Vascular Abnormalities Correlate with Decreased Soft Tissue Volumes in Idiopathic Clubfoot

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Abstract

Background Lower extremity vascular anomalies have been described for patients with clubfoot but few imaging studies have investigated effects on soft tissues such as fat and muscle. To make these assessments we need noninvasive, noncontrast agents to more safely image children.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Questions/purposes We describe a novel noninvasive imaging protocol to identify vascular and soft tissue abnormalities in the lower limbs of patients with clubfoot and determine whether these abnormalities are present in patients who had recurrent clubfoot.

Patients and Methods Three-dimensional noncontrast-enhanced MR angiography was used to identify vascular, bone, and soft tissue abnormalities in patients with clubfoot. We determined whether these abnormalities were more common in patients who had experienced recurrent clubfoot. **Results** Four patients with isolated unilateral clubfoot had arterial anomalies in the clubfoot limb. All patients had less muscle volume in the affected limb, and nine of 11 patients (82%) had less subcutaneous fat, with a mean difference of $0.56 \text{ cm}^3 \pm 0.36 \text{ cm}^3$ (range, 0.08–1.12 cm^3). Vascular anomalies and decreased fat and muscle volumes were present in all three patients with recurrent clubfoot.

Conclusions We found a high frequency of vascular and soft tissue anomalies in the affected limbs of patients with unilateral clubfoot that may correlate with response to treatment.

Clinical Relevance This approach has the potential to enhance our understanding of the anatomy of clubfoot and lead to a larger MRI study that may allow more accurate prediction of the risk of recurrent clubfoot.

Introduction

Clubfoot occurs in one in 1000 live births [40] and is one of the most common birth defects involving the musculoskeletal system. Despite the frequency of this disorder, little is known regarding the etiology. Although clubfoot may be associated with vertical talus, myelodysplasia, arthrogryposis, or multiple congenital anomalies, the majority of

clubfeet occur as isolated birth defects and are considered idiopathic [40]. Many theories have been proposed to explain the etiology of idiopathic clubfoot, including intrauterine compression, neurologic, excess fibrosis, arrest of normal development, and vascular deficiencies [13, 14]. Various morphologic abnormalities of nerve, muscle, bone, and vasculature have been identified in patients with clubfoot to support these theories [4, 15, 17]. Despite the availability of noninvasive imaging technologies such as MRI, few studies have comprehensively evaluated the bone and soft tissue abnormalities in clubfoot.

Of the various anatomic abnormalities, vascular abnormalities have long been recognized and may be the most commonly associated abnormality in clubfoot and in vertical talus [1, 4, 7, 11, 14, 15, 18–20, 33, 37]. Although conventional angiography often is considered the gold standard for the diagnosis of arterial malformations, it is an invasive study with risks, including arterial damage, hemorrhage, ischemia, and reduction in limb growth. Doppler ultrasound is an alternative noninvasive technique to study arterial anatomy but appears less sensitive and specific than arteriography for detecting arterial anomalies in patients with clubfoot [37]. Three-dimensional (3-D) contrast-enhanced MR angiography (MRA) has emerged as a reliable technique for assessment of peripheral vascular disease of the lower extremity in adults [8, 22, 35]. Kruse et al. reported the use of this technique in patients with clubfoot and observed vascular anomalies in the lower extremities of two pediatric patients with clubfoot and a patient with congenital vertical talus [19]. They did not examine bone and other associated soft tissue anomalies in that study [19]. A larger scale study with this same technique is not likely as it requires the use of contrast agents for which the risks are not fully understood.

The etiologic importance of vascular anomalies in clubfoot is unclear, but establishing the importance will require safe noninvasive methods of imaging to be used in a large number of pediatric patients. Although 3-D contrast-enhanced MRA is considered noninvasive, it requires placement of an intravenous line and injection of contrast material, most commonly gadolinium-based contrast agents. There is increasing evidence that links gadolinium-based contrast agents with the development of nephrogenic systemic fibrosis [2, 23, 38], and thus, there is a need for rapid MRA without the use of contrast agents. In addition, in a pediatric population, there is a need for noninvasive techniques that do not require venipuncture. These limitations, along with the added cost of a contrast agent, have led to increased interest in noncontrast-enhanced MRA.

Electrocardiography (ECG)-gated, noncontrast-enhanced MRA initially was described for the chest and abdomen by Miyazaki et al. [26] and Urata et al. [39], and more recently in peripheral arteries of healthy adult volunteers [27]. It is

noninvasive, has a short imaging time, and is able to distinguish arteries from veins. It also can be used to evaluate simultaneously muscle and fat volumes and bone length in the lower extremities. Therefore, it has the potential to be a valuable alternative to more invasive contrast-enhanced MRA, particularly in a young population.

We (1) describe the arterial abnormalities and associated bone and soft tissue abnormalities in subjects with unilateral clubfoot and in one patient with clubfoot on one side and vertical talus on the other using a novel and noninvasive 3-D noncontrast-enhanced MRA method, and (2) determine whether vascular anomalies and additional bone or soft tissue abnormalities are present in patients who experienced recurrent clubfoot.

Patients and Methods

Twelve consecutive subjects who met the inclusion criteria with idiopathic clubfoot deformity were recruited from two institutions: St. Louis Children's Hospital (six patients) and Saint Louis Shriners Hospital (six patients). All but one patient had isolated unilateral clubfoot deformity. The other lower extremity was without congenital deformities except in one patient who had an additional anomaly of a congenital vertical talus on the right side and a clubfoot deformity on the left. All patients were treated with serial casting followed by either a percutaneous tendoachilles tenotomy or an open Z-lengthening of the Achilles tendon. No patient had extensive soft tissue release surgery for clubfoot treatment. Specific exclusion criteria related to MRA imaging included age younger than 6 years, history of claustrophobia, implanted or accidental exposure to metal fragments, and pregnancy. Specific implanted metal fragments included a pacemaker, defibrillator, neurostimulator, artificial heart valve, and cerebral aneurysm clip. One of 12 scanned patients was excluded later owing to motion artifact on the MRA. Thus, 11 patients were included in the final analysis. The mean age of the 11 patients was 16.5 years (range, 6–60 years). There were eight male patients (73%) and three female patients (27%). A positive family history of clubfoot was documented in six patients. Seven (64%) of the 12 clubfeet were right-sided (Table 1). The minimum followup was 60 months (mean, 85 months; range, 50–108 months). Our Human Research Protection Committee approved the study, and written informed consent was obtained for all individuals.

All 11 patients were examined by one author (MBD) who specializes in clubfoot evaluation and treatment of children and adults. Eight of the 11 included patients were treated by one surgeon (MBD) from birth using the Ponseti method of serial manipulations and castings, a percutaneous tendoachilles tenotomy, and foot abduction bracing for

Table 1. Demographics

Patient	Age (years)	Gender	Family history
1	31	Male	Positive
2	60	Male	Positive
3	34	Male	Positive
4	6	Female	Positive
5	7	Male	Negative
6	7	Female	Negative
7	6	Female	Positive
8	8	Male	Positive
9	10	Male	Unknown (adopted)
10	6	Male	Negative
11	6	Male	Negative

3 years [31]. These eight patients had Grade III deformities, using the classification of Dimeglio et al., at the onset of treatment, indicating moderate to severe clubfoot [3]. Three patients experienced a relapse of the clubfoot deformity. In each case, the recurrent clubfoot deformity was treated successfully with repeat casting and no additional surgery. The remaining three patients, who were adults at the time they were seen at our institution, all had their initial clubfoot treatment done elsewhere as infants with serial manipulations and castings, open Z-lengthening of the Achilles tendon, and foot abduction bracing for 2 years. The three adult patients were evaluated at the time of the study by one author (MBD) with physical and radiographic examinations of the feet and lower extremities. Medical records and photographs from birth and early clubfoot treatment also were reviewed for the three patients to ensure an accurate diagnosis. Severity classification was not available for the three adult patients, although clinical records made notation of severe, rigid deformities in all three.

MRA was obtained from 5 to 59 years after completion of initial treatment. No patient was sedated for the purpose of MRA and patients were excluded if they could not lie still for the duration of the MRA study. Noncontrast-enhanced MRA was performed on a 1.5-T system (Magnetom Avanto; Siemens Medical Solutions USA, Inc, Malvern, PA, USA). Coronal scout images, fat-suppressed T2-weighted images, and NATIVE sequences were obtained from the tibial plateau to the ankle. NATIVE is a 3-D angiographic technique that allows acquisition of noncontrast-enhanced images with high resolution using a short scan time. Noncontrast-enhanced arterial phases were acquired by assessing inherent differences in signal between fast flowing blood during the systolic phase and the slower blood during the diastolic phase of the cardiac cycle. An ECG or pulse triggering is used to synchronize the data acquisition to the cardiac cycle. The difference between images acquired during fast- and slow-flow phases

resulted in the angiographic images. A phase-contrast flow quantification with retrospective gating was used to determine trigger times for fast- (systolic) and slow-flow (diastolic) phases before the 3-D acquisition. The 3-D sequence then was acquired with a base resolution of 256, 30 cm field of view, 1.5 mm thickness, TR of 234, TE of 17 ms, bandwidth of 977 Hz/pixel, 2.3 ms echo spacing, centric encoding, trigger delay of 0/600 for slow flow, and trigger delay of 280/300 ms for fast flow. A phase array peripheral extremity surface coil was used with parallel imaging with an acceleration factor of two. The total scan time for imaging was less than 30 minutes. A T1-weighted MR image set was acquired for the same anatomic coverage. This image set was used as a complementary image to the NATIVE sequence to evaluate muscle mass and fat.

Images were transferred electronically to a workstation for analysis. The vascular structures were analyzed independently by two experienced readers (MS, SS) who were blinded to the clinical history (ie, knowledge of which extremity was abnormal). A consensus reading was performed in instances of disagreement. The arterial pattern in the clubfoot limb was compared with that of the contralateral limb. The presence or absence of the anterior tibial, posterior tibial, peroneal, and dorsalis pedis arteries was recorded. The MRA was considered normal when the anterior tibial, posterior tibial, and peroneal arteries were of equal caliber at the ankle. An artery was considered abnormal if it was not detectable (ie, absent) or small compared with the opposite side (ie, hypoplastic).

Volume measurements of subcutaneous fat, muscle, and total mass were made of the affected and unaffected limbs by one observer (LJM) who was trained in volumetric analysis (Fig. 1). Volume measurements were made at the widest calf diameter in both legs. Measurements were acquired using semiautomated image segmentation software implemented in the Analyze software system (Mayo Clinic Foundation, Biomedical Imaging Resource, Rochester, MN, USA). Tibial and fibular lengths were measured from the articular surfaces of each bone.

Continuous variables are presented as the mean and SD, and categorical variables are presented as the frequency (percentage). We determined differences in volumetric fat and muscle mass and tibia and fibula lengths on MR images between affected and unaffected extremities using paired t test analyses. Statistical analysis was performed using the SPSS® software package (SPSS Inc, Chicago, IL, USA).

Results

Vascular, soft tissue, and bone anomalies were seen in some combination in all of the patients studied. Four of

10 (40%) patients with isolated unilateral clubfoot had arterial anomalies in the clubfoot limb. Two of these patients had absent and/or hypoplastic anterior tibial arteries (Fig. 2) in combination with absent dorsalis pedis arteries; one had an absent posterior tibial artery, and one had an isolated absent dorsalis pedis artery (Table 2). In

addition, the patient with vertical talus in one foot and clubfoot in the other had a hypoplastic anterior tibial artery on the vertical talus side. The mean age of the patients with arterial anomalies was 15.8 ± 13.0 years (range, 6–34 years) compared with 17.2 ± 23.9 years (range, 6–60 years) for patients without arterial anomalies.

Fig. 1 A coronal MR image of both lower legs of a 10-year-old boy with right-sided congenital clubfoot deformity is shown. Cross sections of both limbs were taken at the solid line for volumetric analysis of muscle and fat composition. The solid line indicates the widest calf area which in this patient was at the same level in both legs.

Fig. 2 MRA of the lower limbs in a 31-year-old man shows a hypoplastic anterior tibial artery on the right side (arrow).

Table 2. Arterial anomalies and soft tissue volumetric measurements at midcalf by MRI

Patient	Side affected	Arterial anomalies	Affected midcalf muscle volume (cm ³)	Unaffected midcalf muscle volume (cm ³)	Muscle volume difference (affected – unaffected, cm ³), (% difference)	Affected midcalf fat volume (cm ³)	Unaffected midcalf fat volume (cm ³)	Midcalf fat volume difference (affected – unaffected, cm ³), (% difference)
1	Left*	Right AT	11.52	11.81	–0.29 (–2.5%)	7.18	7.19	–0.01 (–0.1%)
2	Right	None	7.32	7.66	–0.34 (–4.4%)	6.71	7.44	–0.73 (–9.8%)
3	Right	Right DP	10.84	11.37	–0.53 (–4.7%)	19.14	15.75	3.39 (17.7%)
4	Right	None	3.84	4.08	–0.60 (–14.7%)	3.65	4.08	–0.43 (–10.5%)
5	Left	None	3.24	3.66	–0.42 (–11.5%)	3.84	4.96	–1.12 (–22.6%)
6	Right	None	4.65	5.76	–0.69 (–12.0%)	6.52	7.39	–0.87 (–11.8%)
7	Right	None	3.09	4.89	–1.80 (–36.8%)	5.78	6.08	–0.30 (–4.9%)
8	Left	Left AT and left DP	2.62	3.35	–0.73 (–21.7%)	4.43	4.91	–0.48 (–9.8%)
9	Right	Right AT and right DP	1.74	4.07	–2.33 (–57.2%)	4.44	4.80	–0.36 (–7.5%)
10	Right	Right PT	2.44	3.34	–0.90 (–26.9%)	3.20	3.28	–0.08 (–2.4%)
11	Left	None	3.14	4.54	–1.40 (–30.8%)	5.82	4.83	0.99 (17.0%)

* Patient affected with clubfoot on left side, vertical talus on right side; MRI = magnetic resonance imaging; AT = anterior tibial artery; DP = dorsalis pedis artery; PT = posterior tibial artery.

Table 3. Bone lengths (measured on MRI)

Patient	Side affected	Affected tibial length (mm)	Unaffected tibial length (mm)	Tibial length difference (affected – unaffected, mm) (% difference)	Affected fibula length (mm)	Unaffected fibula length (mm)	Fibular length difference (affected – unaffected, mm) (% difference)
1	Left*						
2	Right						
3	Right						
4	Right	243.5	251.5	–8.0 (–3.1%)		258.3	
5	Left	245.0	254.4	–9.4 (–3.7%)	238.1	254.4	–16.3 (–6.4%)
6	Right	270.9	276.4	–5.5 (–2.0%)	266.4	274.0	–7.6 (–2.8%)
7	Right	233.0	240.1	–7.1 (–3.0%)	230.5	238.8	–8.3 (–3.5%)
8	Left	243.9	248.5	–4.6 (–1.9%)	250.2	255.9	–5.7 (–2.2%)
9	Right	248.1	257.4	–9.3 (–3.6%)			
10	Right	226.4	231.7	–5.3 (–2.3%)	222.1		
11	Left	237.1	242.6	–5.5 (–2.2%)	233.5	238.9	–5.4 (–2.3%)

* Patient affected with clubfoot on the left side and vertical talus on the right side.

Fig. 3 A MRI axial reconstruction of both lower legs taken at the level shown in Fig. 1 was used as the starting point for volumetric analysis. The tibia (T) and fibula (F) areas were subtracted from both legs. Marked atrophy can be seen in the affected right side of this

patient. Subcutaneous adipose tissue (AT) is highlighted as a hyperdense region for volumetric analysis. Remaining middensity tissue represents muscle (MT).

MRI measurements of tibia lengths were available for eight patients, and in all cases, the tibia was shorter ($p < 0.001$) on the clubfoot side, with a mean difference of 0.68 ± 0.26 cm (range, 0.46–0.94 cm). Fibula length measurements were available for five patients. In all five patients, the fibula was shorter ($p = 0.012$) on the affected side, with a mean difference of 0.87 ± 0.45 cm (range, 0.54–1.63 cm) (Table 3). Measurements were not available for all patients because the entire tibia or fibula could not be observed on one image. All 11 patients, including five with arterial anomalies, had smaller ($p = 0.003$) muscle volume in the affected limb than in the unaffected limb, with a mean difference of 1.05 ± 0.73 cm³ (range, 0.29–2.33 cm³) (Table 2). Nine of 11 patients (82%) had smaller ($p = 0.007$) fat volumes in the affected limb, with a mean difference of 0.56 ± 0.36 cm³ (range, 0.08–1.12 cm³) (Fig. 3). Four of the five patients with arterial

anomalies on the affected side had decreased fat volume in the affected limb. The one patient with an arterial anomaly who did not have a corresponding decrease in fat volume had a distal arterial anomaly (absent dorsalis pedis artery) at the level of the foot.

All three patients with recurrent clubfoot had vascular anomalies on the affected side detected by MRA. In addition, all three patients had decreased muscle and fat volumes on the affected side. This correlated with decreased calf circumference as measured clinically and leg length measured clinically and on MRI for each of the three patients. The clubfoot relapse in each instance was treated with repeat casting alone, without the need for surgery. To mitigate the possible effects of cast immobilization on muscle volume, clinical measurements and MRA imaging were performed more than 2 years after completion of treatment relapse with casting in all three patients.

Discussion

Noncontrast-enhanced MRA, which avoids the need for venous puncture and use of contrast agents, provides diagnostic information equivalent to that seen with standard angiography [6] and with contrast-enhanced MRA in some clinical situations [28], but until now, there has been no reported use of this method for evaluating the vasculature in patients with congenital limb malformations. We used this imaging technology to identify arterial, bone, and soft tissue anomalies of the lower extremities of patients with unilateral clubfoot and for one patient with clubfoot on one side and vertical talus on the other. In addition, we determined whether these anomalies were present in patients who experienced clubfoot recurrence.

We draw the reader's attention to some limitations. First, the analyses were limited to 11 patients. A larger study group might provide stronger evidence to support a higher incidence of arterial and soft tissue anomalies in patients with clubfeet prone to relapse and therefore more difficult to treat. Second, the study was designed only to assess total muscle volume at one area of the leg rather than specifically look at individual muscle compartments. Information regarding which compartments are most involved would provide a better phenotyping opportunity.

Our observations suggest noncontrast-enhanced MRA can detect anomalous vascular anatomy in children and adults with clubfoot. We identified arterial anomalies in four of 10 (40%) patients with unilateral clubfoot in our series and in the limb with vertical talus of one patient in this series with vertical talus on one side and clubfoot on the other. However, because these congenital vascular anomalies may occur in as much as 8.4% (32 of 380) of healthy individuals [36], the presence of a vascular deficiency alone appears insufficient to cause these limb birth defects. Therefore, we consider the possibility that other anatomic abnormalities, including those of bone, muscle, or fat, may correlate more closely with clubfoot abnormality and evaluated these structures using MRI. We hypothesize arterial deficiency is a marker of abnormal early limb development that correlates with other developmental abnormalities of the skeleton or muscle, which together cause clubfoot. This hypothesis is supported by recent genetic data implicating altered transcription factor expression (ie, PITX1, HOX genes) in early limb bud formation in the etiology of clubfoot [9, 12].

Although arterial abnormalities were found in 40% of our patients with unilateral clubfoot, reduced muscle and fat volume were present nearly universally in the affected limb. Ippolito et al. [16] recently identified smaller calf size in fetuses with clubfoot, suggesting this anatomic abnormality is not a result of treatment. Our data are consistent with this observation, as the muscle volume was less in the

affected limbs in our patient cohort, none of whom had extensive surgical releases to correct their clubfoot deformities. Decreased fat volume of the affected limb also provides evidence to refute a myopathic etiology of clubfoot, as these MRI findings are distinct from those seen in children with muscular dystrophies and congenital myopathies in which a fatty infiltration process of the muscles often occurs leading to an increase in total fat volume and a decrease in total muscle volume [24, 25, 30]. Regarding the presence of bone anomalies, our data in nonsurgically treated clubfeet suggest mild tibial deficiency is a primary feature of unilateral clubfoot in the majority of patients.

Although limb-length discrepancy has been described for patients with unilateral clubfoot, this often has been attributed to extensive soft tissue release surgery [21], and there are no studies, to our knowledge, that address the presence of leg-length inequality in patients with clubfoot treated with the primarily nonsurgical Ponseti method [32].

In our study, vascular anomalies correlated with decreased fat and muscle volumes and reduced tibial length and also may correlate with clubfoot recurrence. The three patients in our series with clubfoot relapse all had vessel abnormalities, decreased muscle and fat volumes in the lower leg, and leg-length discrepancies, suggesting a constellation of these MRA findings may correlate with a poorer response to treatment. As clubfoot is heterogeneous in terms of initial severity, response to treatment, and etiology, current classification systems for initial clubfoot severity do not always allow accurate prediction of response to treatment [3, 5, 10, 29, 34]. As a result, there is a need to develop a more specific diagnostic classification system for clubfoot deformities. Instead of basing the classification only on physical examination findings, more accurate phenotyping may be possible with the addition of detailed MRA assessment of arterial structures, muscle, fat, and bone.

We have shown a new method of noninvasive noncontrast-enhanced 3-D MRA and MRI can delineate soft tissue and vascular anomalies in patients with clubfoot. Our data show a high frequency of vascular anomalies, reduced muscle and fat volumes, leg-length discrepancies, and decreased calf circumference in the affected clubfoot limb of patients with a unilateral deformity. Furthermore, vascular abnormalities were present in all three patients with recurrent clubfoot, suggesting these anatomic abnormalities may be predictive of response to treatment. Although additional studies are needed, these studies have the potential to provide valuable insight into the etiology of clubfoot and may allow a more accurate prediction of patient response to traditional treatment methods and risk of relapse. In addition, based on our successful use of noncontrast-enhanced MRA to evaluate vascular structures in the lower extremities of patients with clubfoot, we suggest, with further study, that MRA could be used in

screening family members of patients with clubfoot deformities. This could improve our understanding of basic patterns of normal and abnormal limb development, including the association of vascular anomalies with specific gene mutations

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