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Soft-tissue abnormalities associated with treatment-resistant and treatment-responsive clubfoot: Findings of MRI analysis

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Soft-Tissue Abnormalities Associated with Treatment-Resistant and Treatment-Responsive Clubfoot

Findings of MRI Analysis

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Background: Clubfoot treatment commonly fails and often results in impaired quality of life. An understanding of the soft-tissue abnormalities associated with both treatment-responsive and treatment-resistant clubfoot is important to improving the diagnosis of clubfoot, the prognosis for patients, and treatment.

Methods: Twenty patients with clubfoot treated with the Ponseti method were recruited for magnetic resonance imaging (MRI) of their lower extremities. Among these were seven patients (six unilateral cases) with treatment-responsive clubfoot and thirteen patients (five unilateral cases) with treatment-resistant clubfoot. Demographic information and physical examination findings were recorded. A descriptive analysis of the soft-tissue abnormalities was performed for both patient cohorts. For the patients with unilateral clubfoot, we calculated the percentage difference in cross-sectional area between the affected limb and the unaffected limb in terms of muscle, subcutaneous fat, intracompartment fat, and total area. With use of the Wilcoxon signed-rank test, we compared inter-leg differences in cross-sectional areas and the intracompartment adiposity index (IAI) between treatment-responsive and treatment-resistant groups. The IAI characterizes the cross-sectional area of fat within a muscle compartment.

Results: Extensive soft-tissue abnormalities were more present in patients with treatment-resistant clubfoot than in patients with treatment-responsive clubfoot. Treatment-resistant clubfoot abnormalities included excess epimysial fat and intramuscular fat replacement as well as unique patterns of hypoplasia in specific muscle groups that were present within a subset of patients. Among the unilateral cases, treatment-resistant clubfoot was associated with a significantly greater difference in muscle area between the affected and unaffected limb (−47.8%) compared with treatment-responsive clubfoot (−26.6%) ($p = 0.02$), a significantly greater difference in intracompartment fat area between the affected and unaffected limb (402.6%) compared with treatment-responsive clubfoot (9%) ($p = 0.01$), and a corresponding higher inter-leg IAI ratio (8.7) compared with treatment-responsive clubfoot (1.5) ($p = 0.01$).

Conclusions: MRI demonstrated a range of soft-tissue abnormalities in patients, including unique patterns of specific muscle-compartment aplasia/hypoplasia that were present in patients with treatment-resistant clubfoot and not present

continued

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in patients with treatment-responsive clubfoot. Correlations between MRI, physical examination, and treatment responsiveness may aid in the development of a prognostic classification system for clubfoot.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Isolated clubfoot is one of the most common congenital birth defects, with an estimated birth prevalence of 1 per 1000 live births[1]. Clubfoot treatment consists of manipulation and serial casting, a method that was described by Ponseti[2]. Following initial correction of the deformity, bracing is needed up to the age of five years to prevent clubfoot recurrence[3].

Although many patients with clubfoot treated with the Ponseti method have excellent long-term outcomes with minimal pain or disability, >40% of treated patients fail to respond to initial treatment or develop recurrent deformities requiring additional casting, years of bracing, and/or extensive bone and soft-tissue surgery[4-7]. As a result, many patients may develop lifelong foot pain and arthritis, and quality-of-life measures have shown significant functional impairment among patients with clubfoot[8,9]. However, identifying patients who are at risk for treatment resistance is difficult in most cases because the factors responsible for the failure of conventional clubfoot treatment are largely unknown. Patients with syndromic clubfoot[10-12] and certain genetic abnormalities, including chromosome 17q23 microduplications[13,14], often have clubfoot that is resistant to treatment. Unfortunately, because the genetic basis of clubfoot is unknown for the majority of patients, most patients with treatment-resistant clubfoot have no known risk factors.

The goal of our study was to determine whether structural abnormalities correlate with clubfoot treatment resistance. Magnetic resonance imaging (MRI) was used to compare soft-tissue abnormalities present with treatment-responsive clubfoot with those of treatment-resistant clubfoot. Correlating MRI findings with an initial physical examination of a patient at the time of diagnosis may potentially lead to the development of a new classification system for clubfoot that is more predictive of treatment.

Materials and Methods

Twenty patients with clubfoot were recruited for MRI analysis of their lower extremities from January 2011 to September 2012. Included in the study were patients who had isolated clubfoot treated with the Ponseti method[2] and who had experienced either no relapses (the treatment-responsive group) or relapses that were treated successfully without major surgery (the treatment-resistant group). Patients who had undergone extensive soft-tissue-release surgery were excluded from the study, as were those with any diagnosed genetic syndrome or neuromuscular disorder. Patients in the treatment-responsive group were required to be of such an age that MRI could be performed without administering sedation. Those in the treatment-resistant group had the MRI performed as part of clinical care, and, as a result, were younger and sedated for the one-hour study with use of intravenous anesthetics. For both cohorts, MRI was performed at a minimum of one year from any casting or surgical procedures, with the exception of one patient who had imaging at the age of one month, prior to any treatment. The grade of initial severity before treatment, according to the system of Diméglio et al., was noted within or inferred from medical chart documentation for all patients[15] (Table I). Specific exclusion criteria related to MRI included a history of claustrophobia, implanted or accidental exposure to metal fragments, or pregnancy. The study was approved by the Washington University Human Studies Committee, and informed consent was obtained.

Patient Cohorts

The treatment-responsive cohort included seven patients (five males and two females), with a mean age of 16.1 years (range, seven to twenty-five years) at the time of MRI analysis (Table I). Six of the seven patients had unilateral clubfoot. All of the patients were developmentally normal and had no abnormal physical findings other than clubfoot.

The treatment-resistant cohort included thirteen patients (eight males and five females), with a mean age of 3.9 years (range, 0.17 to eight years) at the time of MRI analysis (Table II). Five of the patients had unilateral clubfoot. Examination results were abnormal for all patients. Eight of the patients had slight or absent dorsiflexion of the great toe (drop toe sign)[16], and four had weak lateral-compartment musculature. Three patients had an additional diagnosis; one had amniotic constriction band in the left hand, one had been diagnosed with mild global developmental delay, and one had choanal and anal stenosis. The results of electromyography/nerve conduction study (EMG/NCS) of the tibialis anterior muscle were abnormal for six of seven patients. Muscle

TABLE I Patient Characteristics: Treatment-Responsive Group

Patient	Age *(yr)*	Sex	Side*	Diméglio Grade†	Treatment	Familial	Other Diagnoses
1	7	M	R	III	Ponseti method	Yes	None
2	9	M	R	II	Ponseti method	No	None
3	25	M	R	IV (MR)	Ponseti method	Yes	None
4	25	F	B	IV (MR)	Ponseti method	Yes	None
5	14	M	R	III	Ponseti method	Yes	None
6	9	M	R	IV	Ponseti method	Yes	None
7	24	F	L	IV (MR)	Ponseti method	Yes	None

*B = bilateral, R = right, and L = left. †MR = inferred from the medical record.

TABLE II Patient Characteristics: Treatment-Resistant Group

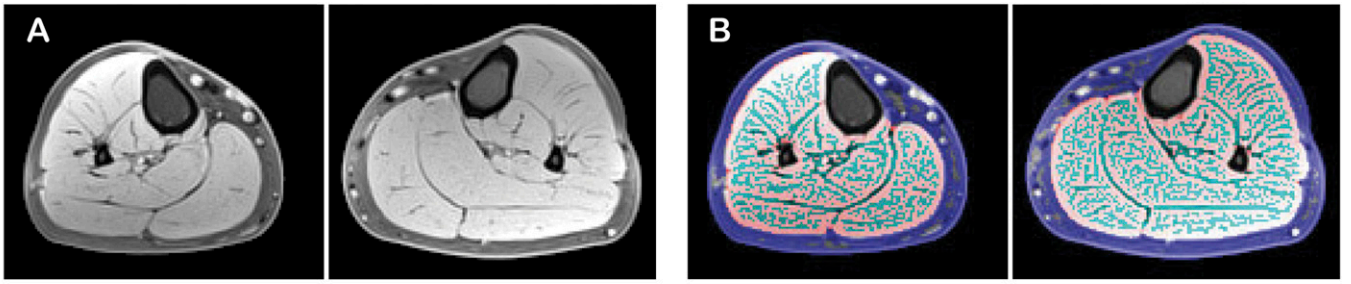
Patient	Age *(yr)*	Sex	Side*	Diméglio Grade	Treatment	Familial	Other Diagnoses	EMG/NCS†	Muscle Biopsy†
8 (A)	2	M	R	IV	Ponseti method, tibialis anterior tendon transfer	No	Amniotic band (hand)	NA	NA
9 (B)	5	M	B	IV	Ponseti method	No	Drop toe sign, weak peroneals	NA	NA
10 (C)	6	F	B (L > R)	III	Ponseti method, tibialis anterior tendon transfer	No	Developmental delay, gastrostomy tube	Bilateral chronic peroneal motor neuropathy	Type-1 fiber predominance
11 (D)	2	M	B	III	Ponseti method, repeat tenotomy, tibialis anterior tendon transfer, distal tibial osteotomies	No	None	Normal study	NA
12 (E)	2	M	B	III	Ponseti method, repeat tenotomy	No	Drop toe sign, weak peroneals	NA	NA
13 (F)	6	F	B	IV	Ponseti method, repeat tenotomy	Adopted, unknown	Drop toe sign, weak peroneals	Peroneal motor neuropathy	NA
14 (G)	3	M	B	IV	Ponseti method, repeat tenotomy	No	None	Low-amp MUPs, (myopathy)	Connective tissue and fat only
15 (H)	8	M	R	III	Ponseti method, repeat tenotomy	No	Drop toe sign, weak peroneals	NA	NA
16 (I)	2	M	R	III	Ponseti method, repeat tenotomy	No	Drop toe sign	Right-side peroneal neuropathy	NA
17 (J)	2	F	R	IV	Ponseti method, repeat tenotomy	No	Drop toe sign	NA	NA
18 (K)	7	F	B (R > L)	III	Ponseti method, repeat tenotomy	Yes	Drop toe sign	Bilateral peroneal neuropathy	NA
19 (L)	0.083	F	R	IV	Ponseti method, repeat tenotomy	No	Drop toe sign, choanal stenosis, anal stenosis	NA	NA
20 (M)	5	M	B	IV	Ponseti method, tibialis anterior tendon transfers, posterior release after MRI	No	None	Low-amp MUPs, (myopathy)	Nondiagnostic

*B = bilateral, R = right, and L = left. †MUPs = motor unit potentials. NA = not applicable.

biopsy of the abductor hallucis was performed for three patients; one showed type-1 fiber predominance, one was nondiagnostic, and one showed only connective tissue and fat.

MRI Technique

MRI was performed on a 1.5-T system (MAGNETOM Avanto; Siemens Medical Solutions). Both the affected and unaffected lower extremity were imaged with use of array coils. Both calves and thighs were imaged. No contrast material was used. Care was taken to position the patients and to adjust the number of slices so that the same anatomic extent of the muscles of interest was scanned for each patient. The patients were placed in a supine position with a Siemens circularly polarizing (CP) no-tune transmit/receive extremity coil placed around the calf muscles. The following MR parameters were used to acquire proton-density-weighted MR images: spin-echo pulse sequence, TR/TE = 1500/12 ms; field of view = 180 mm; bandwidth = 130 Hz/pixel; 30 slices, transverse orientation; signal averages = 1; flip angle = 90°; matrix = 256 × 256; echo



C **Single Leg Metrics**

	Right Leg (Affected)	Left Leg (Unaffected)
Total Cross Section Area (single leg in A):	134.7 cm^2	167.8 cm^2
Subcutaneous Fat (Blue area in B):	42.8 cm^2	49.1 cm^2
Leg Compartments (Pink/Green in B):	81.6 cm^2	108.1 cm^2
Muscle Tissue (within Pink/Green):	78.8 cm^2	104.5 cm^2
Intracompartment Fat (within Pink/Green):	2.8 cm^2	3.6 cm^2
Intracompartment Adiposity Index: (ranging from 0% (no fat) to 100% (all fat))		
$IAI = \left(\frac{\text{Intracompartment Fat}}{\text{Muscle Tissue + Intracompartment Fat}}\right)$	3.4 %	3.3 %

D **Inter-leg Comparisons**

Percentage Difference of Subcutaneous Fat

$$= \frac{\text{(Subcut. Fat of Affected Leg - Subcut. Fat of Unaffected Leg)}}{\text{Subcut. Fat of Unaffected Leg}}$$

$$= \frac{\text{42.8 sq cm - 49.1 sq cm}}{\text{49.1 sq cm}} = -13\%$$

Inter-leg IAI ratio

$$= \frac{\text{IAI of Affected Leg}}{\text{IAI of Unaffected Leg}}$$

$$= \frac{3.4\ \%}{3.3\ \%} = 1.03$$

Fig. 1

Figs. 1-A through 1-D Examples of calculations used in the MRI analysis. **Fig. 1-A** MRI slices of each leg, determined by maximum muscle content. **Fig. 1-B** Shading added to illustrate different single-leg metrics areas. **Fig. 1-C** Example of single-leg metrics data. **Fig. 1-D** Examples of inter-leg comparisons.

train length = 1; acquisition time ≈ 4.5 minutes; and pixel size = 0.703 mm. The MRI spatial resolution ranged from 0.5 mm × 0.5 mm to 1.08 mm × 1.08 mm in the axial plane with slice thickness ranging from 2.0 mm to 5.0 mm. Either T1 turbo spin-echo (T1 TSE) or volumetric interpolated breath-hold examination (VIBE) MRI sequences were obtained for every patient.

Image Analysis

Individual muscle groups and intramuscular fatty infiltration were first assessed subjectively. Fat was characterized as either epimysial (located within the tissue surrounding the whole skeletal muscle group) or intramuscular (visible beneath the muscle fascia, between muscles, and even within the muscle). For quantitative analysis, the slice with the greatest leg muscle area distal to the knee was identified for each sequence and was then analyzed using a semi-automated process that calculated cross-sectional areas of components of the leg. These MRI methods have been previously described[17]. The image-processing methods exploit the difference in the proton density of adipose tissue (brighter intensity) and muscle tissue (lower intensity), which enabled us to identify portions of the MR image corresponding to muscle or fat tissue. Image-processing algorithms automate this sorting of voxels into an intensity histogram of the leg by voxel count, and boundaries of tissue types (muscle and fat) naturally emerge, as the program automatically identifies the threshold value (the histogram's lowest point in the valley between the muscle and fat peaks) used to distinguish the muscle and fat tissues (epimysial and intramuscular).

The intracompartment adiposity index (IAI) was defined as the cross-sectional area of intracompartment fat (epimysial and intramuscular) divided by the total compartment area (intracompartment fat plus intracompartment muscle). This index (ranging from 0% to 100%) quantitatively represents how much fat is present as a percentage of the overall compartment. This index was applied to the muscle compartments in aggregate, although the index could theoretically be applied to individual muscle compartments as well.

Statistical Methods

Correlations were used to determine the association between the various anatomic abnormalities seen on MRI and the measures of anatomy for the unaffected and affected limbs. For patients with unilateral clubfoot, the percentage difference in cross-sectional area between the affected limb and the unaffected limb was calculated in terms of (1) total leg cross-sectional area, (2) area of muscle, (3) area of subcutaneous fat, and (4) area of intracompartment fat, with values presented as the mean and range. The percentage difference for patients with unilateral clubfoot was calculated as: [(Tissue area of affected leg) − (Tissue area of unaffected leg)]/(Tissue area of unaffected leg) (Fig. 1). We used the percentage difference in leg areas as opposed to absolute difference in order to control for age-related differences between patients in overall leg size (e.g., the difference in the cross-sectional area of the leg of a mature adult compared with that of a child). Analysis was also performed to compare the inter-leg differences of the patients with unilateral clubfoot in the treatment-responsive group with those in the treatment-resistant group. Given the small sample size and difficulty establishing normality, a Wilcoxon signed-rank test was applied (Stata statistical software; StataCorp, College Station, Texas).

Source of Funding

The cost of imaging for this study was supported by a grant from the Mallinckrodt Institute of Radiology, Washington University School of Medicine.

Results

Treatment-Responsive Clubfoot

Qualitatively, in patients in the treatment-responsive group, the muscle compartments were well defined in both limbs, with little differences in signal intensity, although the affected

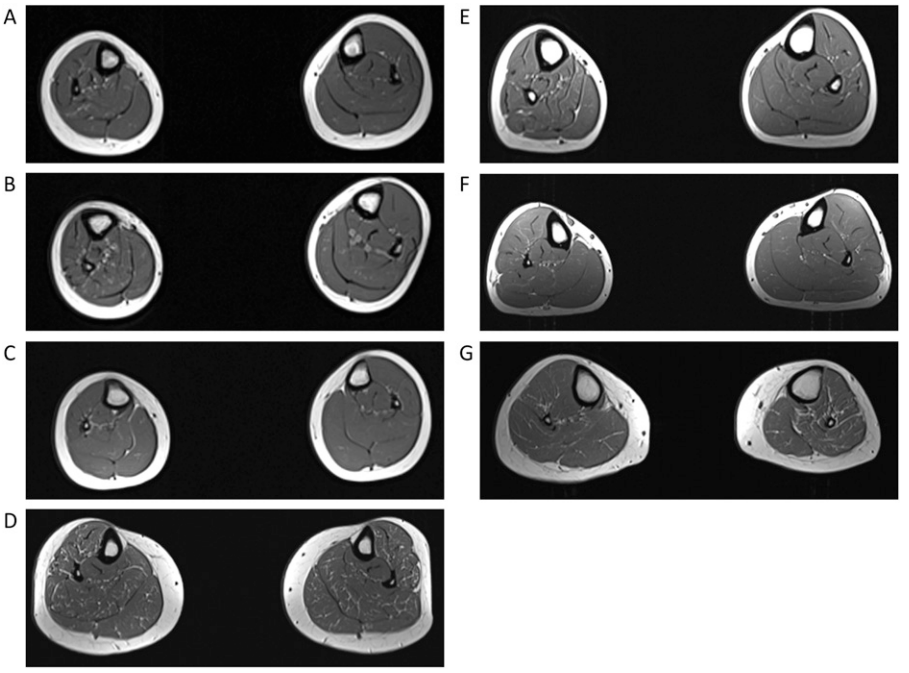


Fig. 2

Figs. 2-A through 2-G Treatment-responsive clubfeet were associated with relatively minor, nonspecific abnormalities on MRI. All cases represented are unilateral, with the exception of **Fig. 2-D**. Among the unilateral cases, the affected limb was only minimally smaller than the unaffected limb. Patient descriptions are provided in **Table I**.

limbs appeared slightly smaller than the unaffected limbs, with globally smaller muscle compartments (Fig. 2).

For the six patients with unilateral treatment-responsive clubfoot, quantitative measurements at the largest cross-sectional area revealed a mean difference of −15.3% (range, −12.4% to −19.7%) in total leg area between the affected and unaffected leg. The affected limb was always smaller. The affected limb also had less muscle area; we noted a mean difference of −26.6% (range, −20.4% to −43.3%) in muscle area between the affected and unaffected limb. The affected leg always had less muscle mass than the unaffected leg in the slice with the largest cross-sectional area. There was little difference in terms of subcutaneous fat quantity (mean difference, 2.0% [range, −12.8% to 14.2%]) or in terms of intracompartment fat (mean difference, 9.0% [range, −53.7% to 116.2%]) between the affected and unaffected leg.

Treatment-Resistant Clubfoot

In the treatment-resistant group, imaging abnormalities noted among the unilateral cases were often present bilaterally, although the findings for the unaffected limb were less severe. Qualitatively, many of the patients with treatment-resistant clubfoot were found to have increased epimysial fat that sharply demarcated muscle compartments (Figs. 3-A through 3-D). Others had diffuse intramuscular fatty infiltration (Figs. 3-E through 3-H). In one case, the gastrocnemius appeared more severely involved (Fig. 3-F), while in another, the fatty infiltration involved nearly all muscles, sparing just a small portion of the peroneus muscle (Fig. 3-G).

Another distinct subset of treatment-resistant patients had hypoplasia or aplasia of a specific muscle group, characterized by well-circumscribed, high-signal-intensity abnormalities within a muscle compartment (Figs. 3-I through 3-M). This group included a patient with complete replacement of the right anterior and lateral muscle groups with fat (Fig. 3-I). The other muscles, while slightly smaller than those of the unaffected limb, were otherwise normal in signal intensity. Slightly increased epimysial fat was present. The patient shown in Figure 3-J had distinct fatty replacement of the tibialis anterior, with otherwise normal muscles, although all compartments were reduced in size. Distinct fatty replacement of the lateral (peroneus) muscle compartment was present in an older child (Fig. 3-K) and in an infant who was scanned at one month of age, prior to any treatment (Fig. 3-L). Finally, replacement of the posteromedial muscle compartments (gastrocnemius) with fat was seen in a child with recurrent clubfoot (Fig. 3-M).

Quantitatively, a study of the five patients with unilateral clubfoot in the treatment-resistant group showed a mean difference of −16.8% (range, −3.6% to −25.4%) in total leg area between the affected and unaffected leg, with the affected limb always being smaller. The mean difference in muscle area between affected and unaffected leg was −47.8% (range, −36.6% to −62.3%), with the affected leg always having less muscle area. Measurement of the subcutaneous fat showed no obvious differences between the affected and unaffected legs, with a mean difference of 2.6% (range, −14.6% to 10.2%). However, the affected legs all had substantially more intracompartment fat compared with the unaffected legs, with a mean difference of

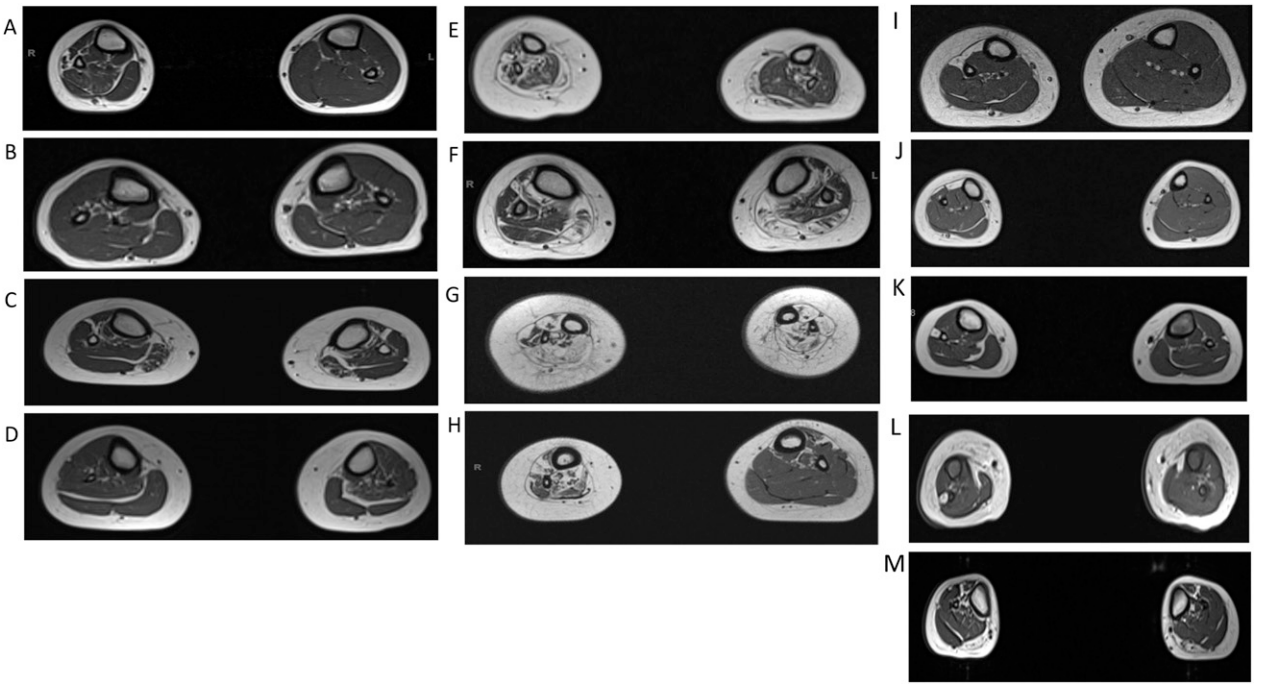


Fig. 3

Figs. 3-A through 3-M Treatment-resistant clubfeet were found to be associated with a spectrum of increased epimyseal and intramuscular fat deposition as well as specific muscle-compartment hypoplasia/aplasia. All cases represented are bilateral with the exception of **Figs. 3-A, 3-H, 3-I, 3-J, and 3-L**. Excess epimysial fat, indicated by bright signal outlining muscle compartments (**Figs. 3-A through 3-D**), and varying degrees of intramuscular fat deposition in various muscle compartments (bright signal, **Figs. 3-E through 3-H**) are shown. Specific muscle-compartment hypoplasia/aplasia was evident in some patients, with replacement with fat (bright signal) involving the anterior and lateral muscle groups (**Fig. 3-I**, right foot, left image), anterior muscles (**Fig. 3-J**, right foot, left image), lateral muscles (**Figs. 3-K and 3-L**, right feet, left images), and posteromedial muscle group (**Fig. 3-M**, bilateral). Patient descriptions are provided in **Table II**.

402.6% (range, 163.9% to 915.4%). In the most extreme case (Fig. 3-H), up to ten times more fat was seen in the affected limb.

Analysis Between Groups of Inter-Leg Differences

Among the six unilateral treatment-responsive cases and the five unilateral treatment-resistant cases, the limb cross-sectional area was always smaller in the affected limb compared with the unaffected limb. Treatment responsiveness was not associated with a significantly greater difference in total leg area (−15.3% compared with −16.8%; $p = 0.47$). Treatment-resistant patients had a significantly greater difference in muscle area between the affected and unaffected limb (−47.8% [range, −36.6% to −62.3%]) compared with treatment-responsive patients (−26.6% [range, −20.4% to −43.3%]) ($p = 0.02$). An analysis of the inter-leg subcutaneous fat differences confirmed that there was no significant association with treatment response/resistance ($p = 0.72$). However, the inter-leg intracompartment fat differences were significantly larger in magnitude for the treatment-resistant group compared with the treatment-responsive group (402.6% versus 9.0%) ($p = 0.01$).

IAI Assessment

The IAI represents the amount of fat within the muscle compartment and was calculated for both the unaffected leg (range, 0.9% to 9.8%) and the affected leg (range, 3.4% to 30.7%) of the patients with unilateral clubfoot. For both treatment-responsive and resistant groups, the affected leg had a higher IAI than the unaffected leg. The highest IAI values were noted for the affected limbs in the treatment-resistant group. The inter-leg IAI ratio between affected and unaffected legs was much larger (8.7 [range, 3.9 to 18.8]) in the treatment-resistant cohort compared with that of the treatment-responsive group (1.5 [range, 0.6 to 3.5]) ($p = 0.01$).

Discussion

The current study provides important new insight into the biological basis of treatment-resistant clubfoot by comparing the imaging characteristics of treatment-resistant clubfoot to those of treatment-responsive clubfoot. These data are an extension of MRI studies that have recently shown that clubfoot, in general, is associated with a reduction in total leg volume and muscle volume, and an increase in fat volume[18-20]. While these earlier small studies established the presence of soft-tissue abnormalities in clubfoot, they did not describe the abnormalities that are unique to treatment resistance. In the current study, we found that treatment-resistant clubfoot was associated with a range of increased epimysial and intramuscular fat that is not present in patients with treatment-responsive clubfoot. Distinct muscle-group hypoplasia was present in a subset of treatment-resistant patients, likely reflecting the heterogeneous underlying etiologies of clubfoot. Finally, our quantitative measurements of inter-leg differences in patients with unilateral clubfoot revealed

that treatment-resistant clubfoot was associated with a greater difference in muscle and intracompartment fat areas compared with treatment-responsive clubfoot.

Increased epimysial fat deposition was more prominent in some patients with treatment-resistant clubfoot and may correspond to the extensive fibrosis initially described by Ponseti in his theory of clubfoot pathogenesis[21]. In our series, the epimysial fat deposition was often found in conjunction with small but otherwise normal-appearing muscle. Unfortunately, the pathophysiological basis for the epimysial fat is unknown. Increased epimysial fat was present in a single patient with amniotic band syndrome. The association of amniotic band syndrome with vascular compromise[22] may explain the overall limb and muscle smallness, perhaps with reactionary increase in epimysial fat.

Muscle-signal abnormalities often occur in patients with congenital myopathy[23,24]. Whereas congenital myopathies are often associated with fat replacement within specific muscle groups, the clubfoot abnormalities identified in the current study do not fit any of these established patterns. Likewise, none of our patients had weakness in the upper extremities, which is necessary for a congenital myopathy diagnosis. As an extreme case, one of our patients had an absence of nearly all muscles in the lower extremities (Fig. 3-G), along with normal spine imaging and a myopathic EMG. A child with similar absence of muscle was described previously[25], although the upper and lower extremities were both involved. Additional studies are necessary to determine the exact mechanism that causes intramuscular fat deposition in children such as these with clubfoot.

Our soft-tissue imaging also identified a small subset of patients with treatment-resistant clubfoot who had specific muscle-group hypoplasia or aplasia. This entity has not, to our knowledge, previously been described in terms of any other disorder. The congenital basis of clubfoot, along with the presence of a distinct and compact muscle compartment filled with fat, suggests that the muscle compartment failed to develop, as opposed to a muscle, present earlier in development, experiencing atrophy. In fact, a developmental process rather than a dystrophic event is supported by the presence of this abnormality in an infant imaged at one month of age, prior to any treatment. Similar lateral muscle hypoplasia was previously described in both humans and mice with a genetic abnormality involving the hindlimb-specific transcription factor PITX1[26]. Loss of muscle has been described previously in patients with upper-limb malformations caused by mutations present with Holt-Oram syndrome of TBX5[27], a gene that is closely related to the TBX4 gene that was recently implicated in clubfoot etiology[13]. Based on our previous studies of clubfoot patients with PITX1 genetic abnormalities, we hypothesize that a lack of regulatory gene expression may result in the failure of specific muscle-group development, either as a primary abnormality or as a secondary consequence of insufficient vascular or neurotrophic factors. It is interesting to note that four of the patients in our study (Figs. 3-C, 3-F, 3-I, and 3-K) had evidence of peroneal neuropathy on nerve conduction studies. Additional studies are needed to distinguish the precise etiology of these unusual cases, as they will likely impact treatment and prevention.

A limitation of our study was that only one patient was imaged prior to having any treatment for clubfoot. To reduce the possibility that surgical iatrogenic injury was responsible for the imaging abnormalities we detected, patients who had undergone extensive soft-tissue release surgery were excluded from this study. Furthermore, all of the patients in the current study were treated with the Ponseti method, which is unlikely to cause compression injuries, although this has been reported in rare cases[28]. Additional evidence that the soft-tissue abnormalities are related to the clubfoot deformity rather than secondary effects of treatment is provided by the presence of lateral compartment hypoplasia in an infant who was imaged prior to the initiation of any treatment. Future serial studies beginning at birth will be helpful to determining whether the abnormalities are static or whether improvements in muscle development may occur over time.

Our data suggest that gross clinical measurements, such as calf girth, may not be sufficient for predicting treatment response. When we restricted our analysis to unilateral cases in which the unaffected limb could serve as a "normal" control, the cross-sectional area of the affected leg was always smaller than that of the unaffected limb, regardless of treatment response/resistance. However, on comparing the magnitude of difference in the total leg area, we found no significant difference between the treatment-responsive and treatment-resistant group. This may be due to the wide range in quantity of subcutaneous fat as well as its large contribution to total leg volume. In contrast, smaller relative muscle and greater intracompartment fat areas were present in the affected versus the unaffected legs of treatment-resistant patients compared with those of treatment-responsive patients. Although previous studies have shown that calf girth is significantly smaller in surgically treated patients with unilateral clubfoot than in those treated nonsurgically[29], our new data suggest that these differences in nonsurgically treated patients are unlikely to predict treatment responsiveness. Instead, quantitative measures of specific tissue types in combination with targeted clinical examination findings may be necessary for reliable prognoses.

In addition to the abnormalities that we identified on MRI in this study, the presence of the drop toe sign at presentation also appears to be predictive of treatment resistance[16] and suggestive of severe abnormalities of either the anterior leg musculature or its innervating nerve. None of the patients with treatment-responsive clubfoot had drop toe sign, while it was present in eight of thirteen patients with treatment-resistant clubfoot. Larger studies are needed to determine whether drop toe sign is always associated with severe morphological abnormalities, and whether clinical signs or MRI abnormalities are more sensitive in the early detection of patients who may fail conventional treatment. It is our hope that predicting which clubfoot patients are at greater risk of relapse can improve care

delivery and allow an individualized treatment plan that may involve longer brace-wear recommendations or early tendon transfers.

While advances in clubfoot treatment such as the Ponseti method have led to many clinical successes, there remain many patients with inadequate responses to treatment. To our knowledge, no uniform method of classifying patients prior to treatment is available to accurately predict treatment response and facilitate personalized treatment plans, such as prolonged bracing or early tendon transfers. Imaging studies of newborns are clearly needed to determine whether abnormalities on MRI that are present at birth correlate with physical examination findings and/or later treatment response. Ideally, treatment would be based on key correlative physical findings to avoid the need for expensive imaging. Nevertheless, advanced diagnostics will likely be essential in identifying the key clinical findings as a classification system is developed, and may remain an important adjunct in the future for individualized clubfoot diagnosis and treatment. ■

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