Title: Natural history of Charcot-Marie-Tooth disease during childhood

Running Head: Natural history of pediatric CMT

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Abstract

Objective: To determine the rate of disease progression in a longitudinal natural history study of children with Charcot-Marie-Tooth disease (CMT).

Methods: 206 (103 female) participants aged 3-20 years enrolled in the Inherited Neuropathies Consortium were assessed at baseline and 2-years. Demographic, anthropometric, and diagnostic information were collected. Disease progression was assessed with the CMT Pediatric Scale (CMTPedS), a reliable Rasch-built linearly weighted disability scale evaluating fine and gross motor function, strength, sensation, and balance.

Results: On average CMTPedS Total scores progressed at a rate of 2.4±4.9 over 2-years (14% change from baseline, p<0.001). There was no difference between males and females (mean difference 0.5, 95%CI -0.9 to 1.9, p=0.49). The most responsive CMTPedS items were dorsiflexion strength (z-score change: -0.3, 95% CI -0.6 to -0.05, p=0.02), balance (z-score change: -1.0, 95% CI -1.9 to -0.09, p=0.03), and long jump (z-score change: -0.4, 95% CI -0.7 to -0.02, p=0.04). Of the most common genetic subtypes, 111 participants with CMT1A/*PMP22* duplication progressed by 1.8±4.2 (12% change from baseline, p<0.001), nine participants with CMT1B/*MPZ* mutation progressed by 2.2±5.1 (11% change), six participants with CMT2A/*MFN2* mutation progressed by 6.2±7.9 (23% change), and seven participants with CMT4C/*SH3TC2* mutations progressed by 3.0±4.5 (12% change). Participants with CMT2A progressed faster than CMT1A (mean difference -4.4, 95%CI -8.1 to -0.8, p=0.02). Children with CMT1A progressed consistently through early childhood (3-10 years) and adolescence (11-20 years) (mean difference 1.1, 95%CI -0.6 to 2.7, p=0.19) while CMT2A appeared to progress faster during early childhood than adolescence (mean difference 10.0, 95%CI -2.2 to 22.2, p=0.08).

Interpretation: Using the CMTPedS as an outcome measure of disease severity, children with CMT progress at a significant rate over 2-years. Understanding the rate at which

children with CMT deteriorate is essential for adequately powering trials of disease-modifying interventions.

Introduction

Charcot-Marie-Tooth disease (CMT) is the eponym for inherited peripheral neuropathies and is among the most common inherited neurological disorders, affecting 1 in 1,214[1] - 2,500[2] individuals of both sexes and all backgrounds. Mutations in more than 80 genes cause CMT (Inherited Neuropathy Variant Browser: http://hihg.med.miami.edu/code/http/cmt/public_html/index.html). The majority of CMT neuropathies are demyelinating, although up to one third appear to be primary axonal disorders.[3,4] Despite a variable phenotype,[5] most patients are characterized by onset in the first or second decade of life, with distal weakness, loss of sensation, and foot deformities (pes cavus and hammer toes). Progression slowly proceeds throughout one's lifespan, although, some patients develop severe, rapidly progressing disability in early childhood (for example, Dejerine-Sottas neuropathy).[6] Scientists are currently developing rational therapeutic strategies for a number of CMT subtypes. However, evaluating interventions in clinical trials remains limited in part by the slow progression of many CMT subtypes and by the lack of natural history data during the first two decades of life when significant progression appears to occur in many subtypes.[7]

The CMT neuropathy score (CMTNS) versions 1 and 2 as well as the most recent Rasch analysis-based weighted version, rCMTNS, and the subscales rCMTES and rCMTSS are simple, reliable and validated standardized assessment tools for adults with CMT.[8,9] However they show limited sensitivity in children, in part due to difficulties with cooperation for subjective components.[10] The CMT Pediatric Scale (CMTPedS) is the only disease-specific scoring system available for children with CMT. The CMTPedS is a well-tolerated psychometrically robust 11-item clinical outcome measure assessing fine and gross motor function, strength, sensation and balance in children aged 3-20 years.[11] The CMTPedS has

been subjected to classical test theory (item, reliability and factor analysis) and item response theory (Rasch modeling) to ensure it can reliably capture changes in disability over time. The CMTPedS is ideally suited to measure the natural history of CMT during childhood because it been shown to be sensitive to CMT genetic subtype, patient age and self-reported levels of pain and disability.[5]

In a small longitudinal study of 15 affected children aged 4-17 years with mixed genetic subtypes, we reported a rate of disease progression of 1.0 CMTPedS points over 1-year (5% change from baseline).[11] In a cross-sectional study of 520 patients with CMT, we observed in CMT1A that CMTPedS Total scores seemed to progress consistency throughout early childhood (aged 3-10 years) and adolescence (aged 11-20 years), while the rate of change in CMT1B, CMT2A and CMT4C seemed to be age-specific.[5] Moreover, the cross-sectional studies suggested that the CMTPedS would be more sensitive to change than the Rasch weighted CMTNS scales in older children.[5] In the present longitudinal study we extend these observations by using the CMTPedS to measure disease progression in a large cohort of children with predominantly CMT1A over a 2-year period.

Materials and Methods

Children aged 3-20 years enrolled across 8 sites of the Inherited Neuropathies Consortium, a member of the NIH Rare Disease Clinical Research Network (http://www.rarediseasesnetwork.org/), were assessed between August 2009 and September 2016. The eight sites included: Sydney Children's Hospitals Network, University of Sydney, Australia; University of Iowa Health Care, Iowa, USA; Wayne State University, Detroit, USA; Children's Hospital of Philadelphia, Pennsylvania, USA; Carlo Besta Neurological Institute IRCCS Foundation, Milan, Italy; National Hospital of Neurology and Neurosurgery

and Great Ormond Street Hospital, London, UK; Nemours Children's Hospital, Florida, USA; University of Rochester, New York, USA. Human ethics or institutional review board approval was acquired from all institutions and written informed consent was obtained from all participants or their parents/guardians. All participants enrolled in the Inherited Neuropathies Consortium with a baseline and 2-year study visit (± 6 months) were included.

Demographic, anthropometric, and physical characteristics including age, height, weight, CMT genotype, and self-reported symptoms (foot pain, leg cramps, unsteady ankles, daily trips and falls, hand pain, hand weakness, hand tremor, and sensory symptoms) were collected at each visit as described previously.[5] Details of assistive device use (for example, ankle-foot orthoses, walkers, wheelchairs) and orthopedic surgery during the 2-year study period were also collected.

Disability was assessed using the CMTPedS,[11] a standardized clinical outcome measure comprising 11 performance-based items: Functional Dexterity Test; 9-Hole Peg Test; hand grip, foot dorsiflexion and plantarflexion strength by hand-held dynamometry; pinprick and vibration sensation; balance; gait; long jump; 6-minute walk test. Raw scores were converted to age- and sex-matched normative reference values from the 1000 Norms Project[12,13] to obtain z-scores. Z-scores were categorized to a Likert scale ranging from 0 (unaffected) to 4 (severely affected) *i.e.* 0 is within ±1 SD of normal, and a score of 1, 2, or 3 is 1-2, 2-3, or 3-4 SDs below normative values respectively, and 4 is > 4 SDs below normal. These categorized scores are summed to produce a CMTPedS Total score between 0-44 (whereby 0 is least severe and 44 is most severe).[11] A score of 0-14 is considered mildly affected, while moderate is defined as 15-29 and severe is 30-44 points on the CMTPedS.

Statistical analysis

Data were analyzed using SPSS v. 22.0 (IBM Corp. Armonk, NY). All data were assessed for normality and the appropriate parametric or non-parametric test subsequently employed. Paired sample t-tests were calculated to assess the significance of change in CMTPedS Total and Item scores between baseline and 2-year study visit. A sensitivity analysis was performed to assess whether the variation in follow-up time around the 2 year study visit (± 6 months) had an effect on the rate of progression by calculating the rate of change over 2 years as the change score / number of weeks between visits x 104 weeks. We compared baseline to the second time point using a repeated measures ANCOVA with time to follow up as a covariate. Independent samples *t* tests were performed to evaluate differences between CMT subtypes, early childhood (aged 3-10 years) and adolescence (aged 11-20 years), males and females, and differences between children receiving or not receiving assistive devices or orthopedic surgery. An alpha level of 0.05 was used for statistical significance.

Results

Natural history data at baseline and 2-years were collected from 206 (103 female) children with CMT (mean follow-up 24.1±3.7 months). Baseline and 2-year demographic, anthropometric, self-report symptoms, and physical characteristics are presented in Table 1. As expected height and weight changed with age over 2 years ($p<0.05$), while BMI percentile and the number of self-report symptoms did not ($p>0.05$). Of the 15 CMT subtypes, the most prevalent were CMT1A (58%), CMT1B (5%), CMT2A (4%), and CMT4C (4%) (Table 2). While all children completed most items of the CMTPedS at baseline and 2-years, 187 participants completed all items to obtain a CMTPedS Total score (Table 3). Participants unable to complete all items were due to reasons other than disease progression (for example

acute injury, behavioral issues). Their remaining item scores were used in the CMTPedS Item score analysis.

Compared to children with CMT1A (14.6±7.1), baseline CMTPedS Total scores were significantly worse for CMT2A (26.7±9.6, mean difference -12.1, 95%CI -18.1 to -6.0, $p<0.001$) and CMT4C (26.1±11.5, mean difference -11.5, 95%CI -17.3 to -5.8, $p<0.001$). There was a borderline difference in baseline severity between children with CMT1B (19.4±5.2) and children with CMT1A (14.6±7.1) (mean difference -4.8, 95%CI -9.7 to 0.0, $p=0.050$) (Table 3). Age did not differ at baseline between any of these subtypes ($p>0.05$).

Mean CMTPedS Total scores for the 187 children with all types of CMT progressed by 2.4±4.9 over 2-years ($p<0.001$) (Table 3). In the sensitivity analysis, the mean CMTPedS Total scores progressed by 2.3±4.8 points between time points 1 and 2 ($p<0.001$). Overall males and females progressed at a similar rate (males 2.1±4.6, females 2.6±5.1, mean difference 0.5, 95%CI -0.9 to 1.9, $p=0.49$). There were no differences in the rate of progression of children who required orthopedic surgery (13 foot and ankle, 1 hand) or received assistive devices (11 ankle-foot orthoses, 1 walking aid, 2 wheelchair) during the 2-year follow-up period ($p>0.05$) (Table 4).

All individual items of the CMTPedS progressed over the 2-year period (Figure 1). The most responsive items were foot dorsiflexion strength (z-score change of -0.3, 95% CI -0.6 to -0.05, $p=0.02$), balance (z-score change of -1.0, 95% CI -1.9 to -0.09, $p=0.03$), and long jump (z-score change of -0.4, 95% CI -0.7 to -0.02, $p=0.04$).

Of the four most common genetic subtypes in this study, 111 participants with CMT1A/*PMP22* duplication progressed by 1.8±4.2 (12% change from baseline), nine participants with CMT1B/*MPZ* mutation progressed by 2.2±5.1 (11% change), six participants with CMT2A/*MFN2* mutation progressed by 6.2±7.9 (23% change), and seven participants with CMT4C/*SH3TC2* mutations progressed by 3.0±4.5 (12% change). While the rate of progression of CMT1A was highly significant ($p<0.001$), small numbers of CMT1B, CMT2A, and CMT4C cases precluded statistical significance ($p>0.05$). Children with CMT2A appeared to have progressed significantly faster than children with CMT1A (mean difference -4.4, 95%CI -8.1 to -0.8, p=0.02) (Figure 2). Table 3 shows the rate of change for other subtypes of CMT, although rate of progression for the smaller disease cohorts (for example, CMT2D/GARS mutation) should be interpreted with caution.

As can also be seen in Figure 2, participants with CMT1A progressed at a consistent rate throughout childhood with no significant difference in the rate of disease progression between early childhood aged 3-10 years (2.4±4.4) and adolescence aged 11-20 years (1.4±4.0, mean difference 1.1, 95%CI -0.6 to 2.7, p=0.19). Younger children with CMT2A (9.5±7.8) appeared to progress faster than adolescents (-0.5±0.7) although this was not significant (mean difference 10.0, 95%CI -2.2 to 22.2, p=0.08). There was only one participant with CMT4C aged 3-10 years and six adolescents aged 11-20 years, which prevented comparison. The CMT1B data were highly variable.

Discussion

This is the first study to evaluate the 2-year natural history within and between genetic subtypes of CMT during childhood. Overall, children with CMT progressed at a rate of 2.4 CMTPedS points, or 14%, and children with the most common form, CMT1A, progressed at

a rate of 1.8 CMTPedS points (12%). Children with CMT2A and CMT4C generally progressed at a faster rate than CMT1A, while progression of CMT1B was highly variable. The increased baseline severity scores of children with CMT1B, CMT2A and CMT4C compared to CMT1A is consistent with our previously reported cross-sectional analysis of 520 participants.[5]

For the CMT1A subtype, the rate of progression was stable throughout early childhood and adolescence, while other subtypes such as CMT2A appeared to progress faster during early childhood than adolescence. Males and females progressed at a similar rate in the most common subtypes of CMT. We were unable to evaluate the rate of progression in males vs. females with CMTX1 because there were no females with CMTX1 in our cohort, most likely due to them being mild or asymptomatic. It has been reported that males with CMTX1 remain mildly affected until the second decade of life with increasing severity occurring in adulthood.[4]

Therapeutic interventions are necessary to slow or halt the progression of CMT in pediatric patients. Previously there has been a lack of responsive outcome measures for clinical trials in patients with CMT, in part because of the slow progression of the most common subtypes.[14] This longitudinal natural history study has shown that the CMTPedS is sensitive to the progression of CMT and would be an acceptable outcome measure for use in clinical trials. Rate of progression differed between the most common subtypes of CMT during childhood with CMT1A progressing slower than the other subtypes. Understanding the rate of change for each genetic subtype of CMT is essential to appropriately design and power future trials with gene-specific interventions. The rates reported in this study can be used to calculate the sample size for therapeutic trials. For example, it is estimated that for a 2-year

randomized (1:1), double-blind, parallel-group, placebo-controlled trial of an intervention aiming to halt the rate of CMT1A progression, a sample of 86 children per treatment arm would be required to provide 80% power (alpha 5%) to detect a difference between group means of 1.8 CMTPedS points (SD 4.2).[15] Note: Adjustments would need to be made for correlation between pre-test and post-test scores, loss to follow-up and non-adherence.

Despite the inclusion of a large international cohort of affected children evaluated prospectively with a well-validated clinical outcome measure over a period of 2-years, there are some limitations to this study. First, while the sample size for children with CMT1A was adequate, numbers for CMT1B, CMT2A, and CMT4C as well as for the rarer genetic subtypes (for example CMTX3, CMT1E, CMTX1, and CMT2D) preclude a conclusive determination of their natural history. Second, children younger than 3 years were excluded from the study because the CMTPedS is validated for children 3-20 years. The Inherited Neuropathies Consortium is currently developing and validating a CMT Infant Scale for affected patients aged 0-3 years.[16]

In conclusion, children with CMT deteriorate significantly over 2-years. Genetic subtype has an influence on this rate of progression. Understanding the natural history of CMT, using well-validated scales like the CMTPedS, is essential for adequately powering clinical trials to alter disease progression.

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Author Contributions:

KMDC, MMR, RSF, MES, and JB performed study concept and design. KMDC, MPM, RRS, IM, EP, DP, TE, SWY, TB, FM, ML, RSF, KJE, DNH, PB, MH, MES, and JB performed data acquisition and analysis. KMDC, MES, and JB drafted the manuscript and figures.

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Potential Conflicts of Interest:

The authors declare no conflicts of interest.

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Figure Legends:

Figure 1: Baseline values and rate of progression for each CMTPedS Item score, based on age- and sex-matched normative reference values.[12,13] Direction of item depends on unit of measure. Pinprick, Vibration and Gait are category scores because z-scores are not calculated for these items. All 206 participants completed Pinprick, Vibration, Balance and Gait items at baseline and 2-years; 205 completed the Functional Dexterity Test, 9-Hole Peg Test, long jump and 6 minute walk test; 196 complete grip strength and 194 completed plantarflexion and dorsiflexion strength. *Significant change from baseline ($p<0.05$).

Figure 2: CMTPedS Total score progression by CMT genetic subtype during early childhood (aged 3-10 years) and adolescence (11-20 years). Each slope represents an individual's change in the CMTPedS Total score over 2-years.

Table 1: Participant demographic, anthropometric and physical characteristics (n=206).

Characteristic	Baseline	Follow-up	Difference
Age, yrs	9.8±3.9 (3 – 18)	11.8±3.8 (5 – 20)*	2.0±1.1 (95%CI, 1.3 – 2.8)
Height, m	1.40±0.22 (0.90 – 1.83)	1.49±0.20 (0.97 – 1.93)*	0.08±0.06 (95%CI, 0.07 – 0.10)
Weight, kg	38.1±16.4 (11.2 – 87.2)	45.2±18.5 (11.6 – 104.0)*	7.1±5.5 (95%CI, 6.2 – 7.9)
BMI percentile	53.8±33.0 (0 – 98.9)	53.1±33.0 (0 – 99.0)	-0.5±21.0 (95%CI, -3.7 – 2.8)
Self-reported symptoms (Sum of 8)	3±2 (0 – 8)	3±2 (0 – 8)	0±2 (95%CI, -0.2 – 0.3)

Data are mean±SD (range) for baseline and follow-up scores and mean±SD (95% Confidence Interval) for Difference scores *Significant change from baseline ($p<0.05$).

Table 2: Frequency of CMT genetic subtypes in the cohort (n=206)

CMT Type	Number	% of Cohort
CMT1A, *PMP22* duplication	119	58
CMT1B, *MPZ*	10	5
CMT1E, *PMP22* point mutation	5	2
CMT1F, *NEFL*	1	0.5
CMT1, unknown	2	1
CMT2A, *MFN2*	8	4
CMT2D, *GARS*	3	1.5
CMT2, unknown	8	4
CMT4A, *GDAP1*	2	1
CMT4B1, *MTMR2*	1	0.5
CMT4C, *SH3TC2*	9	4
CMT4F, *PRX*	1	0.5
CMT4J, *FIG4*	1	0.5
CMTX1, *GJB1*	4	2
CMTX3, Xq27.1 insertion[17]	6	3
HNPP, *PMP22* deletion	2	1
HSN	1	0.5
Unknown	23	11

Gene names following subtype if known. 'CMT1 unknown' indicates individuals with a demyelinating neuropathy without an underlying mutation being identified, while 'CMT2 unknown' indicates individuals with an axonal neuropathy without an underlying genetic mutation.

Table 3: Disease progression over 2-years according to the CMTPedS Total score by CMT genetic subtype.

CMT type	N	Baseline Score	Follow-up Score	Difference	Change (% from baseline)
All cases	187	17.3±9.1 (1 – 40)	19.6±9.4 (0 – 42)	2.4±4.9* (95%CI, 1.7 – 3.1)	14
CMT1A	111	14.6±7.1 (1 – 39)	16.4±6.9 (0 – 36)	1.8±4.2* (95%CI, 1.0 – 2.6)	12
CMT1B	9	19.4±5.2 (14 – 30)	21.7±6.6 (13 – 35)	2.2±5.1 (95%CI, -1.7 – 6.1)	11
CMT1E	5	27.6±9.0 (16 – 37)	31.6±6.7 (23 – 38)	4.0±4.6 (95%CI, -1.8 – 9.8)	15
CMT2A	6	26.7±9.6# (14 – 36)	32.9±9.5 (17 – 42)	6.2±7.9# (95%CI, -2.2 – 14.5)	23
CMT2D	3	22.3±7.2 (14 – 27)	28.7±12.7 (14 – 36)	6.3±5.5 (95%CI, -7.4 – 20.0)	28
CMT2, unknown	6	21.7±8.0 (14 – 36)	26.0±5.5 (21 – 34)	4.3±6.7 (95%CI, -2.7 – 11.3)	20
CMT4C	7	26.1±11.5# (8 – 38)	29.1±11.0 (13 – 39)	3.0±4.5 (95%CI, -1.2 – 7.2)	12
CMTX1	4	9.8±8.2 (1 – 19)	12.3±10.0 (1 – 25)	2.5±3.0 (95%CI, -2.3 – 7.3)	26
Unknown	22	20.8±11.1 (2 – 40)	22.7±10.2 (5 – 38)	1.9±6.9 (95%CI, -1.1 – 5.0)	9

Data are mean±SD (range) for baseline and follow-up scores and mean±SD (95% Confidence Interval) for Difference scores. *Significant change from baseline ($p<0.001$), #Significant difference to CMT1A ($p=0.02$).

Table 4: CMTPedS Total scores for patients requiring assistive devices or orthopedic surgery during the 2-year follow-up.

Intervention	N (%)	Baseline Score	Follow-up Score	Difference	Change (% from baseline)
Assistive devices	12 (6)	16.6±11.9 (1 – 35)	19.0±12.9 (1 – 38)	2.4±5.7* (95%CI, 0.3 – 6.0)	12
Orthopedic surgery	14 (8)	20.4±9.3 (7 – 39)	23.3±7.6 (14 – 37)	2.9±4.3* (95%CI, 0.1 – 6.0)	14
No intervention	161 (86)	17.0±8.8 (1 – 40)	19.3±9.2 (0 – 42)	2.3±4.9* (95%CI, 0.5 – 3.0)	14

Data are mean±SD (range) for baseline and follow-up scores and mean±SD (95% Confidence Interval) for Difference scores. *Significant change from baseline ($p<0.001$). There was no significant difference between children requiring assistive devices or orthopedic surgery, and children who had no intervention in the baseline CMTPedS Total scores or rate of progression ($p>0.05$).

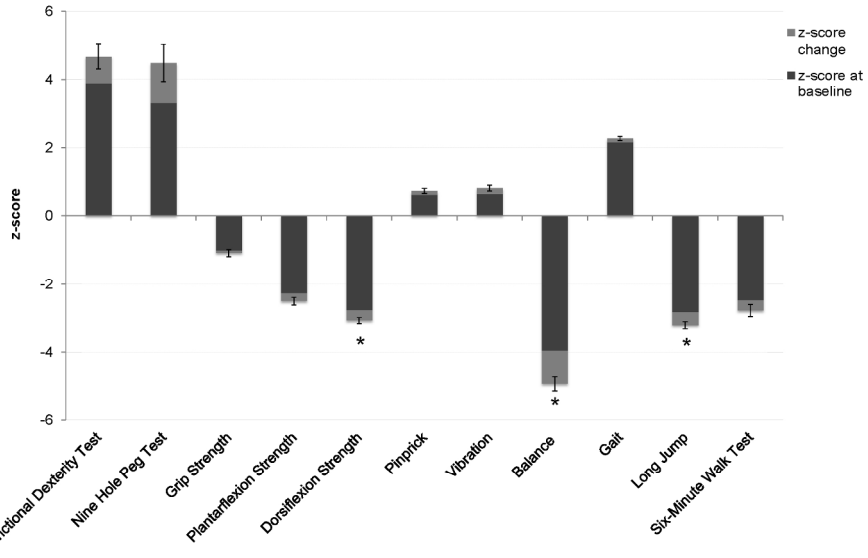

Figure 1: Baseline values and rate of progression for each CMTPedS Item score, based on age- and sex-matched normative reference values.12,13 Direction of item depends on unit of measure. Pinprick, Vibration and Gait are category scores because z-scores are not calculated for these items. All 206 participants completed Pinprick, Vibration, Balance and Gait items at baseline and 2-years; 205 completed the Functional Dexterity Test, 9-Hole Peg Test, long jump and 6 minute walk test; 196 complete grip strength and 194 completed plantarflexion and dorsiflexion strength. *Significant change from baseline ($p<0.05$).

279x215mm (220 x 220 DPI)

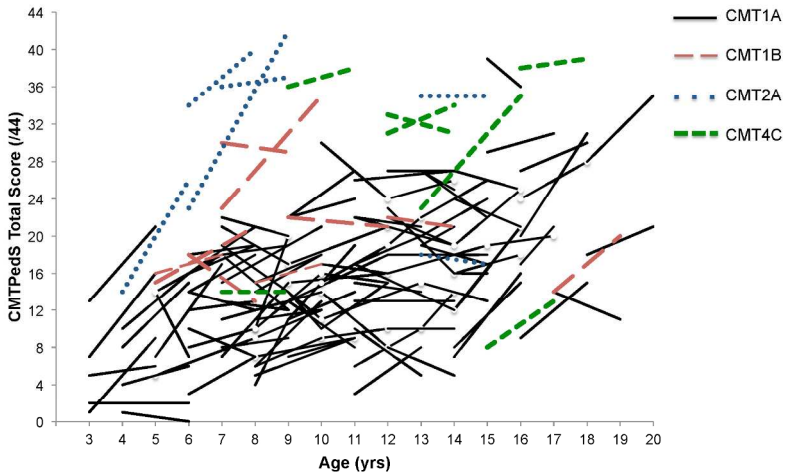

Figure 2: CMTPedS Total score progression by CMT genetic subtype during early childhood (aged 3-10 years) and adolescence (11-20 years). Each slope represents an individual's change in the CMTPedS Total score over 2-years.

297x210mm (216 x 216 DPI)