

Effect of pain in pediatric inherited neuropathies

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ABSTRACT

Objective: Assess the prevalence and impact of pain in children with Charcot-Marie-Tooth (CMT) disease.

Methods: In this prospective cross-sectional study on children with CMT disease seen at study sites of the Inherited Neuropathy Consortium, we collected standardized assessments of pain (Wong-Baker FACES Pain Rating Scale) from 176 patients (140 children aged 8-18 years, and 36 children aged 2-7 years through parent proxies), along with standardized clinical assessments and quality-of-life (QOL) outcomes. We then developed a series of multivariate regression models to determine whether standardized measures of neuropathy severity, functional impact, or structural changes to the feet explained the observed pain scores.

Results: The mean score on the Wong-Baker FACES Pain Rating Scale was 2 (range 0-5). Increased pain strongly correlated with worse QOL scores but not with more severe neuropathy. Independent determinants of increased pain in children with CMT disease included measures of ankle inflexibility.

Conclusion: Pain is present in children with CMT disease and negatively affects QOL. Pain scores do not positively correlate with neuropathy severity but do correlate in limited univariate analyses with measures of ankle inflexibility. Further studies to elucidate the mechanisms of pain may help identify treatments that can reduce pain and improve QOL in patients with CMT disease. *Neurology*® 2014;82:793-797

GLOSSARY

CHQ = Child Health Questionnaire; **CMT** = Charcot-Marie-Tooth; **CMTNSv2** = Charcot-Marie-Tooth Neuropathy Score version 2; **QOL** = quality of life.

There are currently no approved therapies to improve the neuropathy in Charcot-Marie-Tooth (CMT) disease, one of the most common inherited neuromuscular disorders.^{1,2} Understanding what, apart from the neuropathy, affects the patient with CMT disease may help in determining alternative ways of improving patients' lives even as we await definitive cures. We have shown that health-related quality of life (QOL) is significantly reduced in pediatric CMT disease.³ Our follow-up study identified several determinants of reduced QOL⁴ but did not prospectively assess pain measurements in these children. A significant proportion of adults with CMT disease report pain⁵⁻⁹; however, there is no consensus on whether that pain is due to nerve damage or to the relentless structural changes that may occur in the hands and feet of patients with CMT disease. Assessing pain in children with CMT disease, who have less structural changes than adults, may thus offer insight not only into the physiology of the pain but also into the contributors of reduced QOL in children with this disease. Our study objective was to prospectively assess the prevalence and impact of pain in pediatric CMT disease. We hypothesized that pain would negatively affect children with CMT disease and that the etiology of the pain would be structural changes in the feet, as opposed to neuropathy severity.

METHODS Participants. We collected prospective cross-sectional data on children with CMT disease seen through the multicenter natural history study of the Inherited Neuropathy Consortium (U54-NS065712) from 2010 through 2013. Pain data were prospectively collected as contributors of reduced QOL in children with CMT disease. We recruited children aged 2 to 18 years with genetically confirmed CMT disease, or a confirmed test in a first- or second-degree relative with a consistent clinical phenotype and

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Table 1 Demographic data and patient characteristics

Variable	
Sample size, n	176
Sex, % male	49
Race, % white	78
Children aged 8-18 y, n	140 (mean age = 12 y)
Children aged 2-7 y, n	36 (mean age = 5 y)
Mean pain score: Child self-report	1.6 (range 0-5, n = 127 of 140 sample)
Child self-report pain score frequencies, n	
0	25
1	52
2	20
3	15
4	12
5	3
Mean pain score: Parent proxy report	1.8 (range 0-5, n = 157 of 176 sample)
Parent proxy report pain score frequencies, n	
0	23
1	58
2	41
3	13
4	14
5	8
Mean CMTNS, children aged 8-18 y	6.1 (n = 128)
Mean CMTNS, children aged 2-7 y	4.3 (n = 14)
Mean pain score (± SD): Child report by CMT type	
CMT1A	1.7 ± 1.3
CMT1X	2.3 ± 1.2
CMT1	1.5 ± 1.4
CMT2	1.2 ± 1.2
CMT unknown	2.1 ± 1.4

Abbreviations: CMT = Charcot-Marie-Tooth; CMTNS = CMT Neuropathy Score.

confirmatory electrophysiologic testing in the child, through participating sites of the Inherited Neuropathy Consortium in the United States, United Kingdom, and Australia.

Standard protocol approvals, registrations, and patient consents. Institutional ethics review boards approved the protocol

at each participating institution. We obtained informed consent from participants' guardians as well as assent in older children.

Standardized assessments. Demographic data collected included age, sex, race, and ethnicity. The Wong-Baker FACES Pain Rating Scale¹⁰ measured child self-reported and parent-reported (proxy) pain scores. This validated scale has scores ranging from 0 to 5 associated with faces ranging from smiling to crying; the descriptors below each face and score are as follows: 0 = "no hurt" (widely smiling face), 1 = "hurts little bit" (slightly smiling face), 2 = "hurts little more" (neutral face), 3 = "hurts even more" (slightly sad face), 4 = "hurts whole lot" (very sad face), and 5 = "hurts worst" (crying face). The instruction provided with the scale was to rate the average pain the person had experienced over the past year. We measured QOL through the Child Health Questionnaire (CHQ), a validated generic measure of health status in children.¹¹⁻¹³ Clinical measures included sensory information (pinprick and vibration), the standardized 6-Minute Walk Test, the CMT Neuropathy Score version 2 (CMTNSv2) (a validated composite measure including historical, clinical, and electrophysiologic data, shown to correlate with disability),^{14,15} and the validated Foot Posture Index,¹⁶ a clinician-assessed measure of foot position.

Statistical analysis. We calculated descriptive statistics to characterize the study sample and determine the overall prevalence of pain using Stata/IC 11 (StataCorp, College Station, TX) and SAS version 9.3 (SAS Institute Inc., Cary, NC). We calculated Pearson correlation coefficients ($\alpha = 0.05$) to examine associations between pain reported by child or parent proxy and 1) CMTNSv2—a measure of neuropathy severity, and 2) CHQ and the standardized 6-Minute Walk Test—measures of functional impact. Finally, we entered the individual components of the Foot Posture Index as well as the total score into a univariate model (simple linear regression) and multivariate model (multiple linear regression) to explore associations between ankle/foot structural deformity and child-reported pain in pediatric CMT disease.

RESULTS We analyzed data on 176 children assessed through the Inherited Neuropathy Consortium sites. The mean pain score was 2, which correlates to the descriptor "hurts little more" on the 0 to 5 Wong-Baker FACES Pain Rating Scale (parent proxy mean pain score was 1.8 and child self-reported mean pain score was 1.6; we rounded up to 2 because the original scale is not sensitive to the tenth decimal range). The prevalence of pain, as assessed by scores greater than 0, was 80% by child direct report and 85% by parent proxy report. The pain frequencies and demographic data are summarized in table 1.

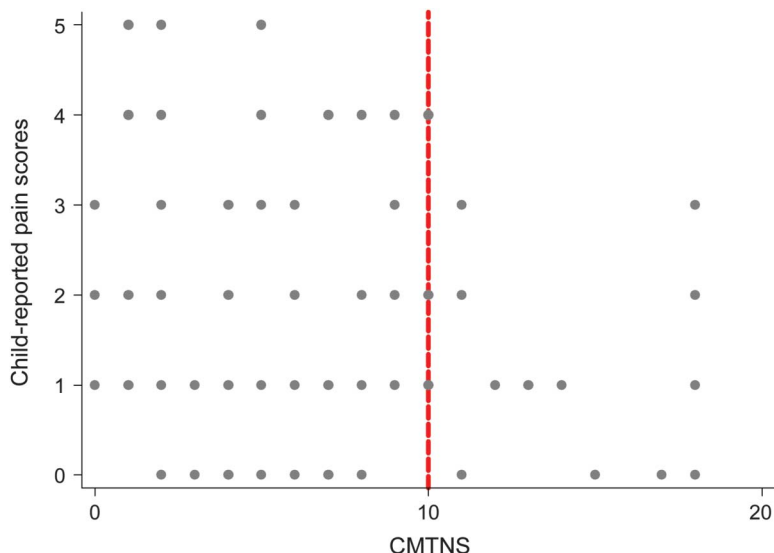
Table 2 Pain correlates in children with CMT disease^a

	Child self-reported pain scores	p Value	Parent proxy-reported pain scores	p Value
Physical QOL	-0.433	<0.00001	-0.488	<0.00001
Mental QOL	-0.293	0.002	-0.110	0.282
CMTNS	-0.102	0.277	-0.051	0.596
Standardized 6-Minute Walk Test	0.011	0.903	0.019	0.827

Abbreviations: CMT = Charcot-Marie-Tooth; CMTNS = CMT Neuropathy Score; QOL = quality of life.

^aCorrelation between child and parent scores = 0.652 ($p < 0.00001$).

Figure Scatterplot of neuropathy severity and child-reported pain scores



The portion to the right of the red line indicates moderate neuropathy; as Charcot-Marie-Tooth Neuropathy Scores (CMTNS) increase, the pain scores decrease.

To assess the impact of pain in children with CMT disease, we generated a Pearson correlation coefficient matrix to examine associations between pain and patient-reported and clinical standardized outcomes (table 2). Increasing pain scores strongly correlated with lower (i.e., worse) QOL physical and psychosocial CHQ composite scores. Standardized 6-Minute Walk Test did not correlate significantly with pain. Pain scores also did not correlate with neuropathy severity, as

assessed by the CMTNSv2: as the CMTNS increased, pain scores decreased (figure).

In univariate regression models, individual components of the ankle/foot index, including features of a supinated foot (straight or convex rearfoot curve below the malleolus, markedly concave forefoot area of talonavicular congruence, high arches that acutely angle toward the posterior end of the medial arch, and easily visible medial toes), correlated with increased pain scores, especially on the nondominant foot. However, in multivariate regression models with child self-reported pain scores, the associations were not significant (table 3).

DISCUSSION This study provides evidence that children with CMT disease report mild to moderate levels of pain, which negatively affects their physical and psychosocial QOL. Worsening severity of neuropathy does not result in increasing pain scores, suggesting that the physiology of the pain in CMT disease is not due to the nerve damage alone. Alternatively, we found that structural changes, particularly in the nondominant foot, showed significant association with pain in the univariate regression models. This association did not hold in more stringent multivariate regression models, suggesting that the measures we used—components of the foot position index—may be proxies of other, more direct measures of structural deformities in the feet.

If mediated by structural changes, the nociceptive pain that originates in pediatric CMT disease could significantly worsen by adulthood due to progressive damage to the joints; rehabilitative interventions would,

Table 3 Univariate and multivariate association between child self-reported pain score and predictors of interest

Univariate model					
Dependent variable	Independent variable	β Coefficient	Standard error	p Value	
Child pain score	Age	0.0256	0.038	0.50	
	Straight or convex rearfoot curve below the malleolus; nondominant foot	-0.38018	0.172	0.0294	
	Markedly concave forefoot area of talonavicular congruence; nondominant foot	-0.38129	0.1365	0.0062	
	Markedly concave forefoot area of talonavicular congruence; dominant foot	-0.26928	0.12912	0.0392	
	High arches that acutely angle toward the posterior end of the medial arch; nondominant foot	-0.27933	0.10761165	0.0108	
	Easily visible medial toes; nondominant foot	-0.2683	0.12829	0.0388	
Multivariate model					
Parameter		Estimate	Standard error	t Value	Pr > t
Intercept		1.605454217	0.58681170	2.74	0.0074
Age		0.005697609	0.04596054	0.12	0.9016
Straight or convex rearfoot curve below the malleolus; nondominant foot		-0.116440186	0.23539141	-0.49	0.6220
Markedly concave forefoot area of talonavicular congruence; nondominant foot		-0.095946371	0.25015619	-0.38	0.7022
Markedly concave forefoot area of talonavicular congruence; dominant foot		-0.119339823	0.22198056	-0.54	0.5921
High arches that acutely angle toward the posterior end of the medial arch; nondominant foot		-0.186401497	0.20347170	-0.92	0.3619
Easily visible medial toes; nondominant foot		0.057913277	0.19810641	0.29	0.7707

Abbreviation: Pr = probability.

theoretically, reduce this nociceptive burden. However, if the pain in adult CMT disease is more neuropathic or central, there are evidence-based guidelines for targeted therapies that have shown effectiveness (e.g., neuropathic: exercise, tricyclic antidepressants, anticonvulsants¹⁷; central: exercise and cognitive behavioral therapy,¹⁸ serotonin-norepinephrine reuptake inhibitors).¹⁹ Characterizing the pain as nociceptive, neuropathic, or structural can therefore help identify targeted, evidence-based treatments to meaningfully improve the QOL of patients with CMT disease.

Chronic pain in children can be difficult to assess and can be influenced by recall bias as well as the cognitive development of the child and other behavioral issues.^{20,21} While these biases cannot be discounted, we believe the strong correlation between the parent proxy report average pain scores and direct child-report average pain scores supports the validity of our obtained scores. The 6-Minute Walk Test did not correlate with pain in our study; the test is a measure of endurance and muscle fatigue, which may not correlate with pain in the CMT population. Planned prospective studies on the associations among the 6-Minute Walk Test, specific pain mechanisms, and gait analyses may provide more information on the impact of pain on daily functioning. Finally, generalization of these results to a nonstudy population of patients with CMT disease must be done with caution because the characteristics of our study patients may differ from general patients.

We urgently need to identify therapeutic interventions that can improve the daily functioning of patients with inherited neuropathies. This need is especially evident in children with CMT disease because the long-term impact of changes occurring during critical developmental stages may result in high adulthood disease burden. We plan to build on these data by multimodal phenotype characterization of the pain in adults with CMT disease, as musculoskeletal, neuropathic, or central. These results would allow a more targeted, evidence-based approach to treatment, to reduce pain and improve the QOL of children, and in the long term, adults with CMT disease.

AUTHOR CONTRIBUTIONS

Dr. Ramchandren: study concept, interpretation, and manuscript preparation. Dr. Jaiswal: data analysis, manuscript revision. Dr. Feldman: interpretation, manuscript revision. Dr. Shy: data acquisition, interpretation, manuscript revision.

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