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Prospective Study of Muscle Cramps in Charcot Marie Tooth Disease

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Abstract

Introduction—This study aims to assess the frequency, location, severity, duration, and fluctuation over time of muscle cramps in Charcot Marie Tooth Disease (CMT).

Methods—Inherited Neuropathies Consortium Contact Registry participants recorded the occurrence and characteristics of muscle cramps using an 11-question survey administered three times over 8-weeks.

Results—One hundred and ten adult patients with CMT completed the survey. Weekly cramp frequency was 9.3 (SD 12.3) and 23% had daily muscle cramps. Twenty-two percent reported a significant impact on quality of life. Over 8-weeks, the daily frequency and severity of muscle cramps did not change significantly.

Conclusions—Patients with CMT have muscle cramps that vary little over an eight-week period, and may interfere with quality of life. These data may be useful in the planning of clinical trials of agents to treat adults with CMT-associated muscle cramps.

Keywords

muscle cramps; Charcot Marie Tooth disease; quality of life

Introduction

Charcot Marie Tooth Disease (CMT) is the most common form of inherited neuromuscular disease.¹ While CMT is genetically heterogeneous, the clinical presentations of these peripheral neuropathies share similarities across subtypes, generally characterized by

progressive distal weakness, muscle atrophy, and sensory loss.¹ Muscle cramps have been reported as a significant detriment to quality of life (QOL) in CMT.^{2,3}

Studies indicate that children with CMT1A have an increased frequency of calf cramps.⁴ Calf cramps worsen with age in both children and adults with CMT1A, and calf cramps are detrimental to overall QOL in CMT1A.⁵ These studies have been cross-sectional, and focused mainly on calf cramps. We would expect cramps to occur in regions of weakness in CMT patients, including regions other than the calves.

In this study, we prospectively evaluated the frequency, location, severity, duration, triggering factors, impact on QOL, and stability of CMT-associated muscle cramps in adults with CMT over a period of time that might be considered for a therapeutic trial for cramps.

Methods

We utilized the web-based Inherited Neuropathies Consortium Contact Registry, which allows patients with all forms of CMT to self-register, to survey patients. All registry participants over the age of 18 were asked to participate in this survey.

The Inherited Neuropathies Consortium (INC) Contact Registry is part of the INC Rare Disease Clinical Research Network (RDCRN), U54NS0657. Patients participating in natural history studies of the INC are subject to rigorous genetic testing and clinical phenotyping. Those in the Contact Registry have a similar distribution of CMT type as those participating in the natural history studies. In the contact registry, 53.45% have CMT1A, 3.77% have CMT1B, 9.69% have CMT2A, 1.97% have CMT4, 4.93% have CMTX, and 26.19% have CMT, without a subtype or genetic classification. These are similar percentages to those enrolled in the natural history studies.

An 11-item questionnaire was developed to assess muscle cramp frequency, location, severity, duration and triggering factors (Supplemental Methods 1). As part of a large, cross-sectional study on quality of life, those participants who completed the larger survey were provided a separate muscle cramps survey (Supplemental Figure 1). Those subjects completing the initial cramps survey were then asked to complete the survey after 3 and 8 weeks. Participants were asked to maintain a diary of their cramp features for seven days prior to completing each survey. Survey instructions defined a muscle cramp as a sudden painful contraction or spasm of a muscle accompanied by visible or palpable hardening of the muscle.⁷ Qualitative interviews with 10 adults who had CMT, prior to development of the survey, were used to ascertain that the criteria for muscle cramps were understandable to patients.

The distributions of frequency, severity, location, and duration of muscle cramps were summarized descriptively. A Spearman rank correlation coefficient was used to describe the association between muscle cramp frequency and age. Wilcoxon rank sum tests were used to compare the distributions of muscle cramp frequency between men and women and between pairs of CMT types. Linear mixed effects models, with random intercepts and slopes, were used to estimate the mean rate of change over time in muscle cramp frequency.

Results

Of the 719 registry members surveyed, 243 individuals (34%) completed the demographic and general QOL survey. Of the 243 individuals, 85% reported currently experiencing muscle cramps, which was a single question on the larger survey. One hundred and ten individuals (45% of the larger survey cohort) participated in the dedicated muscle cramps survey (Supplemental Figure 1). The median age was 56 (range 19-92 years). The median age of symptom onset was 15.5 years (range 0-68 years). Additional demographic and clinical characteristics are provided in Table 1.

Ninety-four percent of respondents experienced muscle cramps. Muscle cramps occurred in both the upper and lower extremities corresponding in general to the pattern of weakness and sensory loss that occurs with most forms of CMT, though a number of participants did develop thigh cramps (Table 2). Also, several participants noted muscle cramps in their face, neck, and jaw (n=6).

On the first survey, over the course of one week, 30% of participants had 0-1 cramps, 50% had between 2-10 cramps, 11% had between 11 and 20 cramps, and 9% of participants had more than 20 cramps over 7 days. The median number of cramps in a week and number of days with cramps are provided in Figure 1. Men had an average of 8.09 cramps per week (SD 12.49) and women had an average of 9.94 cramps per week (SD 12.17), without a significant difference between gender ($p=0.12$). There were no significant associations between cramp frequency and age ($R=-0.074$; $p=0.56$). When comparing axonal and demyelinating forms of CMT (CMT1A vs. CMT2A), there were no differences between number of days with muscle cramps ($p=0.56$) or muscle cramp frequency ($p=0.78$). Similarly, there was no difference in number of days with muscle cramps ($p=.95$) or muscle cramp frequency ($p=0.18$) when comparing CMT1A against all other forms of CMT.

Muscle cramps were of short duration in most subjects. On the first survey, 35% of participants reported their average cramps lasting less than one minute, 41% reported cramps lasting 2-5 minutes, 13% reported cramps lasting 5-10 minutes, and 11% reported cramps lasting more than 10 minutes. On a 1-10 Likert scale evaluating pain, participants rated their average cramp to be 4.5 (SD 2.1) and their worst cramp to be 5.9 (SD 2.5).

Many participants reported their muscle cramps interfered with some aspect of their activities or quality of life (Table 2).

The mean difference in cramp frequency was 0.51 (SD 10.03) between the first and second visit and -0.35 (SD 7.77) between the second and third visit. The average rates of change per 3 weeks in cramp frequency (-0.27 , 95% CI -1.3 to 0.8 , $p=0.62$), average cramp severity (-0.02 , 95% CI -0.20 to 0.16 , $p=0.81$), and impact of cramps on QOL (-0.04 , 95% CI -0.13 to 0.06 , $p=0.46$) were not significant. Cramp duration did decline slightly over time, with the average rate of change per 3 weeks being -0.15 (95% CI -0.29 to -0.01 , $p=0.04$).

Discussion

The present study identified a measurable frequency and severity of muscle cramps in adults with CMT and was stable over time. In a subset of patients with CMT, the occurrence of muscle cramps multiple times a week clearly impacts QOL. We also noted that muscle cramps interfered with sleep, exercise, and daily activities. No FDA approved therapy exists for muscle cramps. Several symptomatic therapies are used to treat muscle cramps in CMT, but data from randomized controlled trials are lacking. Indeed, while some patients do clearly have an impact on quality of life, other patients may experience cramps without an impact on quality of life. Therefore, it is important for clinicians to discuss muscle cramps and impact on quality of life before prescribing medications. Development of an effective therapy for CMT-associated cramps may have a beneficial effect on the overall quality of life in this population.⁵

Our prospective approach to the evaluation of muscle cramps in the adult CMT population differs from those used in prior studies. We utilized a cramps-specific survey rather than general questions on cramps embedded in broader questionnaires. Also, participants were instructed to maintain a diary of their cramp characteristics for 1 week before each survey, rather than retrospectively recall their cramp characteristics. Finally, we collected longitudinal data on cramp features whereas previous studies used a cross-sectional design.

One challenge in the treatment of muscle cramps is their relatively short duration and perceived variability with time. This study shows that over an 8-week period, the characteristics of cramps in adults with CMT remained relatively stable. These data support the feasibility of a clinical trial for muscle cramps in adult CMT, and provide potential clinical endpoints.

Participants had a higher frequency of muscle cramps than that of the normal population. A study of randomly selected individuals previously reported the population frequency of muscle cramps to be 48% in men and 60% in women.⁹ This is significantly lower than the 85% of 243 participants with CMT who endorsed muscle cramps in the general QOL survey. In comparison to previously reported cramp characteristics in patients with idiopathic muscle cramps, participants with CMT had a distinctive cramp phenotype, which more commonly involved their hands, fingers, thighs and trunk.⁸ The presence of muscle cramps in hands, fingers, and other muscles commonly affected in CMT patients is consistent with the hypothesis that motor nerve dysfunction (hyperexcitability) underlies muscle cramps and suggests mechanistically that muscle cramps in CMT are not simply an accentuation of idiopathic cramps, but rather are a function of the underlying disorder.⁹

This study has some potential limitations. Although 110 adults with CMT participated, low representation of less common genetic forms of CMT may bias comparative analyses. A higher percentage of individuals categorized as having an “unknown CMT type” in this study than in the overall contact registry. This relates to the CMT type ascertainment in the survey, which was more stringent and required participants to have a genetic diagnosis for categorization purposes, whereas the contact registry classification doesn't require genetic testing, but can be based on a clinical/electrophysiologic diagnosis, with genetic

confirmation in the family. The CMT subtype distribution of participants in the survey was similar to that of the overall registry when the same subtype schema was applied. Participants with frequent muscle cramps may have self-selected to participate in the survey. The cramp characteristics identified may therefore not be fully representative of those in the wider adult CMT population. The survey employed a clear definition of muscle cramps and evaluated this with qualitative interviews, however, it is possible that participants may have reported some non-cramp symptoms. The INC contact registry was developed through the INC RDCRN, where large numbers of CMT patients are evaluated at specialized centers. While the INC RDCRN is a significant referral source for the INC contact registry, the contact registry is online and patients self-select for enrollment. As such, some participants in this survey may not have been evaluated at a specialized CMT center. This study utilized patient report without other functional measures, so we were unable to examine the associations of muscle strength or other measures of disease severity with muscle cramp frequency.

Overall, muscle cramps in a CMT population occurred frequently, in many muscles, and had a measurable impact on QOL. Muscle cramp features did not vary significantly across 8 weeks. This study identifies one potential focus of symptomatic treatment in CMT. Future clinical therapeutic trials may consider addressing muscle cramps, which were measurable across multiple time points.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Muscle Cramp Frequency over 8 weeks

Figure 1A. Box Plot of Muscle Cramp Frequency Over Time. Interquartile range provided in the box, along with median (middle line) and range (whisker lines). Figure 1B. Box Plot of Number of Days with Muscle Cramps Over Time. Interquartile range provided in the box, along with median (middle line) and range (hash lines).

Table 1

Demographic and Clinical Characteristics of Survey Respondents (n = 110)

Characteristic	Mean
Age (years)	53.6 (14.2)
Age of CMT symptom onset (years)	23.3 (19.2)
Female (%)	61.9%
Require Assistive Devices (%)	56.4%
Require Ankle-Foot-Orthoses (%)	60.9%
Highest level of education (%)	
Grade School	1.8%
High School	18.2%
Technical Degree	9.1%
College	43.6%
Master' s/Doctorate	27.3%
Race (%)	
Caucasian	95.5%
African-American	1.0%
Asian	1.0%
American Indian	1.0%
Type of CMT (%)	
CMT1A	32.7%
CMT1B	4.5%
CMT2A	10.0%
CMTX	3.6%
CMT4	2.7%
Unknown	46.5%

Values are mean (standard deviation) or percentage, as indicated

Table 2

Symptomatic Impact and Location of Muscle Cramps

Cramp Impact	Not at all	A little	A fair amount	A lot
Interfere with Daily Activities	43.6%	36.4%	12.7%	7.3%
Interfere with exercise	48.2%	25.5%	14.5%	11.8%
Interfere with Sleep	36.4%	32.7%	18.2%	12.7%
Interfere with Quality of Life	40.0%	38.2%	8.2%	13.6%

Location	No cramps	Occur any time	Occur with exercise	Occur with sleep
Arms	70.9%	21.8%	6.4%	0.9%
Hands	41.8%	46.4%	10.9%	0.9%
Trunk	62.7%	26.4%	9.1%	1.8%
Thighs	39.1%	31.8%	12.7%	16.4%
Calves	42.7%	27.3%	10.9%	19.1%
Feet	60.9%	26.4%	5.5%	7.3%