Muscle cramp in pediatric Charcot-Marie-Tooth disease type 1A

Prevalence and predictors

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ABSTRACT

Objectives: To identify correlates of calf cramp in children with Charcot-Marie-Tooth disease type 1A (CMT1A).

Methods: Throughout Australia, 81 children aged 2–16 years with CMT1A were recruited. Measures of strength, ankle range, foot posture, balance, agility, endurance, gait, and neurophysiology were collected. Post hoc logistic regression analyses were performed to identify independent predictors of calf cramp.

Results: Of the 81 children, 26 (32%) reported calf cramp, and 1 child each reported toe, quadriceps, or arm cramp. Calf cramp was associated ($p < 0.05$) with older age; the presence of hand tremor; stronger foot inversion, eversion, dorsiflexion, and plantarflexion; and better performance in long-jump and 9-hole peg tests. Logistic regression analysis revealed only increasing age (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.11–1.58; $p = 0.002$) and the presence of hand tremor (OR 3.81, 95% CI 1.18–12.56; $p = 0.028$) as independent predictors of calf cramp.

Conclusion: Calf cramps are common in children with CMT1A and worsen with age. This study revealed a previously unrecognized link between cramp and hand tremor in children with CMT1A. Further investigation of proposed mechanisms and risk factors common to both cramp and tremor will contribute to our understanding of these common complications of CMT1A.

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GLOSSARY

CI = confidence interval; CMT = Charcot-Marie-Tooth disease; CMT1A = Charcot-Marie-Tooth disease type 1A.

Charcot-Marie-Tooth disease (CMT) negatively affects health-related quality of life of children and adults.^{1,2} In one cross-sectional study of 70 Australian children aged 5–16 years with CMT, leg cramps were the strongest independent predictor of reduced quality of life.² In a separate cross-sectional survey of 295 Australian adults with CMT, leg cramps were reported by 79% of the 295 respondents.¹ Leg cramps that occurred very often or constantly (reported by 20%) were associated with lower health-related quality-of-life scores for all physical domains of the Short Form-36.

Despite the high frequency of muscle cramp, there is no accepted treatment in children or adults with CMT, and the cause of muscle cramp in this condition is poorly understood. The aim of this study was to identify correlates of calf muscle cramp in children with Charcot-Marie-Tooth disease type 1A (CMT1A).

METHODS Children aged 2–16 years with proven CMT1A were recruited nationally between June and December 2007 at The Children's Hospital at Westmead (Sydney, NSW, Australia) and Royal Children's Hospital (Melbourne, VIC, Australia) for a clinical trial of ascorbic acid for CMT1A.³ Exclusion criteria were acute lower limb injury, previous foot/ankle surgery, arthritis, diabetes, congenital defects, and neuromuscular disorders other than CMT1A. Post hoc analyses of baseline data were performed to identify

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Table 1 Relationship between calf cramp and physical characteristics and signs and symptoms of CMT1A

Continuous outcome	No. in analysis	With calf cramp	Without calf cramp	Pearson <i>r</i>	<i>p</i> Value	Fisher exact test, two-tailed <i>p</i> value
Age, y, mean (SD)	81	10 (3)	7 (4)	−0.393	<0.001	
Body mass index	81					
Raw data, median (IQR)		17 (15-20)	16 (15-18)	−0.06	0.592	
Transformed data, mean (SD)		0.2 (0.1)	1 (0.1)			
Foot posture index	81					
Raw data, median (IQR)		2 (−3-5)	3 (−2-6)	−0.119	0.289	
Transformed data, mean (SD)		1 (0.2)	1 (0.2)			
Categorical outcome, <i>n</i> (%)						
Gender, male	81	15 (58)	32 (58)			1.000
Hypermobility	75	8 (31)	22 (40)			0.454
Sensory symptoms	81	5 (19)	7 (13)			0.509
Motor symptoms	81	19 (73)	30 (55)			0.146
Hand tremor	77	11 (48)	9 (17)			0.009
Hand/arm pain	80	7 (27)	10 (19)			0.397
Hand sensory symptoms	81	3 (12)	7 (13)			1.000
Pes cavus	81	12 (46)	16 (29)			0.143
Pes planus	81	6 (23)	15 (27)			0.790
Foot pain	81	9 (35)	13 (23)			0.422
Ankle instability	81	20 (77)	38 (69)			0.600
Trips	81	17 (65)	34 (62)			0.810
Falls	81	11 (42)	27 (49)			0.638
Regular trips or falls	81	22 (85)	43 (78)			0.565

Abbreviation: IQR = interquartile range.

correlates of calf muscle cramp. Baseline data included age, height, weight, presence of foot pain and ankle instability, frequency of trips and falls, foot alignment, ankle dorsiflexion range of motion, foot and hand strength, joint mobility, gait characteristics, ability to toe walk and heel walk, balance, fine motor ability, presence of foot drop and postural hand tremor, hand pain, weakness and difficulties, and electrophysiology. Data collection methods have been published.^{3,4}

Children were also asked whether they experienced regular muscle cramp, which was defined as painful involuntary contraction of skeletal muscle. The presence or absence of cramp was determined by the child and parent/guardian after discussion with an investigator (J.B.). The nature of cramp-like symptoms was discussed at length to exclude other diagnoses. Cramp presence and affected muscles were recorded.

Standard protocol approvals, registrations, and patient consents. Parents/guardians gave written informed consent in accordance with approval by the Human Research Ethics Committees of both hospitals.

Statistical analyses. Descriptive statistics were calculated to characterize the sample in SPSS (version 19.0; SPSS, Chicago, IL). Missing data were addressed by excluding cases pairwise. Non-normally distributed data were transformed using an appropriate formula. To assist interpretation of results, medians and interquartile ranges are presented for non-normally distributed raw scores. Means and SDs are presented for transformed normally distributed data.

To examine the relationship between child characteristics and the presence of calf muscle cramp, calculations using Pearson product moment correlation and Fisher exact test were performed for continuous and categorical data, respectively. Factors significantly ($p < 0.05$) associated with the presence of calf muscle cramp were entered into a logistic regression model using the stepwise method. To avoid multicollinearity, only one variable from highly correlated ($r > 0.7$) variables (e.g., plantarflexion and dorsiflexion strength) was included. Age was forced into the model to adjust for its influence on variables related to development.⁵ Removal testing used the backward elimination method based on the Wald statistic. The omnibus tests of model coefficients were performed to provide an overall indication of the model's performance. The Hosmer-Lemeshow test was performed to check model fit. The positive predictive value of the model was calculated. An odds ratio with 95% confidence intervals (CI) was calculated for each independent variable in the model. ZResid values were calculated to identify cases for which the model did not fit well.

RESULTS Participant characteristics. Eighty-one children (47 boys and 34 girls) aged 2–16 years (mean 8.3, SD 3.5) from 50 CMT1A families were included. Of the 81 children, 53 had confirmed 17p11.2 duplication of the *PMP22* gene, and 28 had confirmed 17p11.2 duplication in a first- or second-

Table 2 Relationship between calf cramp and measures of nerve conduction, strength, and function

Continuous outcome	No. in analysis	With calf cramp	Without calf cramp	Pearson <i>r</i>	<i>p</i> Value	Fisher exact test, two-tailed <i>p</i> value
Nerve conduction velocity, m/s, mean (SD)	80	17 (5)	19 (6)	0.162	0.152	
Distal motor latency, ms, mean (SD)	80	8 (2)	7 (1)	0.167	0.140	
Distal compound muscle action potential amplitude, mV, mean (SD)	80	7 (2)	7 (2)	−0.031	0.782	
Ankle lunge angle, degrees, mean (SD)	78	24 (7)	25 (7)	0.038	0.743	
Fist grip adjusted, N, mean (SD)	81	96 (72)	58 (38)	−0.33	0.003	
Tip pinch strength, N, mean (SD)	81	20 (9)	15 (7)	−0.28	0.12	
Ankle plantarflexion strength, N, mean (SD)	81	198 (45)	164 (48)	−0.33	0.002	
Ankle dorsiflexion strength, N, mean (SD)	81	63 (22)	51 (17)	−0.30	0.007	
Plantarflexion/dorsiflexion strength ratio, mean (SD)	81	3 (1)	3 (1)	0.003	0.980	
Foot eversion strength, N, mean (SD)	81	74 (24)	57 (22)	−0.332	0.003	
Foot inversion strength, N, mean (SD)	81	94 (26)	68 (28)	−0.406	<0.001	
Inversion/eversion strength ratio, mean (SD)	81	1 (0.3)	1 (0.3)	−0.144	0.201	
BOT-2 balance total score, mean (SD)	72	9 (4)	9 (4)	0.01	0.933	
BOT-2 agility total score, mean (SD)	71	16 (5)	14 (5)	−0.106	0.381	
9-hole peg test, s, mean (SD)	78	24 (4)	28 (7)	0.278	0.014	
Long jump, cm, mean (SD)	77	88 (27)	73 (27)	−0.252	0.027	
6-min walk test, m, mean (SD)	65	546 (92)	505 (88)	−0.224	0.073	
Walk, mean (SD)						
Velocity, m/s	53	1 (0.1)	1 (0.2)	−0.124	0.377	
Cadence, steps/min	53	130 (18)	135 (17)	0.121	0.389	
Step time, s	53	0.5 (0.1)	0.5 (0.1)	−0.188	0.178	
Step length, cm	53	59 (6)	54 (10)	−0.225	0.105	
Stride length, cm	53	117 (13)	108 (19)	−0.238	0.085	
Base of support, cm	53	9 (3)	9 (4)	−0.014	0.920	
Categorical outcome, n (%)						
Foot drop during gait	81	2 (8)	1 (2)			0.240
Difficulty heel walking	78	24 (92)	44 (80)			0.482
Difficulty tiptoe walking	80	1 (4)	2 (4)			1.000

BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition.

degree relative and consistent phenotype/electrophysiology.

The Kolmogorov-Smirnov statistic demonstrated normal distribution of scores for all but 3 measures. Data were transformed to normal distribution using inverse (severity of hand/arm pain), log10 (body mass index), and reflect and log10 (foot posture index) methods.

Of the 81 children, 29 (36%) reported muscle cramping. 26 children reported calf cramp, and 1 child each reported toe, quadriceps, or arm cramp. Table 1 summarizes the relationship between calf cramp and physical characteristics and signs and symptoms of CMT1A. Table 2 summarizes the relationship between calf cramp and measures of nerve conduction, strength, and function. The following variables were entered into the logistic regression

model: presence of hand tremor, age, strength of foot inversion, long jump, 9-hole peg test, and fist grip strength. Stepwise logistic regression confirmed the presence of hand tremor and age as independent predictors of calf muscle cramping (Hosmer-Lemeshow $\chi^2 = 10.48$, $df = 8$, $p = 0.23$; omnibus test $\chi^2 = 19.31$, $df = 2$, $p < 0.001$). The positive predictive value of the model is 70.6%. The odds of calf muscle cramping are 3.81 (95% CI 1.16–12.56) times higher for a child with hand tremor than for a child without hand tremor, and the odds of calf muscle cramping are 1.32 (95% CI 1.11–1.58) times higher for each increasing year of age.

DISCUSSION Calf cramps are common in children with CMT1A and worsen with age. Although children with stronger distal leg muscles were more likely

to experience cramp, this was explained by their older age. Previous research has demonstrated that despite an increase in ankle dorsiflexion strength as children with CMT1A age, strength scores move further away from the age-equivalent norms.⁶ The relationship between increasing age and calf cramp in CMT1A is supported by previous research identifying a 79% prevalence of lower limb muscle cramp in adults with CMT.¹

Of the markers of CMT1A progression observed in this study (e.g., foot alignment, ankle contracture, balance, and nerve conduction studies), only hand tremor was significantly correlated with calf cramp. Tremor in CMT1A is typically postural, of medium to high frequency (4–12 Hz) and of low amplitude, which increases with voluntary movements.⁷ Postural hand tremor in children with CMT1A may result from a combination of weakness and impaired stretch reflexes, which can act to increase central drive and enhance physiologic tremor.⁷

Although the mechanism of cramp is not well understood, the most popular hypothesis is abnormal excitability of motor nerve terminals. This differs from proposed mechanisms of tremor in neuropathy. Both hand tremor and calf cramp are independently associated with muscle fatigue in people with and without neurologic disease.^{8,9} Children with CMT have upper and lower limb weakness from the earliest stages of the disease.¹⁰ Muscle weakness may reduce time to fatigue and subsequently increase risk of tremor and cramp. Although we did not detect a statistically significant difference in upper or lower limb strength measures between children with and without cramp when accounting for age, we did not measure muscle fatigability. A closer investigation of muscle fatigability might reveal a relationship between muscle fatigability and cramp/tremor.

Tremor in this study was identified by observation. Although this method is well accepted for detection of nonphysiologic tremor,⁷ tremor could be more thoroughly assessed in future research by use of a small, light-weight piezoresistive accelerometer and EMG. Future research could be further strengthened by using a longitudinal study design to track cramp and tremor progression and by conducting exercise testing to trigger cramp in susceptible participants. Inclusion of children without diagnosed neurologic disease could establish whether the relationship between tremor and cramp is limited to children with neurologic disease.

AUTHOR CONTRIBUTIONS

F. Blyton analyzed the data, conducted the statistical analysis, and wrote the manuscript. Dr. Ryan conducted nerve conduction studies in Mel-

bourne, Australia, provided comment on a draft manuscript, and approved the final manuscript. Prof. Ouvrier conducted nerve conduction studies in Sydney, Australia, and approved the final manuscript. Dr. Burns designed the study, collected all data except nerve conduction studies, suggested this post hoc analysis, supervised data analysis, provided comment on draft manuscripts, and approved the final manuscript.

DISCLOSURE

F. Blyton receives a Postgraduate Award from the University of Sydney. Dr. Ryan serves on the Therapeutic Advisory Committee for Treat-NMD; serves as an Associate Editor for the *Journal of Pediatric Neurology* and on the editorial board of the *Journal of Clinical Neuroscience*; and receives research support from PTC Therapeutics, Inc. Prof. Ouvrier serves on the scientific advisory board for the Nerve Foundation of the University of Sydney; serves on the editorial advisory board of *Brain and Development*; and receives publishing royalties for *Peripheral Neuropathy in Childhood*, 2nd ed. (Mac Keith Press, 1999). Dr. Burns receives research support from the National Health and Medical Research Council of Australia, the NIH Rare Diseases Inherited Neuropathies Consortium, The University of Sydney, New South Wales Podiatrists Registration Board, Australian Podiatry Education & Research Foundation, Charcot-Marie-Tooth Association of Australia, and Charcot-Marie-Tooth Association (USA).

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