CMT2A and CMT4C had significantly weaker ankle plantarflexion and dorsiflexion strength than did those with CMT1A and CMTX1 ($P < .05$), as well as reduced long jump and 6-minute walk test distances. Participants with CMT2A had significantly worse scores for ankle strength, long jump, and 6-minute walk test distance than did those with CMT1B ($P < .05$). Participants with CMT1A and CMTX1 had significantly better balance than did participants with CMT1B, CMT2A, and CMT4C ($P < .05$).

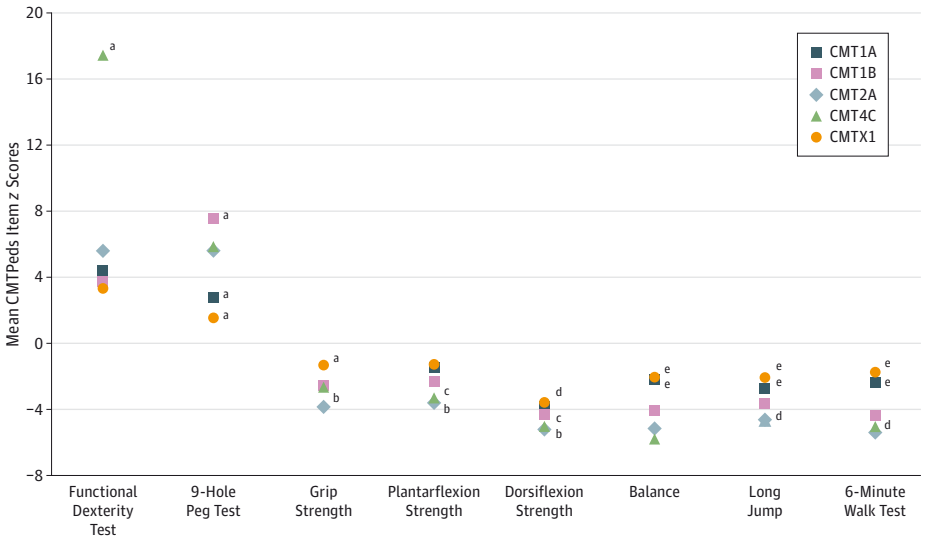
Significant correlations with the CMTPedS score were identified for age, height, weight, body mass index percentile, foot pain, unsteady ankles, leg cramps, hand weakness, hand tremor, and sensory symptoms (**Table 2**). Multiple regression modeling identified increasing age ($r = 0.356$, $\beta = 0.617$; $P < .001$) height ($r = 0.251$, $\beta = 0.309$; $P = .002$), self-reported foot pain ($r = 0.162$, $\beta = 0.114$; $P = .009$), and self-reported hand weakness ($r = 0.243$, $\beta = 0.203$; $P < .001$) as independent predictors of disease severity, explaining 21% of the variance in CMTPedS total score ($r^2 = 0.210$).

Discussion

This sample of 520 children and young adults with CMT is the largest reported to date and shows the phenotypic variability within CMT genotypes and mutation-specific manifestations between types. Disease severity, measured by the well-validated CMTPedS, ranged from 1 to 44 and represents almost the entire spectrum of the scale. Scores for the 5 most prevalent genotypes differed significantly. For instance, the most common type, CMT1A, demonstrated a mean (SD) CMTPedS score of 19 (8), while participants with CMT2A exhibited a markedly higher mean score of 30 (7) and those with CMTX1 had a lower mean score of 15 (7). This study has identified distinct functional limitations and self-reported impairments. For example, participants with CMT2A were significantly weaker for all strength measures, and those with CMT4C performed significantly worse for both hand dexterity measures.

Compared with previous studies exploring the heterogeneity of CMT severity,[3,13] our larger cohort described in this study comprises more than 10 participants for most types, which provides the opportunity to examine phenotypic differences between genotypes. When evaluating CMTPedS scores, children with CMT1A and CMTX1 were less severely affected than those with CMT1B, CMT2A, and CMT4C. Charcot-Marie-Tooth disease type 2A, specifically caused by *MFN2* (OMIM 608507) mutations, has been reported as a more severe phenotype[6] than other CMT2 types; however, it was not compared with CMT1, CMT4, or CMTX. Charcot-Marie-Tooth disease type 4C was recently reported to have a variable phenotype in a study of 10 siblings[7]; however, its severity has not been previously compared with other CMT types. Our find-

Figure 3. Charcot-Marie-Tooth Disease Pediatric Scale (CMTPedS) Item *z* Score Differences Between Charcot-Marie-Tooth (CMT) Types



Because the functional dexterity test and 9-hole peg test are timed tests, a positive *z* score indicates a longer time and therefore a worse performance. For all other measures a negative *z* score indicates a worse performance.

[a] Significantly different from all other CMT types ($P < .05$).

[b] Significantly different from CMT1A, CMT1B, and CMTX1 ($P < .05$).

[c] Significantly different from CMT1A and CMTX1 ($P < .05$).

[d] Significantly different from CMT1B ($P < .05$).

[e] Significantly different from CMT1B, CMT2A, and CMT4C ($P < .05$).

ings confirm this variability in CMT4C, with CMTPedS scores ranging from 15 to 40 in participants with this type. The disease severity of CMT4C (CMTPedS mean [SD] score, 29.8 [8.6]) was similar to that of CMT2A (29.7 [7.1]) and worse than that of CMT1A (18.9 [7.7]), and we identified hand dexterity as a major limitation for children and adolescents with CMT4C. Participants with CMT4C also exhibited significantly reduced sensation compared with those with CMT1A ($P < .001$). Although sensation was only measured by vibration and pinprick in the lower limbs in this study, reduced sensation may be globally limiting hand dexterity in these participants. Variability has also been reported within other CMT types.[4,8] For instance, in CMT1B, different *MPZ* (OMIM 159440) mutations may cause different disease severity.[8] The reason for the variability is not well understood. A recent study reported that participants with CMT had more rare variants in neuropathy-associated genes compared with unaffected participants and hence suggested that mutation burden in participants with neuropathy may contribute to the phenotypic variability.[5] Further studies following our cohort longitudinally will investigate if the disease progression within different types of CMT is also variable.

In our cohort, the 7 males with CMTX1 were marginally more affected than the 3 females with CMTX1, although this difference was not significant. It has previously been reported that males with CMTX1 demonstrate a milder phenotype during the first 2 decades of life, with increasing severity later in life.[4,14] Our findings also suggest that the CMTPedS scores change more rapidly in childhood vs adolescence in participants with CMTX1. Natural history studies into adulthood are required to clarify the severity and progression of CMTX1 in males vs females.

Charcot-Marie-Tooth disease is classically described as length dependent, with lower limb manifestations preceding involvement of the upper limbs.[15] The finding of height as an independent predictor of disease severity supports the length-dependency theory. Our study indicates that ankle dorsiflexion strength and functional hand dexterity are the most affected items on the CMTPedS, suggesting that both upper limb and lower limb manifestations are present from an early age across all CMT types. This finding confirms a previous report that upper limb impairment can be identified in children as young as 3 years with CMT1A.[16] In addition, the significant differences between CMT types for scores of tests of the upper limbs indicate that some forms may have greater hand impairment. Specifically, children with CMT4C performed much worse on the functional dexterity test than did those with all other types of CMT. Children with CMT1B, CMT2A, and CMT4C performed worse on the 9-hole peg test compared with those with CMT1A, suggesting that hand and finger dexterity are more significantly affected in participants with these types.

This study is not without limitations. First, the small number of participants with rarer types of CMT (eTable 1 in the Supplement) prevented a comprehensive comparison between all types of CMT. Second, this cross-sectional analysis provides only a single time point for the CMTPedS score, which limits an understanding of the responsiveness of this outcome measure in children and adolescents with CMT.

However, cross-sectional studies are useful in that they can give some prediction for longitudinal data when one correlates types, as in this case, with age. Figure 1 shows that CMTPedS scores seem to change more rapidly in childhood for those with CMT4C and CMTX1 and more rapidly during adolescence for those with CMT1B and CMT2A, while a consistent progression was observed in participants with CMT1A. Indeed, multiple regression modeling indicated that older age as well as increasing height and self-reported foot pain and hand weakness best predicted the CMTPedS total score. Interventions addressing foot pain and hand weakness at an early age may be appropriate therapeutic targets to reduce disease severity. Although, with only 21% of the variance in the

Table 2. Correlation Matrix of Variables Associated With CMTPedS Score

Variable	CMTPedS Score[a]	*P* Value
Age	0.350	<.001
Sex	−0.085	.06
Height	0.251	<.001
Weight	0.232	<.001
BMI percentile	−0.110	.02
Foot posture index	−0.032	.49
Ankle lunge test	−0.076	.11
Foot pain	0.155	.001
Leg cramps	0.163	<.001
Unsteady ankles	0.191	<.001
Daily trips and falls	0.074	.11
Hand pain	0.055	.23
Hand weakness	0.263	<.001
Hand tremor	0.197	<.001
Sensory symptoms	0.125	.006

Abbreviations: BMI, body mass index; CMTPedS, Charcot-Marie-Tooth Disease Pediatric Scale.

[a] Pearson correlation coefficients.

CMTPedS total score explained by these factors, specifically targeting the most affected CMTPedS items (eg, ankle dorsiflexion strength, functional hand dexterity test) may also be appropriate to reduce levels of disability. In addition, interventions targeting hand function, specifically hand and finger dexterity, might provide further benefits to reduce disease severity. Nevertheless, before trials of treatment can be conducted, it is important to understand the rate of disease progression in prospective natural history studies of children and adolescents with CMT.

Conclusions

This study provides a comprehensive phenotypic characterization of CMT both within and between CMT types seen in childhood. Phenotypic variability within CMT genotypes and mutation-specific manifestations between types were identified. Participants with CMT1B, CMT2A, and CMT4C were more severely affected than those with CMT1A and CMTX1. The most affected aspects of disease severity were ankle dorsiflexion strength and hand dexterity. Our study highlights that significant impairment is present from the earliest stages of the disease, even in participants with the milder CMT1A and CMTX1 forms. Therefore, any disease-modifying therapies that aim to slow or halt progression of CMT should ideally be implemented during childhood. These therapies may have limited benefits once significant axonal degeneration has occurred in older populations. Understanding these genotype-phenotype correlations will assist with accurately targeting future therapeutic trials in children and adults with CMT.

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Author Affiliations: University of Sydney & Children's Hospital at Westmead, Sydney Australia (Cornett, Menezes, Bray, Halaki, Burns); Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City (R. R. Shy); Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Yum); Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Yum); Neuromucsular Program, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Estilow); Istituto di Ricovero e Cura a Carattere Scientifico Foundation, Carlo Besta Neurological Institute, Milan, Italy (Moroni, Foscan, Pagliano, Pareyson); Medical Research Council Centre for Neuromuscular Diseases, University College London Institute of Neurology, Queen Square, London, England (Laurá, Reilly); University College London Institute of Child Health & Great Ormond Street Hospital, London, England (Bhandari, Muntoni); Neuromuscular Program, Division of Neurology, Nemours Children's Hospital, Orlando, Florida (Finkel); Department of Neurology, University of Rochester, Rochester, New York (Sowden, Eichinger, Herrmann); Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City (M. E. Shy).

Author Contributions: Ms Cornett had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: R.R. Shy, Estilow, M.E. Shy, Burns.
Acquisition, analysis, or interpretation of data: Cornett, Menezes, Bray, Halaki, R.R. Shy, Yum, Estilow, Moroni, Foscan, Pagliano, Pareyson, Laurá, Bhandari, Muntoni, Reilly, Finkel, Sowden, Eichinger, Herrmann, M.E. Shy.
Drafting of the manuscript: Cornett, R.R. Shy, Moroni, M.E. Shy, Burns.
Critical revision of the manuscript for important intellectual content: Menezes, Bray, Halaki, R.R. Shy, Yum, Estilow, Foscan, Pagliano, Pareyson, Laurá, Bhandari, Muntoni, Reilly, Finkel, Sowden, Eichinger, Herrmann, M.E. Shy.
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Study supervision: Menezes, Bray, R.R. Shy, Muntoni, Herrmann, M.E. Shy.

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Group Information: The members of the Inherited Neuropathies Consortium are as follows: *University of Iowa Health Care, Iowa City:* Michael Shy, MD. *Children's Hospital of Philadelphia, Philadelphia, Pennsylvania:* Sabrina Yum, MD. *University of Pennsylvania, Philadelphia:* Steven Scherer, MD, PhD. *University of Rochester, Rochester, New York:* David Herrmann, MBBCh. *National Hospital of Neurology and Neurosurgery, London, England:* Mary Reilly, MD, and Matilde Laura, MD. *Dubowitz Neuromuscular Centre, London, England:* Francesco Muntoni, MD. *University of Miami, Coral Gables, Florida:* Stephan Züchner, MD, PhD, and Mario Saporta, MD, PhD, MBA. *The Children's Hospital at Westmead, The University of Sydney, Sydney, Australia:* Joshua Burns, PhD. *Carlo Besta Neurological Institute, Milan, Italy:* Davide Pareyson, MD. *Johns Hopkins University, Baltimore, Maryland:* Thomas Lloyd, MD, PhD. *Vanderbilt University, Nashville, Tennessee:* Jun Li, MD, PhD. *University of*

Washington, Seattle: Michael D. Weiss, MD. *Nemours Children's Hospital, Jacksonville, Florida:* Richard S. Finkel, MD. *National Institutes of Health–Intramural Branch, Bethesda, Maryland:* Kenneth Fischbeck, MD. *Stanford University, Stanford, California:* John Day, MD, PhD. *Cedars-Sinai Medical Center, Los Angeles, California:* Robert Baloh MD, PhD, and Richard A. Lewis MD. *Harvard University/ Massachusetts General Hospital, Boston:* Vera Fridman, MD. *University of Michigan, Ann Arbor:* Sindhu Ramchandren, MD, MS. *University of Minnesota, Minneapolis:* David Walk, MD. *University of Utah, Salt Lake City:* Nicholas Johnson, MD. *University of Connecticut, Storrs:* Gyula Acsadi, MD, PhD. *University of Antwerp, Antwerp, Belgium:* Jonathan Baets, MD, PhD. *Data Management and Coordinating Center; Health Informatics Institute; University of South Florida, Tampa:* Jeffery Krischer, PhD.

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