Statistical Shape Modeling of Foot Morphology in Charcot Marie Tooth

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INTRODUCTION: Charcot Marie Tooth disease (CMT) is a progressive genetic neurological condition that, despite heterogeneity in genotype and expression, presents with characteristic cavovarus foot deformity [1, 2]. This stereotypical consists of a varus hindfoot position with a high arch and valgus forefoot position [2,3]. The classical theory of CMT pathophysiology hypothesizes that the foot shape is a result of alignment change caused by impaired muscle activation, but recent work suggests that changes in bony morphology may also contribute to this deformity [3.4]. Weight-bearing computed tomography (WBCT) has been investigated for characterization of CMT-related foot deformity under load-bearing conditions by measuring specific 3-dimensional angles to characterize alignment, rotation, and osseous morphology [2-4]. Statistical shape modeling (SSM) from WBCT images has been used to quantify variation in morphology and alignment in other foot pathologies but has not been applied to CMT [5]. The objective of this study is to use SSM to analyze differences in foot alignment and osseous morphology between patients with CMT and healthy controls.

METHODS: Retrospective chart review was used to identify patients with CMT who had received WBCT scans before any foot or ankle surgery and healthy controls were identified by retrospective chart review of contralateral limbs from patients receiving WBCT for unilateral acute Lisfranc injury (IRB: 00154634). 9 WBCT scans from 6 patients with CMT were identified (3 female, average age 36 (13-75)) and 15 asymptomatic controls were identified (6 female, average age 39.7 (17-69)). Segmentations were generated semi-automatically (DISIOR, Bonelogic) and then manually edited and verified (Mimics, Materialize). 3-dimensional parts were generated from each segmentation, consistently smoothed and decimated (3-Matic, Materialize), and aligned using an iterative closest point algorithm. A 14 domain SSM was created for the tibia through metatarsals to report mean shape and alignment between control and CMT feet. Single-domain SSMs were created for each individual bone to identify bones with substantial morphology change between groups (ShapeWorks Dev-v6.5, University of Utah). Shape variation between CMT and controls in the multi-domain model was tested with a Hotelling's T^2 test with false discovery rate correction to identify areas with significant differences in the combined morphology and alignment (ShapeWorks, University of Utah). For the multi-domain model and each single-domain SSM, principal component analysis was used to calculate modes of variation and parallel analysis was used to identify statistically significant modes across the population [6]. Along each mode of variation, PCA component scores between CMT and control groups were tested for normality then compared with either a t-test or Wilcoxon rank sum test with a Holm-Sidak correction. All statistical tests used a significance value of α=0.05.

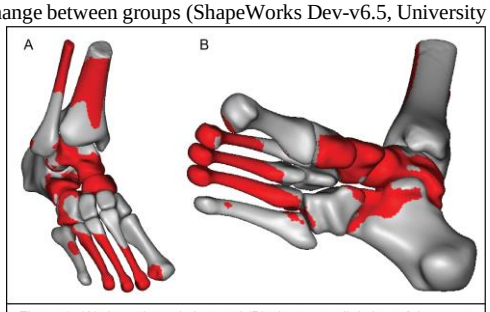

Figure 1: (A) dorso-lateral view and (B) plantar-medial view of the mean foot shape showing results from Hotelling's T² test with false discovery rate correction between CMT and control groups where red indicates particles with a p-value < 0.05

RESULTS: Hotelling's T^2 test revealed significant differences between CMT and control feet at the whole foot level. Corrected p-vales between CMT and control are shown in Figure 1, which s substantial differences in the medial midfoot, distal talus and calcaneus, and distal metatarsals. Parallel analysis of modes of variation showed that the first mode of variation, accounting for 59.4% of the variance in shape among the population, was the only mode of variation with significant differences between CMT and control feet. This mode of variation encompasses elevation of the arch with valgus rotation of the hindfoot (Figure 2). At an individual bone level, significant differences between CMT and control bone morphology within a mode of variation were seen in the 1st, 2nd, and 4th metatarsals, tibia, talus, and calcaneus. Figure 3 shows each of these modes of variation that were significantly different between groups.

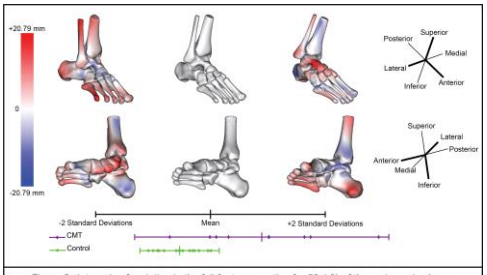

Figure 2: 1st mode of variation in the full foot, accounting for 59.4 % of the variance in shape, showing an antero-lateral view and postero-medial view of the foot and ankle at the mean shape plus and minus 2 standard deviations with distributions of shape scores along the first mode of variation for the control and CMT groups shown underneath with tick marks showing each individual sample

DISCUSSION: The full-foot model shows bony alignment and morphology change in the foot that corresponds with the clinical picture of CMT. However, the mode of variation that is significant between these groups only accounts for slightly more than half the total variance in foot shape in the population, supporting the vast heterogeneity of CMT and indicating that other factors, such as age, sex, or genetic subtype, may further influence foot deformity in CMT. Results for the 1st and 4th metatarsals show an arching of the individual bones, suggesting that the high arch seen in CMT patients is not solely a result of alignment change, but also a change in bone morphology in response to abnormal loading and/or alignment. No significant changes in individual bone morphology were seen in the navicular, cuboid, or cuneiforms, suggesting that the differences between CMT and control feet in the midfoot are primarily a result of changes in alignment. The calcaneus shows a significant morphology difference in the medial wall and posterior edges, which aligns with previous work showing curvature changes in the calcaneus [4]. The talus shows significant differences between groups predominantly at the talar neck, which supports previous investigation into talar neck morphology and angle [3,4]. Future prospective work will aim to explore the mechanism behind these morphologic changes and examine differences between genetic subtypes of CMT.

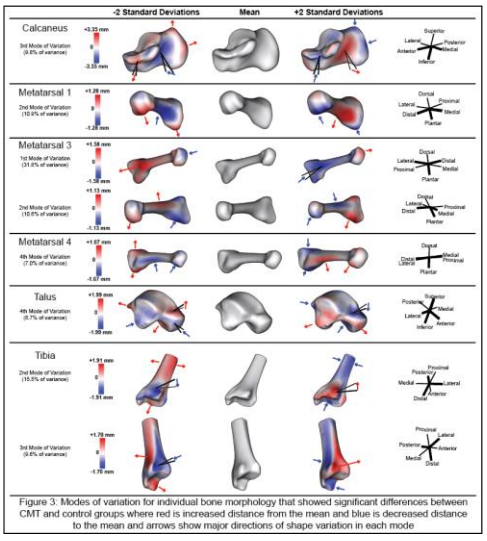

Figure 3: Modes of variation for individual bone morphology that showed significant differences between CMT and control groups where red is increased distance from the mean and blue is decreased distance to the mean and arrows show major directions of shape variation in each mode

SIGNIFICANCE/CLINICAL RELEVANCE: These data quantify morphologic changes in bony anatomy, rather than solely bone alignment, in patients with CMT, which changes the classical understanding of this disease process and may have implications in surgical planning for foot reconstruction in patients with CMT.

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