Differences in Foot Morphology Between Pediatric and Adult Charcot-Marie-Tooth Disease

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INTRODUCTION: Charcot-Marie-Tooth disease (CMT) is a progressive inherited peripheral neuropathy that is strongly associated with cavovarus deformity of the foot [1]. This cavovarus foot shape consists of differences in both individual bone morphology and relative bony alignment, especially in and around the talus [2-6]. While this is a progressive disease, the difference in foot presentation between children and adults with CMT has not been well characterized. Further, there is a lack of consensus on timing and type of conservative and surgical interventions to optimize foot function in this population [7,8]. Understanding age-related differences in bony morphology in CMT may inform treatment approaches. Statistical shape modeling (SSM) from weight-bearing computed tomography (WBCT) has been used to characterize the morphology of several foot deformities, including CMT [4-6,9]. The objective of this study was to utilize these computational tools to identify differences in full-foot and in talus morphology between adults and children with CMT and controls.

METHODS: This study utilized WBCT scans of 73 limbs from individuals with CMT and 33 control limbs that were categorized as pediatric (age ≤ 18) or adult (age > 18). Demographics are given in Table 1. Bones from the tibia through metatarsals were segmented semi-automatically from each image followed by manual verification, consistently smoothed and decimated, and aligned with iterative closest point alignment with all left limbs mirrored to appear as right limbs for modeling and analysis. A 14-domain statistical shape model was generated of this full-foot bony structure and a single domain SSM was generated for the talus [4-6]. Both models were analyzed with principal component analysis (PCA) followed by parallel analysis to identify modes of variation representing a more than random portion of variance. For each of these significant modes, differences in PCA shape scores between groups were analyzed with a Kruskal-Wallis test with Dunn-Sidak post-hoc analysis and Holm-Sidak correction. For each mode with no significant differences between adult and pediatric controls, the controls were combined for comparisons with each CMT group. Sagittal plane Meary's angle was calculated for all scans and compared using the same statistical tests. All tests used a significance level $\alpha = 0.05$.

Table 1: Demographic data and Meary's angle

	Control		CMT	
	Pediatric	**Adult**	**Pediatric**	**Adult**
Age	12.1 (8-17)	41.8 (19-69)	14.6 (10-18)	51.3 (21-73)
Sex	2 F, 7 M	9 F, 15 M	12 F, 10 M	20 F, 31 M
Age at Diagnosis			8.9 (2-14)	40.9 (11-71)
Meary's Angle				
Average	6.8	7.0	24.2	19.5
95% CI	-13.1 – 26.8	-9.2 – 23.2	-5.8 – 54.1	-9.8 – 47.9

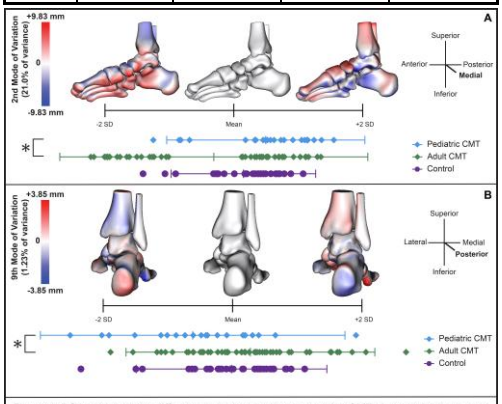

Figure 1: PCA modes with a difference between pediatric and adult CMT showing the mean and +/- 2 standard deviation shapes with red and blue representing positive and negative distance from the mean and distributions of the shape scores of each group shown underneath.

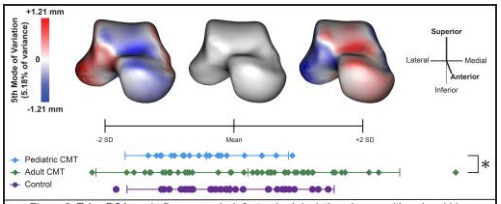

Figure 2: Talus PCA mode 5 mean and +/- 2 standard deviation shapes with red and blue showing positive and negative distance from the mean and group distributions shown below.

RESULTS: There were no differences in sex distribution between groups. The pediatric CMT groups younger than the combined control group and the adult CMT group was significantly older. Between CMT groups, there was no significant difference in genetic subtype distributions. Age at diagnosis was significantly younger in the pediatric CMT group. SSM and PCA analysis of the full foot revealed at least one significant difference between groups along 6 of the 10 significant modes, with differences between pediatric and adult CMT groups along 3 modes. The 1st mode demonstrated a significantly more cavovarus position of the foot in both the pediatric and adult CMT groups versus controls with no difference between pediatric and adult controls. The 2nd mode of variation (Figure 1A) showed a more medial rotation of the talar head in the pediatric CMT group compared to a more lateral rotation of the talar head in the adult CMT group with no difference between either group and controls. The 3rd mode of variation demonstrated increased varus rotation of the calcaneus in adult CMT than controls, with no differences between pediatric CMT and either controls or adult CMT. The 5th mode of variation revealed differences in global joint space, with each pediatric group demonstrating greater joint space than each adult group and no differences between CMT and control groups within each age category. The 6th mode of variation demonstrated a more medial rotation of the talus in pediatric controls than in either pediatric CMT or adult controls. The 9th mode of variation (Figure 1B) showed a more varus position of the calcaneus with decreased subtalar joint space in adult CMT compared to pediatric CMT, with no differences between either group and controls. In the talus, the 1st and 2nd modes showed a flattened talus in both CMT groups in addition to a decreased posterior process in pediatric CMT and longer posterior process in adult CMT compared to controls. The 3rd mode showed a thinner talar neck and smaller talar head in both adult and pediatric CMT than in controls. Differences between adult and pediatric CMT were seen along mode 5 (Figure 2), where the pediatric CMT talus was wider and flatter with a deeper divot in the talar neck compared to the narrower and taller talus in adult CMT. Meary's angle was significantly greater in both CMT groups than controls and was not different between adult and pediatric CMT (Table 1).

DISCUSSION: Both the pediatric and adult CMT groups demonstrate the expected cavovarus position of the foot. This was supported by a greater Meary's angle in both CMT groups than in controls. The adult CMT group had significantly more varus hindfoot than controls, suggesting that continued exposure to muscular imbalances further accentuates foot structural change over the lifespan. This is further supported by medial rotation changes of the talus in the pediatric CMT compared to a more lateral position in the adult CMT suggesting the talonavicular joint is a critical in midfoot adduction changes over the life span. The talus demonstrated flattening in both CMT groups, which aligns with previous research on talar morphology in CMT [4,5]. Interestingly, the pediatric CMT group showed a somewhat flatter and wider talus than the adult CMT group, suggesting that the talus may not continue to flatten with age in this population. The significantly lower age at diagnosis in the pediatric versus adult CMT group may confound these results as the pediatric group may be representative of a more severe presentation of CMT. Further, this cross-sectional study cannot identify disease progression from childhood to adulthood.

SIGNIFICANCE/CLINICAL RELEVANCE: These data indicate differences in the hindfoot and midfoot presentation of CMT-related cavovarus deformity between pediatric and adult patients, which is valuable for surgical and conservative treatment planning and supports the need for further research characterizing the progression of foot deformity in this disease.

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