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Factors Associated With Foot and Ankle Strength in Healthy Preschool-Age Children and Age-Matched Cases of Charcot-Marie-Tooth Disease Type 1A

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Abstract

Charcot-Marie-Tooth disease affects foot and ankle strength from the earliest stages of the disease; however, little is known about factors influencing normal strength development or the pathogenesis of foot weakness and deformity in Charcot-Marie-Tooth disease. The authors investigated factors associated with foot and ankle strength in healthy preschool-age children and compared to age-matched cases of Charcot-Marie-Tooth disease type 1A. In healthy children, ankle dorsiflexion range of motion was one of the strongest independent correlates of foot and ankle strength. Compared with healthy children, those with Charcot-Marie-Tooth disease type 1A had significantly less dorsiflexion strength and range as well as imbalance in inversion-to-eversion and plantarflexion-to-dorsiflexion strength ratios. Given the association between ankle dorsiflexion strength and range in the healthy children, and the abnormality of these parameters in Charcot-Marie-Tooth disease, investigation of the cause-effect relationship is warranted to identify more targeted therapy and further understand the pathogenesis of foot deformity in Charcot-Marie-Tooth disease.

Keywords

Charcot-Marie-Tooth disease, foot, isometric strength, handheld dynamometry

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Charcot-Marie-Tooth disease, the most prevalent neuropathy of childhood, causes selective weakness and imbalance of foot and ankle strength. Recent research into the evolution of foot and ankle problems in children with Charcot-Marie-Tooth disease type 1A, aged 2 to 16 years, has shown that foot and ankle weakness is apparent by the age of 4 years, with ankle equinus preceding this weakness in many cases.[1] Optimal performance of important daily motor tasks such as walking, running, and jumping is dependent on having adequate foot and ankle muscle strength.[2-4] In Charcot-Marie-Tooth disease type 1A, foot and ankle weakness can interfere with the acquisition of these skills and contribute to foot deformity, pain, and difficulty walking.[5,6]

The development of the medial longitudinal arch and associated changes in foot loading patterns and gait dynamics have been extensively investigated in young healthy preschool-age children.[7,8] However, there has been little investigation into the factors associated with foot and ankle strength in this age group. Previous studies have consistently identified body weight, height, and age as strongly predictive of muscle strength in other groups in young children.[9] Gender is also strongly associated with isometric strength in the upper and lower limb from the onset of puberty.[10] There may be other physical and anthropometric factors associated with strength in the growing foot of very young children.

Understanding factors associated with the typically developing foot and ankle in preschool-age children will help diagnose foot and ankle abnormalities in pediatric Charcot-Marie-Tooth disease and contribute to the appropriate selection and timing of therapies. A comparison of foot and ankle strength in healthy and affected children will also help refine pediatric clinical trial outcome measures, similar to the adult Charcot-Marie-Tooth neuropathy score as a measure of disability.[11] Therefore, we investigated factors associated with foot and ankle strength in healthy preschool-age children and compared to foot and ankle

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weakness in age-matched pediatric cases of Charcot-Marie-Tooth disease type 1A.

Materials and Methods

Participants

A total of 60 healthy children aged 2, 3, and 4 years were recruited from the local community to participate in this study. There were 20 children in each age group consisting of 10 boys and 10 girls. Children were included if they demonstrated normal development according to the well-validated Ages and Stages Questionnaire.[12] Children were excluded if they were born prematurely (<37 weeks gestation) or had a family history of a medical condition affecting foot and ankle muscle strength. For comparison, 11 children aged 2, 3, and 4 years with proven Charcot-Marie-Tooth disease type 1A, that is, a 17p.11.2 duplication including the *PMP22* gene, or a confirmed duplication test in a first- or second-degree relative with a clinical phenotype consistent with Charcot-Marie-Tooth disease and confirmatory neurophysiologic testing in the child were identified from the Australasian Paediatric Charcot-Marie-Tooth Registry.[13] The study was approved by the Human Research and Ethics Committee of The Children's Hospital at Westmead (Sydney, Australia).

Figure 1. Measuring ankle dorsiflexion range of motion using the weight-bearing lunge test.

Foot and Ankle Measures

Isometric muscle strength of foot inversion and eversion and ankle plantarflexion and dorsiflexion was measured using a handheld dynamometer (Citec, Centre for Innovative Technics, Groningen, The Netherlands), according to a standardized protocol.[14] The dynamometer was calibrated per the manufacturer's specification to an error margin of 0% to 1% and a range of 0 to 500 N. All testing was conducted with each child in long sitting, looking straight ahead (hips flexed, knees comfortably extended) on an examination table with a back rest. To avoid the child generating extra force by pushing down through the examination table during testing, they were requested to rest their hands gently on their thighs. Heels were positioned over the edge of the table and did not touch the testing surface at any stage. The "make" test was used to assess strength, whereby the assessor holds the dynamometer stationary and the child exerts maximal force against it in the direction of the desired movement. For foot inversion, the dynamometer was positioned against the medial border of the foot, just distal to the base of the fifth metatarsal and for foot eversion, the dynamometer was placed against the lateral border of the foot, just distal to the base of the fifth metatarsal. For ankle plantarflexion, the dynamometer was positioned against the plantar surface of the foot, just proximal to the metatarsal heads and for dorsiflexion, the dynamometer was positioned against the dorsal surface of the foot, just proximal to the metatarsal heads. To ensure all movements were isolated at the foot and ankle and to minimize substitution movements, the assessor stabilized the lower limb just proximal to the ankle joint. The talocrural (ankle) and talocalcaneal (subtalar) joints were positioned in mid-range of the overall length of the muscle, which is considered the optimal position to assess the isometric strength of 2 or more joint muscles.[15] All movements were demonstrated by the assessor and practiced with the child to obtain high-quality contractions of 3 to 5 seconds duration for each muscle group. Three measures were collected for the healthy children by K.J.R. and J.B. and 3 for the children with Charcot-Marie-Tooth disease type 1A by J.B. and averaged for analysis. Assessment of foot and ankle strength using this methodology in preschool-age children has excellent interrater and intrarater reliability.[14] Muscle imbalance ratios were also calculated for the opposing groups: inversion-to-eversion and plantarflexion-to-dorsiflexion.[1]

Foot structure was assessed using a weight-bearing criterion-based, observational rating system, the Foot Posture Index.[16] The Foot Posture Index is a reliable and independently validated, multiple segment, clinical screening tool that allocates a score between –2 and +2 to each of the 6 criteria (talar head palpation, supra and infra malleolar curvature, calcaneal frontal plane position, prominence in the region of the talonavicular joint, congruence of the medial longitudinal arch, and abduction/adduction of the forefoot on the rearfoot) related to foot structure. Scores are allocated for each criterion with a score of 0 denoting a neutral position, –2 for clear signs of supination, and +2 for clear signs of pronation. The aggregated score ranges from –12 (extremely supinated/pes cavus) to +12 (extremely pronated/pes planus). The Foot Posture Index has acceptable reliability and validity, as well as published normative values, for children and adults.[16-19] Foot type was also categorized as pes cavus (Foot Posture Index score = −1 to −12); normal (Foot Posture Index score = 0 to +5); or pes planus (Foot Posture Index score = +6 to +12).[16]

Ankle dorsiflexion range of motion was measured in weight bearing using the lunge test,[20] during which the children were asked to stand with 1 foot perpendicular to a wall and lunge forward using the wall for support if required. The assessor then assisted to move the foot progressively further away from the wall until the maximum range of ankle dorsiflexion was met without the heel lifting (Figure 1). Pronation and supination of the subtalar and midtarsal joint were minimized by ensuring the foot was positioned perpendicular to the wall and by having the child lunge directly over the midline of the foot (second digit). The angle of the lower leg from vertical was measured using a digital inclinometer (Baseline, Fabrication Enterprises Inc, New York). Measurement of ankle dorsiflexion range of motion in weight-bearing lunge has excellent reliability in young children.[20]

Other Factors

Additional variables collected for analysis included participant age (years and months), height (m), weight (kg), body mass index (kg/m^2), gender, and ethnicity (Caucasian, yes/no).

Statistical Methods

In Statistical Package for the Social Sciences 15.0 (SPSS Inc, Chicago, Illinois), descriptive statistics were calculated to characterize the study sample. For all tests, only 1 foot from each child was randomly selected for analysis to satisfy the independence requirement for statistical analysis and to minimize the bias that may have arisen from observer (and participant) limb dominance, improved skill acquisition, or any other cause of systematic error.[21] Normality of data distribution was assessed using the Kolmogorov-Smirnov test with Lilliefors significance correction and the appropriate parametric or nonparametric tests were subsequently used. Data of children with Charcot-Marie-Tooth disease type 1A, including demographics, foot and ankle strength, ankle dorsiflexion range of motion, and foot structure, were compared with the typically developing children using independent samples' t tests. To determine factors associated with foot and ankle muscle strength in the 60 healthy children, a series of multivariate regression models were developed. First, Pearson correlation coefficients were calculated to examine the relationships between strength[22] and physical characteristics of the study participants (age, gender, height, body mass, body mass index, ethnicity, foot structure [Foot Posture Index score], foot type [cavus, normal, or planus] and ankle dorsiflexion range). Characteristics identified to have significant ($P < .05$) associations with strength measures were entered simultaneously into a stepwise multiple regression model, which was reduced to a set of variables that best predicted and could be regarded as independent determinants of each strength measure. Only explanatory variables with the highest association to strength measures, no collinearity, and that were considered plausible predictors of muscle strength were included in the regression analysis. To avoid multicollinearity, only 1 variable from the highly correlated ($r > .7$) variables was included (eg, age or height or weight). β weights for all variables entered into the regression model were then examined to ensure they made meaningful contributions to predicting the individual strength scores.[23]

Results

Participants

The physical characteristics of the 60 healthy children aged 2 to 4 years and 11 children with Charcot-Marie-Tooth disease type 1A aged 2 to 4 years are presented in Table 1. The healthy preschool-age children and preschool-age children with Charcot-Marie-Tooth disease were similar for age, height, body weight, and body mass index. As expected, there were significant differences between children of different ages for height ($F = 115.437$, $P < .001$), weight ($F = 26.225$, $P < .001$), and body mass index ($F = 4.297$, $P < .001$). There were no significant differences between boys and girls for age ($t = –0.035$, $P = .972$), height ($t = 0.680$, $P = .499$), or body weight ($t = 1.709$, $P = .093$), but there were significant differences between boys and girls for body mass index ($t = 2.069$, $P = .043$). Healthy children were predominantly Caucasian (80% of females and 83% of males). The children with Charcot-Marie-Tooth disease type 1A comprised 11 children (3 children aged 2 years, 3 aged 3 years, and 5 aged 4 years). Seven (64%) were male and all were Caucasian.

Foot and Ankle Measures

Table 1 presents strength values for inversion, eversion, plantarflexion, and dorsiflexion. In healthy children, foot and ankle strength increased linearly with age ($r = .696$-$.715$, $P < .001$), height ($r = .699$-$.720$, $P < .001$), and body weight ($r = .574$-$.628$, $P < .001$) but did not differ significantly between boys and girls ($P > .05$). Strength ratios (inversion-to-eversion and plantarflexion-to-dorsiflexion) did not differ significantly between children of different ages or between boys and girls ($P > .05$). In children with Charcot-Marie-Tooth disease type 1A, strength was comparable to normal for inversion ($t = -0.634$, $P = .528$), eversion ($t = –1.393$, $P = .168$), and plantarflexion strength ($t = –1.520$, $P = .133$) but significantly lower for dorsiflexion strength ($t = –2.776$, $P = .007$). Strength ratios also differed significantly between healthy children and children with Charcot-Marie-Tooth disease type 1A for inversion-to-eversion strength ($t = 2.754$, $P = .007$) and plantarflexion-to-dorsiflexion strength ($t = 2.022$, $P = .047$).

Foot structure was pronated in all healthy children but became slightly less pronated with age (Table 1). Girls were slightly less pronated (mean 5.2, standard deviation 2.0) than boys (mean 6.4, standard deviation 2.9; $t = 1.830$ $P = .072$). Foot structure in children with Charcot-Marie-Tooth disease type 1A did not differ from the healthy children ($t = 0.170$ $P = .967$). In healthy children, 25 (42%) had a normal foot type and 35 (58%) children had a planus foot type (Table 1). In Charcot-Marie-Tooth disease type 1A, 5 (45%) children exhibited a normal foot type (1 aged 2 years, 1 aged 3 years, 3 aged 4 years) and 6 children (55%) had a planus foot type (2 aged 2 years, 2 aged 3 years, 2 aged 4 years). No child with or without Charcot-Marie-Tooth disease type 1A had a cavus foot type.

In healthy children, ankle dorsiflexion range of motion increased slightly with age ($F = 2.510$, $P = .092$) but did not differ between boys and girls ($t = 1.038$ $P = .304$; Table 1). Overall, ankle dorsiflexion range of motion in children with Charcot-Marie-Tooth disease type 1A was significantly less than normal ($t = –4.474$, $P < .001$) and decreased with age (28° aged 2 years, 26° aged 3 years, and 23° aged 4 years).

Factors Associated With Foot and Ankle Strength in Healthy Preschool-Age Children

Correlates of strength in the 60 healthy preschool-age children are shown in Table 2. Pearson correlation coefficients revealed a number of explanatory variables significantly associated with the strength measures. These included age ($r = .695$-$.739$, $P < .001$), height ($r = .699$-$.723$, $P < .001$), weight ($r = .574$-$.678$, $P < .001$), and ankle dorsiflexion range of motion ($r = .388$-$.467$, $P < .001$). Table 3 presents the multivariate regression models for inversion, eversion, plantarflexion, and dorsiflexion strength measures. Increasing height and ankle dorsiflexion range of motion were significant independent variables associated with inversion, eversion, and plantarflexion strength. For the model of dorsiflexion strength, increasing age and ankle dorsiflexion range of motion were significant independent determinants.

Table 1. Physical Characteristics of the 60 Healthy Children Aged 2, 3, and 4 years and the 11 Children Aged-Matched Cases With Charcot-Marie-Tooth Disease Type 1A[a]

Physical Characteristics	2 Years	3 Years	4 Years	All Healthy Children	All CMT 1A
Age (months)	28.7 (3.0), 24-34	40.1 (3.2), 36-47	53.9 (3.1), 48-59	40.9 (10.8), 24-59	41.6 (12.0), 24-55
Gender (male:female)	10:10	10:10	10:10	30:30	7: 4
Height (cm)	0.90 (0.03), 0.85-0.97	0.99 (0.03), 0.95-1.06	1.08 (0.05), 1.01-1.18.	0.99 (0.08), 0.85-1.18	1.01 (0.10), 0.85-1.14
Weight (kg)	13.6 (1.7), 11.2-16.5	16.2 (1.4), 12.8-18.0	18.2 (2.7), 26.8-28.2	16.0 (8.4), 11.2-26.8	17.6 (4.0), 12.9-26.1
Body mass index (kg/m^2)	16.8 (1.5), 13.7-20.0	16.3 (1.1), 14.2-19.0	15.5 (1.5), 13.1-19.2	16.2 (1.5), 13.1-20.0	17.1 (1.6), 14.4-20.1
Ethnicity (Caucasian:not Caucasian)	18:2	15:5	16:4	49:11	11:0
Inversion strength (N)	27.6 (8.8), 13.0-40.2	44.8 (13.8), 17.0-66.0	56.8 (15.1), 33.2-83.5	43.1 (17.3), 13.0-83.5	44.4 (17.9), 17.0-70.0
Eversion strength (N)	26.1 (8.7), 12.0-40.3	43.8 (13.2), 15.1-61.1	55.5 (15.1), 32.0-90.1	41.8 (17.4), 12.0-90.1	37.8 (13.2), 14.3-59.0
Dorsiflexion strength (N)	29.4 (7.5), 16.4-44.6	44.7 (11.2), 18.1-61.6	57.2 (12.5), 36.9-80.5	43.8 (15.5), 16.4-80.5	36.1 (11.0), 15.3-49.7[b]
Plantarflexion strength (N)	77.3 (27.8), 22.7-137.6	125.3 (41.0), 45.3-182.1	162.8 (40.6), 89.1-211.5	121.8 (50.7), 22.7-211.5	111.7 (39.0), 41.0-153.7
Inversion-to-eversion strength ratio	1.07 (0.12), 0.84-1.30	1.03 (0.07), 0.89-1.13	1.03 (0.07), 0.87-1.17	1.04 (0.09), 0.84-1.30	1.20 (0.38), 0.55-1.92[b]
Plantarflexion-to-dorsiflexion strength ratio	2.59 (0.60), 1.38-4.26	2.77 (0.44), 2.05-3.50	2.85 (0.39), 2.02-3.48	2.74 (0.49), 1.38-4.26	3.09 (0.72), 1.98-4.20[b]
Foot Posture Index	6 (2), 5-9	6 (2), 5-9	5 (3), 0-11	6 (3), 0-11	6 (3), 0-11
Foot type (cavus:normal:planus)	0:6:14	0:6:14	0:13:7	0:25:35	0:5:6
Ankle range of motion (degrees)	33.2 (5.5), 21.0-40.0	33.3 (6.2), 21.0-45.0	36.6 (3.8), 30.0-45.0	34.5 (5.4), 21.0-45.0	24.9 (7.8), 9.0-33.0[b]

Note: CMT1A, Charcot-Marie-Tooth Disease Type 1A.
[a] Values are mean (standard deviation), range except for gender, ethnicity, and foot type, which are expressed as a ratio.
[b] Significant difference between the healthy children and the children with CMT1A.

Table 2. Associations Between Physical Characteristics and Strength in All 60 Healthy Children Aged 2, 3, and 4 Years

Strength Measure (N)	Age (Years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Gender	Ethnicity	Gross Motor Ability	Ankle Range (Degrees)	Foot Posture Index	Foot Type
Inversion	0.696[a]	0.704[a]	0.650[a]	–0.129	–0.135	0.020	–0.126	0.434[a]	0.038	–0.054
Eversion	0.696[a]	0.719[a]	0.678[a]	–0.119	–0.123	0.034	–0.116	0.388[a]	0.033	–0.057
Dorsiflexion	0.739[a]	0.723[a]	0.650[a]	–0.167	–0.086	0.082	–0.099	0.429[a]	0.027	–0.041
Plantarflexion	0.695[a]	0.699[a]	0.574[a]	–0.254	–0.086	–0.008	–0.094	0.467[a]	0.029	–0.137

[a] $P < .01$.

Table 3. Multivariate Regression Analyses of Factors Associated With Foot and Ankle Muscle Strength in the 60 Healthy Children Aged 2, 3, and 4 Years

Strength Measure (N)	Predictor Variable	β Weight	Multiple r^2 Model
Inversion strength	Height	.632[a]	.564
	Ankle dorsiflexion range	.283[a]	
Eversion strength	Height	.662[a]	.546
	Ankle dorsiflexion range	.231[a]	
Dorsiflexion strength	Age	.644[a]	.553
	Ankle dorsiflexion range	.258[a]	
Plantarflexion strength	Height	.609[a]	.550
	Ankle dorsiflexion range	.322[a]	

[a] $P < .05$.

Discussion

In 60 very young healthy children and 11 affected by Charcot-Marie-Tooth disease type 1A, we identified marked differences in ankle range, dorsiflexion strength, and muscle imbalance but not in foot structure, inversion, eversion, or plantarflexion strength. In the healthy group, apart from body size, restricted ankle dorsiflexion range of motion was the only significant independent correlate of foot and ankle weakness and contributed to all regression models (β weights 0.231-0.322). Although age and physical body size have been shown previously to correlate with strength,[10,24] no studies have identified ankle dorsiflexion range as a factor related to isometric foot and ankle strength in very young children. The muscle length-tension relationship may be a possible explanation for this finding whereby muscles produce greater force at longer lengths than at shorter lengths due to the greater available range through which to generate active tension.[25]

Given the association between ankle dorsiflexion range of motion and muscle strength in healthy preschool-age children, and the obvious abnormality of these factors in children with Charcot-Marie-Tooth disease type 1A, investigation of the cause-effect relationship is warranted to help identify more targeted therapies for affected children. There may be an important clinical indication for preschool age children with Charcot-Marie-Tooth disease type 1A to undergo early intervention to increase ankle range to preserve muscle strength and prevent atrophy. In a recent study of factors influencing foot and ankle weakness in pediatric Charcot-Marie-Tooth disease type 1A, reduced ankle flexibility was significantly associated with weakness of dorsiflexion, inversion, eversion, and plantarflexion, independent of age and physical body size.[1] Future investigation should determine whether foot and ankle strength in children with Charcot-Marie-Tooth disease type 1A can be preserved or improved by increasing ankle dorsiflexion range of motion, such as with manual stretching, serial casting, or surgery.

Interestingly, our results suggest that ankle equinus and muscle imbalance precede foot deformity in pediatric Charcot-Marie-Tooth disease type 1A and may contribute to the characteristic cavus foot deformity. Although foot type in Charcot-Marie-Tooth disease type 1A did not differ from healthy children and no children in either group had a cavus foot structure, ankle dorsiflexion range and muscle imbalance worsened with age and may therefore precede foot deformity in Charcot-Marie-Tooth disease type 1A. Because imbalance of the foot and ankle musculature is thought to play a role in the development of pes cavus deformity,[26,27] early intervention to prevent this disabling problem may be warranted. The weakening and atrophy of the foot and ankle in Charcot-Marie-Tooth disease type 1A, coupled with worsening muscle imbalance and ankle equinus, suggests there may be a critical window of opportunity for intervening in the affected preschool-age child to prevent contracture, deformity, and disability in adolescence and adulthood.

Notably, the sensitivity of our measures to differentiate many aspects of the foot and ankle between healthy and affected preschool children suggests these measures could be a valuable contribution to a pediatric version of the Charcot-Marie-Tooth disease neuropathy score.[11] A pediatric Charcot-Marie-Tooth disease neuropathy score would be important for assessing disability, natural history, and treatment efficacy in clinical trials of childhood Charcot-Marie-Tooth disease.

This study has some limitations. First, due to the very young age of children in this study, we were limited to a relatively small number of variables. Additional measures that may relate to foot and ankle strength could include imaging, neurophysiology, or instrumented gait analysis. However, cost, radiation exposure, and time constraints due to the children's attention span limited our ability to do this, so we chose quick, reliable, and valid measures for preschool-age children. The study was also limited to a small number of preschool-age children with Charcot-Marie-Tooth disease type 1A because it is not often diagnosed in preschool-age children unless the disease has already been identified in the family. Nevertheless, this is the largest reported series of preschool-age children with Charcot-Marie-Tooth disease type 1A.

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Declaration of Conflicting Interests

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